Taking an Economic Approach to Evaluating HIV programs in Australia

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Research program aimed to assess whether Assessing Cost Effectiveness (ACE) approach could be used in priority-setting process to assess interventions for treatment and prevention of HIV in Australia that stakeholders could understand and be engaged in, and that would provide insights that would be useful, relevant and illuminating. Three linked studies of ACE-HIV supported by two studies measuring cost and patient-reported outcomes of people living with HIV in Australia.

Chapter 1 is literature review on HIV interventions in high-income countries. There were few published studies on economic evaluations of interventions for the prevention and treatment of HIV in Australia and few studies of interventions that were relevant in 2008. Chapter 2 reports study using a novel method to derive cost data for 10,951 people living with HIV from Medicare Australia. Data from this study were combined with other available data to estimate total cost of HIV healthcare in Australia for use in models of ACE-HIV project. Study found that it was possible to use Medicare Australia database to estimate costs of HIV healthcare claimed through the Medicare Benefits Schedule.

Chapter 3 describes original study measuring health-related utility in people living with HIV in era of effective antiretrovirals. Australian utility instrument (AQoL) was used for first time in HIV in a sample drawn from existing cohort with available clinical and surrogate data. AQoL was reasonably acceptable for use in sub-set of cohort of HIV patients, but low correlation in scores was seen with different health states associated with HIV.

Chapter 4 reports Assessing Cost-Effectiveness in HIV (ACE-HIV) project, priority-setting exercise that consisted of systematic approach to economic evaluation applied to six different interventions for HIV prevention and healthcare in Australia. The group ranked the interventions according to the economic model results and then re-ranked them after considering non-economic factors.

Chapter 5 reports method, results and discussions of six cost-effectiveness analyses performed for ACE-HIV project. Chapter 6. Thesis concludes that ACE approach could be a sound and useful approach for priority-setting in HIV medicine in Australia and that data required for the economic evaluations could be gathered from existing databases and cohorts.

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## Index

| Introduction | Introduction to purpose and structure of thesis | 3 |
| Chapter 1 | Literature review of economic evaluations of HIV interventions | 11 |
| Chapter 2 | HIV healthcare: costs and resource use | 51 |
| Chapter 3 | Measuring health-related utility in people living with HIV | 82 |
| Chapter 4 | Assessing Cost-Effectiveness in HIV (ACE-HIV) project | 107 |
| Chapter 5 | The ACE-HIV Economic evaluations | 135 |
| Chapter 6 | Discussion and Conclusions | 196 |
| References | References | 219 |
| Appendix A | EURONHEED questionnaire | 242 |
| Appendix B | Instruments used in Chapter 3 | 245 |
| Appendix D | Pamphlet 8 from ACE-Prevention | 265 |
| Glossary | Acronyms and abbreviations |
Abstract

Research program aimed to assess whether Assessing Cost Effectiveness (ACE) approach could be used in priority setting process to assess interventions for treatment and prevention of HIV in Australia that stakeholders could understand and be engaged in, and that would provide insights that would be useful, relevant and illuminating. Three linked studies of ACE-HIV supported by two studies measuring cost and patient-reported outcomes of people living with HIV in Australia.

Chapter 1 is literature review on HIV interventions in high-income countries. There were few published studies on economic evaluations of interventions for the prevention and treatment of HIV in Australia and few studies of interventions that were relevant in 2008.

Chapter 2 reports study using a novel method to derive cost data for 10,951 people living with HIV from Medicare Australia. Data from this study were combined with other available data to estimate total cost of HIV healthcare in Australia for use in models of ACE-HIV project. Study found that it was possible to use Medicare Australia database to estimate costs of HIV healthcare claimed through the Medicare Benefits Schedule.

Chapter 3 describes original study measuring health-related utility in people living with HIV in era of effective antiretrovirals. Australian utility instrument (AQoL) was used for first time in HIV in a sample drawn from existing cohort with available clinical and surrogate data. AQoL was reasonably acceptable for use in sub-set of cohort of HIV patients, but low correlation in scores was seen with different health states associated with HIV.

Chapter 4 reports Assessing Cost-Effectiveness in HIV (ACE-HIV) project, priority-setting exercise that consisted of systematic approach to economic evaluation applied to six different interventions for HIV prevention and healthcare in Australia. The group ranked the interventions according to the economic model results and then re-ranked them after considering non-economic factors.

Chapter 5 reports method, results and discussions of six cost-effectiveness analyses performed for ACE-HIV project.

Chapter 6. Thesis concludes that ACE approach could be a sound and useful approach for priority-setting in HIV medicine in Australia and that data required for the economic evaluations could be gathered from existing databases and cohorts.
Introduction

The research program that makes up this thesis started in 2007, with the fieldwork and stakeholder process being completed by September 2009. The research program consisted of three studies, preceded by a literature search. The three studies were linked, with the largest piece of work being the Assessing Cost Effectiveness in HIV project (ACE-HIV) supported by two studies measuring the cost and patient-reported outcomes of people living with HIV in Australia. ACE-HIV was based on a novel priority-setting approach that consisted of a series of cost-effectiveness analyses combined with stakeholder input to help inform priority-setting for the funding of interventions for the prevention and treatment of HIV. I will explain the thesis structure and flow in more detail below.

There have been major changes in the prognosis and management of HIV infection in high-income countries like Australia since the introduction of highly active antiretroviral medications.

“HIV has changed to a fairly expensive chronic condition rather than an intolerably expensive, mostly fatal illness (1).”

The improvements in morbidity and mortality led to a reduced need for hospital beds funded by state governments for patients with AIDS but the cost of the new antiretroviral agents led to substantial pressure on the Federal government health budget. HIV budgets that had previously been protected or ring-fenced started to be considered part of the mainstream budget, thereby creating the need to compete for funding with programs for the prevention and treatment of other chronic diseases. Programs for the prevention of HIV also came under funding pressures despite rising rates of HIV infection. New biomedical approaches to HIV prevention were proposed, including circumcision and pre-exposure prophylaxis, as well as the early use of antiretrovirals as prevention of HIV transmission rather than just for treatment.

Priorities regarding the funding of treatment and prevention of HIV appeared to be based frequently on historical precedents, political lobbying or media pressure, rather than the result of transparent explicit processes or scientific evidence. Economic analyses had been used extensively in the deliberations of the Pharmaceutical Benefits and Medical Services
Advisory Committees (PBAC and MSAC) about new individual drugs and assays; otherwise, the results of economic analyses had had limited impact in HIV medicine in Australia. Two economic studies related to the state and federal budget spending on certain programs had been performed previously, with limited stakeholder input including clinicians.

There are a number of possible explanations for this situation. Historically, much decision-making in HIV medicine has been reactive for good reasons. The crisis that hit the gay community in Australia with the advent of AIDS in the early 1990s required quick and politically difficult decisions to be made to institute prevention campaigns, even though there was no evidence to support them. When antiretrovirals (ARV) became available, they were provided by the Australian government rapidly, because the mortality and morbidity of AIDS meant that no other option needed to be considered. As the crisis became more manageable and people stopped dying so quickly, review and evaluation of new treatment and diagnostic tools became more extensive, but the processes of the Pharmaceutical Benefits and Medical Services Advisory Committees allow only for one drug or tool to be considered at a time, comparing it to the intervention that it is most likely to replace. This incremental approach leads to an incremental rise in effectiveness and costs, but does not necessarily lead to the removal or reduce the price of, superseded ineffective or inefficient therapies.

Another reason for the lack of use of economic evaluation in priority-setting in HIV medicine could be the lack of priority-setting processes more generally within medicine. Decisions are made to fund services for political reasons; some services or interventions must be funded for a particular geographical area or population or to respond to public and media concern. An example of this is nucleic acid testing of the blood supply, which is not an efficient use of resources (2, 3), but was implemented in Australia to avoid concerns about the blood supply and to reduce the risk of having to pay compensation if infection does occur.

The lack of local data on costs and economic outcomes for HIV prevention and treatment in Australia may have also reduced the likelihood that economic evaluations would be performed and thus be useable for priority-setting. As I will discuss in Chapters 2 and 3, there are very limited recent data on HIV costs and outcomes in Australia. Since completing the studies reported in this research program, there have been a number of requests for the
data to allow economic evaluations to be performed. A study of the cost-effectiveness of routine screening of sex workers in Victoria that used the cost of HIV derived in the cost study, led to a change in government policy (4).

Another reason for the paucity of economic evaluations may relate to the lack of resources to perform them. Economic evaluations require both funding and people trained in the area. Economic evaluations for submissions to Pharmaceutical Benefits and Medical Services Advisory Committees are usually funded by industry. The Government funds studies of public health interventions such as the return on investment study on the cost-effectiveness of needle-syringe programs. There were no health economists studying or working at the National Centre for HIV Epidemiology and Clinical Research (Kirby Institute) before the doctoral research program was initiated. This situation is not unique to Australia; the majority of authors of the global published literature on HIV economic evaluation in high-income countries are based in North America. Economic evaluation studies may appear in the HIV-specific literature but these may be missed or not understood by clinicians.

Finally, a lack of economic evaluation literacy amongst HIV doctors may have contributed to the lack of influence of studies. The majority of HIV clinicians in Australia have not studied health economics or economic evaluation and may therefore be unable to understand the methods, results and implications of an economic evaluation. Doctors may also object to an economic approach to decision-making on the basis of the belief that health should be funded according to need without consciousness of the real cost or the opportunity cost or because they may be opposed to economic rationalist thinking for political or moral reasons. The lack of stakeholder input into many economic evaluations in the past may have contributed to a general sense of disinterest in their findings and implications.

One economic approach that had successfully bridged the gulf between health economists and clinicians in other medical disciplines was the Assessing Cost-Effectiveness (ACE) approach that combined a series of economic analyses with stakeholder input and clear explicit processes (5). The Assessing Cost-Effectiveness method had been applied successfully to priority-setting processes about the treatment and prevention of cancer, mental health and stroke, with the input of clinicians, government and community representatives. In 2007, there was a large National Health and Medical Research Council
(NHMRC) funded program of research using the ACE approach for the assessment of interventions for the prevention of non-communicable diseases. This research program aims to assess whether the ACE approach could be used in a priority-setting process to assess interventions for the treatment and prevention of HIV in Australia that stakeholders could understand and be engaged in, and that would provide insights that would be useful, relevant and illuminating.

Before starting the ACE-HIV project, cost estimates and health outcome measures were needed that could be used in the economic models. These data were not available for Australia. The last published HIV cost study had been conducted in the early 1990s and there had been few studies measuring health-related utility, an economic outcome measure of the preferences of people for different levels of quality of life. Health-related utility scores are used by health economists to value the quality of additional life years gained by healthcare and prevention interventions. Two different outcomes, the quality-adjusted life year (QALY) and disability-adjusted life year (DALY) are used in cost-effectiveness analyses to provide the denominator of the incremental cost-effectiveness ratio, usually expressed as a cost per QALY or DALY. Economic analyses can be used by decision makers to make decisions on the allocation of resources and the implementation of interventions to maximise health outcomes. As one of the key inputs in cost-effectiveness analyses, utilities need to be up-to-date and valid for the Australian population (6).

In Australia, these kinds of study had been mostly conducted in the era before highly active antiretroviral therapy (7). Cost and economic outcome studies can be complex and resource-intensive to conduct. I decided to use novel approaches applied to existing datasets to gather the data. The first study used the Medicare Australia claims database to examine the use and cost of healthcare from 2003-2007 for approximately 11,000 people living with HIV. The second study was based on a sub-set of participants included in an existing large clinical observational database. It used three quality of life/utility instruments and was the first to employ a generic Australian utility instrument in HIV.
The primary research question was

1. Is it feasible and valuable to apply the ACE method to a series of economic evaluations of a range of treatment and prevention interventions, with stakeholder involvement, in a way that will inform decision-makers for priority-setting in HIV medicine in the context of limited time and other resources? A secondary gain from the process of answering this question was the assessment of the cost-effectiveness of six interventions for the prevention and treatment of HIV.

Before embarking on answering this primary research question, data were needed to inform the economic evaluations in the context of limited resources. The second research question was therefore:

2. Can costs and outcomes suitable for use in economic evaluation be measured using existing datasets in novel ways?

**Structure of thesis**

As stated previously, the ACE-HIV project reported in chapters 4 and 5 is the largest piece of work in the thesis. It is supported by the literature review in chapter 1 and two original studies reported in chapters 2 and 3. Conclusions from the research program are presented in chapter 6.

In more detail,

**Chapter 1** is a literature review that incorporates a critical appraisal of the cost-effectiveness studies on HIV interventions in high-income countries that informed the ACE-HIV program process.

**Chapter 2** reports the study using a novel method to derive cost data for people living with HIV from Medicare Australia. Data from this study were combined with other available data to estimate the total cost of HIV healthcare in Australia for use in the ACE-HIV project.

**Chapter 3** describes an original study measuring health-related utility, an economic measure of quality of life, for the first time in Australian people living with HIV in the era of effective antiretrovirals. I used an Australian utility instrument, the Assessing Quality of Life
Instrument (AQoL) for the first time in HIV in a sample drawn from an existing cohort with available clinical and surrogate data. The outcomes of this study were intended to be used in the economic models of the ACE-HIV project.

Chapter 4 is the first of two chapters reporting the Assessing Cost-Effectiveness in HIV (ACE-HIV) project, a priority-setting exercise that consisted of a systematic approach to economic evaluation applied to six different interventions for HIV prevention and healthcare in Australia. This process includes stakeholder input and feedback to a decision making process. The chapter presents an explanation of the ACE-HIV method, the choice of interventions to be evaluated, and the stakeholder input inclusion process. Finally, this chapter illustrates the feasibility, acceptability and reliability of taking an economic approach to priority-setting with stakeholder input in a fast-moving field such as HIV medicine.

Chapter 5 reports the method, results and discussions of the six cost-effectiveness analyses performed for the ACE-HIV project. The six interventions were circumcision, pre-exposure prophylaxis, needle-syringe programs, post-exposure prophylaxis, early use of antiretrovirals as prevention and anal cytology screening. It includes a discussion of new data that emerged from the field that could have affected the findings from the ACE-HIV project, including the HPTN052 study of early use of antiretrovirals as prevention and the pre-exposure prophylaxis studies.

Chapter 6 concludes the thesis addressing a number of aspects including the ways that the studies answered the research questions as well as the essence of the contribution to science; the potential benefits of the application of the research findings to clinical care and population health; further research that would lead on from this work.
Collaborators in research

I conducted this work in collaboration with several colleagues. I will point out the parts played by others throughout the thesis, but summarise here the support provided.

Chapter 2

Cost study: The original idea for the method was inspired by conversations with Dr Susan Hurley. I devised and implemented the study and carried out the analyses. Statistical advice on the most appropriate computer program to analyse the Medicare Australia data was provided by Dr Kathy Petoumenos. Andrew Dalton showed me the method used to analyse the hospital diagnostic related group data. Dr Anne Magnus helped me with the method used for estimating productivity losses and gains.

Chapter 3

Utility study: I devised the study and implemented it in collaboration with staff from five clinical sites who recruited study participants. I carried out the statistical analysis and data matching with the Australian HIV Observational Database with the support of Dr Kathy Petoumenos and her team.

Chapter 4

I set up the ACE-HIV study and ran the stakeholder inclusion process. Professor Rob Carter and Theo Vos developed the original ACE approach adopted in this study and provided much advice through the process. Stakeholders on the panel included:

David Baker
Levinia Crooks
Sean Emery
Robert Finlayson
Andrew Grulich
Jenny Hoy
Michael Kidd
Cipri Martinez
Marion Pitts
Jo Watson
Bill Whittaker

East Sydney Doctors
Australasian Society for HIV Medicine
NCHECR, UNSW
Taylor Square Private Clinic
NCHECR, UNSW
Victorian HIV Service, Alfred Hospital
Flinders University
Western Australia AIDS Council
Australian Centre for Research in Sex Health and Society, Latrobe University
National Association of People Living with HIV/AIDS (NAPWA)
National Association of People Living with
Chapter 5

I designed and implemented all the cost-effectiveness models with collegiate support in some of the epidemiology modelling:

Circumcision: Dr David Wilson developed the epidemiological mathematical model with the collaboration as clinical adviser. I developed and ran the economic model. I was the primary author on the peer-reviewed publication.

Needle-syringe programs: Dr David Wilson and Amy Kwon developed and ran the epidemiological mathematical model with me as clinical adviser. I developed and ran the economic model. I was the co-lead author on the Return on Investment II report and wrote the economic analysis chapters.

Post-exposure prophylaxis: Dr Anna Pierce and Brian Price provided the activity data from the Victorian Non-Occupational Post-Exposure Prophylaxis program.

Anal cytology screening: Dr Richard Hillman and Leon Botes supplied clinical data from the St Vincent’s Hospital screening program and advice on the model.

Tree-Age models: Liliana Bulfone from Deakin University provided me with much advice.
Chapter 1 A literature review of economic evaluations of HIV interventions in the Highly Active Antiretroviral Therapy era from 1996-2007.

1.1 Introduction

I performed this literature review in 2007 with the purpose of informing the ACE-HIV process described in chapter 4 and to understand more about solutions to the challenges of economic evaluation analyses. I included findings from papers published up until early 2009 in the cost-effectiveness models in Chapter 5 where I will discuss how recent published data would have affected the findings of the research program.

1.1.1 Previous reviews

There had been two recent reviews of the literature on the cost-effectiveness of interventions for HIV prevention and treatment. Harling performed an extensive systematic review of HIV interventions with three objectives (i) to review the literature between 1994-2004 (ii) point out the gaps especially related to the developing world (iii) discuss methodological problems with the current literature. He devised and applied a scoring mechanism for study quality. Summary scores were reported for data quality comparatively between the categories of the literature. Most of the studies had been performed in North America and that many used varied and potentially less rigorous sources for inputs. At the end of this extensive and well-conducted review, he concluded that there have been many studies, but not many in topic areas relevant to the majority of people affected and infected by HIV in the developing world. The methodology of many left much to be desired(8).

Hornberger focused on cost-utility analyses using US resources and currency, resulting in a review of studies limited to interventions in the USA. He aimed to examine how comprehensively the literature had covered the topic areas of the Department of Health and Human Services (DHHS) guidelines since the start of the HIV epidemic. He assessed methodological quality and reported a range of results using only the highest quality studies(9). For quality assessment, he used a tool by Chiou(10) with 16 questions that had been used to assess economic evaluations on other disease areas. Having assessed the quality, he reported the costs, benefits and incremental cost-effectiveness ratios (ICER) for
the studies that scored over 90% according to DHHS topic area. The costs reported in studies were adjusted to 2005 dollars using the general consumer price index. For prevention studies, he recalculated the ICER using the average of estimates of the quality adjusted life years lost with HIV infection in 2005(11) and the cost of HIV from 1997(12), that was based on four previous studies in the pre-HAART era(13-16). His review concluded with a table reporting ICERs on 24 interventions from 22 high quality studies. The interventions were described as: cost-saving, cost-effective with an ICER <$100,000 per QALY gained or not cost-effective with an ICER>$100,000 per QALY gained. These results were compared with the recommendations from the DHHS guidelines. The comprehensive analysis demonstrated that health economic analyses were often not cited or taken into account by guideline writers. Some strategies that were cost-saving were ignored by guideline writers and others which were not cost-effective were recommended in the guidelines, such as post-exposure prophylaxis for low risk exposures. The review was limited by the lack of consideration of studies from outside North America or their implications for other healthcare systems.

I concluded from these two reviews that it was helpful to use an instrument or tool to critically analyse the literature.

1.1.2 Approaches to critical appraisal

After reading the previous reviews and an initial search of the relevant literature, it appeared that findings of published economic analyses might not be always directly transferable or useful for decision making in Australia in 2008.

There were a number of factors that were important to me in the choice of tool to help assess the literature. Quality is an important characteristic to consider in the critical appraisal of economic evaluation studies(17). The importance of quality and rigor in methods in economic evaluation are paramount, because the conclusions from a study of poor quality may be misleading or wrong (18-21). Therefore the critical analysis tool needed to include an assessment of quality. Originally the intent was to rate the literature against Drummond’s checklist for economic evaluation that described ten different criteria for a sound economic evaluation(22) but the checklist did not assess the transferability of findings to other settings, so I looked elsewhere.
Spath(23) and Boulanger had all considered the quality and transferability of studies and developed scoring methods and algorithms. Welte emphasised that studies must first score well on quality scores before their transferability could be assessed(18). Boulanger developed a tool with colleagues from the European Network of Health Economics Evaluation Database network of health economists (EURONHEED) from around Europe that focused first on quality, then on transferability.

I decided to use the EURONHEED scale because it provided a systematic approach to assessing the quality and transferability of publications using a set of questions that had been discussed and refined in consultation with a network of health economists around Europe based on the perceived importance of items. There was a scoring system for each category(19) that allowed the derivation of summary scores. There was one direct question on uncertainty analyses with a strong emphasis on probabilistic statistical approaches to uncertainty. The evidence for effect of the intervention was discussed, but there was no rating of the levels of evidence as might be acceptable to clinicians supporting evidence based medicine(19).

Boulanger developed the tool with colleagues from an European network of health economists from around Europe focused first on quality, then on transferability. There is a scoring system for each category(19, 24). The EURONHEED was developed an iterative process with the number of question on a topic reflecting the perceived importance of that issue to the network of colleagues developing it. It does not contain a question on temporal validity and reporting approaches. There is one direct question on uncertainty analyses although there is a strong emphasis on probabilistic statistical approaches to uncertainty and reporting. The evidence for effect is discussed, but there is no rating of the levels of evidence as might be acceptable to the NHMRC and clinicians keen on evidence based medicine. Despite these shortcomings, the EURONHEED was being used extensively in Europe at the moment (19). The EURONHEED scale was used for a quantitative score, with a qualitative focus in my literature search on the areas that it was deficient in, including strength of evidence, temporal validity, uncertainty analyses and reporting approaches. The questionnaire and scoring system are in the appendices.
The scores were used in a presentation that I gave on the quality and transferability of the published literature to the Australian Society for HIV Medicine conference. The analysis also provided an opportunity to explore whether there was a correlation between study quality and transferability. There were separate quality and transferability scores that are reported in the literature review before a summary of the findings of the study.

1.1.3 Limits of depth and breadth of literature review

Each study reviewed in the next literature review reports the key findings from the study with a commentary on the study, including quality and transferability for some. The trade-off between the breadth of the literature search and the depth of the critical analysis was managed by focusing in this chapter only on the findings of studies that were areas of likely inclusion in the ACE-HIV process or to illustrate the point that not all the findings of studies performed overseas are transferable to Australia.

1.2 Literature review of Healthcare Interventions

The literature review is classified into studies that examine prevention and those that look at healthcare interventions. The healthcare studies are first and are sub-classified according to the intervention.

1.2.1 Diagnosis of HIV infection

Studies of early testing were included in the literature review, as it was considered as a potential candidate for the ACE-HIV process. The earlier detection of primary HIV infection could be described as relevant to both individual treatment and prevention. Patients with HIV can be offered treatment at this very early stage which may help preserve the immune system. Individuals identified as having primary HIV infection can be counselled to reduce risk behaviours at a time when the risk of transmission of virus is high and recent contacts can be traced and tested. There is evidence that significant numbers of people with HIV are unaware of their status in some parts of Australia. Stoove showed that 31% of men surveyed anonymously in Melbourne were found to have undiagnosed HIV(25). Data from the Australian HIV surveillance report showed that the median CD4 (cells/μl) at diagnosis for those not diagnosed with newly acquired HIV infection, was 311 for men and 366 for women, with differences according to risk behaviour: for men having sex with men (MSM)
the median CD4 at diagnosis was 443, while in heterosexually infected patients, the median CD4 was 230 for men and 380 for women(26).

Bos published a paper in 2006 that assessed the value of screening patients attending sexually transmitted infection clinics for HIV in the Netherlands using an economic model. He found that the cost per life year gained ranged from €680 to €9300, or €82,000 per secondary HIV infection case averted depending on the assumptions made about behaviour change after diagnosis(27), valued in Euros in year 2000(although € were not formally adopted until 2002).

Comment: The quality score was 64%, the transferability score 78%. The study used an estimate for life expectancy of 16 years from diagnosis. The most recent estimates of life expectancy are around 30 years or more (28, 29). People who were diagnosed by this intervention gained one life-year by earlier antiretroviral treatment and 1 secondary infection would occur for every 4 undetected HIV infections. The model was very sensitive to the assumption that 100% of newly diagnosed people change their behaviour, but the paper did not specify what would be the actual impact on the risk of transmission. Lifetime HIV illness costs (€59,000) were derived from a study from the Netherlands by Postma(30) that was much lower than an estimate from the USA ($385,000) (31). Screening only the group of people diagnosed with a sexually transmitted infection (20%) was more cost-effective than other options, because they were 40% of HIV infections identified, but following that strategy, fewer infections would be diagnosed.

Coco 2005 examined the cost-effectiveness of three diagnostic assays, the p24 antigen, HIV viral load and third generation enzyme immunosorbent assay in a hypothetical cohort of patients with symptoms of primary HIV infection and one HIV risk factor presenting to outpatients clinics in the USA. He found that from a societal perspective, p24 antigen cost $30,000 per QALY compared with no testing and dominated HIV viral load and third generation enzyme immunosorbent assay. From a third party payer perspective, p24 antigen cost $29,000 per additional case detected(32).

Comment: The quality score was 82% and transferability score 97%. The high transferability score related to the clear resource utilisation assumptions, unit costs and inclusion of
statistical analyses. The study included the disutility of anxiety associated with waiting for confirmatory tests(33), as well as HIV infections averted in partners of the patient and decreased quality of life due to awareness of having HIV infection when asymptomatic.

Phillips examined the introduction of routine testing for all new patients attending primary care clinics using a decision tree model, over a one year timeline, comparing it to the introduction of routine risk assessment screening using a risk assessment questionnaire followed by testing as well as current practices(34). She found that routine screening dominated routine risk assessment and cost $4,200 per additional HIV infection diagnosed, $17,600 per life year gained and $22,000 per QALY gained in a population with an HIV prevalence of 0.15%. If the population prevalence was 1%, the incremental cost per HIV infection fell to $700 per HIV infection detected and if it was 0.1%, it cost $6,600 per HIV infection detected. Using risk assessment screening became more cost-effective if fewer than 23% of the patients had risk factors, if the costs of counselling and testing were low or if more than 90% of people with risk factors accepted testing.

Comment: Quality score 79% Transferability 94% .The model inputs and structure was clearly described allowing transfer to another setting. It was assumed that 50% of HIV positive individuals who did not change their behaviour would transmit the virus to another person in their lifetime. The incremental time costs (15 minutes) of achieving pre-test consent in routine testing and providing counselling to a person with newly diagnosed HIV appeared low. The effect of risk assessment as a health education tool was explored. If counselling resulted in behaviour change amongst HIV negative people, the risk assessment became more cost-effective.

Walensky developed a screening model linked with the Cost-effectiveness of Preventing AIDS Complications (CEPAC) disease model to estimate the clinical gains associated with detection of HIV in patients attending hospital. The CEPAC model is a micro-simulation model developed by a group of Harvard University and Johns Hopkins University researchers (35, 36). In Walensky’s study, with an undetected HIV prevalence of 1%, routine inpatient HIV screening cost $35,400 per QALY gained, assuming a 37% uptake with consent and testing cost of approximately $20 per patient. According to the model, the mean CD4 cell count at diagnosis would rise from 196 to 244 cells/microlitre. At an undiagnosed HIV
prevalence of 0.1%, the cost per QALY was $64,500. The analysis showed that “moving even a small number of HIV-infected persons into care...has the single largest effect on the cost-effectiveness of the program”(37).

Comment: Quality score 86% Transferability 82%. The model assumed that 88% of patients would receive their results and be linked into care. Greater screening benefits accrued when the patients detected by routine screening had higher CD4 cell counts. The benefits of the prevention of secondary transmissions were not included. The initial and ongoing training costs for healthcare workers that would be required in a full national routine screening program would make routine screening less cost-effective.

A further study by Walensky on the topic, explored the issue of onward referral into care using an index of participation in both testing and follow-up to examine program efficiency and the optimum way to invest resources. She found that in populations with a low prevalence of undiagnosed HIV infection (0.01%), better follow-up was the more important factor, while in high undiagnosed HIV prevalence populations, the follow-up rate was less critical, although still important. Investments in improving follow-up were more effective than investments in improving participation because those invested in follow-up are definitely spent on people already with HIV while those on testing will only be spent on 1 HIV infected person in 100 in a population with a prevalence of 1%(38).

Comments: the quality score was 60% and 70%. The research question was novel and provided a sophisticated approach to a question but there were limited details of the model structure and inputs used, although it was referenced to previous CEPAC papers. The EURONHEED questionnaire penalised studies that are heavily model-based without details of structure.

The Walensky paper used a cost-effectiveness threshold of $50,000 per QALY which is commonly used in much of the literature. The arguments in favour of a shadow price or willingness to pay based on Gross Domestic Product (GDP) are complex and contested(39) so I will only mention them briefly, but the $50,000 threshold was often used in the literature reviewed without adjustment or increase over time(40, 41). Other authors have suggested decision thresholds of an incremental cost-effectiveness ratio for each disability-adjusted
life year (DALY) saved between 1 times GDP per capita and 3 times GDP per capita (40, 42). This choice allows for differences between countries. In 2006-2007 the GDP per capita in Australia was A$47,954 (43) or US$37,500 using purchasing power adjustment, while the GDP per capita in the USA was US$46,000 (44).

Paltiel 2005 used the CEPAC model to explore the introduction of routine testing using enzyme linked immunosorbent assay to three different populations in the USA:

- high undiagnosed prevalence population with a high incidence,
- population with an undiagnosed prevalence of 1%, similar that suggested for routine testing by the CDC,
- US general population prevalence of 0.1%.

He found that one time screening in a high undiagnosed prevalence population cost was $36,000 per QALY gained. More frequent testing at 5 and 3 years, cost $71,000 per QALY and $85,000 per QALY respectively. At a prevalence of undiagnosed HIV of 1%, the costs for one time, 5 yearly and 3 yearly testing were $38,000, $71,000 and $85,000 per QALY. In the US general population, one time screening cost $113,000 per quality adjusted life year gained. An alternative screening method using rapid testing increased linkage to care that maximised the benefit of routine screening at high prevalence. But in the 1% and general population prevalence, the impact of false positive tests on quality of life, reduced the benefit at high screening frequencies. The authors concluded that “routine voluntary screening for HIV very three to five years is cost-effective by US standards, except in populations with the lowest prevalence of HIV (11).”

Comment: The quality score was 93%, the transferability scores 94%. The disease model used trial data for the effectiveness of ARVs, rather than cohort or observational data. A loss of 14 quality adjusted days was assigned for false positive HIV assays while waiting for confirmatory tests. Secondary transmissions were analysed in sensitivity analyses but were not included as a benefit in the ICER. Costs of testing were based on a study using the ingredients approach (45, 46), sometimes used in the absence of patient-level cost data. The
principal driver of costs and benefits in HIV counselling and testing was the increased number of patients receiving effective yet expensive care.

Paltiel drew on the previous work to examine the role of rapid testing in low and moderate HIV prevalence populations, using updated estimates of life expectancy and costs and incorporating the prevention of secondary transmissions at a population level. One-time routine screening in a population with an undiagnosed HIV prevalence of 1%, cost $30,800 per QALY saved (every five years cost $32300 per QALY and every 3 years $55,500 per QALY). In a population with an undiagnosed prevalence of 0.1%, one time screening cost was $60,700 per QALY(47). Rapid testing led to more people being linked into care, an important driver of cost-effectiveness(38) but was associated with quality of life impacts on cost-effectiveness in populations with lower HIV prevalence.

Comment: The quality score was 91%. Transferability 88% and overall score 90%. The prevention of secondary transmission was an important feature of this paper. Other authors (48-50) had found that the benefits of screening for secondary prevention of transmission of HIV were greater than the benefit of earlier detection of people already infected. Montaner and Hogg argued that over 50% of future infections could be averted by the wider use of ARVs(51). But Paltiel found that the transmission reduction benefits of earlier detection with behaviour change and treatment on the cost-effectiveness were not so significant, as the ICER only improved by 16%. Reasons may have included: a smaller impact of ARVs on HIV infectivity; longer survival leads to a longer period when people with HIV might transmit virus and there are more people with HIV are in the community; time discounting reduces the benefit of future gains from averting a secondary transmission.

The CEPAC model used in this study had been updated with 4 lines of ARVS including 1\textsuperscript{st} line (NNRTI) 2\textsuperscript{nd} line (PI) 3\textsuperscript{rd} line (alternate PI) 4\textsuperscript{th} line (salvage with enfuvirtide, making direct comparison with previous studies using the CEPAC model less certain. Paltiel compared the updated costs of HIV infection used in this analysis with those from his previous 2005 study and found that there was minimal impact, mainly because the effects of any changes for people with HIV are averaged out over a large HIV negative at-risk population. More favourable cost-effectiveness ratios were associated with assumptions about less background testing, higher HIV prevalence or incidence and a greater impact of screening
and treatment on secondary transmissions. At undiagnosed prevalence above 1%, the cost and benefits of healthcare for people with HIV became a key driver of cost-effectiveness. As there is no clear consensus on willingness to pay for interventions, the paper explored the relationship between population prevalence and the effects on secondary transmission on the cost-effectiveness of one-time testing by the use of graphs. This feature increased transferability to other settings since decision makers could use local data to assess the findings of the study.

1.2.2 Rapid testing

Farnham 1996 assessed the value of rapid testing compared to standard testing and counselling, using an ingredients approach. Under the standard counselling and testing approach, the total cost was $103 for an infected person and $33 for an uninfected person compared to $135 for an infected person and $33 for an uninfected person with rapid testing. He estimated average cost-effectiveness for each approach after adjusting for failure of people to return for results: the standard approach cost $68 per person informed; the rapid approach $37. Patients with an initial positive rapid test should be told that it could be a false positive result but would still need to modify their behaviour until the confirmatory western blot was ready. If the initial positive rapid test did not affect behaviour change, then it was no longer as cost-effective(46).

Comments: Quality 71%, Transferability 88%. The study used a literature search and opinion to build an ingredients list for costing the rapid and standard testing approaches in public clinics in the United States. The impact of false positive rapid tests on health-related quality of life was not included; rapid tests are known to have lower specificity especially in population such as pregnant women. The study is limited in value as a cost-effectiveness study because of the use of average cost-effectiveness. But the approach used to estimate the costs could be adapted to other settings because the ingredients were clearly identified, the utilisation of resources in appropriate units presented and the value of each unit set out.

1.2.3 Antiretroviral treatment

Another topic for potential inclusion was different strategies for antiretroviral treatment. The literature contained a number of studies performed with combinations that were no
longer relevant to care in 2008 or comparators such as dual therapy that are not alternatives now (52-56).

Sendi examined the cost-effectiveness of ARVs compared to no ARVs, a null comparator, using a model with data from the Swiss HIV cohort from both a societal perspective and a healthcare perspective. He found that the use of ARVs increased both survival and healthcare costs with an ICER of approx $22,000 per life year gained from the healthcare perspective, but productivity gains compensated for these additional costs, making ARVs cost-saving from the societal perspective. The paper concluded “Society will likely benefit, even in the case where the policy would be based solely on economic grounds.” The inclusion of productivity losses in studies where quality adjustment of life years occurs might be considered as double-counting(57) but they argued that in studies of using unadjusted life years the inclusion of productivity losses was appropriate(58).

Comment: The quality score was 93% and the transferability score 84%. The Swiss cohort collects comprehensive data on health, costs and employment status on 9,000 patients. Unadjusted life years gained, rather than quality adjusted life years, reduced the need for utility measurement, but did not allow the inclusion of adverse effects of ARVs. Productivity gains and losses were calculated by the human capital approach which may overestimate the impact of disability and death on the economy(59).

Freedberg (2001) showed that the incremental cost of ARV compared to no therapy was $23,000 per quality adjusted life year gained with a range of $13,000 to $23,000 per QALY gained. The initial CD4 count and drug costs were the most important determinants of costs, clinical benefits and cost-effectiveness: when ARVs were initiated when the CD4 was above 500, it cost $15,000 per QALY gained, compared with no therapy; when therapy was initiated late (that is with a CD4 cell count below 50) the ICER was $22,000 per QALY. Adjustment of life-years for quality did not make a large difference to the magnitude of the estimates.

Comment: The quality score was 87%, transferability score 91%. Quality-adjusted life years were derived from the patient responses to a single item on overall health scores in a health
profile, during a series of AIDS Clinical Trials Group studies, converted into utility weights using the approach of Torrance[60].

Paton used data from 1200 participants in the Singapore HIV observational cohort study on hospital resource utilisation and outcomes in a five year period leading up to 2001. The study divided patients by Centers for Disease Control (CDC) stages. The cost per life year gained for HAART versus no ARVs was S$22,500 per life year gained (LYG) in stage A, S$21,100 per LYG in stage B and S$16,500 per LYG in stage C. Using a societal willingness to pay threshold of twice the GDP per capita, $74,260, the use of ARVs appeared cost-effective at all stages of HIV infection (61).

Comment: Quality 84%, transferability 88%. The strength of this study was the use of real data on hospital costs and outcomes: its value would be particularly in the decision context of Singapore with a unique medical savings account model of health financing and a diverse population infected with HIV. The use of unadjusted life years may have underestimated the quality gains associated with HAART; on the other hand, there are no locally measured utilities so the use of life years reduced uncertainty in the result.

Beck examined the cost-effectiveness of antiretroviral therapy in two Quebec hospital clinics in the pre-HAART and HAART eras. For patients without an AIDS defining illness, healthcare including antiretrovirals cost $14,600 per life year gained (LYG) in the HAART era compared to the pre-HAART era and for AIDS patients the incremental cost per LYG was $12,800(62).

Comments: the quality score was 96% and the transferability 93%. Health care resource use data was measured in computerised information systems used for inpatients and outpatients and valued using case-mix funding values. A weighted cost average for each antiretroviral regimen was calculated and non-ARV costs were taken from a study in Alberta. Progression times to death could be estimated from the database. Unadjusted life-years were used in the absence of utility weights (63). Despite the high levels of effort taken to obtain real data on costs and outcomes, the authors commented that:“In order to be able to perform the relevant analyses, basic and contemporary information on the use, cost and outcome of HIV service provision needs to be available. ...However, despite the current prevailing rhetoric concerning the need for evidence based-medicine, the
track record of funders of research or governments in many countries has to date, unfortunately, been suboptimal in terms of providing the required resources to set up and maintain those systems which could regularly provide such strategic information (63).”

Sax assessed the cost-effectiveness of enfuvirtide in treatment experienced patients with advanced HIV disease using the CEPAC model and data from the trials of enfuvirtide. The analysis demonstrated that enfuvirtide plus an optimised background regimen cost $69,500 per QALY gained compared to an optimised background alone. (64).

Comments: The quality score was 96% and transferability 69%. The disparity relates to the failure to state a perspective for the analysis, the extent of statistical analyses and the failure to report costs and quantities of resource use separately. The relative lack of transferability could affect the applicability of the findings for decision makers in other settings. Using local inputs in the same model may produce widely different conclusions (65). Noyes showed that using US-specific utility weights in an economic evaluation of a drug for Parkinson disease, resulted in lower incremental effectiveness, higher ICER and a lower probability that the drug was cost-effective (66).

Simpson developed a model to evaluate data from clinical trials. The model was used in a study comparing the use of ritonavir-boosted lopinavir versus nelfinavir as the first line therapy. Data from a clinical trial was extrapolated over a longer time period. The model showed that the use of lopinavir would be associated with lower costs over a five year period and would cost $6,700 per QALY gained compared to nelfinavir (67).

Comments: While the study was high quality, 92%, the transferability was 78%, mainly due to a lack of detail on inputs. The study result illustrates some of the problems with single drug comparisons in economic evaluations: while lopinavir appears cost-effective compared to nelfinavir, it might not be cost-effective compared to other more effective alternative regimens. Nelfinavir is inferior in effectiveness to current first-line regimens and is considered redundant in developed countries. The use of comparators in economic evaluation can lead to incremental creep in drug prices and budgetary impact. If drug A was cost-effective compared to no drug, and drug B is cost-effective compared to drug A, it is not necessarily true that drug B would be cost-effective compared to no drug.
Simpson used the same model to compare the use of boosted lopinavir with atazanavir in antiretroviral naive patients, taking account of the potential impact of coronary artery disease as well as new AIDS defining illnesses. The model assumed that boosted lopinavir was more effective than unboosted atazanavir with an indirect comparison of data from two different sets of clinical trials of each agent. The model found that the boosted lopinavir arm had fewer AIDS defining illnesses but more cardiovascular events in the long term. The number and impact of the former was much greater on the cost-effectiveness than the latter(68). But the CASTLE randomised controlled trial of boosted lopinavir and boosted atazanavir found that they were equivalent in efficacy (69).

Hubben used the Simpson model to assess the cost-effectiveness of tipranavir versus a comparator protease inhibitor regimen in the Netherlands. Data from the tipranavir RESIST studies were entered into the Markov mode with local Dutch cost data. Boosted tipranavir was found to cost €42,500 per QALY compared to the previous standard of care(70).

### 1.2.4 ARVs strategies

Schackman (2001) examined the decision on starting treatment and also the second decision on when States should start funding treatment. The modelling study was set in the context of a rejection of a proposal to revise the Federal Medicaid eligibility rules to include asymptomatic HIV patients, because it was not budget neutral. Initiating therapy at a CD4 cell count of 500 or less was a more efficient use of resources than initiating therapy at a CD4 cell count of less than 200 and had an incremental cost-effectiveness ratio of $17,300 per QALY gained compared with no therapy.

Comments: The quality score was 96%, the transferability score 75%. A clinical trial population was assumed which might lead to higher estimates of effectiveness than a broader population. With a 20% reduction in quality of life while receiving antiretroviral therapies as result of side effects for those on early treatment, the ICER of early versus deferred therapy increased to $67,200 per QALY gained.

In a further study, Schackman 2002 considered starting therapy below 350 compared to below 200 for patients with a viral load between 10,000 and 30,000. The study incorporated the adverse effects of ARVs including hypercholesterolemia and the impact on
cardiovascular risk. Early therapy was a more efficient use of resources in that it was more effective with a gain of 1.15 years and was cheaper than deferred therapy: ICER versus no therapy of $7000 per QALY for early therapy compared to $16,000 per QALY for deferred treatment. The inclusion of cardiovascular risk or the use of pravastatin did not appear to affect the overall ICER of early treatment compared to no treatment substantially, but the ICER for the addition of pravastatin to early treatment compared to early treatment alone was $132,000 per QALY gained, mainly because pravastatin has a small extra benefit for the additional cost (71).

Comments: The quality score was 83%, the transferability score was 76%. The study found that ARVs would have an ICER of $38,000 for a 20% reduction in quality of life and that a 40% reduction would make early treatment no longer cost-effective compared to deferred treatment.

Mauskopf also compared starting ARVs with a CD4 cell count between 350-499 (and a viral load greater than 3000) versus below a CD4 cell count of 350 but used data from a real life cohort from the Johns Hopkins hospital. The incremental cost-effectiveness ratio was $31,266 per QALY gained using a Protease Inhibitor based first line, followed by Non-nucleoside reverse transcriptase second line and composite salvage third line. The authors concluded that there was “little evidence to suggest that the initiation of HAART should be delayed on the basis of cost-effectiveness” (72).

Comments: The quality score was 87%; the transferability score 72%. The use of cohort data for effectiveness increased the likelihood that the result reflected the real world. A meta-analysis provided an estimate of the relative risk of transition from one CD4 cell range to the next, based on the on-treatment 16 week CD4 and viral load response (73). The authors related their findings to Schackman’s work (71, 74, 75), noting that the higher ICER might relate to the use of effectiveness data from a real life cohort rather than a clinical trial.

Merito used data from an Italian cohort from the Italian National Health Service perspective (76) in a model to assess timing of initiation of therapy. Immediate ARV initiation did not affect the incidence of AIDS or death at high CD4 cell counts. Starting ARVs with a CD4 cell count between 200 and 349 compared to deferring treatment until the CD4 cell count was
below 200 proved to be cost-effective with an ICER of €24,124 per disease progression avoided in 100 patients (95% CI €14,389 to €69,491). There was no difference in health outcomes for patients starting ARVs when CD4 cell counts were less than 500, compared to those with a CD4 less than 350. The authors noted that analyses of naïve patients tend to overestimate the benefits of early HAART initiation (76).

Comments: The quality score was 59%, transferability score was 50%. Quality was low due to the lack of justification and sources for input parameters. The characteristics of the study population were not described i.e. MSM, IDU, geographical location, age, sex, nor their representativeness of the general HIV population.

Schackman explored the potential risks and benefits of an induction-maintenance HIV treatment simplification strategy comparing mono-therapy with a boosted protease inhibitor versus standard triple antiretroviral therapy after initial viral suppression. The model showed that there was a gain in quality-adjusted life expectancy for the simplification arm overall, although those who had protease resistance at failure of that line of therapy did worse. The simplification strategy had lower lifetime costs. The critical determinant in the model was the proportion of patients developing resistance at regimen failure in the simplification arm(77).

Comments: The quality score was 77% and the transferability 78%. The model was run to inform the design of a clinical trial that did not proceed. The findings helped show that the long-term benefits of a simplification strategy might not be directly observable during the time-course of the study and some individuals within the apparently beneficial arm would not benefit. It also clarified that resistance testing was a key piece of data and should be used to determine the stopping rules for the trial. On the other hand, the utility and healthcare costs were less important due to the high relative cost of the antiretrovirals and the lack of difference in both types of outcome in an antiretroviral strategy study. These outcomes did not need to be directly collected in the future clinical trial. In an editorial related to the model, Ribaudo commented:

“Trials are expensive and timely to undertake, and they may be unethical if the clinical impact of the intervention at the end of the study is unlikely to impact current standards of
The use of such an economic perspective provides a better understanding of the potential effectiveness of an intervention before hundreds of individuals are exposed to it, and it can also suggest critical data to collect, the choice of population, and the comparator regimen(78).”

1.2.5 Adherence

Adherence to ARVs is crucial for the success of regimens. Data from studies of early protease inhibitor regimens suggested that adherence of less than 95% resulted in high rates of treatment failure (79). Newer regimens may have more ‘forgiveness’ but adherence remains an important issue(80).

Goldie 2003 studied the use of adherence support mechanisms using a threshold analysis with a willingness to pay threshold of $50,000 per QALY gained. She found that interventions costing $100 per month needed to reduce treatment failure by 10% and those costing $500 per month needed to reduce failure by 50% to remain within the cost-effectiveness willingness to pay threshold. In patients with advanced disease or from an inner-city cohort adherence interventions such as directly observed therapy could still be cost-effective even if they cost up to $500 per month as long as failure rates reduced by 25%. The study used the CEPAC model to apply data from three cohort populations to examine adherence. The adherence interventions included electronic reminders automatic dispensers and directly observed therapy(81).

Comments: Quality 95%, transferability 93%. There were limited data on effectiveness of adherence interventions, so the study used uncertainty analysis extensively. The paper provided a helpful way for decision makers to decide on adherence interventions in the midst of great uncertainty over effectiveness and possible costs. The use of different populations allowed the studies to be set within different decision contexts. The lack of data on the duration of benefit of the interventions and the potential set-up costs of new programs meant that careful monitoring of program implementation and outcomes would be required.

Munakata examined the role of adherence in the success of treatments assuming a reduction in efficacy of ARVs with a 4-fold increase in the relative odds of treatment failure
in non-adherent patients compared to adherent patients. The model compared two adherence scenarios, an ideal adherence (90% or more) using data from a clinical trial(82) and typical adherence based on the ATHENA observational cohort study where adherence>95% was 47%(83). In a scenario with ideal levels of adherence, each patient gained 1.2 years spent in full health with a cost per quality adjusted life year of $29400. The authors found that as much as $1600 per year per patient could be spent on adherence interventions before the ICER exceeded a threshold of $50,000 per QALY gained(84).

Comments: The quality score was 72% but transferability score was 28%. There was a low transferability score because: only the first line of ARV therapy was specified which was stavudine-XR, lamivudine and efavirenz; data was drawn from three studies which took place in three different locations. Athena is a cohort from the Netherlands(83) and the other two trials were multi-centred trials with sites in a variety of countries(85-88) and there was no attempt to compare the demographic and other characteristics of the source and hypothetical populations. Utilities for health states were averaged from different studies two of which were derived from studies in the pre-HAART era (12, 89, 90).

1.2.6 Resistance to ARVs

Genotype assisted resistance testing (GART) allows clinicians to detect resistance of HIV to ARVs. The technology is not cheap, costing between $500-800 per test. Some governments and third-party payers have been reluctant to fund it because data on long-term clinical outcomes are not available.

Weinstein used the CEPAC model to evaluate GART from a societal perspective. He found that GART cost $17,000 per quality adjusted life year gained, if used for the first and second ARV regimen failure compared to clinical judgement alone. When used to detect primary resistance, GART cost $22,300 per QALY if the prevalence of resistance was 20% and $69,000 per QALY if 4% of the population had ARV resistance(91). A sensitivity analysis showed that the prescription of newer classes of ARVs would improve the cost-effectiveness of GART.

Comments: Quality 83% Transferability 81%. Effectiveness data was based on the CPCRA 046 (85)and Viradapt studies which were randomised controlled trials(92). Those studies
lasted for 12-26 weeks and relied heavily on surrogate markers extrapolated to a life-time to estimate the long-term consequence from the observed short-term outcomes. The authors argued that the use of GART at regimen failure beyond 1\textsuperscript{st} and 2\textsuperscript{nd} line was likely to be less cost-effective as the incremental benefit was less. In an editorial, Sax argued that the benefits might be greater in salvage patients as they were more likely to have resistance and more likely to be at risk of serious consequences if failure occurred. He also argued that the benefits would be greater in the real world outside a clinical trial(93). This could be a contestable opinion as trial participants were likely to have better adherence than in the real world.

Sax investigated the cost-effectiveness of GART for treatment naïve HIV-infected patients. The authors used the CEPAC model of HIV disease to project life expectancy, costs and cost-effectiveness of resistance testing. They estimated a baseline prevalence of drug resistance of 8.3\% based on a US survey of treatment-naïve patients from the Centers for Disease Control and Prevention. The authors determined that GART had an incremental cost-effectiveness ratio of $US 24,000 per QALY. The cost-effectiveness of GART remained less than $US 50,000 per QALY unless the prevalence of drug resistance was set at $\leq 1.0\%$, a level that the authors noted was lower than those reported in most regions of the United States and Europe(93).

Corzillius reported on a German health technology agency assessment of GART using a decision analysis Markov model. GART after the second and subsequent treatment failure increased life expectancy by nine months and undiscounted life-time costs per case by €16,406. GART cost €22,510 per life-year gained (discounted). Best and worst-case scenarios yielded €16,512 per LYG and €42,900 per LY, respectively. GART prior to the first line of therapy would be equally cost-effective if it could reduce the probability of first HAART failure by at least 36\%. (94).

Comments: Quality 92\% Transferability 88\%. The model population reflected the Swiss cohort study, which has a higher proportion of injection drug users than an Australian population. The increase in costs for the GART arm was due mostly to ARV costs due to an increased lifetime, as the incremental cost of GART per year was assumed to be only €28 per person, because not all patients would need one.
Sendi compared the cost-effectiveness of the availability of GART in Switzerland using a model based on empirical data from the Swiss cohort taking a healthcare and societal perspective. He found that health costs were $2000 greater, life expectancy increased by three weeks and quality adjusted life expectancy by two weeks. GART cost $35,000 per quality adjusted life year gained. In the societal analysis, GART was cost-saving due to the inclusion of productivity losses and gains(95).

Comments: The quality score was 91% and the transferability score was 78%. Costs of care came from a micro-costing study by Haubts using a sample of the Swiss cohort in one academic hospital(96). QALYs were derived from a study on quality of life in patients enrolled in the cohort(97). QALYs were discounted in a societal analysis to take account of the potential double counting of people being in work as well as the productivity gains. In the opinion, this was one of the few societal perspective studies in this literature review that could be said to have taken into account society’s perspective on cost and outcomes.

Yazdanpanah used the CEPAC model based on data from the NARVAL and other randomised controlled studies to estimate the long-term effectiveness and cost-effectiveness of GART. He found that GART was associated with a gain of 15 months in life expectancy compared to clinical judgement alone and cost $88,500 per QALY gained, mainly because of the use of two fully active agents. Costs were greater in the GART arm due to the increased duration of antiretrovirals due to increased life-expectancy(98).

Comments: the quality score was 84% and the transferability score 91%. The regimens used in the model and assumptions on suppression of virus and CD4 T-cell count rises were clearly described, increasing transferability. The model assumed that ritonavir-boosted darunavir would be used instead of boosted-lopinavir in patients with resistance, thus improving the chance of a response.

1.2.7 Anal neoplasia screening

Goldie assessed the clinical benefits and cost-effectiveness of screening HIV infected men having sex with men (MSM) for Human Papilloma Virus (HPV) related anal intraepithelial lesions. Anal cytology tests every two years, beginning in early HIV disease, resulted in a 2.7 month gain in quality adjusted life expectancy for an incremental cost-effectiveness ratio of
$13,000 per quality adjusted life years saved. An increased frequency of testing to yearly provided additional benefit but the cost was $16,600 per quality adjusted life year saved compared to two-yearly screening. If screening was not started until the CD4 cell count was less than 500, then yearly screening was more effective at detection of disease than two-yearly screening and cost $25,000 per quality adjusted life year saved compared with no screening(99).

Comments: The quality was 79% and the transferability 96%. Effectiveness and natural history data were drawn from cohort studies in San Francisco and Seattle that may not have been representative of the wider population of men having sex with men. The cost-effectiveness result was most sensitive to the rate of progression of abnormal anal cytology to anal squamous carcinoma and the effectiveness of treatment of pre cancerous lesions. The authors argued that this study supported the use of anal cytology in HIV infected people. However, uncertainty about the effectiveness of screening and treatment as well as a lack of knowledge of natural history of anal intraepithelial neoplasia, made this statement contestable.

1.2.8 Hepatitis C coinfection

Kuehne used the CEPAC model to examine the cost-effectiveness of alternative treatments and duration of therapy for hepatitis C infection in patients with HIV and moderate levels of liver disease. Data from studies of interventions in mono-infected patients with hepatitis C were used. The study found that for genotype 1, pegylated interferon with ribavarin for 48 weeks cost less than $50,000 per QALY gained compared to no treatment and compared to regular interferon with ribavarin. On the other hand, for non-genotype 1, the incremental benefit of pegylated interferon was not so great compared to regular interferon even though it was cost-effective compared to no treatment and the ICER rose to over $100,000 per QALY(100).

Comment: This was a high quality study (93%) with a high likelihood that the findings could be transferable (96%). The study authors’ reflections on the uncertainties involved in economic evaluation modelling and the potential use of results are germane to a number of other studies:
“Evaluating the effectiveness of HCV treatment in coinfected patients requires specification of the natural history of both diseases (HIV and HCV), consideration of the heterogeneity of risk, treatment efficacy and toxic effects, and accessibility, feasibility, and affordability of medication and health care. Data are not available for all of this information, and our analysis therefore required multiple assumptions.... This analysis was conducted to provide qualitative and quantitative insight into the relative importance of different components of the treatment process and to investigate how results would change when values of key variables were changed. By identifying the most influential variables, these results may be used to help prioritize and guide data collection efforts (100).”

In other words, economic analyses are a synthesis of the currently available data and can magnify any flaws and uncertainties, threatening the ability to have confidence in the value of any conclusions. However, being clear and honest about those uncertainties and exploring them in sensitivity analyses can stimulate thought about future clinical research priorities.

1.3 Literature review HIV prevention interventions

1.3.1 Multiple prevention interventions

I focus here mainly on biomedical prevention studies however I will review three more general studies that illustrate many of the challenges in evaluating HIV prevention interventions.

Cohen (2004) applied a single Bernoulli model to 26 HIV prevention interventions operating at a range of different levels from individual, community and social networks, and structural changes. The study calculated the cost per HIV infection averted from a public health system perspective, and then compared the results of each intervention. The key factors contributing to the cost-effectiveness of interventions were the HIV prevalence in a population and the cost of the intervention. Programs targeting high prevalence populations could be cost-effective even if the implementation cost hundreds of dollars; interventions for low prevalence populations needed to have extremely low price per person; as one might expect, cost-free but effective interventions such as legislative changes were always cost-effective. Targeted interventions were particularly sensitive to the population
prevalence, whereas those for a general population were less sensitive. STI targeted programs were sensitive to the incidence of HIV in secondary partners. A number of programs were not cost-effective: school-based education; programs targeted at youth generally; illicit drug treatment programs; the use of antiretrovirals to prevent secondary HIV transmission. All other interventions targeted at HIV positive people were cost-effective across a range of assumptions(101). The paper argued that

"It is not always necessary to target directly or produce behaviour change to reduce HIV transmission; biomedical Interventions can be cost-effective options(101)".

Comments on the study: Quality was 77%, transferability 61%. The paper stands out because it placed economic evaluation as one of a number of other critical factors for priority-setting including strength of evidence for intervention, effectiveness, feasibility, acceptability, and implementation in the local area. On the other hand, the study demonstrates many of the common challenges of performing economic analyses in HIV. The effectiveness of interventions was established from randomised controlled studies where possible, but for HIV counselling and treatment interventions, observational data was required with meta-analyses. A variety of different types of sources were used for the model inputs. Analyses of some interventions included non-health costs and outcomes. For programs that did not have cost data, a typical prevention program cost was used. The variation in identification, measurement and valuation of costs and outcomes made comparison between prevention and healthcare interventions less reliable. The model time horizons were short, 12 months. There were no comparisons between different programmes within the same population.

A second paper by the same author modelled the impact of a range of public health decisions on women living in the Southern United States(102). The study found that the most cost-effective interventions were alcohol taxes, needle deregulation and needle syringe programs with a cost per HIV infection averted of $3600-$9000. Street outreach, condom availability and mass media cost around $25,000 per HIV infection averted and the latter two averted the greatest number of HIV infections. Opinion leader programs were not cost-effective; each HIV infection averted cost $1m. The authors concluded that in a
population with a low prevalence, HIV prevention interventions would have to reach a large number of people and cost very little per person reached.

Comments on the study: The use of data on intervention effectiveness from Switzerland in a study of the southern USA did not appear appropriate. The paper did not consider the budget impacts of implementing interventions. An intervention could also be ‘cost-effective’ but not affordable, feasible or acceptable. Budgets, implementation and political and cultural considerations may be important. The outcome used, the cost per HIV infection, reduced the chances of comparing interventions with other non-HIV interventions.

Allen Consulting(103) explored the cost-effectiveness of the education and research funded by the Australian government related to HIV. The interventions were the funding of (a) community based organisations to provide education and prevention (b) national research centres (c) World AIDS day activities. The study found that in the period 1985-2005, there was an average cost-benefit ratio of $39 of cost savings by disease averted for each $1 invested in healthcare (HIV research programs $45, HIV community education $21) with an average cost-benefit ratio of $23 for every $1 invested in the years 2000-2005. The benefits were driven mainly by the improvement in quality and quantity of life. A purely financial analysis showed that it was cheaper to fund research and education than pay for the healthcare costs associated with infections averted. The cost-effectiveness analysis showed that it cost $118,000 per HIV infection averted, the net benefit per averted infection was $4.5million and the net financial benefit was $19,500. In other words, the programs funded only had to avert two HIV infections a year to be cost-saving.

The report assumed that 50% of the 504 infections averted each year by HIV prevention interventions are attributable to research and 50% to education through behaviour change. The benefits of the programs were identified as avoidance of treatment costs, years lost of life due to premature mortality and a period of life lived in less than perfect health.

Comment: The programs were not analysed separately, except as categories of education and research, preventing discussion of value for money of the parts. The analysis did not include the funding of programs by State and Territory governments, thus excluding important costs. There was inconsistency in the assumptions about benefits: education
programs were assumed to impact immediately while research programs did not have benefit for five years. The analysis was confined to the particular part of the federal government health budget and stakeholder input into the design or commentary on the results was limited. Changes in sexually transmitted infections and hepatitis C related to the same activities were not included or valued.

While overall the results helped support continued funding of the research centres for HIV and community based-organisations, the study falls into the category of studies done to justify existing policy, rather than an economic analysis to consider alternative options for priority-setting. The study did not examine whether more funding would bring greater returns, or consider alternative ways of providing the funding to researchers or the community.

1.3.2 Condom distribution

Bedimo 2002 explored the cost-effectiveness of a condom distribution program focused on African-Americans in Louisiana, USA. The program was assumed to prevent a total of 170 HIV infections over a three year period of which 107 of the infections were secondary. Condom use during the program had increased from 40% at baseline to 52% at follow-up in men and 28% to 36% in women. The program was cost-saving: it cost around $3m for medical cost savings of $33m; it remained cost-saving as long as condom use increased.

Comment: Quality 72%, transferability 70%. The study assumed that the increased use of condoms in the population resulted purely from the program. It is a common mistake in economic analyses to assume that the effects of the intervention are the sole cause of behaviour or other changes. However, it would be hard to perform a randomised trial of condom provision because it would be unethical to have a control population where condoms were not provided. In these circumstances, Swinburn argued that interventions can be assessed on their ‘promise’, a combination of the certainty of effectiveness of the intervention, judgments of the quality of the evidence, strength of the program logic and its potential population impact (104). Using Swinburn’s criteria, condom distribution could be described as very promising due to the potential population impact. The authors noted that communities without condom distribution programs in place would gain the most. A
threshold analysis showed that the lifetime cost of HIV would need to be less than $17,650 for the intervention to be no longer cost-saving.

1.3.3 Non-Occupational Post-Exposure Prophylaxis (NPEP)

Pinkerton 1998: In a study of non-occupational post-exposure prophylaxis (NPEP) in San Francisco using a Bernoulli model, two scenarios were considered : (1) The potential HIV exposure is an isolated event (2) Repeat post exposure prophylaxis is required in the situation of ongoing risky sexual behaviour.

NPEP was cost-effective in this model, in patient whose risk was receptive anal intercourse with a known HIV positive source (ICER $6,000 per quality adjusted life year saved) but not cost-effective for other sexual acts. In partners of unknown HIV status the ICER for receptive anal intercourse exceeded $100,000 only when the probability that the partner is infected was less than 4%. NPEP was actually cost saving for receptive anal intercourse when the population prevalence was greater than 25%. Repeated episodes of risky behaviour requiring PEP led to a 6% increase in the ICER when the number of episodes increased to 10(105).

Comments: The quality score was 65% and the transferability score was 66%. The population HIV prevalence was set at 18% in the model to reflect the San Francisco population but the findings were said to be generalisable to other parts of the USA. The effectiveness of NPEP was taken from a retrospective observational study(106).

In a later analysis based on empirical data from an observational study of the San Francisco NPEP program from 1997-2000, Pinkerton found that NPEP was cost-effective with an ICER of $14,400 per QALY and cost-saving for those having unprotected receptive anal sex(107).

Comments: Quality 73%, transferability 75%. The importance of the prevalence of HIV infection in the source population, transmission probability of each episode and the proportion of unprotected receptive anal sex behaviours as key drivers in the cost-effectiveness calculations was discussed extensively.
Pinkerton used the data from the study above as inputs to a modelling study of the cost-effectiveness of NPEP in 96 cities in the USA which found that that it was likely to be cost-effective in all cities with an incremental cost-effectiveness ratio ranging between $4137 to $39,101 per QALY saved (108).

Comments: Quality 48%, transferability 75%. The study assumed that the intervention could be implemented in 96 cities around the USA and made the unlikely assumption that the median age and composition of the population in those cities was similar to San Francisco. The model assumed that a program could use existing facilities with only incremental costs of the program delivery. While results were reported for cities where NPEP was most or least cost-effective, individual city results were not reported.

Herida 2006: A decision tree analysis using data on utilisation from the French National NPEP program from 1999 to 2003. Post-exposure prophylaxis was provided to nearly 9000 individuals mostly for heterosexual risk exposures. It was estimated that the overall cost effectiveness ratio was €88,692 per quality adjusted life year gained. Post-exposure prophylaxis was cost-saving in 4.4% of people receiving it and cost-effective in a further 11.3% of cases, assuming a government willingness to pay threshold of less than US$50,000 per QALY.

Comments: Quality score 60%, transferability score 53%. The age, sex or socioeconomic origin of the population was not described although empirical data on utilisation in France were used.

1.3.4 Occupational post-exposure prophylaxis (OPEP)

Shied 2000 used a Markov model to examine the US Public Health Service recommendations for occupational post-exposure prophylaxis that involved the use of two drugs for most exposures and three drugs for highest risk. Use of combination occupational post-exposure prophylaxis cost $81,947 per QALY gained compared to monotherapy (in 1997 dollars). Monotherapy with zidovudine cost $688 per QALY compared to no therapy.

Comments: Features that contributed to the high quality 93% and transferability score 97%:

• a clear specification of the study question, setting and study population;
• admission that only a limited societal perspective was taken as only health costs were included;
• a detailed model with statistical exploration of the risk of exposures and effectiveness of occupational post-exposure prophylaxis;
• specification of the source and calculation of benefits with QALYs based on utilities by time trade off method of healthcare workers (109);
• the use of a range of cost values for HIV in sensitivity analyses (13, 14) including Hurley’s work from Australia (16);
• units of resource used, unit costs and 95% confidence intervals were calculated;
• bootstrap samples of 5000 and 500 trials were created to represent two different sizes of health care worker populations for whom occupational post-exposure prophylaxis strategies might be implemented with confidence intervals for both sample sizes;
• only discounted results were presented;
• the paper compared results obtained with other studies and demonstrated how the use of those assumptions and inputs in the author’s model, gave similar results.

The model explored the impact of better antiretrovirals that lead to improved life expectancy with HIV and hence greater lifetime costs of HIV, on the cost-effectiveness of preventing HIV infection. Inclusion of prolonged survival and increased treatment costs, made occupational post-exposure prophylaxis more cost-effective improving from $88,000 to $62,000 per QALY (110).

Pinkerton and Holtgrave explored changes in the life expectancy and cost of HIV infection for a number of hypothetical prevention interventions using a mathematical model. They showed that improvements in outcomes from better HIV care, improved the cost-effectiveness of HIV prevention interventions with a lower cost per infection averted (less than $55,000 per QALY) but resulted in those interventions with higher cost per infection averted appearing less efficient (111). They claimed that many factors may affect cost per infection, including the costs of an intervention, the number of HIV infections averted, the target population, estimates of the number of quality adjusted life years lost due to HIV infection, the cost of healthcare for HIV, assumptions about timing of ARV initiation, and the discount rate used (111). The finding is important because it suggested that sensitivity
analyses need to be performed to assess the size and direction of effect on the outcome of a model. I adopted this approach in the cost-effectiveness analysis for the ACE-HIV project.

1.3.5 Maternal/neonatal screening and treatment

My research program was focused on the cost-effectiveness of interventions for the prevention and treatment of adults, but I have included the following study because it the most comprehensive cost-effectiveness analysis in HIV from Australia published in the literature.

Graves 2004 examined the cost-effectiveness of universal antenatal HIV screening in Australia during the period of 2001-2002, using a model with a hypothetical cohort of the antenatal population of Australia (112). The intervention would have been cost-effective if the prevalence of undiagnosed HIV in the Australian antenatal population was less than or equal to 0.0044% or 1 in 22,800 women. Applying favourable and unfavourable values of key variables in a sensitivity analysis suggested that the prevalence at which the intervention would be cost-effective was between 0.0016% and 0.0106%, assuming a societal willingness to pay threshold of twice the median per capita income(113). The reported prevalence amongst currently screened women who might be considered high-risk was 0.023% but the current unscreened population prevalence was not known.

The paper compared prevalence in the UK, USA, New Zealand and Canada, and pointed out that the policy of universal screening remained cost-effective at a much lower prevalence than is reported in those countries. The authors recommended that universal antenatal screening should be considered in countries with a very low prevalence, a relatively high per capita income, an established infrastructure for prenatal care and a healthcare system that was already delivering an optimal mix of prevention and healthcare.

Ziegler commented in an accompanying editorial that rates of antenatal testing were only 33% in 1999 in Australia and should be improved(114). Previously it was thought that routine testing was unlikely to be cost-effective in a low prevalence country. Graves’s study appeared to refute the cost-effectiveness argument with a relatively small budget impact of $1.8m that would be exceeded by the cost-offsets due to the detection of HIV in the mother and prevention of transmission to the child.
Comments on Graves study: Quality 86%, transferability 92%. A marginal costing approach was taken that included the incremental cost of adding the delivery of the program to existing services. A sensitivity analysis showed that the additional continuing professional education of the healthcare professionals who would counsel the women and offer the screening affected the cost-effectiveness of the intervention. These costs could be considerable given the number of women having screening each year and the genuine concerns that routine testing might be associated with coercion and a lack of consent (115).

1.3.6 Needle-syringe programs (NSP).

The cost effectiveness of NSPs has been considered in a number of publications including the Commonwealth government first Return on Investment Report (116). The Return on Investment Report (2002) economic analysis demonstrated that there had been significant financial savings accruing from the expenditure on NSPs and that savings were likely to continue in the future (116). The net present value (present value of an investment over time) was estimated to be more than $2 billion dollars (discounted at 5%). NSP cost data was collected from jurisdictions and the lifetime cost of treatment for HIV and HCV were obtained from studies in the pre-ARV era but updated with more recent data from the Australian HIV Observational Database. An ecological analysis estimated the effect of NSPs across numerous international cities and the results of the analysis were applied to estimate the impact in Australia. It was estimated that:

- ~25,000 HIV infections were prevented among injecting drug users (IDUs) by the year 2000 due to the introduction of NSPs.

- The cumulative number of HIV/AIDS deaths by the year 2000 in injecting drug users (IDUs) would be ~200 with the NSPs and ~700 without the NSPs.

- ~21,000 HCV infections were prevented among IDUs by the year 2000 due to the introduction of NSPs (of which 16,000 would have developed chronic HCV).

The cumulative number of IDUs living with HCV in 2000 was estimated to be ~200,000 with NSPs in place; it was estimated that the number would have been ~220,000 without NSPs.
In a systematic review of the international literature, 13 economic evaluation studies of NSPs were identified, most based in North America (117). The studies all concluded that NSPs were cost-saving or cost-effective compared to the lifetime cost of HIV. A range of approaches were used in the economic analyses, depending on the research question of technical efficiency or value for money.

Holtgrave used a hypothetical cohort of one million active IDUs in the United States, to estimate the cost-effectiveness of policies to increase access to sterile syringes and syringe disposal at various levels of coverage. A mathematical model of HIV transmission was employed to link programmatic coverage levels with estimates of numbers of HIV infections averted. A policy of funding NSPs, pharmacy sales, and syringe disposal to cover all injections would have cost just over US$423 million for one year. One third of this cost would have been paid for as out-of-pocket expenditures by IDUs purchasing syringes in pharmacies. Compared with the status quo, this policy would cost an estimated $34,278 US per HIV infection averted, a figure that was well under the estimated lifetime costs of medical care for a person with HIV infection. At very high levels of coverage (>88%), the marginal cost-effectiveness of increased program coverage became less favourable (118).

Comments: Quality was 61% and transferability 69%. This relatively simple approach to modelling the impact of the intervention had a quality score that was reduced by a lack of a statistical analysis of cost results and no discounting of costs. The model would be reasonably transferable to another setting, although the authors did not think outside the United States.

Drucker found that the failure of the federal government in the USA to implement a national needle-exchange program, despite six government-funded reports in support of needle exchanges, might have led to 4000-9700 HIV infections among IDUs, their sexual partners, and their children, during the period 1987-1995. The cost-savings of NSPs could have been between $244m and $538m (119). The paper was a cost and outcomes analysis rather than a cost-effectiveness analysis so it was not scored.

An analysis from the UK on the cost-effectiveness of NSPs in decreasing HIV and HCV infections showed that increasing the number of IDUs receiving full NSP coverage might be
cost-effective if the costs of delivering the increased intervention were not too high and the intervention achieved a moderate decrease in syringe sharing (120). Results suggested that the impact and the cost-effectiveness of NSPs alone were likely to be greater in settings of lower HCV prevalence (120).

Comment: This modelling exercise scored very highly on both quality 97% and transferability 95%. The paper was assisted by being a report, rather than a journal article, where all the details could be included. The authors were from the UK and the paper was written in 2008, so they would have been following the approaches favoured by the European colleagues who helped construct the EURONHEED instrument.

A number of studies have examined the technical efficiency of different programs and their delivery. An HIV prevention program based on the distribution of kits and a needle exchange service which had been in operation in Navarra, Spain was found to cost $16,000 to $88,000 per HIV infection averted (121). Comment: Quality 72%, Transferability 61%. Analysis was focused just on one region of Spain so did not attempt to generalise results for elsewhere. Detailed costing study had been performed but assumptions about the costs of HIV were not clear.

A program including mobile NSPs in Hamilton, Canada returned cost-savings four times greater than the program cost (122). The quality was 90% because the study used a simple cost-benefit analysis rather than estimating quality adjusted life years. This is possible in prevention studies because the costs of an averted HIV infection can be derived from other studies. The transferability was 77% because it was a locally focused study.

Harris showed that the geographical location of NSPs in a city affected cost-effectiveness: sites needed to be located where the density of IDUs was highest and the number of syringes exchanged per client needed to be approximately equal across sites (123). This very sophisticated geographical analysis rated 71% on the quality scale because it was more of a technical analysis of a program delivery than an analysis of different interventions. The transferability was high, 89%, despite the very local nature of the analysis, because all model details were carefully explained.
Pinkerton evaluated the cost-effectiveness of a behavioural risk reduction intervention with injection drug users that emphasised safer sex and injection practices, rather than needle syringe programs alone. The intervention had been implemented in 1996 at 28 sites across the USA; he examined eight of the sites. In a threshold analysis, he found that the program would have been cost-saving if it had cost less than $2,100 per person to implement and would have been cost-effective (assuming a societal willingness to pay of $50,000 per QALY) if it had cost less than $10,300 per person (124).

Comment: Quality 74%, transferability 65%. Pinkerton used his mathematical model to consider the benefits of a boarder public health intervention for people injecting drugs. He used a threshold analysis in the absence of cost data.

Finally Tuli evaluated an HIV prevention intervention for HIV infected injection drug users that was designed to affect risky injection and sexual risk behaviours. The size and duration of the intervention affected the cost-effectiveness: it would be cost-saving if it led to a 53% reduction in the proportion of participants who had unprotected sex in a 12 month period and cost-effective with a 17% reduction. If the impact of the intervention lasted only 3 months, there would have to be a 66% reduction in people reporting risky sexual behaviours and if three years, a 6% reduction(125).

Comment: Quality 82%, transferability 91%. The paper described the method for collection of program costs and set out all cost and outcome data in tables. The authors were realistic that findings from a research study were likely to overestimate the benefits on an intervention in a real-world setting.

1.4 Summary of the literature review

The hypothesis underlying this literature review was that previously published studies from overseas might not be always be directly transferable or useful for decision-making in 2008. There were many issues with the literature reviewed that made it difficult to say that it was of adequate quality and contain enough information to allow to be easily transferred to the Australian context. In the following section, I will use the categories of the EURONHEED instrument to help explain the themes of the issues with quality and transferability.
For many of the studies reviewed, the underlying question or hypothesis was not clearly stated and needed to be inferred from the objectives and outcomes. It was not clear what kind of efficiency was being explored, whether it was technical efficiency (how resources were spent within a program) or allocative efficiency (how resources are allocated between programs).

Economic evaluations should compare two or more alternatives, but often the comparator was not stated or was assumed to be “no program”. But an all-or-nothing approach may not be realistic. Governments in high-income countries are forced by social convention and politics to provide some kind of public healthcare or prevention program, even if it is a less effective or less sophisticated version than the program under scrutiny. Economic evaluations that use unrealistic comparators are also of limited informative value. For example, would a healthcare organisation really restrict access to occupational post-exposure prophylaxis to their employees after only high-risk (?) exposure to HIV?

Another limitation of many of the studies reviewed was that they did not provide sufficient details to understand whether the sample used was representative of the wider community or target population. Assumptions were often made that populations are homogenous or that, for example an intervention that was cost-effective in San Francisco would be so in St Louis or Sydney.

It was difficult to determine the model structure used in many published studies. The CEPAC model, favoured by the Harvard-based research group and which predominates in the HIV healthcare literature, is a mathematical model that requires users to undergo an extensive training course. The inputs to this model were usually listed in their publications but it was not possible to reproduce the model directly. For example, I tried to re-run Goldie’s anal cytology screening model(99)and found that if I used the progression rates stated in the table, 20% of people living with HIV would have anal cancer after 20 years. The papers by Pinkerton and Holtgrave used a simpler mathematical equation that is easier to understand but may lack the ability to take into account multiple factors simultaneously. Few models used in the literature applied the TreeAge software program that is favoured by many modellers now, because it was still in development at the time of this review. Excel-based models are the most transparent because they allow tracking of connections and
relationships within the model and can handle uncertainty by the use of @Risk and other specialist add-ons.

Few economic analyses considered in this literature review were based directly on actual clinical studies. The EURONHEED questionnaire scored real-life studies more highly than models for the real data that they contained. Quality of life is often included in clinical research trials but the results may not be reported or may only be presented as a poster at a conference. Metanlyses were rarely used as the basis for the economic evaluations reviewed, perhaps because HIV is a fast moving field and therefore it is hard to complete a study for the Cochrane collaboration before the field moves on.

In many papers the same utility weights were used across countries and continents, thereby assuming, that the value people place on quality of life does not vary between populations. There are three reasons why researchers may have done this. First, it allows comparisons of results from different interventions across populations by the use of global accepted measures such as the Disability Adjusted Life Year. Second, studies to measure utility are hard to do and take time. As explained in Chapter 4, I needed to use standardised quality of life weights rather than the utility weights from the own study in Chapter 3, because of the pressure of meeting deadlines. Finally, no gold standard exists for utility measurement. Direct methods are complex and cumbersome for people to apply. No multi-attribute utility instrument is accepted universally (as will be discussed in the introduction to Chapter 3), with the Europeans favouring the EQ5D(126), Americans the SF6D(127-129) and the PBAC preferring local instruments like the AQoL(130).

Cost data was reported reasonably well, in terms of the unit costs of interventions. There was a tendency to recycle HIV cost estimates from previous papers, without apparent consideration that these might have changed with better and more expensive treatment. Few studies had performed micro-costing exercises, which may be more relevant to studies looking at the efficient delivery of a particular intervention than those examining the allocation of resources between programs.

Discounting rates varied depending on the country and the researcher, although most followed the standards of Gold et al(57). Some authors explained the rationale for their
choice of discount rate. Results were presented undiscounted or discounted little explanation. Non-economists may struggle with the concepts of discounting health outcomes into the future(131) as it could infer that a year of life lived in ten years is less important than one lived next year.

Most studies performed some kind of sensitivity or uncertainty analysis. One- or two-way sensitivity analyses often provided the most clarity about the factors in a model that affected the result. The EURONHEED instrument particularly favoured probabilistic sensitivity analyses. I decided to do both types where possible because the ACE-Prevention study linked to ACE-HIV used both.

The EURONHEED scores for all the studies rated are listed in table 1 below and plotted in Figure 1. In general, quality appeared to be a correlated well with transferability, although studies could be of high quality but low transferability.

<table>
<thead>
<tr>
<th>Author</th>
<th>Topic</th>
<th>Quality</th>
<th>Transferability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bos</td>
<td>HIV testing in STI clinic</td>
<td>64%</td>
<td>78%</td>
</tr>
<tr>
<td>Coco</td>
<td>HIV testing in Primary care</td>
<td>82%</td>
<td>97%</td>
</tr>
<tr>
<td>Phillips</td>
<td>Routine testing</td>
<td>79%</td>
<td>94%</td>
</tr>
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<td>Walensky</td>
<td>Routine testing hospital</td>
<td>86%</td>
<td>82%</td>
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<tr>
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<td>Testing and referral into care</td>
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<td>70%</td>
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<td>Paltiel</td>
<td>Routine testing in different populations</td>
<td>93%</td>
<td>94%</td>
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<td>Rapid testing</td>
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<td>71%</td>
<td>88%</td>
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<tr>
<td>Name</td>
<td>Treatment</td>
<td>Success Rate</td>
<td>Adherence Rate</td>
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<tr>
<td>Sendi</td>
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<td>84%</td>
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<td>91%</td>
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<td>ARV</td>
<td>84%</td>
<td>88%</td>
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<tr>
<td>Beck</td>
<td>ARV</td>
<td>96%</td>
<td>93%</td>
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<td>Ritonavir boosted lopinavir</td>
<td>92%</td>
<td>78%</td>
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<td>Starting ARV treatment</td>
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<td>75%</td>
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<td>Starting ARV treatment below 350</td>
<td>83%</td>
<td>76%</td>
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<td>Starting ARV treatment 350 to 499</td>
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<td>Starting points for ARV</td>
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<td>Outcome 1</td>
<td>Outcome 2</td>
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<td>Goldie</td>
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<td>79%</td>
<td>96%</td>
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<td>Kuehne</td>
<td>Hepatitis C treatment in HIV</td>
<td>93%</td>
<td>96%</td>
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<td>Cohen</td>
<td>Multiple prevention interventions</td>
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<td>61%</td>
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<td>Bedimo</td>
<td>Condom distribution</td>
<td>72%</td>
<td>70%</td>
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<td>NPEP</td>
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<td>66%</td>
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<td>48%</td>
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<td>Herida</td>
<td>NPEP in France</td>
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<td>53%</td>
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<td>Sheid</td>
<td>Occupational post-exposure prophylaxis</td>
<td>93%</td>
<td>97%</td>
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<td>Graves</td>
<td>Antenatal HIV testing in Australia</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>Holtgrave</td>
<td>Needle Syringe Programs</td>
<td>61%</td>
<td>69%</td>
</tr>
<tr>
<td>Vickerman</td>
<td>Needle Syringe Programs</td>
<td>98%</td>
<td>94%</td>
</tr>
<tr>
<td>Cabases</td>
<td>Needle Syringe Programs</td>
<td>72%</td>
<td>61%</td>
</tr>
<tr>
<td>Gold</td>
<td>Needle Syringe Programs</td>
<td>90%</td>
<td>77%</td>
</tr>
<tr>
<td>Harris</td>
<td>Needle Syringe Programs</td>
<td>71%</td>
<td>89%</td>
</tr>
<tr>
<td>Pinkerton</td>
<td>Needle Syringe Programs</td>
<td>74%</td>
<td>65%</td>
</tr>
<tr>
<td>Tuli</td>
<td>Needle Syringe Programs</td>
<td>82%</td>
<td>91%</td>
</tr>
</tbody>
</table>
Figure 1 Quality versus Transferability in Literature review papers
1.5 Conclusions from this chapter

The topics covered in the published literature appeared, at times, to reflect convenience and opportunity, rather than strategic need or purpose. There were few published studies on economic evaluations of interventions for the prevention and treatment of HIV in Australia and few studies of interventions that were relevant in 2008. Many of the recent publications on the cost-effectiveness of new ARVs were company-sponsored pharmacoeconomic evaluations carried out to assure the public funding of new drugs. Few healthcare systems have genuine needs-based strategic planning and delivery. Healthcare systems for HIV have evolved in response to a rapidly changing disease with little prior planning. The location and mode of delivery of current services may be more suited to the pre-HAART era than to clinical need of patients today. But there are political challenges in moving established resources around within a healthcare system and therefore it is not surprising that few cost-effectiveness analyses have considered alternative ways to deliver services.

The literature review provided me with a good background to the scale and scope of the field. It also led me to appreciate the challenges of performing economic evaluation analyses as well as identify some solutions. I used the process of the literature review to guide me in the execution of the studies reported in the next two chapters on cost and utility measurement. The EURONHEED instrument has 11 questions on costs, 2 on models and 7 on effect. The review provided me with the opportunity to learn from the experiences of previous researchers in the field. The draft list of potential interventions for initial assessment by the stakeholders was developed after doing the literature search. This chapter has focused generally on those relevant to the stakeholder discussions.

In the next chapter, I will discuss the study of the cost of HIV healthcare which aimed to provide some Australian data for the models applied in the ACE-HIV process.
2 HIV healthcare: costs and resource use

Introduction

This chapter is divided into four sections.

Section 2.1 provides a brief overview of the literature on costs and resource use in HIV healthcare in high-income countries, as it stood in 2007. This literature review helped me appreciate that I needed to develop a revised estimate of the cost of HIV healthcare in Australia for use in the ACE-HIV models.

Section 2.2 reports the method and findings of the original study using data from Medicare Australia. This study used a sample of 10,951 people who had ever had an HIV viral load claimed through Medicare Australia in the period 2003-2007 to examine all other items of service that these people had claimed on Medicare in that period, from GP consultations to pathology and imaging items.

Section 2.3 describes how I used utilisation and cost data on hospital admissions by diagnostic-related group to create an estimate of the cost of hospital admissions for people living with HIV in Australia.

Section 2.4 shows how I created a model to estimate the cost of HIV healthcare for use in the cost-effectiveness analyses of the ACE-HIV project in Chapter 4. I also estimated the total cost of HIV healthcare in Australia from the results of the Medicare study, the data from the hospital admissions analysis and the cost of antiretrovirals.

In Section 2.5 I demonstrate the possible impact of HIV disease on productivity in order to illustrate the challenges of this kind of cost estimation.
2.1 Brief literature review on cost of HIV healthcare

The seminal work on HIV cost in Australia was published in two papers by Hurley from 1992-1993. The study was a prospective survey of 128 gay men with HIV who recorded utilisation of different types of hospital and community care using diaries. Mean monthly costs ranged according to disease state from $331 per month for early patients to $4615 per month for AIDS patients, until the last three months of life when costs rose to $13,308 per month until death (15). The average present value of the costs of HIV care were estimated to be $70,000 for a man diagnosed in 1992 with a CD4 cell count less than 500 (16).

Hellinger performed a series of cost studies of HIV in the USA using data from hospital discharge abstracts and health insurance data that provide data from the pre- and post-HAART eras (132-139). In the year 2000, he estimated the average annual cost of managing HIV was between $20,000 and $24,000 per year (139). The costs of HIV that were included in his studies were usually only health sector. One of the frequently quoted studies of HIV costs is Holtgrave and Pinkerton from 1997. The study uses an ideal model of care approach and previous estimates to estimate the lifetime cost of HIV care at $155,000 (discounted at 5%) (12). Both authors have used these estimates, updated usually for medical inflation, in a wide range of economic evaluations of interventions for the prevention and treatment of HIV. Schackman provided a more up-to-date estimate using data from the HIV research network and the CEPAC computer simulation model. He found that from the time that patients entered HIV care, the discounted lifetime costs of HIV healthcare was $385,000 (2004 dollars). The results were sensitive to the costs and efficacy of antiretrovirals and the use of enfuviritide, an expensive agent not used much now (31).

Chen used a healthcare system database in Alabama to measure all encounters including primary care visits. He found that costs ranged from $13,900 per year for patients with a CD4 cell count greater than 350 to $36,500 per year for patients with a CD4 cell count less than 50. Cost of antiretrovirals was $10,500 across all CD4 strata, making up 71-84% of all expenses. Outpatient expenses were $1,600 per year, while only 2% of annual expenses were clinic and physician-related (140). A similar finding was described by Bozette, who showed that from 1996 to 1998, overall expenditures had dropped from $20,300 per patient per year to $18,300, but antiretrovirals made up a greater proportion (141). A retrospective
cohort (n=280) study estimated the average cost to the government or a third party insurer was $20,114 per annum. Independent predictors of cost were CD4 counts, Medicaid eligibility and behavioural co-morbidities(142). This association with costs replicated the findings of an earlier USA study reporting hospitalization rates in 2000-2001 were significantly higher among patients with greater immunodeficiency, women, African-Americans, patients who acquired HIV through drug use, those 50 years of age and over, and those with Medicaid or Medicare. Mean annual outpatient visits decreased significantly between 2000 and 2002, from 6.06 to 5.66 visits per person per year(143).

In terms of studies outside the USA, Beck performed a number of studies of costs of healthcare in the UK and South Africa (144-146) and reviewed studies around the world in 2001, highlighting that in three performed after 1996, the costs of treating people who were asymptomatic had increased to between $3,850-$7,550 per patient per year and for symptomatic persons (non-AIDS) had increased to between $7,350-$13,650 per patient per year(147). He also reviewed studies of the other sectors, patient & family, and productivity losses but all pre-dated effective ARV. The costs of healthcare for HIV have been changing in composition with increasing costs of antiretrovirals and decreasing hospital resource use due to fewer AIDS illnesses.

After the literature review, I decided that I needed a new estimate of the cost of HIV healthcare in Australia. I knew that data were available on hospital admissions and antiretroviral supply, but the size of the Medicare-funded part was uncertain. In Australia, over 50% of HIV healthcare for people living with HIV was being provided in the primary healthcare sector (148) but there were no data on how often people used Medicare services and how much that care cost. I therefore embarked on a study of the Medicare-funded part of Australian HIV healthcare.
2.2 Medicare costs study

Measuring use of resources and cost by micro-casting studies with diaries or surveys relying on patient recall can be very difficult and require large amounts of resource. Many GPs with high HIV caseload were sites in the Australian HIV Observational Database of 2500 people living with HIV, but that database did not collect resource use. There were cohorts and databases overseas that had analyses of claims data for HIV care (149, 150), so I decided to focus on the Australian Medicare claims database.

I realised that there was one unique pathology item, HIV viral load, that all people having their HIV care through their GP were likely to have claimed from Medicare Australia, that no-one without HIV could claim. Patients of outpatient clinics of some hospitals and sexual health clinics also claimed their viral load test through Medicare. I approached Medicare Australia about performing a study that would provide all Medicare claims data during a defined period for any person who had claimed an HIV viral load item. The method would need to protect the confidentiality of people and could not be linked to pharmaceutical benefits data by law. The study would always be limited to people who used Medicare Australia for a viral load measure but the potential size of the sample was large and might mitigate to some extent that drawback. Medicare Australia agreed to perform the data-linkage for the period 2003-2007 after ethical approval from the University of New South Wales ethics review board. This section describes the study of the Medicare claims of 10,951 people who claimed a HIV viral load one or more times during the period 2003-2007.

Medicare Australia administers a funding system that pays health care professionals for the performance of medical activities outside of an inpatient service of a public hospital or public sexual health clinic. Consultations, procedures, pathology and other items are classified by item numbers that relate to the type of procedure. In general practice consultations of different complexity and time are labelled A, B, C, D. The most commonly claimed item is level B, a standard GP consultation.

2.2.1 Method

The primary objective of the study was to measure the use and costs of the Medicare Benefits Schedule (MBS) in individuals with a claim for an HIV viral load test as recorded in the Medicare Australia database from 2003-2007 inclusive.
The secondary objectives were to

- Compare the use and costs of the MBS by individuals with HIV with national averages for use by non-HIV population age and sex-matched to reflect the known epidemiology of HIV.
- Examine the use and costs of Enhanced Primary Care items by people with HIV.
- Assess the use of items apparently unrelated to direct HIV care.
- Observe the use of diagnostic imaging and pathology items.

Medicare Australia agreed to provide the claims data for individuals with an HIV viral load assay claimed through the Medical Benefits Schedule (MBS) in 2003-2007. The data was de-identified before leaving Medicare Australia and assigned a study number by them. The study numbers were consecutive. Data provided included study identifier number, gender, and service date, type of service, charge, benefit paid, and billing method. The data was provided in a Microsoft Access database on a CD-ROM. A list of item numbers for MBS items was prepared to summarise the items according to categories of the MBS schedule (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Categories used in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A GP consults</td>
</tr>
<tr>
<td>B Specialist</td>
</tr>
<tr>
<td>C Miscellaneous either</td>
</tr>
<tr>
<td>D Enhanced Primary Care items</td>
</tr>
<tr>
<td>E Mental health</td>
</tr>
<tr>
<td>F Optometry</td>
</tr>
<tr>
<td>G Allied Health</td>
</tr>
<tr>
<td>H Bulk-Billing</td>
</tr>
<tr>
<td>I Diagnostics</td>
</tr>
<tr>
<td>J Procedures</td>
</tr>
<tr>
<td>K Obstetrics</td>
</tr>
</tbody>
</table>
The second level of classification occurred with the assignment of a new code to 146 different items of particular interest to allow a focus within the main classification areas.

STATA (Stata Corporation, College Station, Texas, USA) was used to produce a series of tables and summaries of the data.

Medicare Australia public data cubes online were accessed for 2007 to provide information suitable for comparisons of age/sex standardised rates with general Australian population (151). Data were limited to claims made on the MBS and no Prescription Benefit Schedule data were available nor were data on services funded outside the MBS such as public hospital inpatient admissions, public sexual health centres or non-Medicare funded outpatient clinics.

2.2.2 Results of Medicare study

Demography: 10,951 people made up the sample of people from 2003-2007. All the Medicare claims items for any type of medical or other service were available. 9944 males and 1007 females had one or more Medicare claim for an HIV viral load. 19.6% were aged over 50 years. (Figures 1 and 2 age and gender). The sample size was limited by the number of individuals who had used the Medicare system to claim a HIV viral load test. The sample probably represented around 63% of people living with HIV in 2008. The small numbers of patients aged 75 combined with relatively few women would mean that some categories are too small for detailed analysis.
Figure 1 Age and Sex distribution of sample

Age range
- 85+
- 75-84
- 65-74
- 55-64
- 45-54
- 35-44
- 25-34
- 15-24*
- 0-14

Number of individuals by age and sex:
- Males:
  - 85+: 85
  - 75-84: 75
  - 65-74: 8000
  - 55-64: 8000
  - 45-54: 8000
  - 35-44: 8000
  - 25-34: 8000
  - 15-24*: 8000
  - 0-14: 8000
- Females:
  - 85+: 75
  - 75-84: 8000
  - 65-74: 8000
  - 55-64: 8000
  - 45-54: 8000
  - 35-44: 8000
  - 25-34: 8000
  - 15-24*: 8000
  - 0-14: 8000
**Figure 2 Women age ranges**

![Bar chart showing women's age ranges with various age groups and their corresponding numbers.](image)

**Total Benefits Paid:** Over 300,000 items of service each year were claimed from 2003-2007 with a total MBS benefit of over $16m per year (Figure 3 and Table 2).
Figure 3 Average claims made per year 2003-2007 by major type

Table 2 Average claims made per year 2003-2007 by major type

<table>
<thead>
<tr>
<th></th>
<th>$m per year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP consults</td>
<td>3.73</td>
<td>23%</td>
</tr>
<tr>
<td>Specialist</td>
<td>1.58</td>
<td>10%</td>
</tr>
<tr>
<td>Miscellaneous either</td>
<td>0.01</td>
<td>0%</td>
</tr>
<tr>
<td>Enhanced Primary Care items</td>
<td>0.47</td>
<td>3%</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.11</td>
<td>1%</td>
</tr>
<tr>
<td>Optometry</td>
<td>0.12</td>
<td>1%</td>
</tr>
<tr>
<td>Allied Health</td>
<td>0.26</td>
<td>2%</td>
</tr>
</tbody>
</table>
GP Consultations: Median annual General Practitioner attendances were 8.25 per year for the whole sample and 25% attended more than 12 times (Figures 4 and 5). The analysis used the data on GP consultation items (i.e. level 3 brief consultation, level 23 standard consultation etc) assuming that a GP type consultation would be claimed if the patient saw a GP.

Use of GPs was much greater for age and gender than the total Australian population for both males and females. Figure 4 shows that difference in frequency of attendance for GP consultations was pronounced in men aged 25-44 who usually visit the GP only twice a year but in this sample the mean number of visits was over 8 times per year. The consultations were also more complex: men aged 25-55 years had more longer and complex consultations with approximately 5 level B standard consultations per year (versus 2.5 in the general population), 2.6 Level C more complex consultations per year (versus 0.3 per year in the general population) and 0.6 Level D long consults over 40 minutes per year (versus 0.03). Young women in the general population tend to visit their GP more often than young men.
because of their need for contraception and pregnancy. The HIV+ women in this sample visited their GP less often than their male HIV+ counterparts with only 2-3 extra consultations per year. Women aged 25-55 had 4.7 level B consultations per year (versus 3.7 in the general population), 1.5 Level C per year (versus 0.68) and 0.4 Level D per year (versus 0.07).

Figure 4 Male GP consultations per year by age group comparing study population with general population
Specialist consultations: 39% had attended any specialist of any type for a consultation claimed against Medicare with a median number of visits of 3 times. Physician consultations are not itemised by specialisation so it is unclear whether these may have been related to infectious disease and immunology visits, some of which are bulk-billed at some hospitals.

Amongst the surgical specialities, colorectal surgery items predominated, with 27% of the age group 35-44 years having a claim once over the 4 year period, most likely related to claims for colonoscopy and the surgical removal of anogenital warts.

Pathology and Imaging: An average of 2.1 HIV viral loads and 3 CD4 T-lymphocyte cell counts were claimed per person per year. Patients may also have been monitored in a non-MBS claiming site. There were 13-18 item claims for pathology per person per year for men
had the individual

e 3 makes interpretation difficult as 13 claims could be 13 items claimed on 13 different dates or 3 each claimed on 4 dates+ 1 on a fifth date. In comparison, the general population made 4.2 pathology claims per person per year in 2006/2007(151).

40-55% of men aged over 45 years had a cholesterol test claimed through the MBS at least once in the four year period. 50-60% of men aged 55 years+ had a prostate specific antigen claimed. Only 1% had a hepatitis C genotype claimed through the MBS. 44% of women aged 15-24 and 25% of women aged 25-34 had a pregnancy test claimed in the 4 yr period.

Rates of imaging were much higher than the comparable general population with more than 1 claim per person per year compared to 0.7 per year per capita for the general population. 37% had a CT scan at least once and 45% an ultrasound over this period. Rates for both procedures were high in younger men also, with 22% of 25-34 year olds having a CT scan at least once during the 4 years.

**Enhanced primary care claims:** 39% of men had a GP management plan claimed that would reflect complex care needs. 18% had claimed a team care arrangement used for individuals with complex medical needs who are seeing 3 or more health care professionals. Only 3% and 1% of the general Australian population have claimed a GP management plan or a team care arrangement respectively. Claims for enhanced primary care items were 50% lower in women than men. However, very few case-conferencing items were claimed by either gender.

Very few diabetes/asthma cycles of care claims were made. While there were 779 individuals for whom claims were made for glycosylated haemoglobin used for monitoring diabetes mellitus, there were only 53 individuals with a diabetes cycle of care item claimed.

**Mental Health:** 10% of males and females aged 25-54 had seen a psychiatrist and claimed the consultation on the MBS. 11% of males and 6% of females aged 25-44 years had ever had a mental health plan claimed compared to 3% of the general Australian population.

**Allied Health and Optometry items:** The optometry claims showed a close relationship with age, with 20% of men age 15-24 visiting the optometrist at least once during the year rising
to 43% in 65-74yo. Relatively few people had any allied health items claimed with only 4% of men and women aged 25-54 making a claim. The dental health scheme only commenced at the end of the study period so only 64 people made claims for dental services during the 4 year period.

**Costs and benefits:** 45% of people were charged privately for GP consultations with an average out-of-pocket cost to the patient of $22 for GP consultations. 61% paid an average $35 out of pocket cost for any specialist consultation. Enhanced bulk-billing items in general practice were claimed for 37-39% people, an indicator of the proportion of concession card holders.

### 2.2.3 Discussion of Medicare study

I showed that it was feasible to use the HIV viral load item number that was used only for managing HIV to capture all use and costs of Medicare items for a large sample of people over a 4 year period. It was possible to use the database to explore the costs of people with different clinical conditions by using a unique item number that was unlikely to be used by people without the disease. I could also explore claims of the use of other services including enhanced primary care items such as GP management and mental health plans for the population. The dataset was likely to be close to complete because most people will claim the Medicare benefit for a consultation. The data were accurate because clinicians have sophisticated systems for claiming the appropriate benefit and Medicare check claims that appear to be inconsistent.

There was a high use of MBS funded services by people in this sample compared to the general population. The benefit paid totalled over $16m a year or an average of $1500 per person per year with the greatest amount spent on pathology $7.8m per year and general practitioner items $3.7m per year. The individuals in the study sample had longer and more frequent GP consultations, more specialist consultations and more frequent use of diagnostic imaging and pathology than the age-gender matched general population. Uptake of enhanced primary care, mental health and imaging items was high. Use of other EPC items was relatively low.
There were high rates of claims for enhanced primary care and mental health items, reflecting the complexity of needs and presence of co-morbidities such as mental health and drug and alcohol problems. On the other hand, uptake of allied health and nursing items was relatively limited and the cycles of care items for asthma and diabetes hardly used. This may reflect either a perception that these services are of limited utility or a focus on particular aspects of health to the detriment of other conditions.

Enhanced bulk-billing items, an indicator of concession card holders, were claimed at one time point or more for around 38% of people, suggesting that a large proportion of people living with HIV are still relying on welfare support, despite the improved clinical situation for many people. 55% of people were bulk-billed, suggesting that at least 18% of people were being bulk-billed despite not having a concession card. Some clinics bulk-bill all patients and most of the others will allow bulk-billing if the patient has a low income. The average out of pocket costs of $22 for GP consultations for those who did pay appears to reflect the inner city urban average at the time. Consultations with specialists were more likely to be charged privately with a larger out of pocket expense but there was likely be a selection bias because the MBS study did not capture all public hospital outpatient consultations as many specialists especially in Victoria do not bill the MBS for public hospital attendances.

It is difficult to compare these results directly to previous studies because this is the first use of the Medicare Australia claims database to look at patterns of utilisation and cost. The BEACH study of general practice included doctors who manage high HIV caseloads in their evaluation(152). GPs completed a log book of patients, but the non-systematic approach used in including patients in these logs, may have led to a bias towards the exclusion of more complex patients whose details it takes longer to record.

What are the limitations? This study was limited to 10,951 people who had an HIV viral load test claimed through the MBS during the period 2003-2007 who were a subset of the estimated 16,500-20,000 people living with HIV in Australia during this period. The sample may not have reflected the same demography or clinical conditions as those who were not included. Those absent from the dataset would have been receiving their HIV care through non-MBS funded services or might not be accessing care at all. MBS claims were made for only a proportion of hospital outpatient visits with wide variation in MBS use, from none at
the major hospitals treating HIV in Melbourne to some at public hospitals in Sydney. This difference was driven by different administrative arrangements between the hospitals. People attending sexual health centres or hospitals might have claimed only the pathology or imaging service. Participants in clinical research studies were likely not to have a MBS claim for their study visits.

The study sample may have been younger and less advanced in their HIV disease than the overall population of people living with HIV because people with more advanced disease might have been seen at the hospital for their care. The sample might have excluded the “working poor” who did not qualify for a Health Care Card and thus may have avoided GP visits that require a patient co-payment.

The amount of data that was available was very large with over 1,200,000 items of service. I needed to apply a two-step classification system to be able to handle the data, initially classifying it by major chapter in the MBS handbook and then applying a sub-classification system that collapsed the items to 120 sub-types. The sub-classification system was focused on topics of interest such as levels of GP consultation, enhanced primary care and mental health items. It could have been equally valid for me to ask for data only from a smaller random sample that would have provided a similar richness of findings but that would have been easier to manage.

The quantity of data also made it difficult to assess if there were any inconsistencies or problems with coding. I found that some codes had changed during the period of the study and that meant that the look-up tables did not find the code easily in previous editions of the MBS to amalgamate it. The codes that I did find did not appear to be for items of interest to the purposes and all had small numbers of users with low frequency of use.

The study provided data on utilisation and costs that could be used to create a synthesis of the costs of HIV in Australia discussed later in this chapter. Next, I will discuss an approach to costing hospital admissions that I used.
2.3 Costing hospital admissions for people living with HIV in Australia

This 3-step method was originally developed by Andrew Dalton, Senior Lecturer in Health Economics at Melbourne University for use in costing studies for a wide range of diseases. I used his method to provide an updated estimate of the cost per admission of a patient with HIV to hospital in Australia.

2.3.1 Method costing hospital admissions

I searched the clinical profiles for all hospital admissions in Australia for 2004-2005 by Australian National Diagnosis Related Group (AN-DRG) looking for HIV in the primary or secondary codes used for case-mix funding(153). The AN-DRG item number in the National Hospital Cost Data Collection Cost Report for 2006-2007 that listed the amount paid according to the case-mix funding formula(154) was entered as average costs per admission in the right hand column of the table below. I estimated a weighted average for any admission of a patient with HIV by multiplying the proportion of each type of admission with the cost per admission. An average cost for any admission where HIV was used as a primary or secondary code was calculated. All costs were converted to 2008 Australian dollars using the health consumer price index and discounted by 3% for the baseline analysis for costs in the future.

The National Admitted Patient Care Collection is conducted by the Australian Department of Health and Ageing. The process includes data submission from hospitals to State coordinators who perform data quality checks before submission to the department. Data was processed with the creation of a population file and national database with adjustment for missing data. Cost weights and tables were created by a technical reference group with sign-off by States and Territory Health departments.

2.3.2 Results costing hospital admissions

According to the analysis, each hospital admission by people living with HIV in Australia cost an average $7,250 in 2008(Table 3). I used the data from this analysis in the section 2.4 of this chapter to estimate a total cost of HIV related healthcare.
<table>
<thead>
<tr>
<th>DRG Code v5</th>
<th>DRG Description</th>
<th>No.</th>
<th>% of total</th>
<th>Average cost per Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>S65C</td>
<td>HIV-Related Diseases - Cscce</td>
<td>152</td>
<td>4.45%</td>
<td>$5,998</td>
</tr>
<tr>
<td>S65B</td>
<td>HIV-Related Diseases +Sccce</td>
<td>151</td>
<td>4.42%</td>
<td>$8,862</td>
</tr>
<tr>
<td>S65A</td>
<td>HIV-Related Diseases +Cccce</td>
<td>128</td>
<td>3.75%</td>
<td>$20,793</td>
</tr>
<tr>
<td>S60Z</td>
<td>HIV, Sameday</td>
<td>58</td>
<td>1.70%</td>
<td>$721</td>
</tr>
<tr>
<td>T63B</td>
<td>Viral Illness A&lt;60 -Cc</td>
<td>4</td>
<td>0.12%</td>
<td>$1,098</td>
</tr>
<tr>
<td>T63A</td>
<td>Viral Illness A&gt;59per+Cc</td>
<td>1</td>
<td>0.03%</td>
<td>$2,044</td>
</tr>
<tr>
<td>TO1C</td>
<td>Or Proc Infect &amp; Paras Dis-Cc</td>
<td>1</td>
<td>0.03%</td>
<td>$5,028</td>
</tr>
<tr>
<td>S60Z</td>
<td>HIV, Sameday</td>
<td>896</td>
<td>26.23%</td>
<td>$721</td>
</tr>
<tr>
<td>S65C</td>
<td>HIV-Related Diseases - Cscce</td>
<td>564</td>
<td>16.51%</td>
<td>$5,998</td>
</tr>
<tr>
<td>S65A</td>
<td>HIV-Related Diseases +Cccce</td>
<td>497</td>
<td>14.55%</td>
<td>$20,793</td>
</tr>
<tr>
<td>S65B</td>
<td>HIV-Related Diseases +Sccce</td>
<td>450</td>
<td>13.17%</td>
<td>$8,862</td>
</tr>
<tr>
<td>Q62Z</td>
<td>Coagulation Disorders</td>
<td>174</td>
<td>5.09%</td>
<td>2,555</td>
</tr>
<tr>
<td>G11A</td>
<td>Anal &amp; Stomal Procedures +Cscce</td>
<td>81</td>
<td>2.37%</td>
<td>6,423</td>
</tr>
<tr>
<td>G44C</td>
<td>Other Colonoscopy,</td>
<td>70</td>
<td>2.05%</td>
<td>1,177</td>
</tr>
<tr>
<td></td>
<td>Sameday</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>-------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>F74Z</td>
<td>Chest Pain</td>
<td>66</td>
<td>1.93%</td>
<td>1,474</td>
</tr>
<tr>
<td>X62A</td>
<td>Poisoning/Toxc Eff Drugs A&gt;59per+Cc</td>
<td>62</td>
<td>1.81%</td>
<td>3,651</td>
</tr>
<tr>
<td>G45B</td>
<td>Other Gastrpy+N-Mjr Digest Dis</td>
<td>61</td>
<td>1.79%</td>
<td>1,047</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>3416</td>
<td>100.00%</td>
<td>$7245</td>
</tr>
</tbody>
</table>

### 2.3.3 Limitations of the hospital admission cost method

Patients with HIV that were admitted with a number of problems would have usually had the top 2 conditions coded. However, the conditions coded were likely to be the most expensive ones, so any that were missed might not be incrementally great. Case-mix allowed for some of this other activity in the costing.

The data on the admissions to hospital was derived from the 2004-5 clinical profiles because that was the data available at the time but the case-mix amount for the item was from 2006-2007. While this might have affected the validity of the results, the exercise aimed to provide a crude estimate that reflected hospital costs during the period of study. Hospitals in NSW did not use case-mix funding during this time, rather they received block grants. But they did contribute data to the case-mix funding process and used the case-mix amounts as indicative markers of costs.
2.4  Estimating the total cost of HIV healthcare in Australia

When I started this research program, I intended to mirror the protocol for the other studies in the ACE-Prevention program that used disease cost data for the cost of disease from the Disease Costs and Impacts Study (DCIS) by the Australian Institute for Health and Welfare (AIHW). I wrote to the AIHW and was provided with a cost estimate for all HIV-related healthcare $24m a year in 2001 but was warned by the AIHW that the data for some disease areas was not certain(155).

The AIHW estimate did appear to be low because there was data from the National Centre for HIV Epidemiology and Clinical Research annual surveillance report that antiretrovirals alone had cost $67m for year 2000/1 (156).

So, I performed the work reported in this section of the chapter to provide:

1. An estimate of the cost of HIV healthcare to use in the cost-effectiveness models for the ACE-HIV project and over a lifetime (sub-section 2.4.1)

2. A synthesis of the data with other data to estimate a total cost of HIV healthcare in Australia annually(sub-section 2.4.2)

2.4.1  Model to estimate the cost of HIV healthcare by CD4 cell count and treatment for use in economic analyses and lifetime cost of care

I created a model of HIV healthcare that was informed by published data and the studies above, including health states according to CD4 cell count and antiretroviral use. This ‘ingredients’ approach had been taken by Hurley et al in their first estimate of the lifetime costs of care in Australia (16) and had been used by other authors(45, 46).

I developed a model of service delivery reflecting current practice in 2008 in an excel spreadsheet. Utilisation data was derived for different health states from the literature and the MBS study data by four CD4 strata and three antiretroviral strata in HIV. I valued outpatient items from the Medicare Benefits Schedule (157) and Pharmaceutical Benefits Schedule (158) in 2008 dollars. As described above in Section 2C, I searched the national health department data on the frequency and proportions of admission to hospital with
different health states of HIV (153) and then derived a weighted average cost per admission in a health state using cost weights for admission to an Australian public hospital (154). All costs were valued in 2008 Australian dollars.

**Identification.** The following items of service for people living with HIV were assumed: medical consultations including general practitioners and specialists; allied Health including psychologists, social workers and dietician; pathology including Full Blood Examination, CD4 T-cell Lymphocyte phenotype, HIV viral load, blood chemistry including liver enzymes, creatinine, urea, electrolytes, glucose, genotype resistance testing; inpatient hospitalisations; medications including prophylaxis and associated non-ARV medications. These items were similar to those identified in a pre-ARV era study of Australian health service use by Hurley (15, 16).

**Utilization:** The utilisation of each type of service was determined from published data, the study above and the clinical experience. Utilisation was the incremental use of health services over and above the use by people of a similar age and gender without HIV. People living with HIV were divided into four health states according to CD4 T cell count >500, 350-499, 200-349 and <200. Antiretroviral costs were calculated separately.

In the Medicare study reported above, men aged 25-54 visited their GP eight times per year, in a study in the United States people with HIV visited outpatients five times a year (159) and in Italy five to six times (160). In the Australian community-based HIV Futures 5 study, 50% of patients were seen by their general practitioner for HIV care, according to patient retrospective self-report (161). Another study in the USA, patients were seen 9.7 times (140). In another study, utilisation rose with lower CD4 cell counts, with 20% more visits when the CD4 was less than 350 (162).

Pathology utilisations were assumed to follow a three monthly monitoring, with a small proportion having a genotype resistance test in a year. This assumption reflect clinical standard of care in 2008. In the model, medications for prophylaxis of herpes simplex virus, mycobacterium complex and pneumocystis pneumonia commenced when the CD4 cell count was low.
Data on hospital admissions from the analysis is reported in section 2C. In the published literature, one study showed that while the risk of AIDS was low with higher CD4 cell counts, people might be admitted with serious non-AIDS events (159). Hospitalisation was rare (1%) in Italy with high CD4 cell counts (143, 160) but higher (11%) in the USA (143, 159, 160, 163). Hospitalisation risk increased in all settings with lower CD4 cell counts (153).

**Valuation:** Outpatient items in the model were valued from the Medicare Benefits Schedule (158), Prescription Benefits Schedule(164) and the Pharmaceutical Benefits Advisory Committee Manual of Resource Items in 2008 dollars(165). The unit costs of inpatient admission were estimated as described above.

**Antiretrovirals:** The use of antiretrovirals in the model was consistent with the Australian commentary on the United States Department of Health and Human Services guidelines (158) with four lines of antiretroviral therapy. In the base case, patients were assumed to start ARVs when their CD4 cell count was less than 350 and continue on them indefinitely. They moved to the next line of therapy when the previous one failed. Antiretrovirals were valued by the Prescription Benefits Schedule (57).

**Disease model for lifetime cost:** To estimate the lifetime cost of HIV, estimates for each health state were placed in a disease model in TreeAge software with 42 health states based on four CD4 levels 0-199,200-349,350-499 and >500 , three treatment lines and viral suppression and a time horizon of 60 years in 3 month cycles . The input parameters such as epidemiology, mortality and changes in viral load were the same as used in the cost-effectiveness models for ACE-HIV reported in chapter 5.

### 2.4.1.1 Cost of HIV healthcare by CD4 T cell count and use of antiretrovirals

The results of the cost model are presented in the table below. The cost of healthcare excluding antiretrovirals and also the cost of each line of antiretroviral therapy is in table 4. I used these estimates as inputs in the cost-effectiveness models reported in chapter 5.

The lifetime cost of HIV healthcare was $359,000 (range $356,000-$391,000) discounted at 3% per annum or $672,000 (range 667,000-$724,900) undiscounted calculated using the disease model.
<table>
<thead>
<tr>
<th>Healthcare excluding antiretrovirals</th>
<th>Annual Cost</th>
<th>Uncertainty intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &gt; 500</td>
<td>$1,523</td>
<td>$1371 to $1676</td>
</tr>
<tr>
<td>350 &lt; CD4 &lt; 500</td>
<td>$2,055</td>
<td>$1849 to $2260</td>
</tr>
<tr>
<td>200 &lt; CD4 &lt; 350</td>
<td>$2,731</td>
<td>$2458 to $3003</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>$5,500</td>
<td>$4950 to $6050</td>
</tr>
</tbody>
</table>

**Antiretrovirals**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line therapy</td>
<td>$14,613</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line therapy</td>
<td>$15,178</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line therapy and subsequent</td>
<td>$27,776</td>
</tr>
</tbody>
</table>
2.4.2 Synthesis to calculate the Annual cost of HIV healthcare in 2008

The data from the Medicare study in section 2.2, the hospital cost analysis in section 2.3 and the reported cost of antiretrovirals in the Australian HIV Observational Database report(166) were used to create a synthesis of the total annual cost of healthcare for people living with HIV, excluding non-antiretroviral medicines.

- The cost to Medicare of healthcare for people living with HIV was approximately $25m per year or $1,500 per patient per year.

- Hospitalisation costs were $25m in 2004, equivalent to $28m in 2008 at a cost per admission of around $7,200 per admission.

- Cost of antiretrovirals was $136m from the Australian HIV Observational Database report (166).

Using these three figures, the total costs of healthcare for people living with HIV were over $186m per year in 2008 dollars, excluding the costs of non-ARV medicines. The average cost of healthcare per person with HIV would be around $10,500 per year if an estimate of the number of people living with HIV of 17,444 people in Australia in 2008 was assumed(167).

2.4.3 Discussion of this section

The process of synthesising a total cost of healthcare for people living with HIV relied on the assumption that the majority of the cost of care was captured in three ways: Medicare, Section 100 of the PBS and hospital admission data. Antiretrovirals cost $136m per year in 2008 that dwarfed the cost of hospital admissions (where HIV was coded) $28m and MBS items claimed $25m. The data did not include the cost of non-ARV medicines or the cost of complimentary therapies. The definition of healthcare was narrowly defined to Medicare-claimable services and so private dentistry, counsellors, psychologists, naturopaths, osteopaths and other health care practitioners were excluded unless the service was provided as part of a team care arrangement enhanced primary care item. The costs of publically-funded outpatient and sexual health clinic appointments were also excluded from the total healthcare cost synthesis although they were included in the ideal model of care.
used in the ACE-HIV models. If data on the use of these services were required in the future, then a detailed micro-costing study might be needed.

I assumed in the overall synthesis of healthcare costs that the healthcare utilisation and cost of consultations of the non-Medicare users were the same as the users. This assumption could have been an overestimate if the non-Medicare users were not using services anywhere else or underestimate if they were attending hospital outpatients or sexual health clinics more frequently than those in the sample. It is probable that some non-Medicare users fall into the first category and some into the second. In a future study, it would be helpful to survey groups of hospital outpatient or sexual health about their use of services, both Medicare funded and non-Medicare funded. A potential long-term study would involve following patients prospectively after HIV diagnosis, with consent to seek their MBS, hospital and PBS data by regular interrogation of the databases and regular surveys to triangulate use of services not-captured in these databases.

In the utilisation model, I assumed that doctors chose a preferred regimen in each line of therapy. It could be argued that this wasn’t a reflection of the real world because adherence to preferred regimens in treatment guidelines was 55% in a study in Australian high-caseload clinics in 2008. However adherence to guidelines was 82% if both preferred and alternate regimens were included(168).

The prices for first line therapy that I used were the costs visible on the PBS website. The cost of first line therapy listed on the website varied from $564 per month for abacavir/3TC to $788 per month for tenofovir/emtricitabine, both nucleoside reverse transcriptase inhibitors and $285 per month for nevirapine to $452 per month for efavirenz, two commonly used non-nucleoside reverse transcriptase inhibitors(169). However, the visible price is not always the price paid by government with agreements on ‘3 for 2’ deals and lower actual prices for some medicines.
2.5 Productivity Losses and Gains

The final section of this chapter is a discussion of the possible productivity losses and gains associated with HIV infection. I have included this section in the thesis because it illustrates well the challenges of estimating the productivity losses and gains a disease like HIV. In the report of the Return on Investment II project on the cost-effectiveness of needle-syringe programs that I co-authored, I calculated productivity losses and gains for both HIV and HCV. The original method was provided by Dr Anne Magnus from Deakin University who assisted me with the application of the process to HIV. I have adapted the section on productivity losses and gains from the Return on Investment II report to focus on HIV. There is one major caveat to point out to the reader: the analysis was focused on HIV infected injection drug users.

2.5.1 Background productivity losses and gains

HIV is a disease that affects the productivity of an individual by reducing both the quantity and quality of years of life. The term productivity costs has been defined as “the costs associated with lost or impaired ability to work or engage in leisure activities due to morbidity and lost economic productivity due to death” by the US Panel on Cost-Effectiveness in Health and Medicine (170).

No studies have attempted to estimate productivity costs associated with HIV infection in Australia. A small number of studies have been conducted overseas, mostly in the pre-ARV era. An analysis of the indirect costs of HIV in the UK in the pre-ARV era that used the human capital approach, found that annual productivity losses ranged from A$2,400 to A$16,600 (1997 prices) depending on clinical state (171); a prevalence-based estimate from the United States argued that productivity losses resulting from morbidity and premature mortality would rise from US$3.9 billion in 1985 to US$55.6 billion in 1991 (172, 173); a recent cross-sectional analysis of patients enrolled in the Swiss HIV cohort estimated a mean annual productivity loss per person of A$19,000 based on the human capital approach (57).

The inclusion of productivity losses and gains in economic evaluations that also include QALYs may be double-counting because the utility used in QALYs takes account of disability and losses in quality of life that may reduce employment (174). However, in the economic evaluation of interventions, it can be valuable in secondary analyses to quantify the
additional potential productivity benefits that may accrue by further expenditure, although it may favour interventions that improve the health of sections of the population with higher levels of employment, over those whom, are not participating in the workforce (175).

2.5.2 Rationale for method

I used the method developed by Deakin Health Economics because it provided a tractable model with relatively simple data needs that had been developed on behalf of decision-makers at the Victorian government Treasury and used in the Assessing Cost-Effectiveness of Prevention studies. The method provided for a choice of two approaches to costing productivity losses. In brief, the Human Capital approach assumed that the productivity losses, associated with a worker who stops work due to illness or dies, were the average annual wage for their age and gender from the time that they stop work until the age of 65. The Friction Cost approach assumes that workers can be replaced and new workers trained to perform at the same level as the injured or deceased worker within a period of time (usually 3-12 months)(59) (174, 176).

The Friction Cost approach is recommended or described as theoretically preferable by a number of reimbursement agencies (174, 177). The Friction cost approach assumes that workers will return to work after a health intervention. This assumption may not hold if recovered workers value non-work life more highly after recovery from a serious illness (177) or have adequate levels of income without the need to work full-time (57).

2.5.3 Method

I used the Friction Cost approach with a secondary analysis using the Human Capital approach for illustration. All cost was discounted to present value at a baseline discount rate of 3%, consistent with the US Panel on Cost-Effectiveness in Health and Medicine (174) varied to 0% and 5%, the latter figure consistent with the recommendations of the Prescription Benefits Advisory Committee (178-180). I assumed that three months would be required to hire and re-train due to a sick or deceased worker; variations of six months and 12 months were carried out to test this assumption.

The Deakin Health Economics model compares the employment status, participation rate, short-term absenteeism and mortality of people with a disease or intervention with people
without the disease or intervention. But I found that data on the workforce participation of people who injected drugs was limited. Studies from the early 1990s reported participation rates of around 30% for injection drug users with and without HCV attending clinics and participating in a coordinated care program (161). On the other hand, in the HIV Futures V study (n=982) carried out in 2005/6 (181), 47% to 50% of the 271 current or previous injection drug users living with HIV were currently employed compared to 62% of those who did not inject drugs with HIV. Given the better economic conditions that were prevalent until 2008, I decided to assume that a population of injection drug users without HCV or HIV would have a workforce participation rate that was 10% less than the general workforce participation rate for age and gender provided in the National Health Survey of 2004/5 (181). The demography of the comparison and disease populations in the productivity model was assumed to match the age and gender mix of the estimates of injection drug users in Australia with 33% women.

Short-term absenteeism rates in the comparison population were presumed to be similar to the general population rates from the National Health Survey when 3% of the population being absent from work daily in Australia (182). Coverage by colleagues and employers for absent workers during sick leave was also assumed to match the general population with 28% of employees not covered by sick leave (183). Training costs for replacement of sick or deceased workers were derived from the Victorian Department of Treasury and Finance Report where outsourced human resources services were costed at 30% for lower paid staff and 75-100% for higher paid staff (184).

The age-sex structure of the population acquiring HIV and HCV in the productivity model mirrored assumptions made for the uninfected IDU population. Inputs for the participation rate, employment status, unemployment rate and short-term absenteeism in people with HIV by age group was provided by the Australian Research Centre in Sex, Health and Society from the HIV Futures V study (161). In the Futures V study the overall employment rate was 51%, with some students, retired people and 10.9% unemployment. 6% reported that they were sometimes unable to attend work due to HIV so the absenteeism rate was assumed to double the rate of the comparison population (29). Age-specific but not gender-specific employment and participation data was used in HIV population in the productivity model.
I estimated extra mortality due to HIV leading to productivity losses for each incident infection at a specific age in a series of separate expected value analyses. I constructed a simple Markov model in TreeAge with annual cycles and two states alive and dead. I drew age-specific mortality for HIV-infected and uninfected populations in the ARV-era (2000-2005) without HCV were drawn from a Danish population study (185, 186). Additional deaths from HIV by 65 years were computed according to the time of infection and included in the model to allow the estimation of mortality-related productivity losses.

Taxation and welfare effects of productivity losses were not estimated due the lack of data on marital status and eligibility for a disability support pension in the IDU population. Taxation and welfare may be considered as transfer payments and therefore excluded from economic evaluations from a societal perspective.

The baseline output from the productivity model was the productivity loss per incident infection of HIV expressed in dollars discounted at 3%, using the Friction Cost approach of replacement in three months with gender specific wage rates. The productivity model was run using the @Risk software package for 4000 simulations to enable the calculation of mean and 95% uncertainty limits. The reference year for costs was 2008.

2.5.4 Results

The baseline mean productivity loss was $21,757 per HIV infection, discounted at 3% with a 95% uncertainty range between $12,322 and $33,939 if the FC period was three months. Using the HC approach the production losses were $493,660 per HIV infection (95% limits 372,306 to 621,463) up to the age of 65 years. An increased time period for recruitment and training of new staff from three months to six months increased the productivity loss to $26,506. Gender free wages increased the productivity loss to $23,222. Using the FC approach, 71% of the cost of productivity loss was due to morbidity, especially in people aged 25-44 years old, reflecting the higher participation rates in the workforce. 29% was related to premature mortality particularly in males infected when aged 35-44. In contrast, using the HC approach, the 50% of productivity cost related to premature mortality. A higher discount rate of 5% reduced the mean loss by FC to $18,167 (95% limits $10,947 to $27,050) and with a zero discount rate the mean loss was $33,619 ($16,325 to $58,151).
2.5.5 Limitations

The method was limited for a number of reasons: I did not have direct data on the employment of IDUs around Australia and therefore made a number of assumptions. Secondly injection drug use may be associated with higher or lower workforce participation than in this model which would alter the productivity loss: if IDUs are already not working, then HIV may make little difference to their employment status. Third, I assumed that the mortality related to HIV would be the same in Australia and Denmark. Since the impact of premature mortality was limited on the result compared to morbidity, it is not likely to have made much difference. Finally a caveat: the results are only relevant to the productivity loss associated with an HIV infection in a population of injection drug users in Australia in the middle of this decade.

2.5.6 Comment on relevance of findings from this analysis

The baseline mean productivity loss was $21,757 per HIV infection using the Friction Cost approach, discounted at 3% if the FC period was three months. An increased time period for recruitment and training of new staff from three months to six months increased the productivity loss to $26,506. When the Human Capital approach was used the production losses were $493,660 per HIV infection up to the age of 65 years.

One can see that the estimates vary widely depending on the method used. From the perspective of an individual, their friends and family or their employer, it could appear obvious that the loss of that person to sickness or death may be devastating economically. From a societal perspective, the person would have contributed to society, paid taxes and consumed goods. But would they have been irreplaceable in their work? There are only a few highly trained individuals with unique expertise that appear irreplaceable when they are sick or die, but the majority of us are not alone in our abilities or experience. This methodological issue makes the results of this productivity losses exercise too uncertain to be useful in economic evaluation.

There is a second reason not to include productivity losses and gains. An economic evaluation of a health intervention for prevention or treatment considers the costs and outcomes of two or more alternatives. It is tempting sometimes to include the productivity losses averted in the outcomes section without including the non-health input costs. This
can make all health interventions appear more cost-effective than they may be from a true societal perspective, beyond just health. A third reason to avoid their inclusion is that the QALY or DALY outcome includes the value of the loss of healthy life in quality and quantity. It could appear to be double-counting to add in the value of the work-life lost, when this may have been considered in the valuation process for the QALY or DALY. For these three reasons, productivity losses and gains were not used in the ACE-HIV studies reported in the next two chapters.

2.6 Summary of Chapter 2

In this chapter, I have shown that it was possible to use the Medicare Australia database to estimate that it cost $25m to provide healthcare for people with HIV claimed through the Medicare Benefits Schedule by using a unique item number that would have been used only for monitoring of the disease. Using data on utilisation from this study and other analyses, the average cost of healthcare per person was $10,500, depending on CD4 cell count and line of therapy.

It was possible to synthesise an estimate of the total cost of healthcare for people living with HIV, $186m per year, excluding non-antiretroviral medicines and healthcare that does not attract a Medicare rebate, and that the uncertainty about the size of productivity losses and gains precluded their use in the ACE-HIV models.
3  Measuring health-related utility in people living with HIV

Introduction
This chapter discusses a study to measure the health-related utility and quality of life of a sample of people living with HIV who were enrolled in the Australian HIV Observational Database. The study used three instruments combined with existing clinical and surrogate marker data. One of the instruments was an Australian designed and valued multi-attribute instrument that had not been used in HIV.

3.1  Background to health utility measurement
Health-related utility is an economic concept that values the preferences that individuals or society may have for a particular set of health of outcomes such a health state or changes of health (187)p14. It is sometimes equated with quality of life related to health, but is different in the sense that it is valued rather than just stated. Utility analysis is a technique that allows adjustment to health outcomes, usually years, according to the quality of life. This can allow analysts to consider the time gained from the benefits of a health intervention in terms of the quality and the quantity of the time gained. There are different ways to measure utility that depend on the theory underlying them and different ways to interpret and use those results also according to the economic theory. In the interests of brevity, I shall not discuss those theories here.

The commonest use of utility weights is in the cost-utility analysis where the parameter of interest is the Quality-Adjusted Life Year (QALY), created by multiplying the time in each health state by the utility weight scored from 0=death to 1=full health for that state of health(188). Another way to adjust years of life is to disability-adjust the time lived and include the time lost to early mortality. This leads to the Disability-Adjusted Life Year (DALY) that has been used extensively by the World Health Organisation as a metric for the burden of disease and to assess the value for money of different interventions (42, 189). The DALY was used in the ACE-Prevention studies that the ACE-HIV project was linked to (see Chapter 4 for discussion).

As I explained above, the ways to measure utility are often linked to particular theoretical approaches. There are direct methods that use special techniques that try to assess the
preferences that people have for different states of health, usually using a clinical vignette or description of life lived with particular severities of conditions. Two types of these are the standard gamble and time-trade off. There are indirect methods that have been created as utility instruments and are based on health states that have been valued by the general population using one of the direct methods (multi-attribute utility instruments). There are also indirect methods that use existing quality of life instruments and then apply an algorithm that reflect valuations made using one of the direct methods.

Utility weights measured in one country may not be appropriate to be used in an economic analysis from another country. Noyes found that the findings of cost-effectiveness analysis of treatments for Parkinson disease differed according to the country of origin of the valuation algorithms used(66). One editorial commented that “all cost-effectiveness analysis is local” (65) because decision contexts, societal values, culture, resources and health care systems vary so much.

Finally, the populations who provide the valuations of preferences for health states may not understand or appreciate the disease states that they are being asked to value. People living with HIV rated their utility higher than people drawn from the general population asked to rate the same health state description(190). While patients showed evidence of adaptation to their disease that explain this difference(191), stereotyping and prejudice by the general population about people with HIV might affect perceptions of the value of life.

3.2 Health utility measurement in HIV

There have been a number of utility studies in HIV, mostly conducted overseas. Mrus used a direct method the standard gamble method (SG) with a group of patients who were both mono-infected with HIV and coinfected with HIV and HCV. The utility weight was 0.87 for HIV positive people, 0.77 for HCV/HIV co-infected people and there was an association with the physical summary score on the SF-12 health status instrument and with symptoms(192).

The utility score may depend on the measurement method employed. Bayoumi used four different methods in a group of patients (n=75) and found varying utility weights depending on the method used(89)(Table 1).
Table 1 Utility weight according to disease state and method of measurement used

<table>
<thead>
<tr>
<th>Method</th>
<th>Symptomatic HIV</th>
<th>Minor AIDS defining illness</th>
<th>Major AIDS defining illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Gamble</td>
<td>0.90</td>
<td>0.65</td>
<td>0.42</td>
</tr>
<tr>
<td>Time Trade Off</td>
<td>0.96</td>
<td>0.75</td>
<td>0.50</td>
</tr>
<tr>
<td>Visual Analogue Scale</td>
<td>0.70</td>
<td>0.49</td>
<td>0.21</td>
</tr>
<tr>
<td>Health Utilities Index</td>
<td>0.86</td>
<td>0.76</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Tsevat used time trade off (TTO) and standard gamble (SG) direct methods in 51 patients attending a HIV regional treatment centre. Standard gamble is based on concepts around risking all for a cure while time-trade off is based on concepts around trading years of life spent with illness for fewer years in full health. In his study utility by time-trade off was higher than by standard gamble, the reverse of the usual situation (193). He postulated that many people living with HIV noted that time was too valuable to trade, but they were used to taking risks in their daily life around HIV treatments (193). Fowler stated in a commentary on using utility methods based on direct methods that invoke concepts about risk:

“For people reluctant to say they will give up any life at all, questions that involve risking or trading life seem likely to be poor measures of the values of health states” (194)

There had been only one published study measuring HIV-related health utilities in Australia (195) prior to mine. The study took place in the early highly active antiretroviral therapy (HAART) era, when the impact of new treatments on mortality and morbidity was unclear and focused on a single AIDS-defining illness, Kaposi’s sarcoma. Using the Time Trade Off method, the mean utility weight for someone with Kaposi’s sarcoma was judged to be 0.27 while those with severe KS were assessed to have a utility weight that was 0.08 (195). The latter score meant that people with severe KS would have given up nearly 90% of their life to live without any disease.
Many instruments have measured health-related utility in HIV studies including the EQ5D(126) and SF6D. The SF6D instrument can be derived using an algorithm from the 36 item health status questionnaire called the Short-Form 36 (SF-36) or the shorter version Short-Form 12 (SF-12) (128, 196).

Studies in HIV have used the SF-36 (197). An early study showed that the mental summary score correlated with the disease specific Medical Outcome Study-HIV scale (197). The SF-36 summary scores had been found to be responsive to HIV disease progression but had ceiling effects with the physical functioning, role /role emotional functions (197) and problems with floor and ceiling effects for some sub-scales (Jenkinson 1999 cited in (198)). There had also been inconsistencies in the SF6D scores derived from the SF-36, possibly related to positive and negative responses within the same domains(127). A review of quality of life measures in HIV concluded that the SF-36 could serve as a useful adjunct to an HIV specific measure such as Functional Assessment of HIV Infection in a trial (196).

The Short-Form 12 (SF-12) instrument was used as a health outcomes measure in pharmacoeconomic studies because it was shorter than the SF-36(128, 199). The Brazier algorithm for the SF-12 was valued on a general UK population and had a range between 0.35 and 1.0. SF-12 had multiple language versions helpful in international studies and could be scored easily. SF-12 summary scores appeared responsive to HIV disease progression (200) and the instrument had satisfactory reliability(201).

Scoring the SF-12 to derive a SF6D score could be performed using a software program with algorithm. There had been different populations used for the algorithms used for valuations of the SF6D with patient derived valuations being 4% to 9% higher than community derived valuation. The impact of the differences in valuation method on incremental cost-effectiveness ratios in HIV was shown to be limited (191). Outside HIV the SF6D has been found to be responsive to change in health states associated with chronic obstructive pulmonary disease(COPD), leg ulcer, osteoarthritis, and elderly exercise (202).

Short instruments for measuring quality of life and utility have been criticised for failing to capture the domains relevant to people living with HIV. Instruments designed in the pre-HAART era were focused on conditions or health states that were not so relevant any more
in the era of effective antiretrovirals (196). The World Health Organisation quality of life group agreed a consensus statement on the areas of health-related quality of life that they believed were affected by HIV (Table 2). They stated that some instruments were too brief or did not cover the domains of health described (198). The AQoL and SF-12 instruments map reasonably well onto four of the WHO quality of life domains covering physical, psychological, levels of independence, social relationships.

<table>
<thead>
<tr>
<th>Table 2. Domains of Health for people living with HIV according to World Health Organisation quality of life group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Pain and discomfort</td>
</tr>
<tr>
<td>Energy and fatigue</td>
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<tr>
<td>Sleep and rest</td>
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<tr>
<td>Symptoms</td>
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</table>
I wanted to perform the study described in this chapter to provide up-to-date utility weights for Australian people with HIV according to different health states based on CD4 T-cell count, viral load and line of therapy. I planned to use the utility weights in the cost-effectiveness models of the ACE-HIV project to estimate the cost per Quality-Adjusted Life Year saved for a number of interventions.

3.3 Study: Measurement of utility in people living with HIV in Australia

3.3.1 Aims and objectives of study

The study aimed to derive utility weights for a range of different clinical and demographic characteristics of people living with HIV.

The primary objective was to derive the utility weight for people in different states of health with HIV. The study sample was drawn from participants in the Australian HIV Observational Database, an existing longitudinal clinical observational database. I planned to measure the utility of a sub-sample of study participants with two different instruments and link this score to clinical and demographic data already collected for these individuals in the database.

The secondary objective was to use an Australian designed and valued multi-attribute instrument, the Assessment of Quality of Life instrument (AQoL) for the first time in people living with HIV. The study also used a second generic health status instrument, the Short-Form 12 that could be converted to utilities using a program to create a score called the Short-Form 6D (SF6D). The scores on the AQoL and SF6D from the study could be compared with each other, AQoL scores with previous studies in the Australian general population and SF6D scores with HIV studies overseas.

Finally, study participants completed a third HIV-specific quality of life instrument, the Functional Assessment of HIV Infection (FAHI), to help assess the relationship between symptoms and utility scores.
3.3.2 Method of Utility Study

3.3.2.1 Site selection and study population

Six sites were selected that were study sites of the Australian HIV Observational Database (AHOD) that was a large clinical database, n=2500, which had been operating since 1998 across primary care and tertiary sites. Data was collated from clinical records at each site and forwarded in a de-identified manner to the central data managers at the Kirby Institute every 6 months. Research using the database had been published in a range of peer reviewed journals and collaborations between AHOD and other databases published in high impact journals such as the NEJM and Lancet.

The study sites chosen were two high HIV-caseload general practices, two hospital sites and two sexual health centres in Sydney, Melbourne and Brisbane to reflect the sites of care and locations of Australians living with HIV(203). The majority (60.3%) of people with HIV in a community survey were from urban areas of capital cities. Over half saw a high HIV caseload general practitioner for their HIV care, whilst others saw a specialist in hospital or a sexual health service(204). One study site did not proceed after initial discussions due to a lack of local research nurse.

The planned sample size was 300. After ethics approval, five sites opened recruitment at the same time and recruited study participants from AHOD study participants using a specific patient informed consent form. The inclusion criteria for the utility study were simple: AHOD study participant, able to understand English, willing to give written informed consent. The exclusion criterion was any condition that might be exacerbated by completing a questionnaire about current health. Each site was allocated an equal quota of sub-study places initially. However when the sixth site withdrew, these places were redistributed according to demand.

No formal power calculations were performed to determine sample size. A sample of 300 patients was considered sufficient for these analyses, as this number was at least as large as the following studies using the first version of the AQoL. Whitfield used the AQoL in a study of people with osteoarthritis with a n=222 and found that there were differences in AQoL scores between people in different disease severity groups(205). Holland administered the AQoL(v.1) to 145 people aged greater than 80 years and detected differences in reported...
health by sex and numbers of drugs at discharge(206). Osborne also used the AQoL (v.I) in a sample of 331 people living in aged care facilities, 220 of whom completed the instrument and found differences according to quality of life and need for care(207).

Participants were encouraged to report any adverse events either during survey or in following 7 days.

3.3.2.2 Instrument choice

The Assessing Quality of Life Instrument (AQoL) that I used in this study was a multi-attribute utility instrument(208). The second instrument used in the study was the Short-Form 12 health status questionnaire that I discussed previously. The scores from the health status instrument were put into a software program that contains an algorithm to calculate the utility weight. The algorithm was developed to relate scores on the health status measure to valuations of health made using the standard gamble method of utility elicitation (128). The whole process was known as SF6D(SF-12)(128). The Functional Assessment of HIV Infection (FAHI) was included to help assess the relationship between symptoms and utility scores.

I will discuss the rationale for choice of the AQoL after describing the instrument methods.

3.3.2.3 Instrument methods

Potential participants were approached by their doctor at the end of a consultation for routine clinical care and asked if they would like to take part in a study on the health quality of life of people living with HIV in Australia. A consent form and information sheet was provided to explain the rationale and risks of the study and the linkage with the data already collected in the AHOD. If people agreed to join the study, an envelope containing all study materials was opened. The study envelopes were numbered with the study identification number. The two utility questionnaires were stapled together with the symptom questionnaire. The order of the two utility instruments varied according to prior random allocation to the envelope by study number using an Excel spreadsheet random number generator function. The clinical staff member wrote the most recent CD4 cell count onto a study front sheet. The first two letters of the first and last names and date of birth were included on the front sheet with the AHOD study number if known.
The study participants were encouraged to complete the questionnaire in a quiet space at the clinic although they could take it home if they would prefer and return it in a self-addressed envelope to the study team. Once completed the questionnaire was placed back in the envelope and returned to the study site coordinator. The questionnaire was copied and retained in the study site folder and the copy forwarded to the central research team.

3.3.2.4 Choice of Assessment of Quality of Life instrument mark 2 (AQoL)

The Assessment of Quality of Life instrument AQoL version 2 (AQoL) was chosen because it was a theoretically sound Multi-Attribute Utility Instrument (MAUI), was based on well conducted domain and item choice, and had scaling techniques with a multiplicative and econometric model. AQoL had been valued in a survey of the Australian general population using the Time-Trade off method (209-214). Interviews were conducted with a random sample of 350 Australians stratified to represent a general population. Respondents were asked to evaluate each item response on an 'item best-worst' response scale (214). AQoL measured utility from a handicap perspective across six domains of quality of life, including pain, mental health, coping, level of independence, social relationships and sensory perceptions (130, 208). The underlying concept of handicap placed people in their social context. The orthogonal nature of AQoL reduced the chance of double counting. Domain coverage appeared to me to be wide enough to capture the disutility associated with HIV disease. In terms of coverage of domains likely to be affected by HIV described by the WHO-QoL group, AQoL with a focus within and outside the skin appeared better than other health utility measures that focus within the skin.

The features of the AQoL was claimed to reflect a rational design. It aimed to have increased sensitivity in the region of full health to allow evaluation of health promotion programs (130) with a broad range from -0.04 (worst) to 1.00 (best). In a study of people who are elderly using the AQoL, there were ceiling effects for the social relationships and physical senses scales with 25% scoring highest score but no floor effects noted (207) and had equal interval properties reflecting a responsive instrument (207).

A study performed in Victoria showed a relationship between the first version of AQoL and actual patient expenditures. The authors concluded that “very significant predictive power
and capacity to distinguish between patients requiring intensive and less intense medical care”(215).

Patients with a cochlear implant operation were found to have improved AQoL score (215). Psychosis patients had utility weights 19% lower than the general population (216). In the elderly, AQoL had substantial associations with the SF-36 scales especially physical function, mental health, and general health, vitality. The subscale of physical senses in AQoL had the weakest correlations with other scales(207). In stroke patients, overall AQoL score and individual domains correlated highly with disease specific scores and scores at 3 months after stroke predicted death and institutionalisation at 12 months (217).

In osteoarthritis, the AQoL domain independent living correlated with the physical function scale on the SF-36, psychological well being with bodily pain, but physical senses unlike other scales(205). The AQoL had reasonable discriminatory validity in a study of people with osteoarthritis with the summary utility weight correlating (r=0.66) with disease state. The receiver operator characteristics were estimated to be equivalent to the SF-36 physical function. (205).

As I explained previously, HIV-specific quality of life instruments do not necessarily allow cross-comparison with other disease areas. I was interested to use AQoL in this study because it offered the potential for sensitivity to the areas of quality of life affected by HIV (198) and was an Australian designed and valued instrument with a rigorous econometric origin that had been used in other diseases and the general population(207).

I used the SF-12 instrument because it was a health status profile that had been used extensively in HIV that could be translated to health-related utility weights using an algorithm(218). The preferences and valuations which make up the SF6D utility score used have been derived using the Standard gamble direct method, from a sample of the general population in the United Kingdom (128). I also had experience of using a previous 20 item version of the instrument the Medical Outcome Study Instrument in a validation study I performed in Britain(219).

To help assess validity, I chose a HIV-specific quality of life instrument that had been frequently used was the Functional Assessment of HIV Infection (FAHI) (220) that asked
about symptoms of the disease. The FAHI had been used in a number of HIV studies (220) (221, 222).

3.3.3 Data analysis plan

The AHOD research team provided me with de-identified clinical and immunological data linked to the study number.

The primary endpoints of the study were the quality of life scores for the AQoL questionnaire and the derived utility score. The secondary endpoints for the study were the derived SF6D scores and the FAHI symptom scale scores. The quality of life scores and utility scores were calculated using the algorithms available for each questionnaire (128, 208) that were available as computer software. The FAHI summary scores were calculated using the available scoring method(220).

Descriptive statistics were used for the mean, median, standard deviation and inter-quartile range of utility scores. Utility scores were plotted by frequency of scores to assess the distribution. If the data was not normally distributed, the utility data was transformed using a logarithmic transformation. Multivariate regression analysis was used to assess the following clinical and surrogate marker explanatory variables including: CD4 cell counts, HIV log viral load, FAHI symptom scale score, age, years since diagnosis and categorical variables of gender, modified CD4 cell count band(0-199, 200-349, 350-499, >500), HIV viral logarithm, treatment status (1st combination, 2nd combination, 3rd combination, 4th and subsequent combination), co-infection with hepatitis C or not, co-infection with hepatitis B or not, prior AIDS defining illness.

No formal power calculations were performed to determine sample size. A sample of 300 patients was considered sufficient for these analyses, as this number was at least as large as the following studies using the first version of the AQoL. Whitfield used the AQoL in a study of people with osteoarthritis (n=222) and found that there were differences in AQoL scores between people in different disease severity groups (205). Holland administered the AQoL to 145 people aged greater than 80 years and detected differences in reported health by sex and numbers of drugs at discharge(206). Osborne also used the AQoL in a sample of 331
people living in aged care facilities, 220 of whom completed the instrument and found differences according to quality of life and need for care (207).

3.3.4 Results of utility study

240 participants consented to the study at five sites. AHOD data and AQoL questionnaires were available from 211 participants who completed both instruments and could be identified from the AHOD database.

23 participants did not complete all the questions of the AQoL instrument, 10 did not fully complete the SF12 (SF6D) questionnaire, with 3 not completing both questionnaires. Only 1 person did not answer any of the questions in the AQoL instrument. The rest failed to answer 1-3 questions, mostly in questions 4-7 that ask about physical functioning and role function. There was no consistent pattern to the omissions in the SF12 responses, although they tended to run in 3-4 questions in a row, suggestive that participants turned two pages at once. One study participant wrote on the questionnaire that the constructs used around family and friends did not apply to them. The order of questionnaires did not seem to make much difference: 8/23 of those failing to complete the AQoL, were due to complete it after the SF6D, while 6/10 of those failing to complete the SF12 were due to complete it after the AQoL.

Demography: The mean age of the study population was 49.8 years, median 49.0 years, with a range from 23 to 83 years old. Of those who completed both questionnaires, 97.6% were males with median CD4 cell count 554 (IQR 424-808). 94% of the study population had been treated with antiretrovirals (ARV), which is consistent with their prior participation in the AHOD cohort that was a closed cohort from 2001-2008 with mostly antiretroviral-experienced participants. Most utility study participants had been on antiretrovirals for longer than 9 years (94%) with only 12 ARV naïve participants.

AQoL and SF6D scores: Mean AQoL and SF6D scores for the populations were 0.74 and 0.72 respectively with a higher median AQoL of 0.81 compared to the median SF6D of 0.68. The scores on both instruments correlated strongly ($r=0.77$ $p<0.001$) (Figure 1) as well as with the Functional Assessment of HIV Infection symptoms score (Spearman’s $R=0.71$, $p<0.001$). The SF6D showed a floor effect: there were no scores below 0.405 while 23 people
scored less than 0.4 on the AQoL with 5 scoring less than zero. However all of those scoring less than zero scored less than 0.6 on the SF6D.

Figure 1 Correlation between the AQoL score (y axis) and SF6D score (x-axis)

Relationship to clinical variables of AQoL scores

AQoL values for different demographic and clinical variables are listed in Table 3.

The few females in the study had lower scores than the males, mean scores 0.61 versus 0.75.

Those not currently on ARV had higher scores than those on therapy. 12 people who were ARV naive had mean AQoL scores of 0.82, while 6 participants previously on therapy but not currently on ARV 0.88 and those on ARV 0.74. Numbers are too small to infer any differences.

Univariate and multivariate linear regression analysis was performed against a number of clinical categories (Table 4). The mean AQoL score was 0.09 units lower in the 49 participants with a CD4 cell count of less than 350 compared to those with a count above 350 (Figure 2). The correlation was fairly weak in univariate analysis (R=0.027 Spearman’s)
and did not reach statistical significance. More recent commencement of ARVs after year 2000 was associated with a higher AQoL score. AQoL scores were lower with increasing age, more years since diagnosis and a greater number of prior ARV regimens. There was little difference between the mean score of those with a prior AIDS diagnosis (0.71) and those without (0.74).

In a multivariate analysis controlling for the factors tested in the univariate analysis, only time since diagnosis remained significantly negatively correlated with the AQoL score (Table 4 and Fig 3) (R=-0.24, p<0.01). All study participants with scores of less than zero on the AQoL had been diagnosed for more than 10 years.

### Table 3  AQoL scores according to demography, clinical disease & surrogate markers

<table>
<thead>
<tr>
<th>Covariate</th>
<th>AQoL mean</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.74</td>
<td>211</td>
</tr>
<tr>
<td>Male</td>
<td>0.75</td>
<td>206</td>
</tr>
<tr>
<td>Female</td>
<td>0.61</td>
<td>5</td>
</tr>
<tr>
<td>ARV Naive</td>
<td>0.82</td>
<td>12</td>
</tr>
<tr>
<td>Current ARV</td>
<td>0.74</td>
<td>193</td>
</tr>
<tr>
<td>Prior ARV not on Rx</td>
<td>0.88</td>
<td>6</td>
</tr>
<tr>
<td><strong>Year started ARV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-1996</td>
<td>0.69</td>
<td>66</td>
</tr>
<tr>
<td>1996-1999</td>
<td>0.74</td>
<td>97</td>
</tr>
<tr>
<td>2000-2005</td>
<td>0.85</td>
<td>22</td>
</tr>
<tr>
<td>&gt;=2006</td>
<td>0.81</td>
<td>14</td>
</tr>
<tr>
<td>ARV Naive</td>
<td>0.82</td>
<td>12</td>
</tr>
<tr>
<td>No prior AIDS</td>
<td>0.75</td>
<td>167</td>
</tr>
<tr>
<td>Prior AIDS</td>
<td>0.71</td>
<td>44</td>
</tr>
<tr>
<td>CD4 &lt;200</td>
<td>0.67</td>
<td>5</td>
</tr>
<tr>
<td>CD4 200-349</td>
<td>0.68</td>
<td>24</td>
</tr>
<tr>
<td>CD4&gt;350</td>
<td>0.76</td>
<td>173</td>
</tr>
<tr>
<td>Viral load &gt; 50cp/ml</td>
<td>0.78</td>
<td>36</td>
</tr>
<tr>
<td>Viral load &lt; detection</td>
<td>0.74</td>
<td>172</td>
</tr>
</tbody>
</table>

95
<table>
<thead>
<tr>
<th>Table 4 Univariate and multivariate linear regression analysis of AQoL against clinical categories</th>
</tr>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age every 5yr older</td>
</tr>
<tr>
<td>Years since diagnosis</td>
</tr>
<tr>
<td>ARV Naive</td>
</tr>
<tr>
<td>Currently on ARV</td>
</tr>
<tr>
<td>Previously on ARV</td>
</tr>
<tr>
<td>Current regimen</td>
</tr>
<tr>
<td>PI, no NNRTI</td>
</tr>
<tr>
<td>PI+NNRTI</td>
</tr>
<tr>
<td>NNRTI, no PI</td>
</tr>
<tr>
<td>No PI/No NNRTI</td>
</tr>
<tr>
<td>ARV Naive</td>
</tr>
<tr>
<td>Not currently on ARV</td>
</tr>
<tr>
<td>Number of previous ARV regimens</td>
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<tr>
<td>Year started ARV</td>
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<tr>
<td>Pre 1996</td>
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<tr>
<td>1996-1999</td>
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<tr>
<td>2000-2005</td>
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<tr>
<td>&gt;=2006</td>
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<tr>
<td>ARV naive</td>
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<tr>
<td>Prior AIDS</td>
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<tr>
<td>Viral load&lt;50</td>
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<td>CD4&lt;200</td>
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<td>---------</td>
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<tr>
<td>CD4 200-349</td>
</tr>
<tr>
<td>CD4&gt;350</td>
</tr>
<tr>
<td>Missing value</td>
</tr>
</tbody>
</table>

Figure 2 Correlation between the AQoL score (y axis) and current CD4 (x-axis)
3.4 Conclusions from this chapter

The utility study demonstrated that it was feasible to measure health-related utility weights as a nested sub-study within an existing clinical observational database study using an Australian designed and valued multi-attribute instrument. There are two important contributions to science from this study.

First, the study showed that the utility scores of people living with HIV enrolled in a long-term observational cohort were negatively correlated with time since HIV diagnosis rather than absolute CD4 cell count or age. The correlation with time since diagnosis rather than age could suggest that the long-term impacts of living with HIV might have masked the reduction in utility scores that have been associated with ageing in other studies and the improved CD4 cell counts associated with ARV. Patients with long-term HIV may have experienced AIDS-defining illnesses prior to the introduction of HAART; the duration of time with HIV might be a surrogate for time on antiretrovirals that may have caused long-term toxicities such as lipodystrophy.
Second, a reduced quality of life persisted for people living with HIV despite improved surrogate markers and better mortality outcomes. The AHOD cohort study participants were recruited since 1999 with a second cohort recruited in 2006-2008. Most of them had HIV for 10-20 years and had probably experienced the early antiretrovirals that had significant tolerability and long-term toxicity problems. The association between time with HIV and lower scores on AQoL instrument could reflect the legacy of the past or could be related to depression or other mental health conditions. The higher use of mental health services in the Medicare study would support this hypothesis. HIV remains associated with stigma and guilt for many people despite the great strides that have been made to remove barriers to healthcare and other services. HIV has become a chronic disease and the depression of chronic disease is well known.

The AQoL was reasonably acceptable for use in a nested sub-study of a cohort population but did not correlate well with different health states of HIV based on clinical surrogate markers such as CD4 and viral load, when factors such as time since HIV diagnosis and age are included in a multivariate model. Since these surrogate markers are most closely linked to morbidity and mortality, the utility weights derived in this study may not be particularly useful for the economic analyses planned in Chapter 4. But the study did show that there was a wide range of scores on the AQoL instrument reflecting the diverse and complex impact of HIV on health.

Some participants with high current CD4 cell counts valued their quality of life as being very poor, despite apparently good immune status. Other factors may impinge on physical, mental or social health including co-morbidities, drugs and alcohol over-use, employment and relationship problems. The AQoL is supposed to be orthogonal, in that it measures different domains separately and avoids double-counting. However pain, side-effects, stigma or depression may affect the perception of the value of someone’s quality of life in more than one domain: depressed people cope less well with pain; someone who has been rejected in a relationship due to their HIV may feel despondent and lethargic. Scores less than zero on the utility scale reflect the perception of life to be worse than death and in other studies have occurred in people experiencing the side-effects of chemotherapy for cancer(223).
The range of scores on the AQoL scale was much greater than those elicited on the SF6D instrument, with a floor effect observed for the SF6D. However, the mean score on the SF6D was lower than that on the AQoL. It could be argued that the SF6D is a truer reflection of life as scores that are less than zero are not realistic (223). On the other hand, the wider spread of scores at the top and the bottom of the scale for the AQoL might reflect a greater sensitivity of the instrument to differences in different domains.

The study participants had more difficulty in completing the 20 questions of the AQoL than the 12 questions of SF12. Shorter questionnaires are likely to be easier than longer ones. The topics covered in the two questionnaires are similar and the Likert scale is used commonly. It could have been that some questions were not answered because they were perceived as being irrelevant to the lives of people living with HIV and their health issues. While the AQoL was used first in patients with arthritis and other age-related related conditions (206, 207, 224), there is much discussion in HIV clinical research about accelerated ageing in patients with HIV (225) and the different contributions of intrinsic and extrinsic factors in increased diagnoses of frailty at an earlier age (226); perhaps a questionnaire that probes on these topics is appropriate.

The AQoL was reasonably acceptable for use in a sub-set of a cohort of HIV patients, but little correlation in scores was seen with different health states associate with HIV, as measured by clinical surrogate markers such as CD4 and viral load, when factors such as time since HIV diagnosis and age were included in a multivariate model (Table 4). Since these surrogate markers are most closely linked to morbidity and mortality, the utility weights derived in this study may not be particularly useful for the economic analyses planned in Chapter 4 and 5. However, the study did show that there was a wide range of scores on the AQoL instrument, reflecting the complex and diverse impact of HIV on health.

How do the results of this study compare with previous studies of utility in HIV? A meta-analysis reviewed the literature for utility measures used in HIV and found that the utility weight for asymptomatic patients was 0.94, for people with the classification of symptomatic HIV 0.82 and for patient with a previous AIDS defining illness 0.70 (190). The
scores in this study were generally lower than this and there is only a small difference in AQoL score between those with a prior history of AIDS 0.71 and those without 0.75. Few patients in this study are likely to have been experiencing symptomatic AIDS defining illnesses and so the low utility weights scored are surprising.

The relative scores may have been affected by the methods used to elicit the utility weights as has been discussed previously. The scores are higher than those for patients with symptomatic KS in the previous Australian study 0.27 (195), as one would expect, but lower than the SG method elicited score 0.87 from Mrus(192). They are similar to the scores for people with a minor AIDS-defining illness in Bayoumi’s study using 4 different methods (89) but much lower than the symptomatic HIV (0.86 to 0.96). The utility weight elicited with the Multi-Attribute Utility Instrument (HUI) in that study had the smallest range and appeared closest to the scores on the AQoL in our study. It may be that the complex interplay of health, valuation and risk are too complex to allow consistency using different methods when trying to value an individual or group’s state of health.

The patients with the very low scores on the AQoL could reflect design issues with the instrument. AQoL II domains aim to be orthogonal (at right angles) to each other with a hierarchical descriptive structure and structural independence achieved by factor analysis of the descriptive system(227). But previous studies have shown some cross-loading on the scales between social relationships with independent living and physical senses(communication with others) with anxiety (207).

The SF6D mean score was lower than the AQoL despite a narrower range. An explanation could be that the SF6D may have a problem of under-predicting the value of good health states and over-predicting value of poor health states(127) . The SF-12 was known to have floor and ceiling effects in the physical functioning, and role/role emotional function scales(197).The SF6D algorithm was valued on a British population that has some similarities to an Australian population but may be different in terms of the life experiences and cultural values.

The additive models for calculating the SF6D assumes that there are no important preference interactions. However if a person suffers a loss of function in two different
domains for example cognition and emotion, it is likely to be worse than losing function in only one, but not as bad as the sum of both losses individually (228). The original AQoL used a multiplicative models (227) allowing lower scores and also because in additive models the sum of different item and domain importance weights can exceed 1.0 in full health. But multiplicative models can lead to a bias for summary scores to be lower, so the AQoL uses mathematical functions with econometric models to try to smooth out any inconsistencies. However, there could still be lower scores because of residual effects of multiplication.

The way that instruments were originally valued may cause their overall valuations of complex health states to be lower. In the development of AQoL, the general population that were valuing the health states were asked to deliberate about the valuation of the different health states and not assume that other parts of a person’s life would be affected by ill health in one domain (227). But people tend to believe that if one domain of health is bad, all other states will be affected, for example, a person with limited hearing will be unhappy and have limited functioning.

Other factors could have affected the scores in this study relative to other studies: Patients who were sick at the time of presentation to the physician are often excluded from utility studies but perhaps these patients were less likely to be excluded by study sites that are experienced in clinical research.

Before effective treatment, immune system dysfunction, measured by CD4 T-cell count was associated with poorer quality of life and increased symptom counts on HrQoL measures. (Lubeck and Fries 1997 cited in (229)). When early HAART was used, some of the patients were noted to have HrQoL scores that decreased due to continuing immune dysfunction and drug side effects. Other patients, with improved immune function, appeared to have better physical and mental health summary scores, Chan and Revicki 1998 cited in(229). In another longitudinal study in the early HAART era, HrQoL scores stayed stable over a 4-year period in a cohort of patients, despite very significant immunological and virological improvements. Regression analysis of the scores on HrQoL measures showed that there was a complex interplay between clinical outcomes and changes in symptoms and side-effects over time. CD4 cell count increases and their effect on the risk of HIV related illness, seemed to partially mitigate the deleterious consequences of side-effects from these early HAART
drugs(229). Although 40% of the longitudinal sample reported improvements in mental health over 4 years, 25% showed significant declines, and the overall sample mean remained well below that of the general population. The author concluded that “the respective contributions of virological, immunological and treatment side-effect factors to self-reported well being are difficult to tease out in a cohort study” (229). The very low scores on the AQoL scale reported in this study may reflect mental health problems such as long-term depression.

Other studies have shown that the measured quality of life and utility score of people with HIV may rise after diagnosis(230) due to changes in emotional social support and coping provided by social welfare, peer support programs and a focus on health behaviours (Friedland 1996 cited in (198). This apparent paradox could be misunderstood by an outside observer as a perverse incentive for HIV acquisition. But instead, it is best seen as a salutatory tale or reflection on the relative inadequacies of all instruments that attempts to summarise a person’s complex life and health into a score or series of scores.

The AQoL scores from the study can be compared with the results of studies using AQoL in other populations. A population of people aged 79 years or more about to be discharged from hospital in the UK had a mean utility score on the AQoL of 0.45(206). People with all stages of lung cancer attending a Melbourne hospital clinic had a median utility score of 0.67(231). Chronically ill elderly people participating in a randomized controlled trial of care coordination in Australia had a mean score of 0.33(207). People with arthritis recruited from hospital and community had a mean AQoL score of 0.47(224).

The median AQoL scores for the study population were 0.06 units (8%) lower than age-matched scores for men of the similar age deciles in a general population study in South Australia using the AQoL-1, n=3010, with mean utility score of 0.83 (232). The same study found that the minimum important difference on the AQoL was 0.06 using data on changes in self-reported health over time (Table 4).
Table 4 AQoL scores in the general population by gender and age group from (232).

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Gender</th>
<th>n</th>
<th>AQoL utility scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>15-19</td>
<td>Female</td>
<td>119</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>126</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>246</td>
<td>0.87</td>
</tr>
<tr>
<td>20-29</td>
<td>Female</td>
<td>262</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>271</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>533</td>
<td>0.87</td>
</tr>
<tr>
<td>30-39</td>
<td>Female</td>
<td>292</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>285</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>578</td>
<td>0.85</td>
</tr>
<tr>
<td>40-49</td>
<td>Female</td>
<td>272</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>268</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>540</td>
<td>0.85</td>
</tr>
<tr>
<td>50-59</td>
<td>Female</td>
<td>188</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>190</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>378</td>
<td>0.80</td>
</tr>
<tr>
<td>60-69</td>
<td>Female</td>
<td>154</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>147</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>301</td>
<td>0.79</td>
</tr>
<tr>
<td>70-79</td>
<td>Female</td>
<td>156</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>107</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>263</td>
<td>0.75</td>
</tr>
<tr>
<td>80+</td>
<td>Female</td>
<td>58</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>39</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>96</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Female</td>
<td>1,501</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1,433</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>2,934</td>
<td>0.83</td>
</tr>
</tbody>
</table>
There were limitations with the study. The Assessment of Quality of Life Mark II instrument, AQoL, required some language modification about families and communities to account for the diverse cultures of many people living with HIV. While it is a generic instrument, it can appear more focused on the handicaps related to health problems of older people, like reduced mobility and sensory capacity. If I was to do it all again, I would pilot the questionnaire with a group of people with HIV and ask them to suggest different wording prior to conducting the main study. Some study participants found the cognitive burden of completing three questionnaires excessive, although the SF-12 and the FAHI were used for validation of the AQoL.

The process of matching dates of birth and initials with AHOD numbers was more challenging than expected as some patients had moved clinic and others used different names or initials than when first enrolled in AHOD. It would have been better to provide the study data at the time of the regular data transfers from the sites to the coordinating centre.

Longitudinal data on quality of life and utility over years would provide more ability to discern the impact of changes in clinical state or treatment. The AHOD has been running since 1999, but has always been relatively passive in the collection of data so recruitment of a sub-cohort might be required. Future studies would be improved by the addition of symptom-focused questionnaires about mental health and relationships.

The utility study would have been improved by the collection of individual-level data on utilisation of health system resources. This would require consent from individuals to use their personal details including date of birth and Medicare number to collate data from the Medicare Australia database, state data on admissions and national prescription level data. However, the levels of consent required may have decreased the likelihood that some patients would agree to participate and the study might be biased towards patients with uncomplicated disease who were open about their HIV status to others.

The time taken to conduct the study made it difficult for me to use the utility estimates in the ACE-HIV models because I had not completed the data analysis before I needed to run the models for the second stakeholder meeting. I decided to use published disability
weights instead so that the study results could be consistent with the ACE-Prevention studies. The lack of association between utility scores and CD4 cell count in the multivariate model suggested that scores in the ACE-HIV models was another factor in the decision.

The study was limited because it is cross-sectional rather than longitudinal, and therefore could not conclude whether AQoL would be useful for the measurement of the effect of healthcare or public health interventions. A future study would regularly survey a subset of AHOD participants using a health-related quality of life measure and ask about recent hospital admissions and other health system utilisation.

20 study participants could not be linked to an AHOD data file. Study participants were asked to provide their 4 letter name code and date of birth to allow matching with their AHOD data but it was still not possible to match them easily. However, this study was the first nested study within the AHOD. Use of the existing dataset reduced the burden of reporting data for the participant and the clinic, although separate ethical approval, consent and study management was still required.
4 Assessing Cost-Effectiveness in HIV (ACE-HIV) project

Introduction

In this chapter, I assess whether it was possible to apply the Assessing Cost-Effectiveness in HIV (ACE-HIV) method for priority-setting in a way that would inform decision-makers in HIV medicine in the context of limited time and other resources. The methods, models, results and discussion of the six economic analyses performed for the ACE-HIV stakeholder process are in Chapter 5.

The research question for chapter 4 was “what are the priorities for funding from a range of interventions for the prevention and management of HIV”.

Section 4.1 starts the chapter with a brief description of the ACE-HIV project and how it was developed from the methods used in the linked ACE-Prevention program. This section includes a brief discussion of the theoretical rationale underlying the approach.

Section 4.2 describes the methods used for ACE-HIV process including the first stakeholder meeting that provided advice on the choice of interventions.

Section 4.3 discusses the review meeting when the stakeholders ranked the interventions first using the economic results and then again according to second stage non-economic filters.

Section 4.4 concludes the chapter with a summary of the findings of the ACE-HIV process.

Before I start this chapter, I would remind the reader that ACE-HIV was a project that ran in 2008-2009. The two stakeholder meetings were held in September 2008 and 2009 with the final report written in October and November 2009. Therefore the findings of other studies that were concluded after September 2009 were not included in the economic analyses that were done in the period between the first and second stakeholder meetings. This is particularly relevant for the analyses on pre-exposure prophylaxis and early antiretrovirals as prevention because the results of major field-based studies were presented on these topics in the following year. The economic analyses presented in this chapter were those used in the ACE-HIV project. In the relevant sections of Chapter 5, I discuss the ways in
which the results from these studies might have altered the economic results and hence the deliberations of the stakeholder group.

4.1 **ACE-HIV project in context of ACE-Prevention**

The ACE-HIV project was based on the Accessing Cost Effectiveness method that had been developed by Professors Rob Carter from Deakin University and Theo Vos from University of Queensland. The ACE approach had been used in priority-setting exercises for cancer, mental health and stroke. At the time that I decided to start on ACE-HIV, there was a National Health and Medical Research Council funded program called ACE-Prevention that aimed to assess 150 prevention interventions across a range of non-communicable and communicable diseases to help determine potential “best buys”. I was able to adapt the methods being used by ACE-Prevention for the project, where appropriate, although there were a number of differences in the approach. The results from the ACE-HIV project fed into the ACE-Prevention program as benchmarks to the non-communicable disease interventions. I was the author of pamphlet number 8 used to explain the results (Appendix D) and provided the results of the ACE-HIV project for the ACE-Prevention project summary report(233). Pamphlet 8 from ACE-Prevention was written by me.

4.1.1 **ACE approach theoretical foundation**

The ACE-Prevention was based on a priority setting approach known as Program Budgeting and Marginal Analysis (PBMA). As an economic approach to priority setting, PBMA emphasises both the notions of opportunity cost as well as reallocation of resources at the “margin” where additional costs of an additional unit of benefit are assessed. The PBMA approach typically involves a multidisciplinary advisory panel whose role is to identify areas for potential efficiency improvement through reallocation with consideration to the available resource. One key feature of the PBMA approach is its pragmatic guidance for decision-makers throughout the prioritisation process(234).

The ACE prevention project applied standardized evaluation methods to avoid methodological confounding and to promote a balanced approach to priority setting. The following are key features of the approach taken as reported in the ACE-Prevention project protocol(235). I have provided excerpts to assist the understanding:
• The economic evaluations are undertaken as an integral part of the priority setting task (rather than relying on pre-existing studies in the literature);

• The economic evaluations are based on modelling best available information on costs and benefits from a range of data sources for demography, health system costs and cost offsets, disease incidence/prevalence, risk factors and disease burden that best describe the context of Australian health services;

• A common setting (the Australian population) and decision making context (recommendations for change that can be applied on an Australia-wide basis) is applied across all interventions and options for change;

• The rationale for selecting interventions is clearly specified and consistently applied (a key factor in operationalising “opportunity cost”);

• The economic evaluation methods are standardised, documented and open to scrutiny;

• Information is assembled by a multidisciplinary research team;

• The technical cost-effectiveness results (i.e. cost per DALY saved) are presented within a broader decision-making framework provided by the PBMA approach;

The specific aims of the ACE-Prevention were to improve the effectiveness and efficiency of current Australian health services for the prevention of non communicable disease by:

- Directing available resources towards “best practice” cost-effective services;

- Providing best practice cost-effective services that address “unmet needs” in the Australian community;

- Modifying ineffective services to improve their cost-effectiveness (“need met ineffectively”);

- Targeting services to those in need as opposed to people with low risk profiles who are unlikely to benefit in a cost-effective manner (i.e. eliminating “meet unneeded services”);
Informing policy makers in the area of prevention about the best bundle of interventions, given alternative levels of budget availability (235).

4.2 The ACE-HIV project

The aim of the ACE-HIV project was to assist a group of stakeholders, who were decision makers, in strategic planning and priority setting about the funding of interventions for HIV. I adopted the ACE method that uses explicit decision rules that takes account of evidence of effectiveness and cost-effectiveness along with due consideration of second stage filters or factors such as ethics, feasibility, acceptability, equity, due process, politics and social justice. I needed to show that the ACE-HIV method was acceptable and potentially valuable to the stakeholders, compared to historical methods of ad hoc, implicit or reactive decision making.

In the next sections, I discuss some of the theoretical considerations that were relevant to the methods used by me including the decision context, perspective, and process of selection of interventions.

4.2.1 Decision context for ACE-HIV

The decision context for the ACE-HIV project was the relative scarcity of resources for the prevention and management of HIV. There were a range of options for intervening to prevent and manage HIV related conditions. These diseases cause harm to individuals, their families, their communities and the country as a whole. Some of these options were currently in operation and some of them were ones that might have been used in the future. However these interventions required money to pay staff, buy materials, rent land etc and most of this money in Australia, originated with State and Federal governments. Only a small amount came from patient co-payments and not-for-profit community organisations. The amount of government money to do this was limited in the short-term by health budget allocations to specific program areas and in the long term by competing programs, both health and non-health which were also aiming to further the good of society as well as the state of the economy.
4.2.2 Perspective for economic evaluations in ACE-HIV

The perspective for the ACE-HIV was informed by the decision context as well as other theoretical considerations. I did not want to rewrite sections of lecture notes or textbooks into this thesis, so I would refer the reader to the Drummond’s text book on economic evaluation for more background(22). A range of different perspectives could have been used: healthcare, government as third party payer, societal etc. It is worth briefly considering the costs and consequences associated with HIV at a high level to help understand why I chose the base-case perspective for the ACE-HIV evaluations.

In Australia in 2008/9, most funding related to HIV prevention and healthcare came from either Federal or State/Territory governments. However the costs and outcomes of HIV did not just accrue to the healthcare sector. Patients and their families would have experienced costs associated with illness such as co-payments and over the counter medicines. Partners and families of people with HIV might have sought counselling or professional support or required time and travel to visit sick relatives. The exact extent of these patient and family costs was unknown although 30-40% of people living with HIV/AIDS surveyed in the HIV Futures 6 study reported some difficulties with costs due to HIV healthcare(236).

Other sectors of the government and the private sector might have also accrued cost or receive benefits as a result of HIV and interventions related to it. For example, social support programs for housing people with late stage disease were required although perhaps not to the same extent since the introduction of effective antiretroviral treatment. Productivity losses due to HIV/AIDS and productivity gains due to the prevention and treatment of HIV affected the whole of society. In many countries around the world, HIV/AIDS had significantly affected economic growth and stability due to the loss of trained and productive workers, who might have been hard to replace(237). Beyond social welfare, professional sports codes had ‘blood rules’ for games which required teams to have spare sets of clothing and to rest players when they were actively bleeding.

While the impact of HIV went beyond the healthcare sector, the precise identification, measurement and valuation of patient and family costs and non-health sector costs was challenging. There had been no prospective studies of the patient-related cost of HIV in Australia. It was unclear what costs accrued outside the health sector because the
government intervened to provide social welfare for people on the basis of needs. Attributing the aetiology of these needs directly or indirectly to HIV could have been an over-simplification. Private sector costs were also difficult to measure or value since the costs may not just relate to HIV: for example the ‘blood rules’ in sport were developed for all blood borne viruses and not just HIV(238).

As I showed at the end of Chapter 2, production losses related to HIV could be estimated using methods used for other diseases, but the health of some people living with HIV waxed and waned. A late-presenting patient with an AIDS defining illness at HIV diagnosis might recover to full employment or have been left with a significant disability. The various methods used to estimate productivity losses depended heavily on prior assumptions of the availability of spare workforce capacity to train and replace a sick worker.

Mindful of the issues discussed above, what were the possible perspectives for the economic evaluations that I could have taken in the ACE-HIV project?

1. Societal: health economic evaluations publications often take a ‘societal perspective’ (see Chapter 1) because this perspective is most valued by regulatory authorities such as the PBAC(6). Some studies that claimed to take a societal perspective did not include non-health sector cost and cost offsets. The conduct of studies from a true societal perspective could require methods and techniques, such as cost-benefit analysis and willingness to pay, that might not be embraced by health economists that rejected the orthodox market model of healthcare. The general public had become accustomed to the government purchasing and providing the majority of healthcare on their behalf(239).

2. Program –based perspective: I could have taken a program-based perspective and considered each HIV intervention as it applied to a program population. However that would have had some restrictions. People not able to access the program or providing services not funded by the program would not have been included in the analysis. The perspective would not have permitted an estimate of an opportunity cost to other health sector areas beyond the confines of the program, nor would it have allowed any adjustments to maximize the benefit at the margin.
3. Jurisdiction: the perspective of one level of government such as a State or Territory government. While this would have reflected the way that decision-making often occurs in Australia, it would have prevented inclusion of Commonwealth-funded interventions beyond those related to a specific program, particularly primary healthcare and primary prevention programs.

4. Human services: Since HIV/AIDS was first described, it has caused huge health and community repercussions. The responses required to deal with HIV were not limited to health but involved community and other human services that had to provide social welfare programs such as housing and day centres, enact anti-discrimination laws and help rebuild affected communities. Therefore I could have taken a human services perspective which could also be called a ‘narrow’ societal perspective. Health and community sector costs and consequences for the government and the patient/family would have been assessed for each option and compared to an alternative. However it might have been hard to identify measure and value these human services costs and cost-savings. Many HIV specific community support programs were being mainstreamed at the time, as people with HIV were perceived to have “a fairly expensive chronic condition rather than an intolerably expensive fatal illness” (1).

5. Government as third party-funder of healthcare: this perspective allowed the inclusion of costs and outcomes that could be identified, measured and valued with a reasonable degree of certainty. The perspective informed health decision makers and had potential to assist in the comparison of HIV interventions with other disease areas. I should point out that some of the other ACE-Prevention protocols took a broader societal perspective because the interventions were outside the health system. On the other hand, the government as third party funder of healthcare perspective had been used in the ACE approach to cancer (240) that had similarities to HIV in that a high proportion of the costs and outcomes in HIV relate to antiretroviral treatment costs and outcomes (140).
So in summary, I chose government as third-party funder of healthcare perspective for the base-case analysis in the economic evaluations. Productivity and patient & family costs were included in one evaluation, needle syringe programs, for illustration purposes.

### 4.2.3 Initial selection of Interventions for ACE-HIV

The choice of competing alternative options or interventions for economic evaluation could never have been exhaustive in a doctoral research program with limited time and resources. The ACE approach emphasises the principle that clear criteria for choosing the options can be important to avoid favouritism towards certain projects and help make rational explicit decisions(235). Interventions that can increase or decrease or are novel are most amenable to economic inquiry because the greatest value of economic evaluation can be at the margin, where further spending may bring further benefits or less spending may free up resources to be spent elsewhere for greater good.

There were a number of possible ways to go about choosing the interventions:

- I could have chosen the interventions.
- The project stakeholder group could have nominated a range of interventions.
- Interventions that had been discussed at recent scientific conferences and in peer reviewed journals could have been chosen as a short-list.
- Interventions from the Australian Fifth National Strategy for HIV (2005-8) could have been used as a shortlist.
- Members of the HIV taskforce groups established by the Victorian government at the time could have nominated the interventions.
- Cochrane collaboration reports on effectiveness of interventions could have been used as the shortlist.
- A consultation process on the Victorian HIV service could have provided a short-list.

I looked at the ways that other ACE studies had gone through the process of choosing the interventions. In the ACE cancer study, the working party classified the interventions into one of five groups and only examined the top two groups(240).
1. Options for change
2. Possible options for change
3. Monitor developments
4. Research strategies
5. Parenthood strategies

The criteria they used to determine the classifications were:

• A clear and concrete intervention could be specified;
• There was sufficient evidence to make an assessment of efficacy/effectiveness possible;
• Both increments (i.e. options that involve additional expenditure) and decrements (i.e. options that involve reduced expenditure) are included;
• Options from across the complete disease pathway, from prevention to palliation, are included;
• Options be included that tested the assessment of both mortality and/or morbidity impacts on health status;
• The a priori perceived importance of options be taken into account(240)

So after considering the factors above, the four key criteria that I used for selection of the interventions for ACE-HIV were:

1. On the policy agenda and relevant in 2008;
2. Mix of interventions;
3. Data available;
4. Practical in a PhD program.

It was important to me that economic evaluation informed priority-setting around current topics of interest in order to provide value to decision makers. I wanted to examine a mix of both healthcare and prevention interventions, including some classic and some new biomedical ones. New modalities like circumcision and pre-exposure prophylaxis would compete with classic prevention modalities such as needle syringe programs for budget funding. Prevention and healthcare competed with each other in the overall spending on HIV, even though they came from different budgets in States, Territories and Federal government. I needed data to inform the modelling. Evidence for the effectiveness of
Interventions was to be drawn from randomised controlled studies and cohort studies where possible, although there were also different types of evidence that might inform economic evaluations (104) (241). The interventions had to be limited to a practical number that could be completed in the time between the stakeholder meetings and that could be brought together into a doctoral research program.

4.2.4 Initial interventions chosen from literature review.

Using the criteria listed above, I chose 17 interventions for further assessment and provisional selection prior to the ACE-HIV stakeholder first meeting. The interventions are listed in Table 1 below with a brief description of the intervention and setting, target population and number, policy agenda relevance, chance of increased or decrease spending, evidence, type and clarity of specification. This table was provided to the stakeholder group prior to the first meeting.

Before the meeting, I chose 12 interventions that were possible candidates for inclusion and ranked them according to the criteria used in the ACE-Prevention program that ranked interventions by three types of options for change: likely options for change, possible options for change, options for change which require monitoring (235) (Table 2 and Figure 2).
<table>
<thead>
<tr>
<th>Intervention and Setting</th>
<th>Target population</th>
<th>Target number</th>
<th>Policy relevance</th>
<th>Increase Decrease Spending</th>
<th>Evidence Type</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media campaign raising awareness of HIV</td>
<td>All sexually active adults MSM</td>
<td>12000000 1800000(203)</td>
<td>Often in media</td>
<td>Increase</td>
<td>Experimental(242, 243)</td>
<td>Clear</td>
</tr>
<tr>
<td>Education/prevention campaign on safe sex via social marketing</td>
<td>MSM Indigenous Australians</td>
<td>180000(203) 458500(244)</td>
<td>In progress</td>
<td>Increase/Decrease</td>
<td>Observational(245) multiple</td>
<td>Many different options</td>
</tr>
<tr>
<td>Needle syringe programs</td>
<td>Injection Drug Users</td>
<td>130000-350000(246)</td>
<td>Returns on Investment</td>
<td>Increase/Decrease</td>
<td>Observational(246-250) multiple</td>
<td>Clear +education/screening</td>
</tr>
<tr>
<td>Behaviour change program</td>
<td>HIV- MSM risk HIV+ MSM MSM /drug use</td>
<td>20000-60000 10000(203) 5000</td>
<td>Always</td>
<td>Increase/Decrease</td>
<td>Experimental(251-253) multiple</td>
<td>Group or individual Components?</td>
</tr>
<tr>
<td>Condom education and supply</td>
<td>MSM Young Indigenous Australians</td>
<td>180000 125000(254)</td>
<td>Uncertain</td>
<td>Increase</td>
<td>Experimental(255, 256)</td>
<td>Clear</td>
</tr>
<tr>
<td>Adult male circumcision</td>
<td>MSM</td>
<td>40000-180000</td>
<td>WHO</td>
<td>Increase</td>
<td>Observational(257-259) + extrapolated(260-262)</td>
<td>Clear</td>
</tr>
<tr>
<td>Post-exposure prophylaxis</td>
<td>MSM</td>
<td>4000</td>
<td>Yes</td>
<td>Increase/Decrease</td>
<td>Observational(106, 263)</td>
<td>Clear</td>
</tr>
<tr>
<td>Pre-exposure prophylaxis</td>
<td>MSM</td>
<td>40000-180000</td>
<td>Trials in progress</td>
<td>Increase</td>
<td>Extrapolated(264-266)</td>
<td>Clear</td>
</tr>
<tr>
<td>Mental health interventions</td>
<td>MSM Young adults</td>
<td>30000(267)</td>
<td>Uncertain</td>
<td>Increase</td>
<td>Extrapolated(268) (267)</td>
<td>Upstream or individual?</td>
</tr>
<tr>
<td>Sexually transmitted infection detection and treatment</td>
<td>Young adults MSM HIV+ MSM</td>
<td>Uncertain 40000-180000 10000(203)</td>
<td>yes</td>
<td>Increase</td>
<td>Extrapolated from overseas studies(269-274)</td>
<td>HSV or urethritis or syphilis?</td>
</tr>
<tr>
<td>Antiretrovirals as prevention</td>
<td>Sexual partners of HIV+ people</td>
<td>12000+</td>
<td>Swiss(275-277)</td>
<td>Increase</td>
<td>Extrapolated (51) (278)</td>
<td>Clear</td>
</tr>
<tr>
<td>Setting of care</td>
<td>HIV+</td>
<td>16000</td>
<td>complex</td>
<td>Increase/Decrease</td>
<td>Observational Cochrane(279)</td>
<td>Options</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>------------</td>
<td>-------</td>
<td>---------</td>
<td>-------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Routine testing for HIV</td>
<td>Inpatients STI clinic pts MSM Indigenous Australians People from high prevalence countries</td>
<td>Uncertain</td>
<td>Uncertain 180000 458500 Uncertain</td>
<td>In USA</td>
<td>Increase</td>
<td>Observational(243, 280-284)</td>
</tr>
<tr>
<td>Early treatment</td>
<td>HIV+ with CD4 350-500</td>
<td>2000-3000</td>
<td>START study</td>
<td>Increase</td>
<td>Experimental-indirect(285)</td>
<td>Clear</td>
</tr>
<tr>
<td>ARV Strategies</td>
<td>HIV+</td>
<td>10000-12000</td>
<td>PBAC</td>
<td>Increase or Decrease</td>
<td>Experimental-multiple RCTs.</td>
<td>Clear if follow guidelines approach</td>
</tr>
<tr>
<td>Frequency of Monitoring of HIV+</td>
<td>HIV+ people</td>
<td>12000-16000(286)</td>
<td>Models of care</td>
<td>Decrease</td>
<td>Extrapolated(287)</td>
<td>Clear</td>
</tr>
<tr>
<td>Anal cytology</td>
<td>HIV+ MSM HIV+ people</td>
<td>10000(203) 16000</td>
<td>Intermittently</td>
<td>Increase</td>
<td>Extrapolated(99, 288)</td>
<td>No RCT evidence on treatment options</td>
</tr>
<tr>
<td>Cardiovascular screening and management</td>
<td>HIV+</td>
<td>16000</td>
<td>Abacavir risk</td>
<td>Increase/Decrease</td>
<td>Opinion(289)</td>
<td>Options</td>
</tr>
<tr>
<td>Adherence interventions</td>
<td>HIV+</td>
<td>12000(290)</td>
<td>Uncertain</td>
<td>Increase/Decrease</td>
<td>Experimental(291-294)</td>
<td>Options</td>
</tr>
</tbody>
</table>

HSV=Herpes Simplex Virus; RCT=Randomised Controlled Trials; Swiss=Swiss statement on infectiousness; START study=study on initiation of ARV; PBAC=Prescription Benefits Advisory Committee; CD4=CD4 T-cells;
### Table 2 Ranking of interventions according to options for change and evidence

<table>
<thead>
<tr>
<th>Rank order</th>
<th>Group</th>
<th>Definition</th>
</tr>
</thead>
</table>
| **1**      | Likely options for change                  | • Interventions where sufficient ‘evidence’ exists to indicate that strategies involving additional investment would be associated with significant reductions in the prevalence of the risk factor/disease and little or no likelihood of causing harm.  
• Interventions where sufficient ‘evidence’ exists to indicate that strategies involving reduced investment would be associated with no increases or insignificant increases in the prevalence of the risk factor/disease and little or no likelihood of causing harm. |
| **2**      | Possible options for change                 | • This group includes:  
  (i) Interventions where some evidence exists to indicate that strategies involving additional (less) investment would be associated with significant reductions (insignificant change) in the prevalence of the risk factor/disease and little or no likelihood of causing harm.  
  (ii) An intervention for which it is difficult to conduct rigorous trials, but program logic strongly suggests their likely effectiveness and/or their place within a coherent package of interventions. |
| **3**      | Other options for change which require monitoring | • This group includes:  
  (i) Ideas for action that are considered to have merit but are too broad and abstract to evaluate (and for which specific research work has not been developed), or are politically sensitive.  
  (ii) Interventions that are currently being worked on and/or implemented in another context, or which require more research before they can be evaluated, that is, evidence does not exist to sustain their efficacy/effectiveness credentials and a clear intervention cannot be specified. |
**Figure 1 Provisional list of Interventions before first stakeholder meeting.**

*Colour code: in green were the first preference, blue second, orange third.*

### Interventions

<table>
<thead>
<tr>
<th>Likely options for change</th>
<th>Possible options for change</th>
<th>Other options for change that require monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle Syringe Programs</td>
<td>Pre-exposure prophylaxis</td>
<td>Cardiovascular screening</td>
</tr>
<tr>
<td>Early use ARV as treatment and/or prevention</td>
<td>Routine testing</td>
<td>Setting of Care</td>
</tr>
<tr>
<td>Post-exposure prophylaxis</td>
<td>STI diagnosis and treatment</td>
<td>Mass media campaigns</td>
</tr>
<tr>
<td>Condom education</td>
<td>Circumcision</td>
<td>Adherence supports</td>
</tr>
</tbody>
</table>

### 4.2.5 ACE-HIV Stakeholder Panel

The first meeting of the ACE-HIV stakeholder panel was in September 2008 at the Australasian Society for HIV Medicine conference. The panel met twice in September 2008 and 2009 for two hours meetings. The role of stakeholders in the ACE-HIV project was to:

- comment on the choice of the specific interventions to be evaluated;
- discuss the objects of interest for the economic evaluations;
- assist in the development of second-stage filters;
- review the findings and help apply the second-stage filters;
- consider the policy implications of the data.

Stakeholders invited to the meeting included clinicians, community representatives, academics, health department staff, and an industry physician. The panel members were chosen for their extensive experience in HIV and their previous or current role in decision making and advisory groups for government agencies. A list of panel members is reported in the introduction to the thesis.
Clinician panel members were offered reimbursement for their time at a rate similar to the fees paid to advisory board members by industry. Funding for the stakeholder payments and travel costs of the stakeholder meetings of the ACE-HIV study were provided in small research grants from MSD Australia, Gilead, BMS Australia and Pfizer. The funds were held in trust by Medicines Australia. Donors had no control or input over the choice of interventions or stakeholders, content, outcomes or publications of the study.

4.2.6 Process in stakeholder first meeting

The stakeholders were provided with a copy of the agenda and the data on the 17 possible interventions before the meeting (Table 1). The purpose of the first stakeholder meeting was to comment on the selection criteria and provisional choice of the specific interventions.

Before any presentation, the stakeholders were asked to rate a number of possible interventions from 1(highest) to 13 (lowest) in terms of their preference to fund the intervention in the setting of a limited budget. These results are presented in Table 3 below.

<table>
<thead>
<tr>
<th>Table 3 Stakeholder ranking of interventions before presentation (1=Highest priority)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>1. Treat All: most effective and safe antiretrovirals (ARV) available to all with minimal limitations</td>
</tr>
<tr>
<td>2. Needle Syringe Program</td>
</tr>
<tr>
<td>3. Routine HIV testing for men having sex with men (MSM)</td>
</tr>
<tr>
<td>4. Early treatment</td>
</tr>
<tr>
<td>5. STI diagnosis and treatment in MSM</td>
</tr>
<tr>
<td>6. ARVs as prevention</td>
</tr>
<tr>
<td>7. Rapid HIV testing in hard to reach populations</td>
</tr>
<tr>
<td>8. Routine HIV testing for Indigenous Australians</td>
</tr>
<tr>
<td>9. Monitoring of T-cells and viral load every three or six months</td>
</tr>
<tr>
<td>10. STI diagnosis and treatment in Indigenous Australians</td>
</tr>
<tr>
<td>11. Pre-exposure prophylaxis in MSM</td>
</tr>
<tr>
<td>12. Circumcision in MSM</td>
</tr>
<tr>
<td>13. Circumcision in indigenous Australians</td>
</tr>
</tbody>
</table>
The presentation at the first stakeholder meeting consisted of an introduction to economic evaluation, an explanation of the ACE-HIV method, and the data on the interventions initially chosen by me and the provisional list of possible interventions to be studied. The data was presented (Table 4).

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Agenda</th>
<th>Increase Decrease</th>
<th>Specification</th>
<th>Relev. 2008</th>
<th>Efficiency question</th>
</tr>
</thead>
<tbody>
<tr>
<td>media</td>
<td>possible</td>
<td>often</td>
<td>yes</td>
<td>difficult</td>
<td>yes</td>
</tr>
<tr>
<td>condom</td>
<td>sufficient</td>
<td>?</td>
<td>yes</td>
<td>Education</td>
<td>yes</td>
</tr>
<tr>
<td>NSP</td>
<td>sufficient</td>
<td>ROI</td>
<td>yes</td>
<td>NSP+</td>
<td>yes</td>
</tr>
<tr>
<td>circumcision</td>
<td>possible</td>
<td>WHO</td>
<td>yes</td>
<td>yes</td>
<td>Alloc/tech</td>
</tr>
<tr>
<td>PrEP</td>
<td>possible</td>
<td>yes</td>
<td>inc</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>STI</td>
<td>possible</td>
<td>yes</td>
<td>inc</td>
<td>HSV or all?</td>
<td>yes</td>
</tr>
<tr>
<td>routine</td>
<td>possible</td>
<td>In US</td>
<td>inc</td>
<td>Testing/linkage</td>
<td>yes</td>
</tr>
<tr>
<td>ARVs early</td>
<td>possible</td>
<td>START</td>
<td>inc</td>
<td>CD4&lt;500</td>
<td>yes</td>
</tr>
<tr>
<td>ARVs prev</td>
<td>?</td>
<td>SWISS+</td>
<td>expansion</td>
<td>Primary/second</td>
<td>yes</td>
</tr>
<tr>
<td>CVS</td>
<td>Good idea</td>
<td>ABV</td>
<td>inc</td>
<td>challenging</td>
<td>yes</td>
</tr>
<tr>
<td>Setting</td>
<td>More re complex</td>
<td>change</td>
<td>difficult</td>
<td>yes</td>
<td>technical</td>
</tr>
<tr>
<td>adherence</td>
<td>limited</td>
<td>less</td>
<td>inc</td>
<td>variety</td>
<td>less</td>
</tr>
</tbody>
</table>

Table 4 Provisional list of possible interventions to be studied

Media=Mass Media Interventions; Condom=condom education; NSP=Needle Syringe Programs; PrEP=Pre-exposure Prophylaxis; STI=Sexually Transmitted Infection diagnosis and treatment; Routine=Routine Testing for HIV; ARVs early=use antiretrovirals early in HIV disease for patient benefit; ARVs prev=Use of antiretrovirals early in HIV disease for patient and prevention of transmission benefit; CVS=cardiovascular disease screening and management; Setting= clinical setting for care; Adherence=adherence interventions.

The stakeholders commented on the options with extensive discussion and were particularly keen to see needle syringe programs, pre-exposure prophylaxis and early use of antiretrovirals included. They did not see any value of including condom education or routine HIV testing because they thought that there was little interest in changing policy on either of these interventions. A trial of Sexually transmitted infection diagnosis and treatment was underway but they thought that it would be better to wait for data. Anal cytology screening was included because a number of invitees who had been unable to attend the stakeholder meeting expressed an interest in seeing an Australian economic analysis of an anal cytology screening program.

The final list of interventions for economic evaluation ACE-HIV after the first stakeholder meeting was:

1. Needle Syringe Programs for people injecting drugs;
2. Pre-exposure Prophylaxis for men having sex with men;
3. Early use of antiretrovirals as (a) treatment (b) treatment and prevention;
4. Adult male circumcision for men having sex with men;
5. Non-occupational post-exposure prophylaxis after sexual exposures;
6. Anal cytology screening in HIV positive men having sex with men;

The interventions ranked according to evidence levels, following the classification of evidence from the ACE Prevention program (Table 5).

<table>
<thead>
<tr>
<th>Evidence from Level I-III study designs</th>
<th>Evidence from Level IV studies, indirect or parallel evidence and/or from epidemiological modelling using a mixture of study designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient evidence of effectiveness</td>
<td>Likely to be effective</td>
</tr>
<tr>
<td>Needle syringe programs</td>
<td></td>
</tr>
<tr>
<td>Limited evidence of effectiveness</td>
<td>May be effective</td>
</tr>
<tr>
<td>Circumcision</td>
<td>Pre-exposure Prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Early treatment as prevention</td>
</tr>
<tr>
<td></td>
<td>Non-occupational post-exposure prophylaxis</td>
</tr>
<tr>
<td>Inconclusive evidence of effectiveness</td>
<td>No evidence of effectiveness</td>
</tr>
<tr>
<td></td>
<td>Anal screening</td>
</tr>
</tbody>
</table>

### 4.2.7 First stakeholder meeting comment

Overall the stakeholders appeared to engage enthusiastically in the process and appeared to understand their role. Feedback was positive with expressions of intent of involvement in the second stakeholder meeting. They completed the task of providing commentary on the provisional selection that helped inform the choice of the final list. In the meeting, it emerged that ‘evidence’ and ‘being on the policy agenda’ were the two important criteria for inclusion. They were also
concerned that the evaluation should be limited to six interventions for the sake of completion of the project.

There was little commentary on the objective to be used in the economic evaluations, quality-adjusted or disability-adjusted life years. There was not time to discuss comparators for the economic models.

4.3 Second stakeholder meeting

The stakeholders met for the second time in September 2009 to consider the results of the economic analyses and discuss second stage filters. I presented them with the results of the economic analyses in a number of ways that all shown below.

1) In summary form (Box 1);
2) In a table of the results (Table 14);
3) Ranked according to: size of population at risk; HIV cases prevented; DALY gain; budget impact; cost per DALY; strength of evidence (Table 15).

4.3.1 Intervention rankings from economic analyses

NSP ranked highest in terms of HIV cases prevented, closely followed by PrEP. NSP, targeted circumcision and digital rectal examination for anal disease were cost-saving, while anal cytology and PrEP were cost-effective if the cost-effectiveness threshold is $50,000 per DALY. Early ARV including the treatment and prevention gains was close to the cost-effectiveness threshold. NPEP was not cost-effective and had the smallest DALY gain. PrEP and circumcision had the biggest budget impact.
Box 1

**Summary of results of economic analyses as presented to stakeholders**

**Needle-syringe programs** were cost saving at current levels and there would be increased healthcare cost-savings if the funding and provision of sterile injection equipment were increased by 50-75% compared to current levels of funding. Decreased funding would be associated with greater decreases in health care cost-offsets than would be saved in program costs.

**Adult male circumcision** would be cost-saving if targeted to predominately to insertive men; it is likely to be cost-effective if implemented for all men but there would be high program costs, especially initially; programs for young men would have a substantial likelihood of not being cost-effective.

**Pre-exposure prophylaxis** could have a big impact on incidence and prevalence of HIV in men having sex with men but at high budget costs at current antiretroviral prices, and uncertain cost-effectiveness.

**Post-exposure prophylaxis**, as currently provided in Australia, is not cost-effective, with a very limited impact on HIV incidence. If targeted to HIV-negative men having unprotected receptive anal sex only, the incremental cost-effectiveness ratio is below $50,000 per DALY.

**Early use of antiretrovirals as treatment alone** would not be cost-effective at $140,000 per DALY compared to current ARV guidelines but the inclusion of the associated benefits of prevention improved the incremental cost-effectiveness ratio to $59,000 per DALY, mainly by additional healthcare cost offsets related to fewer HIV infections. **The use of antiretrovirals based on current guidelines** was highly cost-effective at $1,300 per DALY gained for treatment benefits alone.

**Anal cytology screening** may be cost-effective compared to no screening but there is substantial uncertainty surrounding the associated incremental cost-effectiveness ratio. However, digital rectal examination is cost-saving compared to no program.
Table 14: Health impact, costs and incremental cost-effectiveness ratios for ACE- HIV interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Health impact (95% CI or interquartile range-IQR)</th>
<th>Budget per year</th>
<th>ICER $ per DALY versus comparator</th>
<th>95% CI ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Needle Syringe Programs</strong></td>
<td>75,000 HIV infections (IQR 41,000-84,000) 190,000 HCV infections (IQR 185,000-206,000) prevented 365,703 DALY gained</td>
<td>$24m a year</td>
<td>Cost-saving $2.3bn</td>
<td>IQR $1.7-4.0bn</td>
</tr>
<tr>
<td><strong>Circumcision</strong></td>
<td>240 to 650 HIV infections prevented 1.4%-3.7% of expected incidence 1,800 to 4,900 DALY</td>
<td>Initial $5m to $140m Ongoing $3m to $5m a year</td>
<td>Insertive cost-saving All MSM $8,900 per DALY 35-44yo $9,100 per DALY Young $35,000 per DALY</td>
<td>cost-saving to $45,000 cost-saving to $22,000 $700 to $110,000</td>
</tr>
<tr>
<td><strong>Pre-exposure prophylaxis</strong></td>
<td>675 HIV infections prevented per year. 95,000 DALY (55,000 to 160,000)</td>
<td>Continuous $420m per DALY Intermittent $210m per DALY</td>
<td>Continuous $46,000 per DALY Intermittent $5,600 per DALY</td>
<td>$24,000 to $69,000 cost-saving to $18,000</td>
</tr>
<tr>
<td><strong>Post-exposure prophylaxis</strong></td>
<td>3 HIV infections prevented per year 540 DALY (430 to 660)</td>
<td>$3m-$5m</td>
<td>$190,000 per DALY</td>
<td>$170,000 to $210,000</td>
</tr>
<tr>
<td><strong>Early Rx alone</strong></td>
<td>11,000 DALY (3,600 to 20,000)</td>
<td>$40m a year</td>
<td>$140,000 per DALY</td>
<td>$65,000 to $300,000</td>
</tr>
<tr>
<td><strong>Early Rx with prevention effect</strong></td>
<td>12,000 DALY (5,400-14,000) including Rx and prevention</td>
<td>$40m a year</td>
<td>$59,000 per DALY</td>
<td>cost-saving to $143,000</td>
</tr>
<tr>
<td><strong>Anal cytology</strong></td>
<td>2000 DALYs (0 to 14,000 )</td>
<td>DRE $450,000 pa Cytology $5m a year</td>
<td>DRE cost-saving Cytology $33,000 per DALY versus nil $53,000 per DALY versus DRE</td>
<td>Cost-saving to $37,000 cost-saving to $330,000 cost-saving to $700,000</td>
</tr>
</tbody>
</table>

CI=Confidence Intervals. ICER=Incremental Cost-effectiveness ratio; DALY=Disability Adjusted Life Year; DRE=Digital Rectal Examination; Early Rx =Early antiretrovirals; MSM=Men having sex with men
Table 15 Rankings of interventions according to economic analyses

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Size of population at risk</th>
<th>HIV cases prevented</th>
<th>DALY gain</th>
<th>Budget (smallest)</th>
<th>Cost per DALY</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Circumcision</td>
<td>NSP</td>
<td>NSP</td>
<td>NPEP</td>
<td>NSP</td>
<td>NSP</td>
</tr>
<tr>
<td>2</td>
<td>NSP</td>
<td>PrEP</td>
<td>PrEP</td>
<td>Anal cytology</td>
<td>Circ</td>
<td>Circ</td>
</tr>
<tr>
<td>3</td>
<td>Early Rx/P</td>
<td>Early Rx/P</td>
<td>Circ</td>
<td>NSP</td>
<td>AIN screen</td>
<td>PrEP</td>
</tr>
<tr>
<td>4</td>
<td>PrEP</td>
<td>Circ</td>
<td>Early Rx/P</td>
<td>Early Rx/P</td>
<td>PrEP</td>
<td>Early Rx/P</td>
</tr>
<tr>
<td>5</td>
<td>NPEP</td>
<td>NPEP</td>
<td>Early Rx</td>
<td>Circ</td>
<td>Early Rx/P</td>
<td>AIN Screening</td>
</tr>
<tr>
<td>6</td>
<td>AIN screen</td>
<td>AIN Screen</td>
<td>PrEP</td>
<td>Early Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Early Rx</td>
<td>NPEP</td>
<td>NPEP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSP=Needle Syringe Programs; Early Rx=Early antiretrovirals for treatment; Early Rx/P=Early antiretrovirals for treatment and prevention; NPEP=Non-occupational post-exposure prophylaxis; Circ=Circumcision; AIN screen=Anal cytology; PrEP=Pre-exposure Prophylaxis

Stakeholder ranking process after economic analyses

Following presentation of the results, the stakeholders ranked the interventions according to the economic analysis results and the evidence that supported those analyses. The conclusions and rankings after the economic analyses are listed below in Table 16. Stakeholders were asked to say if interventions should be funded, could be funded or should not be funded. After seeing the summaries of the economic analysis results, the stakeholders decided that: Needle Syringe Programs and Pre-Exposure Prophylaxis should be funded, circumcision and early use of ARVs for treatment and prevention could be funded, early use of ARVs for treatment alone, Non-occupational post-exposure prophylaxis and anal cytology should not be funded.
4.3.2 Re-ranking by non-economic factors: second stage filters

At this point in the meeting, the stakeholders were asked to discuss the second stage filters or non-economic factors to be taken into account. I have summarised the discussion in Table 17 according to three main themes that emerged: acceptability, feasibility, and equity. Other considerations are listed as well.
Table 17: Stakeholder comments in the second stage filter process

<table>
<thead>
<tr>
<th>Stakeholder Focus Area</th>
<th>Acceptability</th>
<th>Feasibility</th>
<th>Equity</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Needle syringe programs</strong></td>
<td>Some media and political opposition to further expansion</td>
<td>NSP program running well</td>
<td>Recent rises in young IDUs may reflect temporal and geographical barriers</td>
<td></td>
</tr>
<tr>
<td><strong>Adult Circumcision of MSM</strong></td>
<td>Resistance by MSM to operation.</td>
<td>Surgical services already over-stretched. Indemnity insurance issues for GPs to perform op.</td>
<td>Potential for outing and discrimination against MSM</td>
<td>Safe-sex messages blurring with potential for risk disinhibition. One-off intervention that is present in every sexual encounter.</td>
</tr>
<tr>
<td><strong>Pre-exposure prophylaxis</strong></td>
<td>Need for low side-effect Rx.</td>
<td>Expansion of current primary care for MSM.</td>
<td>MSM clinics concentrated in inner-urban areas. MSM, not self-identified, may not access.</td>
<td>Long-term adherence required. Resistance. Risk disinhibition. Moral imperative to use available effective technology.</td>
</tr>
<tr>
<td><strong>Post-exposure prophylaxis</strong></td>
<td>Surveys suggest acceptable to MSM but low uptake relative to incidence of risk behaviours. Restricting or removing current service could be opposed.</td>
<td>Running on small scale but challenges of expansion outside inner city with reluctance of emergency depts.</td>
<td>Rural and regional.</td>
<td>Indemnity risks if person denied service acquired HIV. Community reassurance for sero-discordant couples Earlier diagnosis of people already HIV+ during screening process not captured in analyses. Moral imperative to use available effective technology.</td>
</tr>
<tr>
<td><strong>Early ARV treatment + pre-exvention</strong></td>
<td>Most people living with HIV will follow treatment strategy of treating doctor. But some currently not on treatment have other objections to ARVs</td>
<td>Networks and workforce already in place but evidence of scarcity in trained doctors.</td>
<td>Significant undiagnosed HIV particularly in CALD and young populations. Lost to follow-up and reduced use of healthcare due to cost and temporal/geographic/cultural availability of services.</td>
<td>Ethical issues of little health gain for individual and potential for adverse events relative to population benefit.</td>
</tr>
</tbody>
</table>
After describing the second stage filters and factors, the group was asked to re-order the rankings of the interventions by moving pieces of paper up and down on whiteboard (Table 18). Second-stage filters were non-economic factors that affected their ranking of the priorities for interventions. They were chosen by the stakeholders and the themes elicited during the second meeting. The order of rankings changed because of these second stage filters (Table 19).

<table>
<thead>
<tr>
<th>Anal cytology screening</th>
<th>Discussion and examination of anus embarrassing</th>
<th>Few clinicians trained in high resolution anoscopy. No MBS item number</th>
<th>Rural and regional. Cultural issues for CALD populations increasing resistance to anal screening.</th>
<th>Potential for additional STI screening at same time as examination.</th>
</tr>
</thead>
</table>

NSP=Needle Syringe Programs; IDU=Injection Drug Users; CALD=People from Culturally and Linguistically Diverse Backgrounds; MBS=Medicare Benefits Schedule; STI=Sexually Transmitted Infection; Early Rx =Early antiretrovirals for treatment; Early Rx/P=Early antiretrovirals for treatment and prevention; NPEP=Non-occupational post-exposure prophylaxis; Circ=Circumcision; AIN screen=Anal cytology; PrEP=Pre-exposure Prophylaxis

<table>
<thead>
<tr>
<th>Stakeholder decision</th>
<th>Intervention</th>
<th>Summary of second stage filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should fund</td>
<td>Needle Syringe Programs</td>
<td>Generally acceptable now</td>
</tr>
<tr>
<td>Pre-exposure prophylaxis</td>
<td>Moral imperative to use available technology and intermittent use may make more cost-effective</td>
<td></td>
</tr>
<tr>
<td>Non-occupational post-exposure prophylaxis</td>
<td>Indemnity risks if person denied service acquired HIV.</td>
<td></td>
</tr>
<tr>
<td>Could fund</td>
<td>Early use of treatment and/or as prevention</td>
<td>Easy to implement</td>
</tr>
<tr>
<td>Doubtful</td>
<td>Circumcision</td>
<td>Feasibility and acceptability</td>
</tr>
<tr>
<td></td>
<td>Anal cytology</td>
<td>Feasibility and acceptability</td>
</tr>
</tbody>
</table>
Non-occupational post-exposure prophylaxis moved up to ‘should fund’ from doubtful, mainly because there could be indemnity or litigation risks if a person who had been denied NPEP subsequently was shown to have acquired HIV from that episode. The lack of cost-effectiveness was seen in the context of a relatively low national budget and uptake rate for the service, compared to the number of risk episodes.

Early ARVs as treatment alone moved to ‘could fund’ from doubtful because it was easy to implement with an existing workforce, supply chain and mechanism for funding. The smaller possible clinical benefits of early ARVs were perceived as related to a lack of data that the START study would answer. The stakeholders were unanimous in this change in priority.

Circumcision dropped from ‘could fund’ to doubtful due to concerns about feasibility with a lack of trained staff and indemnity issues for GPs to perform the procedure. MSM were also seen as unlikely to willingly undergo the procedure for fear of pain and loss of sexual function.

Pre-exposure prophylaxis was reinforced in the position of ‘should fund’ because of “the moral imperative to use available technology.” One stakeholder expressed a belief that intermittent use might make it more cost-effective.
<table>
<thead>
<tr>
<th>Stakeholder decision</th>
<th>First stage</th>
<th>Second stage</th>
<th>Summary of second stage filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should fund</td>
<td>Needle Syringe Programs</td>
<td>Needle Syringe Programs</td>
<td>Generally acceptable now</td>
</tr>
<tr>
<td></td>
<td>Pre-exposure prophylaxis</td>
<td>Pre-exposure prophylaxis</td>
<td>Moral imperative to use available technology and intermittent use may make more cost-effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-occupational post-exposure prophylaxis</td>
</tr>
<tr>
<td>Could fund</td>
<td>Circumcision Early use of ARVs treatment + prevention</td>
<td>Early use of treatment and/or as prevention</td>
<td>Easy to implement</td>
</tr>
<tr>
<td>Doubtful</td>
<td>Early use of ARVs treatment</td>
<td>Circumcision</td>
<td>Feasibility and acceptability</td>
</tr>
<tr>
<td></td>
<td>Non-occupational post-exposure prophylaxis Anal Cytology</td>
<td>Anal cytology</td>
<td>Feasibility and acceptability</td>
</tr>
</tbody>
</table>

There were changes in the rankings through the process. At the start of the first meeting, I asked the stakeholders to rank a list of all the potential interventions from first to last. In table 20, I have noted the ranking at the end of second stage compared to the ranking before the meeting. Pre-exposure prophylaxis had been ranked 11th out of 17 in the initial rankings but it rose to ‘should fund’ after the results of the economic analyses. That change may reflect changes in sentiment about the impending pre-exposure prophylaxis study results, but appeared also to be influenced by the potential impact on HIV incidence and cost-effectiveness. Circumcision started as doubtful to fund and stayed that way, despite the data from the economic models that suggested it could also be cost-effective. However the impact on the HIV incidence was likely to be much lower than PrEP because it would only affect men who were predominately insertive in their sexual behaviours and would require an operation on the penis that would deter men.
### Table 20
End of second stage rankings compared to start of first stakeholder meeting rankings

<table>
<thead>
<tr>
<th>Stakeholder decision</th>
<th>Second stage</th>
<th>Ranking before 1st meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should fund</td>
<td>Needle Syringe Programs</td>
<td>2nd</td>
</tr>
<tr>
<td></td>
<td>Pre-exposure prophylaxis</td>
<td>11th</td>
</tr>
<tr>
<td></td>
<td>Non-occupational post-exposure prophylaxis</td>
<td>NR</td>
</tr>
<tr>
<td>Could fund</td>
<td>Early use of treatment and/or as prevention</td>
<td>4th</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6th</td>
</tr>
<tr>
<td>Doubtful</td>
<td>Circumcision</td>
<td>12th</td>
</tr>
<tr>
<td></td>
<td>Anal cytology</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR=Not ranked at initial meeting

Overall the results of the re-ranking in the second-stage filter process suggested that stakeholders valued the feasibility of providing an available intervention highest. In other words, if it is easiest to do with the existing resources or is already being done, we should do it first, even if it is less cost-effective in the medium to long-term.

### 4.4 Conclusions from the ACE-HIV second stakeholder meeting

The conclusions of the second stakeholder group of the ACE-HIV project can be summarised as below.

Funding of needle syringe programs should continue and could be increased to improve temporal and geographic availability of needles.

Pre-exposure prophylaxis is modelled to have a major health impact, but at considerable cost. It may be more cost-effective if taken intermittently. The moral imperative to use available technology was perceived as a major factor in future decisions on its availability.
Non-occupational post-exposure prophylaxis is currently funded. Continuation of funding should be considered for concerns about indemnity risks if denied, and it could be more cost-effective if targeted to MSM after receptive anal sex, rather than all potential exposures.

Early treatment with or without the putative benefits of prevention would be easy to implement. While the addition of the prevention benefits improves the cost-effectiveness, early use of antiretrovirals is still cost-ineffective at current prices and given the uncertainty surrounding their effect on infectiousness.

Circumcision of MSM could be recommended on cost-effectiveness grounds but could lead to large up-front costs if all eligible men were circumcised. There would be significant cultural and social barriers to overcome.

Anal cytology screening is cost-ineffective compared to annual digital rectal screening for anal cancers and there are barriers to implementation.

I will discuss the findings of the individual cost-effectiveness analyses and implications of the ACE-HIV project in greater detail in the next chapter of the thesis.
5 The ACE-HIV Economic evaluations

This chapter describes the methods and results of the six economic evaluations that I performed. First I will describe the features that were common to all the models to avoid repetition in the description. Second, I will go through each intervention with the specific methods, results and findings, including the impact of more recent data from the field included in my models on the results.

5.1.1 Model inputs

Health benefits
Originally when I planned the studies, I intended to use utility weights from the own study in the models. However I decided to change to Disability-Adjusted Life Years (DALYs) as the object of interest in the models for two main reasons. Firstly, the main ACE-Prevention studies used DALY weights rather than QALYs and so I needed to provide results in this format. The results of the ACE-HIV study were to be reported as part of that larger ACE-Prevention study, so there was a need for consistency across the projects. Second, the preliminary results of the utility weights study in Chapter 3 suggested that there was no consistent correlation with CD4 cell count measured with the two utility instruments. I did not have time to revise the model structures away from the CD4-based health states and decided to use disability weights for the results for the second stakeholder meeting. So health benefits in these models were estimated in Disability-Adjusted Life Years (DALYs) using disability weights for HIV health states related to CD4 T-cell count and other diseases from the Victorian Burden of Disease project(295).

Cost of HIV healthcare
I used the cost of HIV healthcare from the synthesis reported in Chapter 2. The perspective for all the analyses was the health sector (government as third party payer) because of the absence of any reliable data on patient/family costs of HIV in Australia. Table 1 below is copied from Chapter 2, table 4.
<table>
<thead>
<tr>
<th>CD4 Cell Count Range</th>
<th>Healthcare Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &gt; 500</td>
<td>$1,523</td>
</tr>
<tr>
<td>350 &lt; CD4 &lt; 500</td>
<td>$2,055</td>
</tr>
<tr>
<td>200 &lt; CD4 &lt; 350</td>
<td>$2,731</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>$5,500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiretrovirals Type</th>
<th>Annual Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line therapy</td>
<td>$14,613</td>
</tr>
<tr>
<td>2nd line therapy</td>
<td>$15,178</td>
</tr>
<tr>
<td>3rd line therapy</td>
<td>$27,776</td>
</tr>
</tbody>
</table>
In the next section, each of the six cost-effectiveness analyses is reported including a brief description of methods, results and discussion of the results. I have summarised the methods used below to assist the reader (Table 2).

### Table 2 chosen interventions, evidence type, population and methods used.

<table>
<thead>
<tr>
<th>Description of intervention</th>
<th>Evidence of impact for the intervention</th>
<th>Likely effectiveness</th>
<th>Comparator</th>
<th>Population and size</th>
<th>model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle syringe programs</td>
<td>Ecological</td>
<td>100% if sterile injection equipment used</td>
<td>No public funded NSP. Private supply only (15%)</td>
<td>Injection drug users n=173,500 (105,000-236,500)</td>
<td>Mathematical population With Excel analysis</td>
</tr>
<tr>
<td>Adult Circumcision of MSM</td>
<td>Prospective cohort MSM Australia+ RCTs MSW Africa</td>
<td>60-80% reduction of acquisition for insertive</td>
<td>Status quo</td>
<td>MSM n=180,000</td>
<td>Mathematical Population With Excel analysis</td>
</tr>
<tr>
<td>Pre-exposure prophylaxis</td>
<td>Animal studies</td>
<td>90-100%</td>
<td>Status quo</td>
<td>MSM with high risk behaviour n=45,000</td>
<td>Dynamic Markov TreeAge</td>
</tr>
<tr>
<td>Post-exposure prophylaxis</td>
<td>Retrospective case-control study</td>
<td>99.7% if fully adherent 70% if not</td>
<td>status quo prior to program</td>
<td>MSM with high risk behaviour n=60,000</td>
<td>Dynamic Markov TreeAge</td>
</tr>
<tr>
<td>Early ARV treatment</td>
<td>Cohort data</td>
<td>Reduction mortality, incidence Opportunistic Diseases and serious Non-AIDS events by 50%.</td>
<td>Status quo</td>
<td>People living with HIV n=16,500</td>
<td>Dynamic Markov TreeAge</td>
</tr>
<tr>
<td>Treatment + prevention</td>
<td>Ecological studies</td>
<td>92% reduction in infectiousness</td>
<td>Assumed no reduction in infectiousness due to ARVs</td>
<td>People living with HIV n=16,500 + MSM n=76,500</td>
<td>Dynamic Markov TreeAge</td>
</tr>
<tr>
<td>Anal cytology screening</td>
<td>Single arm studies of treatment of high grade AIN</td>
<td>50-75% reduction progression to anal cancer</td>
<td>No program</td>
<td>HIV+ MSM n=12,000</td>
<td>Markov TreeAge</td>
</tr>
</tbody>
</table>

NSP=Needle Syringe Programs; Early Rx=Early antiretrovirals for treatment; Early Rx/P=Early antiretrovirals for treatment and prevention; NPEP=Non-occupational post-exposure prophylaxis; Circ=Circumcision; AIN screen=Anal cytology; PrEP=Pre-exposure Prophylaxis DRE=Digital Rectal Examination
Individual Cost-Effectiveness Models

5.2 Needle Syringe Programs (NSP)

The Needle Syringe Programs economic analysis was carried out in collaboration with David Wilson and Amy Kwon. I performed all the economic analyses and was the principal author for the chapters reporting those results and co-author on the discussion section. I have adapted text from that report where I was the principal author. In the discussion section, I wrote the paragraphs on the economic results and David Wilson covered the epidemiology results.

The NSP analysis explored the impact of NSPs on both HIV and hepatitis C, with a sub-analysis covering only HIV. I have included the results for HCV + HIV as well as those for HIV alone because there were some findings regarding increasing and decreasing supply of clean injecting equipment. The research questions was: what are the costs and consequences of the current provision of NSPs in Australia for the prevention of HIV and Hepatitis C, compared to a hypothetical situation where there was no public provision of clean injection equipment?

5.2.1 Methods

Needle Syringe Programs in Australia consisted of the provision of 27 to 31 million sterile needles and syringes at no or low cost through 84 primary sites, 732 secondary sites, 23 enhanced secondary sites, and 118 vending machines as well as advice on injection behaviour, safe sex and referral to other services. NSPs were a ‘classic’ form of HIV prevention but had been controversial politically in some jurisdictions and locations. The intervention used in the model was specified as the current levels of NSP provision as well as decreased and increased levels of funding and provision of sterile equipment.

Evidence of impact and likely effectiveness of NSP

Sharing of syringes by injecting drug users (IDUs) is an important mode of global transmission of blood borne viruses, such as HIV and hepatitis C virus (HCV). Both HIV and HCV infection are associated with significant morbidity and mortality. Needle and syringe programs (NSPs) are a public health measure designed to reduce the spread of these infections among IDUs. There are large differences in HIV epidemics among IDUs between different international settings (296-298). Ecological studies suggest that where NSPs are not easily accessible, HIV prevalence tends to be substantially greater than in locations where NSPs are available (299-307). An ecological analysis in
the first Return on Investment report estimated the effect of NSPs across numerous international cities and the results of the analysis were applied to estimate the impact in Australia. It was estimated that 25,000 HIV infections were prevented among injecting drug users (IDUs) by the year 2000 due to the introduction of NSPs, the cumulative number of HIV/AIDS deaths by the year 2000 in injecting drug users (IDUs) would be ~200 with the NSPs and ~700 without the NSPs (308).

**Description of current practice**

There are now more than 3000 NSP sites across Australia, with the sector comprising primary and secondary NSP outlets, mobile and outreach services, syringe vending machines and a significant number of pharmacies that offer NSP services (309) (310). More than 30 million syringes are distributed each year through Australian NSPs (311).

In the model, injection drug users were the target population.

**Description of comparator**

The comparator in the scenario was a situation where no public NSPs had been opened or all existing NSPs had been closed. In this scenario, only private purchase of clean needles and syringes occurred. According to the cost data provided by the States and Territories for the project, around 15% of clean injecting equipment had been purchased privately.

### 5.2.2 NSP Epidemiology Model

*The epidemiological model was developed by the collaborators Amy Kwon and David Wilson with my input on the clinical aspects of the model.*

The NSP models consisted on an epidemiological model and an economic model. The results of the epidemiological model fed into my economic model.

A mathematical epidemic model was developed to simulate HIV and Hepatitis C (HCV) transmission among IDUs in Australia (309). The model was used to determine the population-level effectiveness of NSPs in preventing transmissions of HIV and HCV. The model considered heterogeneity in injecting behaviour, including frequency of injecting and sharing of injecting equipment as well as rates of cleaning equipment. Mathematical associations were derived to describe the coverage of injecting equipment among IDUs for different levels of NSP distribution of sterile injecting
equipment. The model tracked the changing number of IDUs in the population, including the entry of new injectors and the rate of ceasing injecting behaviour. The structure of the analysis was a compartmental model based on a large system of ordinary differential equations. The infection of IDUs with HIV and/or HCV was simulated based on injecting behaviour and mixing in the population. All available Australian behavioural and epidemiological data and international disease-related data were used as inputs to calibrate the model to the State, Territory and Australian populations. The model accounted for the total number of needles and syringes distributed to IDUs in each population, as informed by each State and Territory health department.

The epidemiological model was run for 200 simulations over different time horizons. The time horizon was varied to reflect different decision contexts: the period 2000-2009 to reflect past investment in NSPs, 2010 to 2019 and 2029 to reflect the impact of choices made in 2009 in relation to the next 10-20 years, and 2010-2059 and 2010-2080 to consider whole of lifetime impacts (309), clinical model in Figure 1.

We tested different scenarios for the levels of supply of clean injection equipment, including increases and decreases in supply. The model was run for Australian populations at a national and jurisdiction level to produce a series of excel spreadsheets for each situation of population and assumption about provision and coverage of clean injection equipment during injecting behaviour.

The outputs of the epidemiological model were:

- Number of people in each HIV and HCV health state
- Deaths
5.2.3 Economic model

The economic model was devised and run by me.

The epidemiology model outputs were taken and inputted into a separate economic analysis model written in Excel spreadsheets. Disability weights for health states were used to estimate for each year the number of disability adjusted life years for the population. The number of DALYs was estimated by applying the DALY weight of being in particular health state and multiplying it by the number of people in the health state (189). I then added the number of years lost to a death that was estimated using a DALY weight of 1.0 for the 10 years following a death assuming the loss of 10 unadjusted life years for patients with Hepatitis C compared to people without Hepatitis C (312). DALYs for HCV and HIV were reported separately and combined.

Cost of NSP

I used budget data provided by State and Territory health departments to derive the cost of NSPs and their associated interventions (309) (Table 3). State and Territory health departments provided...
data on the budgets for NSPs in responses to a standardised questionnaire that I developed after a stakeholder meeting. Two main categories of costs were identified that related to the activities of NSPs: (i) consumables including sterile injecting equipment, disposal costs and safe sex-equipment, and (ii) support for the NSP sector including primary NSP operations, support of secondary sites, transport and vending machines. Some jurisdictions separately identified costs such as grants, peer-support programs, and telephone information services on safe disposal of needles and training. These costs were included in the support for primary NSPs subcategory unless identified as relating to one of the other subcategories.

Table 3: Expenditures made by financial year in 2008 Australian dollars (unadjusted financial expenditures and adjusted for consumer price index)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONSUMABLES ($'000)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile injecting equipment</td>
<td>5,658</td>
<td>5,140</td>
<td>5,633</td>
<td>6,677</td>
<td>6,928</td>
<td>6,571</td>
<td>7,404</td>
<td>6,857</td>
</tr>
<tr>
<td>Disposal equipment</td>
<td>911</td>
<td>884</td>
<td>952</td>
<td>941</td>
<td>1,184</td>
<td>1,122</td>
<td>1,274</td>
<td>1,474</td>
</tr>
<tr>
<td>Safe sex packs</td>
<td>15</td>
<td>52</td>
<td>70</td>
<td>69</td>
<td>246</td>
<td>245</td>
<td>289</td>
<td>293</td>
</tr>
<tr>
<td>Sub-total</td>
<td>6,583</td>
<td>6,076</td>
<td>6,655</td>
<td>7,686</td>
<td>8,358</td>
<td>7,938</td>
<td>8,968</td>
<td>8,624</td>
</tr>
<tr>
<td><strong>NSP SUPPORT ($'000)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary NSP Operations</td>
<td>8,851</td>
<td>10,510</td>
<td>10,417</td>
<td>11,261</td>
<td>12,505</td>
<td>12,274</td>
<td>14,450</td>
<td>15,929</td>
</tr>
<tr>
<td>Support for Secondary NSPs</td>
<td>380</td>
<td>653</td>
<td>745</td>
<td>788</td>
<td>951</td>
<td>1,264</td>
<td>963</td>
<td>1,222</td>
</tr>
<tr>
<td>Transport</td>
<td>89</td>
<td>82</td>
<td>92</td>
<td>105</td>
<td>117</td>
<td>184</td>
<td>198</td>
<td>192</td>
</tr>
<tr>
<td>Vending Machines</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>246</td>
<td>441</td>
</tr>
<tr>
<td>Sub-total</td>
<td>9,331</td>
<td>11,245</td>
<td>11,254</td>
<td>12,154</td>
<td>13,573</td>
<td>13,742</td>
<td>15,856</td>
<td>17,783</td>
</tr>
<tr>
<td><strong>TOTAL ($'000)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(unadjusted for CPI)</td>
<td>15,914</td>
<td>17,321</td>
<td>17,909</td>
<td>19,841</td>
<td>21,931</td>
<td>21,680</td>
<td>24,824</td>
<td>26,407</td>
</tr>
<tr>
<td><strong>TOTAL ($'000)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(adjusted for CPI)</td>
<td>20,119</td>
<td>21,236</td>
<td>21,312</td>
<td>23,064</td>
<td>24,850</td>
<td>23,897</td>
<td>26,500</td>
<td>27,380</td>
</tr>
<tr>
<td><strong>Total Client Costs ($'000)</strong></td>
<td>7,608</td>
<td>7,296</td>
<td>6,548</td>
<td>6,769</td>
<td>6,825</td>
<td>6,230</td>
<td>6,176</td>
<td>6,160</td>
</tr>
</tbody>
</table>
5.2.4 NSP Results Economic analysis

The economic and epidemiological models were run for two time periods,

1. from 2000-2009
2. 2010-2079 to represent a lifetime

Analysis of current NSP provision compared to no government funded NSPs (2000-2009)

During the period 2000-2009, gross funding for NSP services was $243m with healthcare costs saved of $1.28 billion ($1.12bn-$1.45bn, IQR) compared to no program and more than 140,000 DALYs gained. The net financial cost-saving was $1.03 billion ($876m-$1.98bn, IQR) undiscounted. NSP activities were cost-saving so the incremental cost-effectiveness ratios were not calculated.

The net present value allows a funder to assess an investment in an intervention from the perspective of the start of a time period, as if a decision was being made at a point in time (i.e. year 2000 about funding of NSPs for the period 2000-2009). Costs were valued to a specific year (2008) and then costs and outcomes were discounted from the time of the start of the intervention (see economic methods section) at 3% or 5%. The net present value at year 2000 of $190m spent on NSPs over the period 2000-2009 (in year 2008 prices) was $896m (discounted at 3%) and $817m for $172m spent (discounted at 5%). In other words, for one dollar invested in NSPs, more than four dollars would be returned in healthcare cost-savings after deduction of the cost of the program.

The net monetary benefit of the intervention can be calculated in economic analyses: if one assumes that a government would be willing to pay $50,000 per DALY gained through healthcare interventions, then the net monetary benefit of NSPs would have been more than $8 billion undiscounted and $6.2 billion discounted at 3%.

The majority of the gain was related to the prevention of HCV disease. If the benefits of prevention of HCV disease were not included, the net cost of providing NSPs was $94.8m over ten years, with a gain of 4,034 Disability-Adjusted Life Years. NSP funding was cost-effective for HIV alone in the time period, costing $4,500 per DALY gained.
Analysis of increases and decreases in NSP provision compared to no government funded NSPs (2010-2079)

Data from the epidemiological transmission model were generated for a number of different scenarios in which provision and funding of NSPs was less or more than current levels. Each scenario was compared to the no-program scenario using the start date of 2010 for the intervention and discounting to take the position of a decision maker in 2009. Costs were valued in 2008 Australian dollars.

Expenditure on NSPs was cost-saving at all levels of NSP funding when analysed for the periods 2010-2019 (10 years), 2010-2029 (20 years), or 2010-2059 (50 years) with undiscounted cost savings for current levels of NSP of $782m (10yrs), $3.23bn (20yrs), $17.75bn (50 years), and $28.71bn (70 years). The cost savings or net present value increased with more spending on NSPs, although the incremental net present value (NPV) started to reduce as spending increased beyond 50% above current levels of funding (Table 4 and Figure 2). Analyses with longer time horizons showed greater gains and increased returns for each dollar invested.

Table 4: DALYs and Net Present Value with changes in NSPs after ten years (2010-2019) and 20 years (2010-2029) discounted at 3%

<table>
<thead>
<tr>
<th>Level of funding for NSPs</th>
<th>NSP investment</th>
<th>Gain in DALY</th>
<th>Net Present Value of NSPs</th>
<th>Return on investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 2010-2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% of current levels</td>
<td>$225m</td>
<td>97,229</td>
<td>$631m</td>
<td>current investment + 380%</td>
</tr>
<tr>
<td>110% of current levels</td>
<td>$248m</td>
<td>98,562</td>
<td>$633m</td>
<td>current investment + 360%</td>
</tr>
<tr>
<td>125% of current levels</td>
<td>$282m</td>
<td>104,005</td>
<td>$647m</td>
<td>current investment + 330%</td>
</tr>
<tr>
<td>150% of current levels</td>
<td>$338m</td>
<td>111,254</td>
<td>$656m</td>
<td>current investment + 290%</td>
</tr>
<tr>
<td>175% of current levels</td>
<td>$395m</td>
<td>116,874</td>
<td>$650m</td>
<td>current investment + 270%</td>
</tr>
<tr>
<td>200% of current levels</td>
<td>$451m</td>
<td>121,303</td>
<td>$635m</td>
<td>current investment + 240%</td>
</tr>
<tr>
<td>300% of current levels</td>
<td>$676m</td>
<td>132,595</td>
<td>$514m</td>
<td>current investment + 180%</td>
</tr>
</tbody>
</table>
Figure 2: DALY gain versus Net Present Value 2010-2019 (NB: DALYs start at 50,000 and net costs are expressed as negatives (i.e. are cost-savings) and discounted at 3%)

Decreased funding from current levels would be associated with increases in HIV and HCV infections, with associated loss of health and life. The reduced return on investment would exceed any savings associated with reduced spending on NSPs: if funding was reduced by $22m or 10% over the time period 2010-2019, 7,600 DALYs would be lost and the return on investment would be reduced by $36m (Table 10 below). If funding was cut by 50%, over 36,000 DALYs would be lost with a reduction in the return on investment $197m Figure 3.

<table>
<thead>
<tr>
<th>NSP funding</th>
<th>Reduction in NSP spending</th>
<th>Loss in DALY vs. current</th>
<th>Reduced return on investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% of current levels</td>
<td>$112m</td>
<td>36,370</td>
<td>$197m</td>
</tr>
<tr>
<td>75% of current levels</td>
<td>$56m</td>
<td>16,473</td>
<td>$98m</td>
</tr>
<tr>
<td>90% of current levels</td>
<td>$22m</td>
<td>7,607</td>
<td>$36m</td>
</tr>
</tbody>
</table>

Table 4: Loss of life and reduced return associated with decreased funding period 2010-2019 (all discounted at 3%)
5.2.5 Secondary analyses

Inclusion of patient & client costs, productivity gains and injection-related injuries & disease: Inclusion of productivity gains and losses (with patient costs) increased the net present value of current provision of NSP to $5.85bn in the period 2000 to 2009. Most of the productivity gains were related to HCV disease. I used the Friction Cost approach to estimate productivity losses as reported in section 2.5. The cost savings to society are shown in Table 5.
Table 5: Societal costs averted, including productivity losses, and net present value for current funding of NSPs (undiscounted)

<table>
<thead>
<tr>
<th>Year</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Societal costs averted $ m (IQR, undis)</td>
<td>993 (931-1075)</td>
<td>949 (881-993)</td>
<td>410 (360-450)</td>
<td>348 (306-369)</td>
<td>380 (353-419)</td>
<td>448 (407-501)</td>
<td>521 (466-582)</td>
<td>580 (509-662)</td>
<td>676 (566-779)</td>
<td>783 (635-901)</td>
</tr>
<tr>
<td>NPV $m (current program)</td>
<td>973</td>
<td>928</td>
<td>388</td>
<td>325</td>
<td>355</td>
<td>424</td>
<td>494</td>
<td>552</td>
<td>648</td>
<td>756</td>
</tr>
</tbody>
</table>

If no NSPs were available, one could speculate that there would be an increase in injection related injuries and disease (IRID). If NSPs prevented 50% of the IRID that might occur in their absence, then one might assume that the additional cost-saving with current levels of NSP would be more than $20m a year or $200m in ten years (undiscounted).

Return on investment of NSPs associated only with HIV: The benefit of preventing HIV alone was considered in a secondary analysis for increases in funding scenarios from 2010-2019. Current levels of NSPs funding would be $226m (discounted) over the period 2010-2019 with healthcare costs saved of $56m and a net cost of $170m. 11,990 DALYs would be gained compared to no program for a cost of $14,200 per DALY gained. In other words, current levels of NSPs were cost effective compared to no program if only gains related to the prevention of HIV were considered over a future ten year time horizon.

The incremental cost of provision of NSPs at 150% compared to current levels was $444,000 per DALY gained when considering just the healthcare costs of HIV disease alone; in other words it would not be cost-effective to expand services on the basis of HIV alone in this ten year time horizon. If both analyses were conducted at the 20 year time horizon, both current provision and 150% provision were cost-saving compared to no program for HIV alone, although the incremental cost per DALY gained comparing 150% funding with current program was $55,000 per DALY gained.

5.2.6 Discussion and conclusions of economic analysis of Needle-Syringe programs (NSP)

The economic analyses of the results of the epidemiological transmission model suggested that spending on NSPs had provided substantial healthcare cost savings to government related to the prevention of HCV and HIV in the past decade. The majority of the cost savings and gains in life
years related to the prevention of HCV because more people were prevented from acquiring HCV than HIV in the population at risk. However prevention of HIV alone by current levels of NSPs was cost-effective in the short-term and cost-saving in the long-term. These cost savings had been associated with substantial gains in quality and quantity of life in the population of NSPs clients. For every ten dollars spent on the activities of NSPs currently, nearly forty dollars was returned and approximately two days of disability-adjusted life gained.

Projections into the future suggest that maintenance of current levels of NSPs funding would continue to provide substantial and increasing healthcare cost savings and gains in life years. Increases in the funding and provision of NSPs would have averted additional HCV and HIV infections with further increased cost savings. However, the marginal return on investment would reduce as funding increased to 200%, due to saturation of the market.

NSPs were not only cost-effective but cost-saving if HCV was included. There was significant financial return for the investment made in these programs. The analysis suggested that it was appropriate from a health sector (government) perspective to consider further expansion of NSPs in all Australian jurisdictions. The quantum of additional resources required to increase syringe distribution depended on the methods employed to achieve this aim. Expansion of opening hours and the establishment of new NSP outlets would require significant additional resources and these measures would most likely be necessary to achieve a large increase in syringe distribution. However, other measures to increase syringe distribution, such as the relaxation of restrictions on the quantity and range of syringes freely available to NSP clients, the removal of impediments to allow secondary exchange by IDUs, and the installation of additional syringe vending machines or more mobile services, could all be implemented at relatively low cost (313). In Australia, the costs associated with procurement of needles and syringes were estimated at approximately one quarter of total NSP service budgets. If the above-mentioned low cost measures were implemented across Australia, a 10% increase in syringe distribution could theoretically be achieved with a modest ~2% increase in the total NSP budget. The key issue was determining how much extra demand exists for NSP services and the feasibility of meeting the demand.

On the other hand decreased funding in NSPs of just 10% could have cost more in the next decade in HIV and HCV infections, with loss of health and life and associated extra healthcare costs leading to a reduction in the return on investment greater than the immediate NSP expenditure savings.
5.2.7 Limitations of analysis

There were several limitations to the epidemiology modelling approach taken in this analysis. While assumptions were based on the best available data, these data were based on non-random samples or case notifications. Different prospective observational studies, using different methods and sampling techniques, were explored where possible to obtain robust assumptions. Furthermore, wide-ranging uncertainty analyses (defining ranges of uncertainty around key assumptions) were performed to provide a sense of the robustness of results. There was a lack of data for some factors, such as rates of HIV treatment among active IDUs. However, the model was calibrated to current levels of HIV transmission, and so the results were broadly applicable as long as current rates of HIV treatment in active IDUs remained stable.

All models are abstract simplifications of reality and do not incorporate much of the large heterogeneity that exists between people. The mathematical transmission model was a population-based system of ordinary differential equations. An agent-based computer micro-simulation model would be required to capture networks of IDUs and to incorporate greater variation in behaviour between individuals. However, the model used in this analysis was a significant advancement over previous models of HIV and HCV epidemics among IDUs in Australia (or overseas) and over the methodology used in the previous return on investment analysis (116).

The economic analyses also had a number of limitations. First, I assumed that individuals in each health state of HIV or HCV had homogenous use of healthcare and medications. If the economic model had been incorporated into the population model, I could have sampled stochastically to generate uncertainty boundaries around our cost estimates. However, the method did not allow this and I was aware that this limited the ability to deal with heterogeneity and uncertainty in cost. Second, I only used patient and carer cost and productivity gains in secondary analyses and may have underestimated the potential health sector and societal benefit of NSPs. On the other hand, the approach reflected the lack of reliable recent local data on patient & carer costs and workforce participation of NSP clients and people living with HCV. In the productivity analysis, I used the Friction Cost approach rather than the Human Capital approach because this approach was recommended by local and international funding agencies and because it reduced the risk of amplifying any uncertainty in the estimates of productivity gains excessively. Finally, in the analyses of increasing or decreasing funding, I assumed that all costs were variable in the short-term, which
is unlikely in reality as infrastructure and wind-down/start-up costs would create ‘lumpiness’ in cost. The analyses of increases and decreases in funding were included to illustrate that NSP funding could be increased substantially without reduction of cost-savings.

It is important to note that the analysis was based on the effectiveness of NSPs in averting HIV and HCV infections among IDUs only and not on the many other benefits of NSPs, such as avoided mental health episodes and injecting related injury, psychosocial benefits, overdose education and prevention. Thus, the analysis was highly conservative of the true return on investment associated with NSPs.
5.3 Adult male circumcision

I was the first author of the peer-reviewed publication of this analysis in Journal of Infectious Diseases (paper in Appendix C). The published paper reported results in US Dollars but the original modelling was performed in Australian Dollars, so I have used the Australian dollar amounts here.

5.3.1 Method

Description
An adult male circumcision HIV prevention intervention would consist of a program to circumcise men having sex with men (MSM), with the circumcision procedure being carried out in public hospitals with pre- and post- procedure medical care and counselling. Four target groups were compared: young MSM; MSM aged 35-44 years (highest incidence of HIV acquisition); insertive MSM; and all MSM. The comparator was the status quo with falling prevalence of circumcision in adult males by age group.

Evidence of impact and likely effectiveness of the intervention
Adult male circumcision has been shown to be effective for the prevention of acquisition of HIV in three randomised trials in heterosexual men in Southern and Eastern Africa (260-262). A meta-analysis of observational data on the effect of circumcision in MSM revealed insufficient recent evidence that male circumcision protects against HIV infection or other STIs but reported a protective association of circumcision with HIV in studies of MSM conducted before the introduction of highly active antiretroviral therapy(314). In 2008, a large Australian community-based cohort reported a significant reduced risk of HIV seroconversion among circumcised MSM who predominantly took the insertive role in anal intercourse (33% of the cohort) with an 89% reduction in the acquisition of HIV for predominantly insertive MSM with 95% certainty that the true value lay between 20% and 97%(315).

Current practice
Paediatric circumcision had been declining in popularity in Australia steadily from rates of 80% in the 1960’s to less than 10% in the recent decade and hence the prevalence of circumcision in adults had also been declining(316). Adult male circumcision in Australia was generally performed in hospital as a day procedure with an average length of stay of 1-2 days(317).
5.3.2 Model Circumcision

The intervention was modelled as four strategies for the implementation of circumcision including:
1) young men having sex with men (MSM) close to time of sexual debut;
2) MSM aged 35-44 years (highest incidence of HIV acquisition in Australia);
3) MSM practising only insertive anal intercourse (i.e. not receptive);
4) All MSM.

The comparator was the current status quo with a prevalence of circumcision in adult males by age group that fell steadily since the 1970s until the decade until 2010 when paediatric circumcision is rare; hence the proportion of men currently aged 35-44 who have been circumcised with no change in practice would be greater than the 25-34 age range.

The epidemiological model was built using the Mathlab program by my collaborator David Wilson with the extensive input into the clinical variables and inputs to be used (Figure 5). The epidemiology model was constructed with the assumption that only men having unprotected insertive anal sex would be affected by the intervention (Figure 4). The model had 4 age groups with ageing over time. It was assumed that sexual mixing occurs across all age groups but is primarily assortative within each age group with 75% of episodes between men in the same age group(318).
The model included data from existing studies of MSM in Australia of age-specific circumcision status (range 50% 18-25 years to 83% aged >45 years) (316, 319, 320) (321) and HIV prevalence (range aged 18-25 years 0.5% to aged >45 years 18%) (203); probability of acquisition and transmission of different sexual acts (0.008 for receptive anal sex and 0.0008 for insertive anal sex) (322-324); frequency of sexual acts (125 acts per man/year) (325, 326); condom usage (65%) (327, 328) and efficacy (90%) (255, 329); use and impact on infectiousness of antiretroviral therapy (70-75% on ARV, 80% achieve viral suppression, that reduces infectiousness by 95%) (330-334); strategic positioning and role preference (33% engage only in insertive anal sex) (335). The model was calibrated to accurately reflect the population of Australian MSM and the HIV epidemic in this population (203). Using the model input ranges and adjusting the per-act transmission probabilities (to the levels indicated above), the model simulations produced estimates of HIV incidence (680 cases per year mean, 95% CI 456-963) that matched the HIV epidemic in Australia (681 HIV diagnoses in this population in 2006). Outputs from the epidemiology model for each strategy and the comparator were

- number of number of circumcisions
- number of HIV infections for each strategy

A separate excel spreadsheet was constructed by me to perform the economic analyses. Inputs include the number of circumcisions; number of HIV infections for each strategy (from the transmission model); cost of intervention and costs of HIV healthcare (see below); lifetime loss of disability adjusted life years due to HIV infection (see below). In the analysis, each incident HIV infection accrued a DALY loss and the cost of HIV care; both cost and DALY loss were discounted.
amounts that were discounted again at the time in the model that the infection was assumed to occur.

Circumcision was assumed to have an effectiveness of 60%, based on data from three RCTs in Southern and Eastern African heterosexual men (260-262) with sensitivity analyses from 40% to 80% to illustrate the impact of our assumption and the results of a published meta-analysis (336). The putative direct benefit of circumcision would be only in men practicing insertive sex. In the HIM cohort reported sexual behaviours correlated well with the initial declared preference (337).

Health benefit. The peer-reviewed publication uses loss of quality adjusted life years associated with HIV from the published literature (9) but for the stakeholder group version I made the assumption that the loss of disability adjusted life years was similar to the loss of quality-adjusted life years as most of the adjusted years lost would be years lost to death rather than small differences in the DALY or QALY weight for disease states. I tested this assumption in a sensitivity analysis and confirmed that the model was relatively insensitive to the impact of changes in the QALY/DALY loss. 7.5 QALYs were estimated to be lost over a lifetime per incident HIV infection in an estimate of the QALY loss associated with HIV infection from a large systematic review of the cost-effectiveness of interventions for HIV (9).

Costs of intervention Cost of circumcision included the operation cost (338), medical visits including any adverse effect management and prevention counselling (339) (340), all derived from published cost-estimates.

Time horizon. The time horizon of the economic analysis was 25 years in one year cycles. In the analysis, each incident HIV infection accrued a QALY loss and the cost of HIV care; both cost and QALY loss were discounted amounts at 3% that were discounted again at the time in the model that the infection was assumed to occur.

Calculation of cost-effectiveness. The costs (intervention and disease-related costs) and outcomes (HIV infections and quality adjusted life years) were estimated and the incremental cost-effectiveness ratios (ICER) calculated comparing the net costs and net outcomes of each strategy with the status quo. I assumed that a strategy was cost-effective compared to the status quo when the incremental cost-effectiveness ratio was less than A$60,000 per DALY or QALY gained, a
shadow price used in a government-published economic analysis of public sector interventions including for HIV(341).

**Uncertainty and Sensitivity Analyses.** I entered the 95% confidence intervals for the number of HIV infections from the results of the population model for each strategy into the Excel spreadsheet used for the economic analyses and then ran 2000 simulations for each strategy compared to the status quo using the @Risk software program (www.palisade.com/risk/). In the results below, 95% confidence intervals and probabilities that the ICER will be less than the cost-effectiveness threshold of $60,000 per DALY are reported. One-way sensitivity analyses were performed to account for other important model assumptions and uncertainties in input parameters, including the impact of risk disinhibition. For variables without a range of published estimates, the ranges for sensitivity analyses represented the judgement of the variations likely to be encountered in the implementation of the intervention. In the baseline analysis, my model included the costs of the management of post-operative complications of circumcision; in a sensitivity analysis it included a 10% loss of quality of life in a 4 week post-operative period, extrapolated from the literature on quality of life in men with erectile dysfunction(342). The inclusion of program costs such as marketing, administration, monitoring and evaluation were explored.

**5.3.3 Circumcision Results**

Over 25 years of the population model, there were 241 (1.4%) fewer infections compared to the status quo in the strategy of ensuring all MSM are circumcised prior to sexual debut, 318 (1.8%) fewer by circumcising all men in the 35-44 year old age group, 363 (2.0%) fewer by circumcising men who practice predominantly insertive penile-anal sex, and 655 (3.7%) fewer if all MSM are circumcised. 3-5% of HIV infections per year would be averted after 25 years. 118 circumcisions would be required to prevent one HIV infection in the insertive strategy and 338 circumcisions if all MSM were circumcised (Figure 5). 10 to 27 disability adjusted days (undiscounted) would be gained per circumcision performed depending on the strategy. The expected change in incidence due to any of the circumcision interventions is relatively modest and thus overall prevalence was not found to change substantially over 25 years due to circumcision (a maximum change of 0.15% in absolute prevalence).
Circumcision and medical costs for the first year of the intervention would be $5.1m for the sexual debut strategy, $29.5m for the 35-44 years old, $47.6m for the strategy targeting insertive MSM and $136m for the all MSM strategy. Once the initial start-up phase had passed, the yearly costs would range from $2.9m to $7.9m a year.

The insertive strategy saved $31m over 25 years compared to the status quo for an overall investment of $89m (discounted), with 2% likelihood that it would not be cost-saving and 0.4% likelihood of not being cost-effective. The cost-effectiveness threshold for interventions in Australia is not explicitly stated by funding advisory bodies such as the PBAC or MSAC. If an incremental cost-effectiveness ratio of less than $50,000 per DALY gained was assumed, all other strategies were cost-effective (Table 6), with 1% likelihood that the all MSM strategy was not cost-effective, but a 3.6% and 25% likelihood that the 35-44 year old and sexual debut strategies would not be cost-effective. The insertive strategy was cost-effective after 7 years of the model, while the sexual debut strategy took 21 years until becoming cost-effective. The total investment over 25 years for the 35-44 year old strategy would be $120m (discounted) and for the all MSM strategy $254m.
<table>
<thead>
<tr>
<th></th>
<th>HIV infections averted</th>
<th>ICER $ per DALY</th>
<th>Probabilistic sensitivity analyses</th>
<th>Budget impact First year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young MSM</td>
<td>146</td>
<td>$38,000</td>
<td>3.6% not cost-effective</td>
<td>$5.1m</td>
</tr>
<tr>
<td>35-44 years</td>
<td>204</td>
<td>$14,000</td>
<td>25% not cost-effective</td>
<td>$29.5m</td>
</tr>
<tr>
<td>Insertive</td>
<td>246</td>
<td>cost-saving</td>
<td>2% not cost-saving</td>
<td>$48m</td>
</tr>
<tr>
<td>Insertive</td>
<td></td>
<td></td>
<td>0.4% not cost-effective</td>
<td></td>
</tr>
<tr>
<td>All MSM</td>
<td>444</td>
<td>$11,000</td>
<td>1% not cost-effective</td>
<td>$136m</td>
</tr>
</tbody>
</table>

If men who had been circumcised in the intervention reduce their use of condoms by 10%, none of the interventions are effective and therefore none could be cost-effective. If only 80% of all MSM are circumcised the intervention would cost $21,020 per DALY and if 90% of all MSM are circumcised the intervention costs $12,900 per DALY.

One-way sensitivity analyses around cost and discounting are presented in Figure 6 for the all MSM strategy. Results of the sensitivity analyses are similar for the other strategies (not shown). The model is most sensitive to the effectiveness of circumcision, proportion of predominately insertive men, costs of circumcision and the management of HIV infection. The intervention would have been cost-saving for all strategies if circumcision is 50% cheaper. It remained cost-effective for three of the four strategies, if the cost doubled due to program and marketing costs. HIV disease in Australia could have cost 50% less than the baseline assumption and the intervention would have remained cost-effective in most scenarios. The incremental cost-effectiveness ratio was less affected by the discount rate. If men being circumcised had a temporary loss of quality of life, there was little effect on cost-effectiveness.
The probabilistic sensitivity analyses are presented in figure 7 as scatter plots that show that 3.6% of the simulations for the young MSM are not cost-effective; 25% of the simulation models for men aged 35-44 are not cost-effective; 2% of the estimates for the insertive strategy are not cost-saving and 0.4% are not cost-effective. Circumcising all men has a 99% likelihood of being cost-effective.
5.3.4 Discussion and conclusions circumcision

The economic analysis explored the cost-effectiveness of circumcision as a prevention intervention for MSM in a well-resourced setting. The model suggested that circumcision could be cost-effective or cost-saving under a range of implementation strategies. The investment required would be considerable for limited impact on the epidemic. Furthermore, the effectiveness could be undermined by plausible levels of increased risk behaviour.

An estimated one-third of gay-community-attached MSM in Sydney predominantly took the insertive role in anal intercourse(337). Circumcision of predominately insertive MSM would save $21.7m over 25 years with a $62.2m investment. However, the epidemiological model assumed that the sexual preferences of MSM in our model would remain stable over 25 years. This is contestable as sexual behaviour and preference may be fluid in the long run, depending on emotions, setting, partnership dynamics, age and culture.

The analyses of the uncertainty related to population model inputs suggested that there was only 75% likelihood that a strategy of circumcising young MSM would be cost-effective, although there was less uncertainty about the cost-effectiveness of a strategy of circumcising all MSM. Lower
levels of coverage for the all MSM strategy would be still be cost-effective and would have smaller initial budget impacts. The one-way sensitivity analyses also demonstrated that the results were very sensitive to assumptions about the effectiveness of circumcision, the proportion of men who are predominately insertive and the costs of circumcision and HIV healthcare.

In a paper published after ACE-HIV was complete, Sansom examined the cost-effectiveness of neonatal circumcision for the prevention of HIV from heterosexual transmission in the USA and found that it cost $87,792 per QALY saved for Caucasian males. Results were most sensitive to the discount rate, and circumcision efficacy and cost(343). A systematic review of economic evaluations of adult male circumcision for prevention of HIV acquisition by heterosexual males reported that the intervention was generally cost-effective or cost-saving. The key driver of cost-effectiveness models was circumcision efficacy(344).

There are a number of limitations. First, models are only approximations of the real world and simplifying assumptions must be made. For example, there were not data available on the degree of assortative-disassortative mixing across age groups; the epidemiological model used estimates consistent with a recent modelling study that estimated mixing patterns across age groups in Australian MSM(345). Second, the epidemiology model used the efficacy of circumcision from the randomised controlled trials in heterosexual men in Southern and East Africa(260-262). However, this estimate fell within the confidence intervals of the estimated reduction of HIV risk conferred by being circumcised in a large prospective in MSM(337). Third, I used estimates of the discounted quality adjusted life years lost and costs of lifetime of HIV infection in the original paper, but these were derived and valued in the USA that has a very different health system to Australia(9) and I then assumed that the DALY loss was the same when I re-ran the model for the ACE-HIV process. Finally I did not consider the potential additional benefits in the reduction of other sexually transmitted infections associated with circumcision and may have therefore underestimated the potential benefits.

In conclusion, the study was the first cost-effectiveness analysis of adult male circumcision in men having sex with men and used data from rigorously conducted studies in the population. I showed that circumcision could be cost-effective and even cost-saving using a range of strategies. However, the investment required would have been considerable and the impact on the overall epidemic limited. In addition, if a perception of being protected from HIV led to increased HIV risk
behaviour, then the effectiveness of the intervention could easily be lost. In such a setting, it was not inconceivable that the intervention could lead to an increase rather than a decrease in new HIV infections. A single technology such as circumcision is unlikely to be effective in a complex epidemic; combinations of new and classical health promotion actions are likely to be needed (346).
5.4 Non-occupational Post-exposure prophylaxis

5.4.1 Method

Description of NPEP

The Victorian NPEP program was used to provide a model for the intervention to be analysed. It consisted of a NPEP advice line 24 hours a day, staffed by a roster of specially trained on-call nurses with onward referral to either community primary care clinics, a public sexual health centre, a regional hospital or the emergency department of a tertiary public hospital. If a significant high-risk exposure was determined to have occurred, the person was offered one week’s supply of two or three drug NPEP, depending on the exposure, at the first consultation. During the same consultation appropriate counselling was performed and baseline blood samples for pathology were taken. An on-call infectious diseases physician is available for secondary consultation.

Follow-up occurred at one week with a clinical review that includes sexually transmitted infection screening, adherence support, advice on side-effects and follow-up supply of enough medication to complete a four week course. Repeat HIV testing was recommended after 4-6 weeks and 12 weeks. A psychologist was available to see any patient who presents for NPEP, but principally was concerned with those who present on multiple occasions. After patient consent, data was collected and stored centrally at the Victorian NPEP service, Figure 8.

Figure 8: Description of NPEP and no program

<table>
<thead>
<tr>
<th>Intervention: NPEP program</th>
</tr>
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<tbody>
<tr>
<td>Risk behaviour</td>
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<table>
<thead>
<tr>
<th>Comparator: no program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk behaviour</td>
</tr>
</tbody>
</table>

Abbreviations:
MSHC: Melbourne Sexual Health Centre
GP: General Practitioner
ID: Infectious Diseases
Evidence of impact and likely effectiveness of the intervention

Animal models suggested that the administration of antiretrovirals early (<72 hours) after a high-risk exposure to HIV-like viruses protects against subsequent infection(347). There had been no RCTs of NPEP use in humans: a retrospective case-control study showed a reduction of ~ 80% after PEP taken for occupational exposures to HIV;(106) a study of persons who received NPEP in San Francisco showed that 3 of 702 persons acquired HIV after fully adherent NPEP(348), that translated to 99.58% efficacy in a fully adherent person. However 22% of individuals in the Victorian NPEP program failed to collect follow-up medication after one week, so overall effectiveness in the model was 78%(349).

Current usage at time of the analysis for the ACE-HIV project

The Victorian NPEP program saw 592 people in 2008, mostly MSM(349). Data from the Melbourne gay community survey 2008 was used to try to calibrate the probability of accessing the NPEP program: 4.9% of MSM reported using NPEP in the six months prior and 25% reported high-risk sex in the previous 6 months(350). However if it was assumed that 20% of the 25% of MSM having high-risk sex in the model accessed NPEP, then the NPEP program would see over 2,000 MSM per month. Therefore in the model, it was assumed that 0.52% of those with a high-risk behaviour access NPEP, resulting in 600 MSM attending for NPEP each year. This assumption was explored in threshold and sensitivity analyses, using a range of 0.052% to 100%.

Description of the Comparator for NPEP

Prior to the NPEP program being established, there was no formal program for the provision of NPEP in Australia, even for cases of rape or unprotected sex with a person known to be HIV infected, although a pilot NPEP scheme commenced in two jurisdictions in 2002. The comparator for the analysis was no program.

5.4.2 Model for NPEP

I used the same TreeAge model structure for NPEP and PrEP.

Participants could progress through the three health states, HIV negative, HIV positive and death. Death was the absorbing state of the model. A fourth health state was used to represent people entering the population over time, Figure 9.
• HIV negative individuals in the model could engage in high-risk sexual behaviours, defined as unprotected anal sex with a man of unknown or HIV positive serostatus.

• Individuals with recent high-risk sexual behaviours might access NPEP or be taking PrEP or may not be, depending on the scenario for coverage.

• If individuals engaged in high-risk behaviours, there was a risk of acquiring HIV. The risk of HIV acquisition was determined by type of sexual behaviour, source partner HIV status and the use of NPEP/PrEP. To simplify the model, it was assumed that all sexual risk related to unprotected anal sex.

High-risk sexual behaviour was defined as unprotected anal sex with a man of unknown or HIV positive serostatus: in the Melbourne gay community survey 2008, 26.9% of HIV negative men and 25.4% of unknown HIV serostatus reported having engaged in unprotected anal intercourse with casual sexual partners (350); 25% of HIV negative MSM in a sero-discordant relationship with an HIV positive man, reported unprotected receptive anal sex. In the prospective Health in Men (HIM) cohort study of initially HIV negative MSM in Sydney, 36% reported risky sex, defined as sex with a man of unknown or positive HIV status in the previous six months with a median of 11 risky acts (326). In the model, we assumed that 25% of MSM had high-risk sexual act each month in the model. The model was calibrated to Australian HIV incidence data (351).

The probability of acquisition or transmission risk for a type of sex act was derived from the consensus opinion contained in the Australian National NPEP guidelines, in which the estimates of the transmission risk of receptive anal unprotected sex was based on an original prospective study (352). The probability of HIV infection after receptive anal sex with an HIV infected source used in this model without PrEP or NPEP was 0.008 (352) with sensitivity analyses based on a range of alternative estimates for risk; a higher estimate of 0.02 used in the empirical study of the San Francisco program (107) and a lower estimate reflecting antiretroviral therapy in people living with HIV with a 92% reduction to 0.00064 (353, 354).

Baseline HIV prevalence in the model was assumed to be 9% with the subsequent prevalence in the model calculated from the probability of being HIV positive at the start of each model cycle using a state probability function in the TreeAge software (203). Adverse events related to the antiretrovirals in NPEP/PrEP were modelled and included using local and published data (355).
Time horizon

The time horizon was 25 years with monthly cycles.

Cost of NPEP

Intervention costs were fixed or variable: fixed program costs included staff wages and marketing; variable costs included provision and distribution of antiretrovirals; and medical consultations associated with the program. In the model it was assumed that the program continued to require similar fixed annual costs to operate.

Marketing and operational costs were provided by the Victorian NPEP program. Program staff wages and overheads were annualised from the 11 months of data available. Overhead costs were estimated as 25% with 12.4% salary on-costs and 12.6% of program overheads and consumables. Staff costs were contained to staff directly working within the NPEP program(349).
Antiretroviral costs used in NPEP were assigned based on the fractions of patients using a 2 or 3 drug regimen for NPEP and the types of drugs used(349). Since in the Victorian program, 22% of patients did not return after a week for their follow-up drugs, a similar proportion of NPEP users, had starter pack costs only assigned, to create a weighted average of cost per participant starting NPEP. It was assumed that one week of NPEP was ineffective and so the overall effectiveness of NPEP was reduced by 22%. The cost of NPEP for one month of tenofovir/emtricitabine (2/3) or tenofovir/emtricitabine/boosted lopinavir(1/3) was based on the published Australian government reimbursement tables for antiretrovirals(169).

NPEP-related clinical consultation costs were estimated as follows: General practice costs were estimated at the Medicare rebate for an initial longer consultation followed by standard follow-up consultations with the patient paying a co-payment in 50% of the consultations. At public sites, the consultation was costed for a standard ambulatory care episode in the infectious diseases unit using VAXS copayment and sexual health centre without patient co-payments(349).

5.4.3 Results NPEP

A NPEP program would have cost $3m-$5m per year if operated Australia-wide, preventing 3 HIV infections per year at a cost of $190,000 per disability-adjusted life year gained (95% CI $170,000-$210,000 per DALY).

Sensitivity analyses NPEP

NPEP could be more likely to be cost-effective if a higher transmission risk of unprotected receptive anal sex was assumed in the model (Figure 10), a higher proportion of sources were HIV infected, more of the risk behaviours were receptive anal sex and with a higher probability of accessing NPEP. The cost-effectiveness improved despite an increase in total program cost. NPEP could also be cost-effective if the cost of ARVs and healthcare for a NPEP course was lower (One way sensitivity analyses Tornado plot (Figure 11). The inclusion of a 10% decrement in utility for people who engaged in risky sexual behaviour related to anxiety in the three months after the exposure, led to a result suggesting that NPEP could be cost around $63,000 per DALY saved.
Figure 10 Incremental Cost-Effectiveness Ratio vs assumed Transmission Risk Receptive Anal Sex
5.4.4 Discussion and Conclusions Non-Occupational Post-exposure prophylaxis (NPEP)

A Non-Occupational Post-exposure prophylaxis program would not be described as cost-effective according to the model. I used the Victorian Non-Occupational Post-exposure prophylaxis program and assumed that this would be applied across the country. I valued only the reduction in HIV infections associated with the program, but the objectives of the program were wider than economic efficiency and these gains were not captured in the model. The program aimed to provide timely and equitable access to high quality clinical care and advice in the setting of rigorous data collection and stakeholder consultation. In addition to the provision of antiretrovirals for NPEP, other services included behaviour modification, management of repeat presenters and monitoring of adherence to prescription guidelines and follow-up. To do this, the program had a central “hub” of supporting staff and an advice line. If the program costs were removed from the model, the cost-effectiveness improved significantly, although the quality of the program might be reduced. If more people accessed the program, the cost-effectiveness improved but the total program costs increased.

Earlier detection of previously unknown HIV infections can help reduce further transmission by changes in sexual behaviour and allow management to avoid mortality and morbidity. STI screening
can result in the detection of a treatable infection such as chlamydia, gonorrhoea or syphilis. These patients might not have attended a doctor for HIV testing or STI screening had they not required NPEP. The model did not capture these secondary benefits.

The prevention of infection benefited both the individual and their future sexual partners, reducing secondary transmissions. In the model, I did not take account of secondary infections prevented. In studies where this benefit has been included, the cost effectiveness of an HIV prevention intervention may significantly improve, by up to 50%. (356).

The sensitivity analyses in the study provided useful insights on possible efficiency improvements. Encouraging men who have engaged in recent unprotected receptive anal sex with a known HIV infected partner to use NPEP would be a good idea. The program in the model became cost-effective with an Incremental Cost-effectiveness ratio of $17,000 per DALY when all NPEP recipients had engaged in unprotected receptive anal sex with known HIV infected source partners.

The results were comparable with another Australian study of the cost-effectiveness of NPEP. In a decision analysis model of people accessing NPEP in New South Wales, Queensland and Victoria conducted by Guinot et al, the cost per QALY saved was A$176,000 and A$1,740,134 per HIV infection averted (357).

Comparison with an earlier economic analysis of the San Francisco program discussed in Chapter 1 is also illuminating (358). The key drivers for the difference between the model and the San Francisco study appeared to be the transmission risk estimate for unprotected receptive anal sex (1 in 120 versus 1 in 50) and the proportion of source partners who were definitely HIV infected (46% versus 24%). These differences should caution against extrapolating the results of one study in one population at one time, to a wider population or a different setting in a different era.

5.4.5 Limitations NPEP model

The model had a number of limitations. Markov models are ‘memory-less’ and do not take into account prior experience or behaviour. A person who has used NPEP may change their behaviour afterwards. While over 10% of program users have received NPEP before, it is difficult to assess whether their re-presentation is due to: (a) continuing or increasing risk behaviour; (b) awareness of the service; or (c) higher levels of baseline anxiety. When a 10% quality of life decrement after high risk behaviour was included in a sensitivity analysis for those not receiving NPEP, the program
became nearly cost-effective in the model. There are no studies measuring the impact on health quality of life associated with having recent high risk behaviour reported in the literature, but clinicians report that people attending after high risk episodes are often severely anxious, ashamed and may report significant mental health issues in the three months before the follow-up HIV antibody test. In micro-economic terms, patients seek NPEP to satisfy this disutility.

In conclusion, the model showed that a Non-Occupational Post-exposure prophylaxis program was not cost-effective. Better targeting of the intervention might result in it being better value for money.
5.5 Pre-exposure Prophylaxis (PrEP)

5.5.1 Method

Description of Pre-exposure Prophylaxis

In the model, a pre-exposure prophylaxis (PrEP) program would consist of the supply of two antiretrovirals in a fixed dose combination pill, emtricitabine and tenofovir, taken by HIV-negative MSM with risk behaviour as well as prevention counselling and medical monitoring. PrEP could be taken continuously or intermittently in anticipation of high risk sexual behaviour. PrEP could be accessed through primary care clinics in most capital cities which tend to be concentrated in inner urban areas where many gay-identified men live. The comparator for PrEP would be no public health program, the status quo in 2008.

Evidence of impact and likely effectiveness of Pre-exposure Prophylaxis

At the time of the model, animal studies had demonstrated a high degree of protection, 90-100%, against HIV-like viruses in monkeys who had been previously been administered two antiretroviral medications (265). Human studies in heterosexual and homosexual populations were in progress and were about to report data, since reported in 2010 and 2011 (359-361). The level of protection assumed in the PrEP model was 90% with a sensitivity analysis from 50-100%. The subsequently published data for the iPrEx study in men having sex with men showed a population effectiveness of 44% and an effectiveness of 73% in study participants with more than 90% adherence (361).

Cost Pre-exposure Prophylaxis

Costs of PrEP were estimated from the PBS costs of the fixed dose combination pill Truvada most commonly used in published research studies and a hypothetical activity-based costing of medical consultations and pathology. Inputs are listed in Table 7.

5.5.2 Pre-exposure Prophylaxis Model

The Pre-exposure Prophylaxis model structure was the same as the Non-Occupational Post-exposure prophylaxis model.
### Table 7 Key Inputs to model

<table>
<thead>
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<th></th>
<th>Baseline</th>
<th>Range</th>
<th>Source/Comments</th>
</tr>
</thead>
<tbody>
<tr>
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<td>$5,867-$8,800</td>
<td>ARVs +monitoring PBS S100 list price</td>
</tr>
<tr>
<td>HIV management</td>
<td>$14,913</td>
<td>$13,422-$16,404</td>
<td>Cost data from Chapter 2</td>
</tr>
<tr>
<td>Proportion of MSM having high risk sex</td>
<td>25%</td>
<td>15%-35%</td>
<td>Community survey(350)</td>
</tr>
<tr>
<td>Risk per episode unprotected receptive anal sex</td>
<td>1 in 125</td>
<td>1 in 50</td>
<td>Vittinghoff(362)</td>
</tr>
<tr>
<td>Baseline HIV prevalence</td>
<td>9%</td>
<td>5%-15%</td>
<td>Surveillance data(203)</td>
</tr>
<tr>
<td>Effect of PrEP on acquisition</td>
<td>90%</td>
<td>50-100%</td>
<td>Assumed</td>
</tr>
<tr>
<td>Effect ARVs on transmission in 70% HIV+ on ARVs</td>
<td>0%</td>
<td>92%</td>
<td>Wilson(275) Attia(353)</td>
</tr>
<tr>
<td>Adverse events or Resistance</td>
<td>0%</td>
<td>0%-10%</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

PrEP=Pre-exposure prophylaxis

#### 5.5.3 Pre-exposure prophylaxis results

Continuously taken Pre-exposure prophylaxis by men having high risk behaviours would prevent 675 HIV per year and HIV prevalence could fall to 5.8% over 25 years compared to a rise to 12% with no program, assuming 90% effectiveness, Around 95,000 disability-adjusted life years would be saved (IQR 55,000 to 160,000) with a total program cost of $420m per annum. Continuous Pre-exposure prophylaxis would cost $46,000 per DALY saved (95% CI $24,000 to $69,000 per DALY). A program of intermittent Pre-exposure prophylaxis taken 50% of the time would cost $5,600 per DALY (95% cost-saving to $18,000 per DALY saved).

**Sensitivity analyses**
In a probabilistic sensitivity analysis, it was 18% likely that incremental cost-effectiveness ratio for continuous Pre-exposure prophylaxis would be more than $50,000 per DALY. Use only in sero-discordant couples would make Pre-exposure prophylaxis more cost-effective around $11,000 per DALY.

Any use outside those with high-risk behaviours would render Pre-exposure prophylaxis much less likely to be cost-effective. The results in the model were most sensitive to the effectiveness and cost of Pre-exposure prophylaxis. Figure 12 is a tornado plot of the one-way sensitivity analyses for a number of different inputs and their effect on the incremental cost-effectiveness ratio. Figure 13 is a two-way sensitivity analysis of the cost of PrEP and assumptions about the effect of PrEP on acquisition of HIV. In the blue hashed area of the graph, PrEP is cost-effective compared to no program and demonstrates that the cost of PrEP could vary from $8000 per year if highly effective to $1000 a year for low effectiveness PrEP.

In the model, small increases in the frequency or prevalence of high-risk behaviour or the use of Pre-exposure prophylaxis by MSM with low risk behaviour would render intervention less cost-effective. If I assumed that antiretrovirals reduced infectiousness by 92% in MSM with HIV, Pre-exposure prophylaxis would no longer be cost effective costing over $600,000 per DALY gained.
Figure 12. Tornado plot of key inputs into Pre-exposure prophylaxis cost-effectiveness

Figure 13 Two way sensitivity analysis of cost of PrEP and effectiveness showing that continuous PrEP is the cost-effective in the blue hashed area.
5.5.4 Discussion and Conclusions pre-exposure prophylaxis (PrEP)

In the model, I found that PrEP could have a large impact on HIV prevalence and be cost-effective if greater than 90% effective and if targeted to MSM at high risk. Low levels of resistance to ARVs and more than 3% of people experiencing a 10% decrease in quality of life could make it no longer cost-effective. The model had significant uncertainty around the input parameters especially the targeting of provision to men with only high risk and I will discuss the impact of including the iPrEx results on the model outcomes.

The Preexposure Prophylaxis Initiative (iPrEx) study that reported results in 2011, showed that use of a combination of tenofovir and emtricitabine in a population of 2500 HIV negative MSM was associated with a 44% reduction in the incidence of HIV compared to a placebo arm by the primary intention to treat analysis. But adherence levels were low overall around 50%. The impact of PrEP was a reduction by 73% in the number of new infections in participants who were more than 90% adherent to study drug or placebo. Tenofovir/emtricitabine was reasonably well tolerated with few discontinuations due to adverse effects of study drug. However, a sub-study showed reductions in bone mineral density (BMD) with a 1.1% net decrease in mean BMD in the tenofovir/emtricitabine versus the pre-treatment/placebo group at the femoral neck (95% CI 0.4-1.9%) over the study period.

How might the results from the iPrEx study have affected the ACE-HIV process? Firstly, the study could have changed the perception of the strength of evidence and policy agenda that was important to the stakeholders in their choice of interventions for analysis. The strength of evidence was perceived as being one of the key factors to be considered in the first stage, along with the economic analysis results. The evidence for PrEP was rated as a possible option for change and the intervention was ranked 11thper13 prior to the ACE process. If the data from iPrEx had been available, the stakeholders may have seen it as being on the policy agenda.

The population in the iPrEx study were MSM living in Latin America, USA, South Africa and the Thailand, mostly aged less than 30 years. 80% had unprotected anal sex with a partner of unknown or positive HIV status in the past 6 months, with 60% having unprotected receptive anal sex in the previous 12 weeks, with an average of 18 sexual partners in the previous 12 weeks. In the model, I had assumed that 25% of HIV negative MSM had risky sex in the previous 6 months with a median
of 11 risky acts derived from a study in Sydney(326). The rate of HIV infection in the model was calibrated to reflect the incidence of HIV in MSM in Australia in 2008, around 788 new diagnoses from an estimated population of 165,000 gay and bisexual men with an incidence of around 1% per annum(203). In the study, there were 64 new infections in the 1248 men in the placebo group with a median follow-up of 1.2 years; the incidence was just under 5% per annum. In the model, the efficacy of PrEP was assumed to be 90%, whereas in the study it ranged from 44% by intention to treat to 73% in the more adherent population.

I ran the model again using the iPrEx study results, varying the effectiveness from 44%-73% and also changing the likelihood of having unprotected sex from 25% to 80%. The results show that PrEP would not have been cost-effective as a population intervention costing $117,000 per DALY gained due to low rates of adherence (Table 8). If patients were 90% or more adherent to PrEP it might be more likely to be more cost-effective, assuming the high rate of sexual risk behaviour of the study population.

The original PrEP model was most sensitive to the assumptions about efficacy (Figure 14), adverse effects of PrEP (Figure 15) and cost of medicines. A two-way sensitivity analysis of the model showed that assuming an incidence of HIV reflective of Australia, TDF/FTC would need to cost less than A$360 per month to be cost-effective, half the current list price on the Prescription Benefits Schedule, (Figure 16). A manufacturer might chose to discount for volume for a PrEP indication, but might risk pressure to lower the price of the medicine for the existing ARV indication and erode margins.

How would the existence of the data have affected the findings from the ACE-HIV project? PrEP was recommended as a ‘should fund’ option by the stakeholders with some uncertainty associated with the potential study outcomes. If I had presented the results according to the population efficacy 44%, the ICER would have suggested that PrEP was not cost-effective. But, I would expect that the stakeholders would have been aware that the adherent population had a better efficacy resulting in a more cost-effective intervention. They would have expected also that the manufacturer might discount the cost of TDF/FTC as a fixed dose combination for the prevention indication because the company now had three other single tablet regimens soon to reach the market that would reduce the need for the two drug fixed drug combination. Gilead had also
started to develop a follow-up compound for tenofovir that would allow them to discount or restrict the use of tenofovir to the prevention indication.

As I discussed previously, feasibility and the moral imperative to use available technology were key second stage factors, so I imagine that stakeholders would have seen the field evidence of efficacy as strengthening the case of funding, despite the impact on cost-effectiveness. On the other hand, the loss of bone mineral density in the treated group may have reduced some of the enthusiasm for the introduction of PrEP. The reduction in bone mineral density associated with TDF has not been directly linked to fractures (363). At least one observational study has shown an association of tenofovir with fractures, but the bone mineral density data was lacking (364). In the end, the best revealed preference of the importance of the bone data for physicians might be reflected in the continued dominance of tenofovir in the ARV market.

<table>
<thead>
<tr>
<th>Table 8 Impact of iPrEX results on incremental cost-effectiveness PrEP</th>
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<tbody>
<tr>
<td><strong>PrEP Model</strong></td>
</tr>
<tr>
<td><strong>Likelihood high risk behaviour last 6 months</strong></td>
</tr>
<tr>
<td><strong>Reduction in infectiousness PrEP</strong></td>
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<tr>
<td><strong>ICER $ per DALY</strong></td>
</tr>
<tr>
<td>Original</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>90%</td>
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<tr>
<td>$46,000</td>
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<tr>
<td>Study results Intention to treat Study population</td>
</tr>
<tr>
<td>80%</td>
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<tr>
<td>44%</td>
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<tr>
<td>$117,000</td>
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<td>Study results 90% adherence Study population</td>
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<td>73%</td>
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<td>$63,500</td>
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<tr>
<td>Study results Intention to treat Australian MSM population</td>
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<td>25%</td>
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<td>44%</td>
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<td>Study results 90% adherence Aus MSM population</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>73%</td>
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<td>$76,630</td>
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Figure 14 Sensitivity of ICER to assumption about infectiousness of Pre-exposure prophylaxis

![Graph showing ICER $/DALY vs Reduction in Infectiousness PrEP](image)

Figure 15 Sensitivity PrEP results on Adverse events

![Graph showing Sensitivity Analysis on percentAE](image)
The cost-effectiveness model was relatively insensitive to low rates of adverse events but more sensitive to higher rates of adverse events in the model.
5.6 Early use of antiretrovirals for treatment and treatment & prevention

5.6.1 Method

The model considers one intervention in two ways:

(a) Early use of antiretrovirals for the treatment of an individual
(b) Early use of antiretrovirals for the treatment of an individual and the potential prevention benefits to the population associated with reduction in infectivity.

Early use of antiretrovirals for treatment (Early Rx)

HIV antiretroviral guidelines at the time of the analysis recommended initiation of treatment when the person had a CD4 T-cell count less than 350 cells per microlitre reflecting moderate immune system damage and/or when there is evidence of clinical progression to an AIDS defining illness(164). There had been recent observational and indirect data supporting the earlier use of antiretrovirals for treatment with a reduced risk of opportunistic diseases and serious non-AIDS events(365) (285). A large RCT of early initiation of ARVs for treatment was underway in Australia as well as other countries called Strategic Timing of Antiretroviral Treatment (START), (clinicaltrials.gov NCT00867048).

The early use of antiretrovirals for treatment and prevention (Early Rx/P)

Early antiretroviral treatment as treatment and prevention of HIV (Early Rx/P), also known as “test and treat” had been proposed after observational studies showed that a low HIV viral load in a person with HIV is associated with a low risk of transmission to their sexual partners(353, 366-368). See below for further discussion of effect.

In the model, early use of antiretrovirals for treatment or treatment/prevention was explored in 2 scenarios compared to the status quo of starting when the CD4 was less than 350 and/or an AIDS defining illness.

The two scenarios were:

1. initiation of ARVs in all patients with HIV independent of CD4 T-cell count
2. ARV initiation when the CD4 T-cell count fell below 500 and/or with clinical progression.
In the model, antiretrovirals would be used after initiation according to the standard of care reflected in the Australian commentary on the US guidelines(164).

**Evidence of impact and likely effectiveness of early ARVs for treatment**

At the time of the model, data and guidelines supported the initiation of antiretrovirals in patients with a CD4 T cell count of less than 350 or who have been diagnosed with an AIDS defining illness(164). Recent data from the SMART study have shown that those who were naïve to ARVs and then initiated on ARVs with a CD4 cell count between 350 and 500 had lower rates of Serious Non-AIDS events(SNAEs), opportunistic diseases(ODs) and mortality compared to those who stayed off ARVs(369). Data from observational cohorts showed that those who started on ARVs with a CD4 cell count greater than 350 fared better than those who wait until the CD4 cell count fell below 350(365). There is a randomised controlled trial of early initiation of ARVs (START) that is currently underway around the world in which one group with a CD4 cell count greater than 500 will initiate treatment immediately, while the control arm will wait until the CD4 cell count falls below 350.

**Evidence of impact and likely effectiveness/implementation of early ARVs for treatment**

At the time of the economic analysis for ACE-HIV, there were observational studies that suggested that persons with HIV with a very low viral load were less likely to transmit HIV to their uninfected regular partner (353, 366-368). A meta-analysis concluded that heterosexual serodiscordant people with HIV with a very low or below detection HIV viral load are less likely to transmit HIV to their sexual partners(353). There was no data on the reduction in transmission in MSM although there was some biological plausibility that there will be a similar effect, but perhaps to a lesser extent (334, 354). Studies were underway in serodiscordant couples of men having sex with men (MSM) to assess the impact of antiretroviral treatment on infectiousness. For this analysis, the expected reduction in transmission associated with use of antiretrovirals was estimated at 92% a figure drawn from a metanalysis by Attia and estimates by Wilson(275, 353). The HPTN052 study published after I had completed the ACE-HIV project showed that effect was a reduction of 96% in infectiousness (370). The model was re-run after the ACE-HIV project using the HPTN results.
5.6.2 Description of model used for early use of ARVs for treatment & prevention

The benefits were modelled in TreeAge with a dynamic Markov model with 43 health states in three monthly cycles over a 20 year time horizon. Model health states represented HIV negative and HIV positive men with health states determined by four CD4 strata, treatment and viral load. Population was distributed in the model at baseline according to the Australian HIV Observational database (371). The model population represented 180,000 homosexual and bisexual men with age range reflecting the best estimates of prevalence of homosexuality in the Australian population (203). The HIV incidence was derived from the Australian National Annual HIV Surveillance Report where 75% of the 1000 people diagnosed with HIV reported male to male sexual activity(351). HIV prevalence was assumed to be 9%(203). The mortality data of HIV negative and positive people were taken from large population cohorts according to CD4 T-cell and HIV viral load (372-374). A reduction in infectiousness of 92% was applied for HIV+ individuals on fully suppressive therapy in the prevention model(353). The effectiveness of four lines of combination antiretroviral therapy including incidence of viral rebound was derived from randomised controlled trials and observational cohort data (373, 375-385). An disability adjusted loss due to serious non-AIDS events and opportunistic diseases was estimated for people with CD4 cell counts>350, not on ARVs, using data from the SMART study(285).

The use of antiretrovirals was consistent with the Australian commentary on the United States Department of Health and Human Services guidelines (158) with four lines of antiretroviral therapy. Patients were assumed to start ARVs and continue on them until there was treatment failure, when a new line of therapy was commenced. Antiretrovirals were valued by the Prescription Benefits Schedule (57).

5.6.3 Results for early treatment alone and early treatment with prevention

The treatment benefits of individuals starting ARVs at any CD4 cell count cost $140,000 per DALY compared to SOC (95% CI $65,000-$300,000 per DALY). If the additional benefits of prevention were added, the cost fell to $59,000 per DALY (95% CI cost saving-$143,000 per DALY. The incremental cost of treating the additional people who are not currently treated was around $40m a year, an increase of a third on the estimated ARV costs of $136m that I described in Chapter 2.
Treating all would lead to a reduction of 33% in the number of new HIV infections in population over 20 years but a rising HIV prevalence still, because I assumed that not everyone with HIV was diagnosed immediately and not everyone on ARVs had a viral load below detection.

Starting all patients at a CD4 cell count of 500 would not be cost-effective on individual treatment benefits alone with a cost of around $80,000 per DALY saved but would cost less than $40,000 per DALY if the prevention benefits were included.

**Sensitivity and Threshold analyses**

The reduction in infectiousness in the model due to ARVs needed to be greater than 88% for the starting ARVs at any CD4 including the prevention benefit to have a cost of less than $50,000 per DALY. For the start at a CD4 less than 500, the reduction in infectiousness needed to be greater than 65%.

The model outcomes were less sensitive to any reduction in quality of life due to the adverse effects of ARVs, the development of increased ARV resistance due to more widespread use.

In a probabilistic sensitivity analysis starting ARVs at any CD4 (including the prevention benefits) had a 11% likelihood that it would cost greater than $100,000 per DALY and starting CD4 less than 500 including prevention a 19% likelihood cost that it would cost more than $100,000 per DALY. Different factors operated in each of the model analyses. The assumed reduction in infection was the largest driver of cost-effectiveness above CD4 500 and the smaller individual patient clinical benefit drove the model for start under CD4 500.

Figure 17 below shows the sensitivity of the model of starting at a CD4>500 including the prevention benefits to the assumption about the size of the reduction in infectiousness.
Figure 17  Treatment as prevention sensitivity analysis reduction in infection
Start any CD4 incl prevention
5.6.4 Discussion and conclusions early use of ARVs

Early use of antiretrovirals at any CD4 cell count could be cost-effective in Australia if the possible prevention benefits were realised at a population level but would not be cost-effective on individual treatment benefits alone. Starting treatment at a CD4 cell of 500 would be still not cost-effective unless the prevention benefits were included.

The HPTN052 study was completed after I had completed the ACE-HIV project. The study was conducted in a number of sites, mostly in Africa and Asia. The population was serodiscordant couples, mostly heterosexual. The data showed that early use of ARVs in a population of ARV-naïve people with a CD4 cell count between 350 and 550 was associated with a 96% reduction (95% CI 73-99%) in the risk of acquisition of HIV in their HIV-uninfected partner(370). The study showed also a reduction in the occurrence of serious non-AIDS events or death by 41% in the early treatment group, although 90% of the people with these events in the comparator arm were living in Africa or Asia with pulmonary tuberculosis(370). There was no difference in drug-related adverse events.

I re-ran the early use of ARVs models with the effectiveness set at 96% assuming all patients started below and above a CD4 cell count of 500 but I did not adjust the risk of serious non-AIDs events because the disease risks were substantially different to the risks of an Australian MSM population. The cost per DALY improved to $42,900 for start CD4 under 500 (from $44,500) and to $56,100 for start CD4 greater than 500 from ($59,000), (Table 9).
How would these results have affected the rankings? In the ACE-HIV stakeholder process, early use of ARVs was only listed as doubtful initially because of a lack of certainty about the size of the reduction of infection. The intervention moved up to ‘could fund’ in the second round, because it was perceived to be feasible using existing infrastructure and the stakeholders were convinced by the observational data. If the HPTN052 study data had been available, I expect that it would have been listed as ‘should fund’ in both rounds.

There are some caveats on my assumptions. The study population of mostly heterosexuals in Africa and Asia in HPTN052 was different to an Australian population of MSM. However the HIV incidence was 10% over 5 years in the control arm, so there was a yearly incidence of 1-2 new infections per 100 person years, consistent with Australian MSM. On the other hand, the ARVs that were used in HPTN052 were less effective than the standard of care in Australia, so the impact may have been even greater.

The model assumes that all ARVs have the same impact on infectiousness. There is data suggesting that different ARVs have different penetration into the genital tract and fluids(386), although this has not been directly linked to infectiousness.

<table>
<thead>
<tr>
<th>CD4 ARV starting point</th>
<th>Reduction in infectiousness</th>
<th>ICER $ per DALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td>92%</td>
<td>59,000</td>
</tr>
<tr>
<td>&gt;500</td>
<td>96% (95% CI 73-99%)</td>
<td>56,145 (54,000-73,000)</td>
</tr>
<tr>
<td>&lt;500</td>
<td>92%</td>
<td>44,500</td>
</tr>
<tr>
<td>&lt;500</td>
<td>96% (95% CI 73-99%)</td>
<td>42,900 (41,700-51,800)</td>
</tr>
<tr>
<td>&lt;500 (assuming infection rate in serodiscordant couples from HPTN052 that double rate original model)</td>
<td>96%</td>
<td>29,900</td>
</tr>
</tbody>
</table>
In summary, the studies strengthened the case for PrEP and early use of ARVs by adding to the evidence of the efficacy of intervention. The economic argument was weakened for PrEP but the additional evidence would likely be valued more highly. The effectiveness of early use of ARVs would have been confirmed in the priority list, probably at a higher level than PrEP, because physicians might believe that the START study will provide further evidence of the individual benefits in terms of prevention of serious non-AIDS events.
5.7 Anal cytology screening for anal intraepithelial neoplasia

Anal cytology screening for anal intraepithelial neoplasia, the precursor of anal cancer, has been discussed by some clinical guidelines due to rising rates of anal cancer in MSM especially those with HIV(387, 388). Anal cancer is related to oncogenic Human Papilloma Virus (HPV) infection in a similar way to cervical cancer and high grade anal epithelial neoplasia appears to be the precursor of anal cancer similar to cervical intraepithelial neoplasia in relation to cervical cancer(389).

5.7.1 Method

Description of intervention

The intervention modelled was annual anal cytology in HIV+ MSM using liquid based cytology and follow-up of high grade cytology by high resolution anoscopy with biopsy and treatment of lesions with topical therapies. Two alternative comparators were used (a) no program (b) annual digital rectal examination to detect early anal cancers.

Evidence of impact and likely effectiveness of the intervention

People with HIV have at a 28-30 fold higher risk of anal cancer(390, 391) compared to the general population rate of 1/100,000 per year in 2005(392).

At the time of the model there was parallel indirect evidence from cervical intraepithelial neoplasia that the anal cytology is likely to be effective in identifying pre-cancerous lesions and Australian evidence that oncogenic HPV infection is common in MSM with HIV(393). There had not been any randomised controlled trials that had shown that local treatment such as topical imiquimod (394) or infrared coagulator ablation(395, 396) and/or therapeutic vaccination reduce progression(397) or are likely to lead to long-term resolution of high-grade lesions.

Digital rectal examination (DRE) is used clinically to detect abnormalities of the anal canal, rectum and prostate. There have been no randomised controlled trials of the use of DRE for the detection of anal cancers. As it could have provided an alternative or interim approach to the detection of early anal cancers, it was included in the model.
Anal cytology screening with high resolution anoscopy

Anal cytology can be performed easily by a clinician with brief training using a Dacron swab and liquid based medium used for cervical cytology. Pathologists can read anal cytology tests after additional training. High resolution anoscopy requires a colposcope, a trained operator, an assistant, wire biopsy forceps, acetic acid, iodine and a suitable table. There are few clinicians in Australia with extensive experience of performing anal cytology and only a handful trained and experienced in high resolution anoscopy. However there are substantial numbers of gynaecologists and sexual health physicians with training in cervical colposcopy who work in a facility with a colposcope. Patients may be reluctant to have anal cytology performed due to embarrassment about intimate examination; work commitments and the need to abstain from sexual contact before and after the procedure may deter patients from HRA.

Digital rectal examination (DRE)

Digital rectal examination is a clinical skill that is acquired during basic medical training and used frequently by general practitioners. However non-colorectal specialists may have limited recent experience of performing DRE. Patients may avoid DRE for fear of embarrassment as prostate cancer screening programs have found; on the other hand, MSM may be less anxious about DRE than heterosexual men because of the role of the anus in male to male sexual activity.

Description of comparator

The comparator was no program for both interventions, although at the time of the model there had been research-based anal cytology programs in Sydney and Melbourne.

5.7.2 Description of model

Benefits were modelled in TreeAge software with a Markov model with eight health states related to grades of anal intraepithelial neoplasia and anal cancer, before and after diagnosis and treatment. There were yearly cycles over a 25 year time horizon to allow for long-term costs and outcomes.

The baseline AIN prevalence and the rates of progression and regression of AIN were drawn from the St Vincent’s Hospital HIV clinic where a number of anal cytology studies had taken place in the past few years, Figure 17. Rates of progression and regression of normal and low grade states were
based on cytology while those for high grade were based on histology, because HRA was only performed on those with high grade cytology.

**Figure 17 Progression and regression rates from data from St Vincent’s Hospital (398)**

Adverse events related to the detection and management of HRA were modelled with disutility related to pain and bleeding. Cost of cytology, high resolution anoscopy and treatment were informed by the cost of liquid based cytology and the cost of high resolution anoscopy performed at St Vincent’s Hospital (399). Treatment costs for anal cancer were taken from an economic evaluation performed in the United Kingdom (400).

Detection and treatment by anal cytology and HRA was assumed, without any data to support it, to reduce the progression of detected high grade lesions by 50% and to detect small cancers earlier than those found as a result of symptoms (Table 10).

<table>
<thead>
<tr>
<th>Table 10 Key input parameters for anal cytology model</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity anal cytology</td>
<td>81%</td>
</tr>
<tr>
<td>Specificity anal cytology</td>
<td>63%</td>
</tr>
<tr>
<td>Baseline prevalence HSIL</td>
<td>23%</td>
</tr>
<tr>
<td>Effect of screening and treatment on progression of HSIL</td>
<td>50% reduction</td>
</tr>
<tr>
<td>Probability of cancer being found at digital screening &lt;3cm</td>
<td>75%</td>
</tr>
<tr>
<td>Probability of cancer being found after symptoms &lt;3cm</td>
<td>44%</td>
</tr>
<tr>
<td>Cost digital rectal examination</td>
<td>$33</td>
</tr>
<tr>
<td>Cost cytology</td>
<td>$91</td>
</tr>
<tr>
<td>Cost high resolution anoscopy</td>
<td>$300</td>
</tr>
<tr>
<td>Cost treatment HSIL</td>
<td>$900</td>
</tr>
<tr>
<td>Cost treatment cancer less than 3cm</td>
<td>$19,600</td>
</tr>
<tr>
<td>Cost treatment cancer more than 3cm</td>
<td>$29,000</td>
</tr>
</tbody>
</table>
5.7.3 Results Anal cytology model

An anal cytology screening program for HIV+ MSM would cost $5m a year and cost $33,000 per DALY saved compared to no program with a 95% uncertainty of cost-saving to $333,000 per DALY. But an anal cytology program cost $53,000 per DALY saved compared to digital rectal examination, because digital rectal examination was cost-saving compared to no program, with a 95% likelihood that the cost-effectiveness was either cost-saving or cost-effective. Digital rectal examination had a smaller impact on the budget, costing $450,000 per year.

Sensitivity analyses

The cost-effectiveness of anal cytology screening was very uncertain demonstrated in the plot of the probabilistic sensitivity analysis shown below in Figure 18.

![Figure 18 Scatterplot of ICER](image)

The model outcomes were particularly dependent on the unknown progression of high grade disease to cancer, particularly the rates of progression of undetected disease. Figure 19 is a Tornado diagram of sensitivity of incremental cost-effectiveness ratio to input assumptions.
Figure 19 Tornado diagram of sensitivity of results to inputs

Tornado Diagram at
Is screening for AIN cost-effective in HIV+ MSM?

5.7.4 Discussion and conclusions anal cytology screening

Anal cytology screening appeared cost-effective when I used the point estimate of incidence and progression rates of anal high grade cytology changes to cancer, but the result was very uncertain with a wide range of results depending on the assumptions about progression of high-grade anal neoplasia to cancer.

The results from the study were different to that from the Goldie paper discussed in the literature review that showed that anal cytology screening every 2 years cost $13,000 per Quality Adjusted Life year (QALY) gained(99). I tried to use Goldie’s estimates of progression of high grade disease in the model and found that 16% of people would have anal cancer after 15 years. The results were also different to a more recent cost-effectiveness of anal cytology screening in the United Kingdom that showed that screening was more costly and less effective than no screening due to assumptions on the impact of screening on quality of life. If the quality of life impact was removed, the intervention cost $120,000 perQALY(400). A third recent analysis examined the technical efficiency of different approaches for detecting disease and found that the direct use of high
resolution anoscopy was the most cost-effective strategy (401). All of these studies, including the own, used estimates of progression and regression rates from fairly small clinic-based populations that would increase the uncertainty around the estimates. Larger datasets are required from population samples of people living with HIV.

5.8 General strengths and limitations of the ACE-HIV models

I embarked on the research program with the aim of using the same or similar model for all the analyses to improve comparison. However, there were differences in populations, intervention type, comparator or base-case and modelling software used. All the prevention studies were modelled on populations of HIV negative men having sex with men in Australia, except the needle syringe program analysis. Five of the interventions related to HIV prevention while one was for early detection of pre-cancerous lesions or anal cancer in people who were already HIV infected. It was difficult to draw an expansion curve because the comparator for each model was slightly different.

There were some other general themes that are worth exploring as they applied to most of the models. I used some of the questions from Drummond’s checklist for economic evaluation (187) pp28-29 to help explain the technical limitations of the research.

Was a well-defined question posed in an answerable form? The studies always involved a comparison of alternatives, although the alternatives varied between a ‘do nothing’ that was sometimes the status quo (PrEP, Early use of ARV, anal cytology, circumcision) or sometimes a counterfactual removal of the service (NSP, NPEP). The costs and effects of the intervention were considered generally, although for some studies it was difficult to isolate only the costs and outcomes directly relevant to HIV.

The models were all designed & applied in the context of decisions about HIV programs as that was the focus of the project, although the results were included as benchmarks in the ACE-Prevention program focused on non-communicable diseases. The ACE-HIV stakeholders were all involved in the HIV sector and so that could have affected the way I framed the questions. I did not compare alternative uses of the money within the health sector using the same models or use a technique, such as cost-benefit analysis, that would have allowed me to compare with investments in transport or infrastructure. But a cost-benefit analysis would have required other studies that
valued health outcomes in dollars such as conjoint analysis that can be difficult to perform for a complex disease like HIV.

Was a comprehensive description of competing alternatives given? The stakeholder process helped specify the interventions, particularly in the initial selection process. Data on the population to be reached and the evidence for the intervention were important to the stakeholders. A number of possible interventions such as mass media were removed from the list because they were not clearly specified, such as few mass media campaigns that had occurred in Australia since the initial Grim reaper campaign more than 20 years ago. It was hard to be precise over the population to be reached for some interventions due to different estimates of the proportion of MSM having risky sex, so I calibrated the models to the incidence data.

Was the effectiveness of the programs or services established? The source on the data on effectiveness of the interventions in the models varied from randomised controlled trials (RCT) for circumcision through retrospective observational data for NPEP to data from animal models for pre-exposure prophylaxis. Some interventions such as NSP only had ecological data to prove their effectiveness and needed to be assessed on their ‘promise’, a combination of the certainty of effectiveness of the intervention, judgments of the quality of the evidence, strength of the program logic and its potential population impact (104). In 2009, when I was completing the models, the Cochrane reviews of circumcision(402) and ARV as prevention in discordant couples(403) were not completed and the review on PrEP advised waiting for the results of the field studies(404). The other topics were not covered.

I wanted to include some biomedical prevention interventions that were novel and on the policy agenda such as PrEP and treatment as prevention so I necessarily needed to speculate about the possible effect of the interventions using indirect data from animal models and observational cohorts. There were risks in examining interventions without established data but I was willing to take them for the sake of fostering enthusiasm for the project from the stakeholders. They had little appetite to reconsider interventions that ‘everyone’ agreed were effective and likely to be cost-effective such as condom provision. This preference for the new over the established is a potential bias to all priority-setting exercises, but particularly likely in a fast-moving field like HIV, given the history of early adoption. Any future version of the ACE-HIV process would need to
include all the current major interventions for prevention and treatment from community media campaigns to standard ARV use.

Was allowance made for uncertainty in the estimates of costs and consequences? The one-way analyses were more useful as a preliminary step to identify the key factors in the model and confirm that the model appeared to be functioning correctly. The probabilistic approach is potentially more useful to be able to provide some bounds of uncertainty around a point estimate of cost-effectiveness. It worked well for circumcision, where we had randomised controlled data but with other models, the inputs did not have distributions so I had to apply standard distributions((405)pp77-120) to the point estimates using the TreeAge distribution function that creates a distribution according to standard formulae. In some ways that could give the appearance of being a distribution based on a sample from field work, rather than an artificial constructed distribution. The values of costs were particularly difficult to create distributions around, because many of them were predetermined point amounts paid by the Medicare or the PBS.

Joint use of resources was a common problem with all the ACE-HIV models, as it is likely that people with HIV would visit their GP and need prescriptions with or without HIV and clean injection equipment prevents HCV, HIV and injection site infections. I tried to adjust for joint use in the healthcare cost model for the number of GP visits by using the incremental additional number of visits compared to the general population in the base-case but it was clearly a potential bias in the model. On the other hand, I may have underestimated the cost of hospital admissions by counting only the admissions where one of the Australian National Diagnostic Related Group (ANDRG) codes for HIV was mentioned in the National Admitted Patient Care Collection(153).
6 DISCUSSION and CONCLUSIONS

Introduction

In this chapter I will discuss the essence of the contribution to science including priority-setting, clinical medicine and population health and discuss possible future research.

The aim of this research program was to seek evidence about the empirical application of the ACE approach to HIV medicine and the feasibility of using existing datasets to collect the inputs required for economic modelling. The hypotheses were that the ACE approach was feasible and could be valuable for priority-setting in HIV medicine in Australia and that the data required for the ACE process could be gathered from existing databases and studies. The first questions to answer in this chapter relate to the primary hypothesis: Did ACE-HIV represent a sound priority-setting exercise? Was it better than existing approaches?

6.1 Did ACE-HIV represent a sound priority-setting exercise?

ACE-HIV needed to be a sound priority-setting exercise for it to reliably inform stakeholders. The process did seem to follow most of the tenets of a sound priority-setting exercise, as described by Rob Carter (who developed the ACE method) (Box 1). He based these criteria on economic theory, ethics and social justice, lessons from empirical experience and the needs of decision-makers(5). I will use these criteria to show that there was an explicit process for generating options for change; marginal analysis was an integral component; decision rules and the role of judgement were clearly specified; the need for due process was recognised; and the rigour was generally appropriate.
Box 1 criteria for an ideal priority-setting exercise from Carter paper (5).

| Criterion 1: Is there clarity in the research question? |
| Criterion 2: Is there a clear concept of benefit? |
| Criterion 3: Is there an acceptable process for generating options for change? |
| Criterion Four: Is marginal analysis an integral component? |
| Criterion 5: Are the decision rules clearly specified? |
| Criterion 6: Is the role of judgement clearly specified? |
| Criterion 7: Are the data needs tractable? |
| Criterion 8: Is the need for ‘due process’ recognised? |
| Criterion 9: Do the measurement methods demonstrate appropriate rigour? |
| Criterion 10: Reporting/implementation |

I will examine ACE-HIV against each of Carter’s checklist questions

Criterion 1: Is there clarity in the research question? The research question for chapter 4 was “what are the priorities for funding from a range of interventions for the prevention and management of HIV”. However the options were relatively limited and the decision context was an academic exercise rather than the deliberations of a government committee or advisory panel. Therefore, stakeholders may have perceived their decisions as risk-free unlike the real world where a decision to decrease funding means unhappy clients or patients, media attention and political challenges.

Criterion 2: Is there a clear concept of benefit? There were two forms of benefit in the economic analyses of ACE-HIV, health and cost-savings, but the second-stage process showed that the stakeholders valued outcomes such as a cultural acceptability intervention, an intervention that was feasible for the health system, the use of available technology for good, a lack of media reaction and political acceptability. ACE-HIV allowed these forms of benefit to be explicit in the priority-setting, rather than requiring advocacy or political lobbying as occurred in the historical approach.

Criterion 3: Is there an acceptable process for generating options for change? The options for change were generated from the literature search and discussions with the supervisors. I wanted a mix of classic and newer forms of prevention and treatment, particularly biomedical prevention
interventions. In an ideal world, I would have asked the stakeholders to review the outputs of the literature search prior to the nomination of a provisional list, but the realities of limited time and resources meant that I only had the opportunity for 2-3 stakeholder meetings.

The preferences were weighted towards economic evaluations of biomedical interventions for prevention because I was a primary care physician who was interested in their potential role in the future. The initial choice of Needle Syringe Programs was encouraged subsequently by the request to evaluate the intervention by the Australian government. The choice of anal cytology was probably biased by the previous participation in studies around anal cytology screening programs and the desire to obtain another perspective on the issue. So the choice of interventions was probably not always as objective as the ACE method generally suggests. The stakeholders did provide comment and direction on the provisional decisions and were aware of the other factors that were impinging on the preferences.

Criterion Four: Is marginal analysis an integral component? In most of the ACE-HIV projects, I considered partial or increased provision of the intervention including more or less funding of NSP, different strategies to implement circumcision in a population, intermittent use of PrEP, early use of ARV at different thresholds, digital rectal examination rather than anal cytology. Marginal analysis provided a way to understand the technical efficiency of different potential strategies.

An expansion curve is a way of representing the health gains and costs of different interventions to determine the order that the interventions might be implemented, given limited resources. I did not present a graph of an expansion curve in ACE-HIV for two reasons: first, we did not have a set budget to allocate so it did not seem likely to assist the stakeholders in their priority-setting; second, the concepts of allocating to the most efficient first or for portions up to a certain amount that underlay expansion graphs did not seem easy for non-economists to grasp when I introduced the idea in the first stakeholder meeting.

Criterion 5: Are the decision rules clearly specified? The decision rules were clear from the start. The ACE-HIV project allowed the stakeholders to rank the interventions according to the economic results and then re-rank them according to non-economic factors. No interventions were unable to be ranked in either stage and all were discussed at some length. The stakeholders found the
categories ‘should fund’, ‘could fund’ and ‘don’t fund’ easy to comprehend and functional. At the end of the second meeting there was a clear list with group consensus.

Criterion 6: Is the role of judgement clearly specified? Judgement was clearly expressed throughout the second stage process. The big movers in ranking from the first stage to second stage were early use of antiretrovirals, post-exposure prophylaxis and circumcision. The key factor for the re-ranking of early use of antiretrovirals for treatment and/or prevention was feasibility. It was perceived as a natural extension to current practice that would not require any changes in infrastructure or training and would have been easy to implement immediately. The stakeholders were fairly convinced already by the observational data that ARVs reduced the risk of transmission.

The stakeholders judged that stopping services was harder than starting them. Post-exposure prophylaxis was seen as something that was already happening, so impossible to stop. In this situation, stakeholders feared a backlash from the community and concerns about being sued, if someone who was unable to access a closed NPEP service, subsequently acquired HIV. This kind of barrier to closing or stopping inefficient services is not unique to HIV medicine, but HIV is a disease area that has generally seen expansion of services over the years. The need for beds in wards for AIDS patients has decreased since the introduction of antiretrovirals with dramatic improvements in morbidity and mortality. Some of the existing services have utilised the funds previously earmarked for HIV care that is no longer needed for inpatient care for their other projects and programs, for example the NPEP program in Victoria, rather than assess whether the funds could be spent for more benefit to meet an unmet need elsewhere in the health system. The feasibility and acceptability of circumcision was seen as the biggest challenge for implementation with cultural barriers amongst MSM and a lack of trained staff to perform the procedure.

Criterion 7: Are the data needs tractable? As I did not use the Disease Costs and Impacts Study (DCIS) costs of disease, I needed to conduct the own cost study and develop a cost model. The intervention costs were usually easier to capture, especially with the published data on hospital costs for circumcision and antiretroviral costs through the PBS schedule. The published literature provided data on effectiveness from RCTs and observational cohorts. The disease and surrogate marker progression and improvement data were challenging to incorporate because the studies had covered different populations to Australia or had examined AIDS and mortality in different studies.
It took me three years to complete the whole process, but one year between the stakeholders meeting. I spent time learning to model using different techniques and performing the field studies. A full ACE process could be repeated in a shorter time by someone who had expertise in it, had support for data collection, modelling skills and study implementation. I didn’t perform metanalyses because there were not enough studies to bring together.

Criterion 8: Is the need for due process recognised? A number of stakeholders said that the ACE-HIV project was a refreshing way to do decision-making because there was a clear process that we were following that had been set out from the start. However, during the initial economic ranking process in the second stakeholder meeting, the group found it hard to ignore the second stage filters that they had already formed in their minds. I actually had to remind the group a number of times to try to ignore the second stage filters as we did the initial ranking. But there was a sense that the second stage filters started to creep into their thinking again during the first stage process, particularly the factors of feasibility and equity. Once we started the second-stage filter process, there was a collective sigh of relief that they were able to express their concerns particularly around feasibility.

One stakeholder who was unable to attend the second meeting expressed discontent that economic results were being discussed first. He had been involved previously in another of the ACE projects as a stakeholder. He said that the discussion of economic results first was an inherent bias in the ACE method towards economics taking precedence above other non-economic factors. He suggested that the first and second stages could take place together, rather than being separated artificially. It did appear that this might be a more realistic method reflecting a process of decision-making where all perspectives and values are on the table at once. Other stakeholders reported afterwards that they had felt that the separation was rather contrived and agreed that it did not reflect their usual ways of working.

There was pressure from other directions that could have impacted on the due process of ACE-HIV. As I have mentioned throughout this thesis, ACE-HIV was associated with the ACE-Prevention program of the cost-effectiveness of non-communicable diseases as an infectious disease benchmark. ACE-Prevention covered alcohol, tobacco, physical activity, nutrition body mass, blood pressure/cholesterol, osteoporosis, illicit drugs, cancer, diabetes, kidney disease, mental disorders,
cardiovascular disease, and other prevention. The studies covered 123 preventive interventions and 27 treatment interventions.

The ACE-Prevention report was published using the results soon after the second ACE-HIV stakeholder meeting. I wrote a pamphlet on the ACE-HIV results. The leaders of the project were keen to have a similar style to all the pamphlets that had the effect of emphasising the economic results in the wording, although the second stage filters were mentioned. The changes made in the pamphlet emphasised the economic aspects of the analyses above the second stage filters. The full report of ACE-Prevention (2010) took a similar approach with tables and summaries emphasising the first stage results over the second stage. For example, in Table 0.1 from the executive report(233), interventions were listed that were most cost-effective with the largest population health impact measured in DALYs prevented. Taxation and regulation items topped the list because they didn’t cost anything to implement.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>DALYs prevented</th>
<th>Intervention costs (A$ billion)</th>
<th>Cost offsets (A$ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco tax 30%</td>
<td>270,000</td>
<td>0.02</td>
<td>-0.7</td>
</tr>
<tr>
<td>Alcohol tax 30%</td>
<td>100,000</td>
<td>0.02</td>
<td>-0.5</td>
</tr>
<tr>
<td>Alcoholic volumetric tax 10% above current excise on spirits</td>
<td>110,000</td>
<td>0.02</td>
<td>-0.7</td>
</tr>
<tr>
<td>Unhealthy foods tax 10%</td>
<td>170,000</td>
<td>0.02</td>
<td>-3.5</td>
</tr>
<tr>
<td>Taxation</td>
<td>110,000</td>
<td>0.07</td>
<td>-3.5</td>
</tr>
<tr>
<td>Preventive treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three blood-pressure-lowering drugs to replace current practice of preventive drug treatments</td>
<td>20,000</td>
<td>-1.9</td>
<td>-0.3</td>
</tr>
<tr>
<td>Polypill to replace current practice</td>
<td>50,000</td>
<td>-7.0</td>
<td>-0.8</td>
</tr>
<tr>
<td>Laproscopic gstric banding (body mass index &lt;35)</td>
<td>140,000</td>
<td>1.7</td>
<td>-4.9</td>
</tr>
<tr>
<td>Health promotion</td>
<td>120,000</td>
<td>2.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>Intensive SunSmart</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The economic evaluation analysis results from ACE-HIV were included in a summary table of the main report. On the table 0.2 below, only one of the ACE-HIV interventions was described as cost-saving (NSP), two were very cost-effective (Intertmittent PrEP and Circumcision), three were categorised as not cost-effective because the incremental cost-effectiveness ratio was greater than $50,000/DALY (early use of ARV, NPEP and anal cytology). I was concerned that the second stage filter results were not included in the summary table of all interventions at the back of the main report, (table 0.2)although they had been included in the HIV pamphlet.
I would argue that ACE-HIV maintained due process, as much as was possible, under pressure from the ACE-Prevention project to focus on the first stage filters as being more important than the second-stage filters. The ACE-Prevention report that set out to be more than league tables of cost-effectiveness reverted in the end to a more economic perspective.

Criterion 9: Do the measurement methods demonstrate appropriate rigour? I deviated from the protocol set by the ACE-Prevention program that specified that all the interventions should be modelled with the same model for a number of reasons. I wanted to learn how to perform different types of modelling through the PhD program to understand better the advantages and disadvantages of each. Epidemiology models were hard to model in Tree-Age requiring a special function called state probability that determined the current proportion of people with HIV in the model population at the end of each cycle of the model. Math-lab based models required
collaboration with an expert in the technique. The excel spreadsheets for analysis of the epidemiological model were simple to construct for circumcision but required multiple interlinking files for the outputs from the NSP epidemiology model.

The stakeholders stated during the meeting that they needed to trust that the economic modelling was done correctly as they had no knowledge of economic evaluation methodology. This situation contrasted with their usual technical knowledge and extensive experience with the methods and tools of clinical research studies. They were accustomed to understanding the science behind presentations and being able to challenge a presenter on their methods, but could not do this due to a relative lack of literacy in economic analyses. This potential barrier to their involvement was probably surmounted by their previous experience of me as a clinical researcher that was keen to make sure that studies were performed with rigor to high standards. They did know that I was being supported in my work by a number of experienced economic and epidemiological modellers, which helped their trust in the black box of the models. The inputs and structures of the models were available for their discussions but they chose not to question those during the stakeholder meetings. On the other hand, that could have made them less confident in the economic evaluation skills because they knew that I was a clinician doing economic evaluations to provide another perspective to inform priority-setting as part of a PhD program, not a fully-fledged economist.

Criterion 10: Reporting/implementation. The economic outputs from the ACE-HIV project were provided to the stakeholders in the form that I have described in chapter 4. They appeared to find the simple summary tables most able to be comprehended including the rankings according to different health and economic outcomes.

The economic analysis findings from ACE-HIV were incorporated in the ACE-Prevention program that was published as a report(233). The individual studies were all presented or published in their own right: the circumcision study was published in a peer-reviewed international journal; the economic analysis of needle-syringe programs presented as a report to the Federal Minister of Health and released to the media as part of the public debate on continued funding; the treatment as prevention study was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) ; the pre-exposure prophylaxis analysis to a PrEP workshop organised by the Australian federation of AIDS organisations; and the anal cytology study as a paper at the ASHM conference.
where it contributed to a decision to start a study on the use of digital rectal examination for the
detection of anal neoplasia. In addition the Needle Syringe Program analysis has been used
extensively for advocacy for increased funding both in Australia and overseas.

In summary ACE-HIV could be described as a sound priority-setting exercise with explicit process
for generating options for change; marginal analysis was an integral component; decision rules and
the role of judgement were clearly specified; the need for due process was recognised; and the
rigour was generally adequate. External factors such as data availability and internal needs such as
limited time and a preference to consider biomedical interventions, may have affected the choice
of interventions and hence the process may have been less objective and systematic than in a
perfect world.

6.1.1 Assessment of the usual decision-making in HIV against Carter’s criteria for a sound
priority-setting process

The usual approach to priority-setting in HIV medicine had been a mixture of need and advocacy,
especially during the pre-ARV era. Carter argued that these forms of priority-setting in other
disease-areas had deficits in four of the criteria used in his checklist: a clear concept of benefit, a
process for generating options for change, clear decision rules and marginal analysis(5). The usual
approach to priority-setting in HIV medicine appeared to have similar issues.

The determination of clinical and epidemiological needs was very effective at identifying the need
when HIV first emerged. Community advocacy helped mobilise resources to try to address those
needs. Few other sectors of health in Australia have enjoyed such a successful partnership between
community, medical professionals, government and academics. The partnership helped foster the
rapid introduction of mass education around condoms, needle syringe programs, funding of
community based-organisation, formation of ministerial advisory councils and funding of
specialised and community HIV health services. But when HIV changed from a serious life-
threatening disease that was almost invariably fatal to a chronic manageable disease, the services
and programs that had been developed did not always change easily.

There were no clear decision-rules for changes in services and a lack of marginal analysis to
determine if a reduction or increase in the amount or depth of service might be useful. For
example, services that had been good at providing volunteer terminal care for people dying of AIDS
councils were not necessarily experts in avoiding dependency of clients of housing support services who were no longer dying and had chronic mental health or drug & alcohol issues. They did not know whether to make that support more intensive or withdraw services.

The services changed without a clear concept of benefit or a process for generating options for change. They used freed up resources to fund new services that were not necessarily effective or clearly knew what benefit they were providing. Examples of this included: outreach clinics to areas that were already well served with health services; media advertisements by AIDS councils that appeared to be about promoting the continued existence of the organisation rather than the any health message; hospitals set up programs such as the Victorian NPEP program without explicit consideration of the alternative options for funding. Organisations and health services became very adept at changing to meet the needs of funders or to respond to lobbying by existing clients rather than the needs of the broader community.

In addition to the issues common to many disease areas, priority-setting HIV had suffered from a lack of due process at times, despite the veneer of consultation that the multiple ministerial committees appeared to provide. Decisions were made without due process, to fund interventions such as auto-retractable needles to address the risk of transmission of HIV from discarded needles, despite the lack of evidence of transmission. Recommendations from ministerial advisory councils were ignored or sucked into a never-ending vortex of working groups and bureaucratic review processes that meant that they never reached the light of day again.

The reviews of funding that occurred at the Federal and State levels were set up without clear decision rules and with little due process on the choice of interventions or any options for change. The reporting of these reviews was focused on the technical aspects of the financial side of funding mechanisms, rather than potential increases in the services.

In summary, the usual approaches to priority-setting lacked due process were not performed with clear decision rules nor an acceptance of the role of judgement, did not consider different options for change and were based on reporting that was not clear or transparent.
6.2 Impact of findings from studies on clinical medicine and population health

In this section, I will discuss the broader clinical and population health implications of the findings from the research.

6.2.1.1 Cost

Australian governments had been concerned about the growth in healthcare costs and had tried a number of mechanisms to control them, including increased policing of Medicare claims and reduced claim benefits. The cost study showed that the cost of ARVs was a much greater part of the healthcare costs for people living with HIV than the cost of providing primary or tertiary healthcare. Governments should focus on making sure that ARVs are being used more efficiently to improve health outcomes for the same budget either by encouraging ARV use where they are effective and cost-effective or reducing the cost of ARVs.

My cost study and the economic models suggest ways for a more efficient use of ARVs. First, the early use of ARVs as treatment and prevention model showed that diagnosing and treating everyone with a CD4 cell count less than 500 would be cost-effective, reducing morbidity and decreasing new infections. Treating everyone with a CD4 cell count greater than 500 could be cost-effective, depending on whether most people with HIV have been diagnosed and linked into care. Second, increased government efforts to reduce the total cost of procuring and providing ARVs would be more likely to lead to reduced budget pressures than checking Medicare claims. The government might need to work with clinicians and community to agree a smaller formulary of ARVs with a tendering process for the procurement of standardised first, second or third line regimen. An initiative like this would require political and financial investment in consensus building, education of clinicians and patients, re-engineering of healthcare systems and negotiations with industry. One example of a similar approach has been the London consortium that included a tendering process and a standard model of ARV care. Third, the government could examine the prospects for the removal of less effective or cost-effective medicines from the S100 list. These kinds of initiatives might not immediately reduce costs but they would certainly be a more efficient use of resources.
The high uptake of EPC items within a short period after their introduction showed how resources could be mobilised to address issues through Medicare. GPs caring for people living with HIV were willing to take time to manage complex issues, rather than only see patients for a standard consultation. The relatively high and rapid rate of uptake could also be a function of physician behaviour incentivised by the fee available. Some clinics have software and systems to facilitate the completion of these care plans and may complete them for patients more readily than others.

The cost study data cannot differentiate whether the use of EPC items was associated with better clinical behaviour, nor can it show if clinical outcomes were improved because of it. However, I would argue from professional experience that the impact of EPC items had been to mitigate some of the negative incentive that the standard consultation item numbers and payment created, where a consultation of 6 minutes was paid at the same rate as a consultation of 18 minutes. The incentive against caring for people with complex diseases had led to a number of GPs leaving HIV medicine and shortages of new entrants. Therefore, whether the funds were being applied in a focused way or not, the study shows that GPs working in HIV medicine were using the items. It also suggests that governments can quickly increase funding to primary healthcare using these kinds of items through Medicare Australia, without setting up new funding processes or requiring new organisations to be established.

One key future change, that the cost estimates used in the models ignored, was the recent PBS reforms that have the potential for the introduction of generic ARV to the market from 2012 onwards that will automatically drive down the cost of existing branded versions by 12%-16%, including fixed dose combinations containing one of the agents(406). These cost reductions could affect the cost-effectiveness estimates for some of the models, as the cost implications of acquiring HIV and the cost-offsets associated with preventing acquisition were major factors in the incremental cost-effectiveness ratio. The potential uptake of generic-based regimens is contestable: on one hand, newer branded regimens have fewer adverse-effects and improved long-term toxicities; one the other hand, their efficacy in recent studies have been non-inferior to the drugs like efavirenz that will be generic soon. However, if I assume that the use of generic-based treatment combinations increases, the cost of HIV care would fall. For circumcision and needle-syringe programs, a lower cost of managing HIV would make these interventions less cost-effective. Cheaper treatment regimens would make PrEP less cost-effective unless the cost of PrEP came
down. The patent on the fixed dose combination of tenofovir/emtricitabine will last until the end of this decade, although tenofovir alone may be generic by 2015/16. Early use of ARVs for treatment would become more cost-effective, while the additional incremental benefit of prevention would be less significant. The budget impact of lower cost antiretrovirals would be significant as well.

The high Enhanced Primary Care item claim rate in the Medicare study could be useful for patient advocacy groups and their clinicians to support arguments about the need to maintain funding for primary care programs that address people with chronic diseases. Patients also required mental health plans at a higher rate than the general population supporting the need for continued mental health services, particularly for marginalised groups.

Women with HIV appeared to use MBS-funded services at a lower rate than men with HIV. In the general population, women attend primary care services more frequently than men because of reproductive health needs and gynaecological issues and the reciprocal tendency of men to avoid seeking medical attention for health problems. There are a couple of possible explanations: Women with HIV do not have access to primary care services so easily because they are marginalised, live in areas with doctor shortages or do not have an HIV-friendly GP who is also experienced in seeing women. Gay men with HIV have a number of HIV-friendly GP clinics with male sexual health expertise, with lower cultural barriers to attendance and located close to the neighbourhoods with high proportions of gay men.

The Medicare study had implications for other diseases. The method could be used by researchers interested in other diseases such as Hepatitis C and diabetes mellitus. The HCV viral load could be used to assess the use of GP services by people who are perceived as being marginalised by health services, although it may only capture those that are engaged with the system. The glycosylated haemoglobin item number could be used for diabetes, where specialist care may be delivered through private as well as public clinics.

6.2.2 Utility

The utility study participants had a quality of their life score in relation to health that was 8% lower than that of men of comparable age in general population (232). The continued impact of side-effects of antiretroviral therapy or previous AIDS defining illnesses might explain that finding. There are a number of other non-HIV factors that may be affecting health quality of life in people living
with HIV, including high levels of drug, alcohol and tobacco use and discrimination related to sexuality or injection drug use. Without data from a matched cohort of HIV-uninfected men, one cannot discount an alternative explanation.

The finding of some people with very low scores on AQoL suggests that doctors could try to identify the group of patients who perceive their health quality of life to be very low. While one might assume that poor mental health might contribute to this perception of global handicap, the AQoL covers five other domains of health, including pain, coping, level of independence, social relationships and sensory perceptions. The AQoL is not designed as a clinical screening tool, but there are other quality of life questionnaires and clinical prompts that might be helpful in the clinic as patients experiencing poor health may not be able to communicate easily with their doctor. The study does provide a pointer to a good place to start, as low scores correlated with duration of HIV infection.

On a broader level, did the utility study support the concept of using a generic utility instrument for people with a chronic disease? The AQoL was developed as an instrument for use in all populations but had been implemented in diseases of the elderly such as arthritis. AQoL required some minor changes to be used in a population of people living with HIV, including changes in language about family and activities. The tone of the first questions on suggested physical activities are those of older people, such as gardening, walking, washing, toileting, dressing, eating or looking after appearance. Other questions that talk about communities in local neighbourhoods may not fit with a MSM culture with a mostly non-geographically located community. Three questions at the end on hearing, speech and vision may be more questions about handicap for older people than for people with HIV. There is a question on sexual relations, but nothing on stigma or disclosure of HIV status that may impact on emotional relationships. AQoL scores were correlated with symptom scale scores and utility measured using the SF-12(SF6D). Most significantly for this project, AQoL scores did not relate to CD4 T-cell count or viral load in the multivariate analyses, although this could be a function of the changes in HIV disease, rather than a failing of the instrument.

It could be argued that this study shows that a more HIV specific AQoL should be developed to provide greater sensitivity to HIV disease issues because the CD4 was not significantly correlated in the multivariate analysis. There are two key arguments against the development of a new scale: any new scale would become redundant after a few years as HIV is a complex disease that affects
multiple areas of health and the impact on the health of people living with HIV has changed in scale and scope over time; an HIV-specific AQoL would remove the opportunity to explore the cost-effectiveness of HIV interventions compared to non-HIV interventions. Decision-makers may need quality of life and utility information to allow priority-setting between disease areas.

6.2.3 Impact on clinical care and population health: ACE-HIV project

One of the drivers for this research program was the perception that clinicians were missing out on the opportunity to think about economic analyses because of the way the results can be presented out of context, without the non-economic factors. The research program showed that clinicians, who were amongst the stakeholders, could understand and engage in the ACE-HIV process in a way that they found useful and interesting. The feedback from all the clinicians that were involved was positive with one remarking that it had provided him with a completely different perspective that he would never have considered otherwise.

Although, the ACE-HIV studies were aimed at informing priority-setting exercise that operated at a program or national level, the findings could be helpful to inform clinical practice and guidelines. I will discuss the implications of each of the individual cost-effectiveness analyses.

6.2.3.1 NSP

The NSP economic analysis showed that spending of $27 million per year (total $243m) in NSPs from 2000 to 2009 had resulted in net cost-savings of $1.28bn due to the prevention of HCV and HIV. During the same time period more than 140,000 DALYs would have been saved. Projections that continued the program to 2019 or 2029 suggested that continued substantial savings of costs and gains in years of life would occur for a similar level of funding of NSPs. The majority of savings related to healthcare for HCV, although the program would still have been cost-effective if only HIV disease was considered. Expansion of the program to 150% of the current level with additional spending of $13m per year would have led to further savings of $5.5m per year with evidence of a decreasing marginal return on further spending. Decreased funding from current levels would have been associated with increases in HIV and HCV infections, with associated loss of health and life. The reduced return on investment would exceed any savings associated with reduced spending on NSPs.
While HIV remains low and stable among IDUs in Australia, even relatively minor reductions in current levels of NSP coverage could result in an important increase in incident infections. The situation is more severe for HCV, where the background prevalence is high and increased viral infectivity implies that large control is very unlikely.

If productivity gains associated with the prevention of HCV and HIV were included, $5.85bn of financial savings to society would have occurred from 2000 to 2009 (for every one dollar invested, $27 is returned in healthcare cost savings). If the costs of IRID prevented are included, NSPs could provide additional cost-savings of $20m per year. The costs of secondary HIV and HCV infections prevented would also add 30% more savings from HIV healthcare costs averted and 10% more savings related to HCV costs.

Clinicians are generally supportive of the provision of clean injection equipment at NSPs. The ACE-HIV study reinforces the need to continue and perhaps expand supply. Injection drug users are everywhere and many Australians who have used recreational drugs by injection do not fit the “junkie” stereotype. General practitioners can assist in the process of increasing supply of needles to people who may not be reached by current programs by allowing distribution at their clinics and hospitals by acting as secondary NSP or by allowing a vending machine.

6.2.3.2 Circumcision

Circumcision is a unique biomedical HIV prevention intervention: it is delivered once only, requires no further adherence, cognition or purchases, and is present at every sexual encounter for the lifetime of the individual. But the impact of circumcision was estimated to be low, averting only 2 to 5% of infections in the model. A total of 118 to 338 circumcisions would be needed to prevent one HIV infection; a substantially higher number than the estimated 72 circumcisions required to prevent one HIV infection among African heterosexual men (336).

Globally, circumcision as HIV prevention programs are being targeted at young men, supported by the data from randomised controlled trials in Africa assessing effectiveness (260-262, 336) and cost-effectiveness (407, 408). In the model, circumcision of young men close to sexual debut was the least cost-effective strategy. In Australia, a young gay men circumcision strategy could also involve significant challenges in implementation due to difficulties in identifying young gay men early in their sexual life. Circumcision of men in the age group with the highest incidence of HIV in Australia
(35-44 years) (351) was almost as cost-effective as circumcision of all MSM, with a much smaller initial investment. The study suggested that if circumcision were to be adopted as a public health intervention in Australia, it would be best targeted at this age group.

The scale and effectiveness of a circumcision program could be limited by resource constraints and fiscal burden (409). In Australia adult male circumcision is currently mostly performed by a surgeon as a day case or with an overnight stay. Hospitals had significant waiting lists due to limited human and other resources, especially in regional and remote settings. Primary care practitioners would have required extra training to perform the procedure and funding for higher levels of indemnity insurance. Australian Federal and State governments spent different amounts on HIV prevention and education campaigns but none exceed $10m per year (410). The likelihood they would decide to invest a large amount of money in a single prevention technology was low.

One could argue that a focus on circumcision might also reduce the funding and attention available to other cost-effective prevention, both for HIV and other diseases(411) and might have other negative externalities: the model showed that a 10% decrease in the level of condom use would render the intervention ineffective. However, there was no evidence of disinhibition among participants in the African randomised trials (412).

In the model, I assumed that all members of the MSM population would accept circumcision and would have equal access to health services. However, acceptance of circumcision may be reduced by personal and cultural beliefs, although there is no data from Australian MSM. Men may fear pain from the operation or believe that sexual pleasure is reduced without a foreskin, despite evidence to the contrary on the latter from the African setting. A study from the USA suggested that MSM would consider adult circumcision if it reduced sexual transmission of HIV(413).

The study supported the provision of the intervention but the stakeholders reduced the ranking during the ACE-HIV process because of the cultural and feasibility challenges. Others have advocated for neonatal rather than adult circumcision, since a major change in society would not be required(414). The numbers of people requesting circumcision is likely to be low initially, therefore the health system may be able to slowly adapt to the increased demand. A single technology such as circumcision is unlikely to be effective in a complex epidemic; combinations of new and classical health promotion actions are likely to be needed(346).
6.2.3.3 NPEP

In the context of limited resources that could be used elsewhere for other benefits, it would have seemed prudent to target and/or reserve NPEP for unprotected receptive anal sex. The advice for men with lower risks would be to prioritise education and counselling for future risk reduction, perhaps with counselling or psychological therapy. The risk of litigation that featured in the ACE-HIV second stage discussions suggested that it might be difficult for clinicians to stop providing any NPEP, so this compromise may be more acceptable.

6.2.3.4 PREP

Despite the potential population benefit, the budgetary costs of a large PrEP program could be too high at current ARV prices, over $400m a year and are very unlikely to be affordable for the healthcare system. Cheaper PrEP would obviously reduce the budget. Other than the obvious reason of reduced profits, pharmaceutical companies may not be keen to reduced prices for PrEP because it may lead to pressure to reduce them for antiretroviral therapy for people with HIV. This risk might be mitigated by the government agreeing to price ARVs differently by indication or by price-volume deals that may allow a decreased cost of goods with greater volume of production. One pharmaceutical company has applied to the US FDA for registration of this indication, but the likely pricing and access in Australia is not clear yet.

It is not clear if the net reduction in bone mineral density (1%) seen after 24 weeks in one of the PrEP studies using tenofovir/emtricitabine will translate into a clinical effect and longer term follow-up will be needed. Although, the participants did start with low bone mineral density, 7% more participants experienced greater than 5% bone mineral density loss at the femoral neck in the tenofovir versus placebo groups (p = 0.13) (360). The impact of bone mineral density changes and renal dysfunction on the risk-benefit ratio for the use of antiretrovirals would be different for HIV negative compared to HIV positive people.

6.2.3.5 Early use of ARV

Early use of antiretrovirals for the treatment of an individual patient must depend on the clinical, virological and immunological situation and will be informed in the long run by data from strategy studies like the START study. But in situations where the decision is not clear or marginal, the early
use of ARVs may have some added prevention value especially in situations where there is a discordant couple or where the patient does not appear to be using condoms for all sexual acts.

The population health impacts beyond fewer new infections should not be forgotten. The communities affected by HIV but with a lower community viral load may gain value from the reassurance that the risk of transmission to between serodiscordant partners is reduced and so discrimination against HIV positive people may be lessened.

6.2.3.6 Anal cytology

Performing anal cytology on HIV patients as a routine would require a significant amount of resources and training for few cases of anal cancer detected and treated earlier, and the resources may be better used performing a regular digital rectal examination or helping patients to stop smoking. Digital rectal examination was more likely to be cost-effective or even cost-saving, because it was a technique that all doctors could perform and the model assumed that it would lead to the detection of smaller and more treatable anal cancers earlier.

6.2.4 Impact of findings on economic modeling for HIV

In all three research projects in this thesis, there were findings that suggest that the previous approaches to modelling HIV may need to be updated. In the cost study, I showed that the cost of ARVs dominated costs from hospital admission or Medicare claims. In the utility study, there was no correlation between utility scores on either instrument and CD4 T-cell count. In ACE-HIV, the cost and cost-offsets related to antiretrovirals were the greatest drivers of the cost-effectiveness models.

Economic models for HIV treatment may need to be rebuilt, to move away a framework for modelling that reflects a different era of HIV disease and outcomes. As the efficacy and tolerability of ARVs improves, clinical researchers have argued that new goals for interventions for HIV need to be set, including reduction in immune activation, treatment of virus in sanctuary sites, lower viral load levels etc (415). These outcomes may not be captured in the standard economic models of HIV, nor will the utility gain associated with better treatments if most people are well. These gains may be small relative to the impact of HIV on other parts of an individual’s life such as stigma, discrimination, fear of disclosure and relationship issues.
Modelling HIV may need to change therefore. It could become more complex with the use of utility weights for each health problem in a population living with HIV including mental health, stigma and discrimination, physical health and adverse-effects. Or it could become simpler, with the use of 1 or 2 utility or disability weights: for someone with HIV without clinical disease; someone with a current serious non-AIDS event or AIDS event or even simpler, with a single weight for people living with HIV more generally. In chapter 5, I showed that the ACE-HIV models were relatively insensitive to the value of the quality-adjusted or disability-adjusted weights. The recommendation would be to use the simplest approach in models that will be driven by ARV cost and mortality and only consider using more detailed utility weights for interventions around mental health or other HIV associated condition. In treatment models that compare two antiretroviral first line combinations, the greatest value is often represented in the delay of use of more expensive regimens due to efficacy, resistance and adherence, rather than the impact of small differences in adverse effects on quality of life or utilisation of healthcare resources.

Reimbursement agencies prefer to see both generic and disease-specific patient-reported outcome measures to allow decision-making across interventions for different diseases(174). The impacts of living with HIV today may not be captured in generic quality of life or utility instruments because few other diseases are so associated with social factors such as discrimination. Many industry studies use the short utility questionnaires that may be fairly insensitive to small changes in quality of life (202, 416). Symptom distress scales, that are more sensitive to changes in quality of life, may not be able to be converted to utility weights(220). HIV specific scales have become outdated as the impact of the clinical disease changes(197).

6.2.5 Implications of findings on transferability and generalisability of findings from elsewhere.

The ACE-HIV project supported the argument that the results from international studies cannot always be transferred to the Australian environment. If the stakeholder group had been provided with the results from the analyses of the cost-effectiveness of circumcision in Sub-Saharan Africa(408), the group might have come to the conclusion that a program for circumcision would be relatively cheap and would be definitely cost-saving, however it was implemented. If we had used the previously published analysis of anal cytology that used data from one centre in the USA(99), we might have based a conclusion on inputs that suggested unrealistic rates of anal cancer. If we had adopted the findings of early use of treatment as prevention from British Columbia(51), where
the impact of the intervention was greater because existing rates of ARV uptake were only 50% and clean needles were not widely available, we could have assumed that early use of ARV was cost-saving and a very worthwhile investment. All these examples support the notion that, not only all cost-effectiveness, but also all priority-setting, is local or at least national.

6.3 Future research

A future expanded ACE-HIV project could be performed more efficiently by avoiding some of the challenges that I experienced during the research program and building on some of the learnings from this program.

ACE-HIV covered only six of a possible 17 interventions that I identified during the literature search. Time and resource issues were the most important factors in this decision but also the evidence required for modelling interventions. If I had more time or human resource to perform the modelling, it could have been informative to look at more of the classic interventions for prevention of HIV including mass and narrow media awareness campaigns, condom distribution and education, and community development for marginalised communities affected by HIV. Other topics that were becoming more topical were control of sexually transmissible infections as HIV prevention, interventions in remote and regional Indigenous communities, earlier diagnosis and management of HIV for people from a culturally and linguistically diverse background, appropriate screening for non-AIDS cancers, drug/alcohol/tobacco issues.

One idea for a future project might include all interventions for blood borne viruses including Hepatitis C as well as sexually transmissible infections (STIs). Australian governments had often seen the similarities rather than the differences between these diseases over the past 15-20 years and brought together advisory panels that covered all three in one committee. But clinicians and communities could often see that the differences were greater than the similarities, with only limited cross-over between the populations, interventions and outcomes. The stakeholder pane for an ACE-BBV and STIs would suffer from the same increase in numbers and dilution of focus that the ministerial advisory councils had experienced. However, beyond populations and interventions such as injection drug users and NSP, in general, it may be better to model Hepatitis C and STIs separately to HIV. The colleagues and I identified that it could be useful to perform an ACE-STI and managed to be successful for an NHMRC project grant on the topic that is currently underway. An
ACE-Hepatitis C project could be very useful to help identify the most effective and efficient ways to organise services for the large numbers of people living with Hepatitis C who cannot be serviced by existing tertiary-based services.

During the past decade, HIV funding has been under pressure from the disappearance of ring-fenced funding, with the move towards mainstreamed services typical of other chronic manageable diseases. HIV had a small burden of disease relative to non-communicable diseases related to tobacco use, obesity and lack of exercise. The inclusion of ACE-HIV in programs like ACE-Prevention helped demonstrate the continuing value of prevention and treatment of HIV, relative to other disease areas, using metrics that were becoming more widely accepted and understood in population health. While the study had limitations, this may have been the greatest value of the ACE-HIV project to stakeholders, as at least HIV was represented at the table. A relatively small disease such as HIV in Australia may be overlooked compared to the burden of diabetes and heart disease. The HIV sector has lost the power of the disease that AIDS disease had always provided and community advocacy has became more nuanced and complex. It could be worth repeating or extending an ACE-like process to help continue to provide relevant information about the value of current and future interventions.

There are a number of ways that a larger ACE-HIV process could be quicker in the future: avoid performing a detailed utility study, adapting the cost estimates from chapter 3 and use a single model for all interventions that was a linked agent-based prevention and treatment model.

The Medicare study results raise a series of questions that may require further study around mental health and the use of enhanced primary items, particularly in terms of the drivers and benefits of the use of enhanced primary care and mental health items in HIV.
6.4 Final conclusions

I have demonstrated in this thesis that the ACE approach could be a sound and valuable approach for priority-setting in HIV medicine in Australia and that the data required for the economic evaluations could be gathered from existing databases and cohorts.

The research program provided extensive evidence including:

1. The successful application of the ACE method using a series of economic evaluations and a stakeholder process;

2. A database study of Medicare Australia claims to measure the use and cost of healthcare for 10,951 people living with HIV;

3. A field-based sub-study in an existing ongoing cohort study that used a generic Australian health outcomes instrument for the first time;

4. Six economic evaluation analyses that examined interventions for the prevention and treatment of HIV.
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### Appendix A  EURONHEED questionnaire

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<td></td>
</tr>
<tr>
<td>E6. Are the side-effects or adverse effects addressed in the analysis?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1. Do the authors specify any summary benefit measure(s) used in the economic analysis?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2. Do the authors report the basic method of valuation of health states or interventions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3. Do the authors specify the source(s) of health states (e.g.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Transferability Questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>P</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT1. Is the intervention described in sufficient detail?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT2. Is (are) the comparator(s) described in sufficient details?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE2. Is (are) the country (ies) in which the economic study took place clearly specified?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1. Did the authors correctly state which perspective they adopted for the economic analysis?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP1. Is the target population of the health technology clearly stated by the authors or when it is not done can it be inferred by reading the article?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SP3. Does the article provide sufficient detail about the study sample(s)?

E5. Have the principal estimates of effectiveness measures been reported?

E7. Does the article provide the results of a statistical analysis of the effectiveness results?

B5. Is the level of reporting of benefit data adequate (incremental analysis, statistical analyses)?

C1. Are the cost components/items used in the economic analysis presented?

C5. Are unit prices for resources given?

C6. Are costs and quantities reported separately?

C7. Is the price year given?

C9. Is the currency unit reported?

S1. Are quantitative and/or descriptive analysis conducted to explore variability from place to place?

O1. Did the authors discuss caveats regarding the generalisability of their results?

“Each question in the checklist had four possible responses for the assessor to select. To facilitate the calculation of a percentage score, the responses were given the following scores: 1 for “Yes”, 0.5 for “Partial” and 0 for “No/No information”. “No information” was penalised to the same level as “No,” since the provision of the relevant information was considered to be essential for the assessment of the transferability of study results. When the response to a question was “N/A”, the question was excluded from the scoring by reducing the denominator accordingly. A summary (percentage) score was therefore derived using the following formula:

\[ \text{Summary score (\%)} = \frac{1}{n - x} \sum_{i} S_i \times 100 \]

where \( i = 1, \ldots, n \), ‘\( n \)’ is the number of questions, ‘\( x \)’ is the number of questions for which the response was N/A and ‘\( S \)’ is the score of each question.” (Reference Nixon(21))
Appendix B Instruments used in Chapter 3
FAHI instrument

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some -what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP1 I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP2 I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP3 Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP4 I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP5 I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP6 I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP7 I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>BMT6 I get tired easily</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HI7 I feel fatigued</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HI12 I feel weak all over</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

<table>
<thead>
<tr>
<th>EMOTIONAL WELL-BEING/ LIVING WITH HIV</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some -what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE1 I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE4 I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE5 I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE6 I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th></th>
<th>FUNCTIONAL AND GLOBAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some -what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>I am unhappy with my appearance</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2</td>
<td>It is hard to tell other people about my infection</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H4</td>
<td>I worry about spreading my infection</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td>I am concerned about what the future holds for me</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B7</td>
<td>I worry about the effect of stress on my illness</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H10</td>
<td>I am embarrassed by my illness</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>SOCIAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some-what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS1 I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS2 I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS3 I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS4 My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS5 I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS6 I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HI3 I have people to help me if I need it</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Q1 Regardless of your current level of sexual activity, please answer the</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>following question. If you prefer not to answer please tick this box, it, please</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>check this box And go to the next section</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS7 I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>COGNITIVE FUNCTIONING</td>
<td>Not at all</td>
<td>A little bit</td>
<td>Some-what</td>
<td>Quite a bit</td>
<td>Very much</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>------------</td>
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<td>-----------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>L1 My thinking is clear</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H18 I have trouble concentrating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H19 I have trouble remembering things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Thank you for completing this form. Now please complete the second form.
Assessment of Quality of Life Instrument II (AQoL)

This survey asks about questions that may or may not be relevant to your health. You answer the questions by ticking the box next to the response that best fits your situation.

Q1 How much help do I need with household tasks (e.g. preparing food, cleaning the house, or gardening):
- I can do all these tasks very quickly and efficiently without any help
- I can do these tasks relatively easily without help
- I can do these tasks only very slowly without help
- I cannot do most of these tasks unless I have help
- I cannot do any of these tasks by myself.

Q2 Thinking about how easy or difficult it is for me to get around by myself outside my house (e.g. shopping, visiting):
- Getting around is enjoyable and easy
- I have no difficulty getting around outside my house
- A little difficulty
- Moderate difficulty
- A lot of difficulty
- I cannot get around unless somebody is there to help me.

Q3 Thinking about how well I can walk:
- I find walking or running very easy
- I have no real difficulty with walking or running
- I find walking or running slightly difficult. I cannot run to catch a tram or train, I find walking uphill difficult
- Walking is difficult for me. I walk short distances only, I have difficulty walking upstairs
- I have great difficulty walking. I cannot walk without a walking stick or frame, or someone to help me
- I am bedridden.

Q4 Thinking about washing myself, toileting, dressing, eating or looking after my appearance:
- These tasks are very easy for me
- I have no real difficulty in carrying out these tasks
- I find some of these tasks difficult, but I manage to do them on my own
- Many of these tasks are difficult, and I need help to do them
- I cannot do these tasks by myself at all.

Q5 My close and intimate relationships (including any sexual relationships) make me:
- Very happy
- Generally happy
- Neither happy nor unhappy
- Generally unhappy
- Very unhappy

Q6 Thinking about my health and my relationship with my friendship group or family:
- My role with my friendship group or family is unaffected by my health
- There are some parts of my role in my friendship group or family I cannot carry out
- There are many parts of my role in my friendship group or family I cannot carry out
- I cannot carry out any part of my role in friendship group or family.

Q7 Thinking about my health and my role in my community (that is to say local neighbourhood, sporting groups, work, cultural groups or religious groups):
- My role in the community is unaffected by my health
☐ there are some parts of my community role I cannot carry out
☐ there are many parts of my community role I cannot carry out
☐ I cannot carry out any part of my community role.

Q8 How often did I feel in despair over the last seven days?
☐ never
☐ occasionally
☐ sometimes
☐ often
☐ all the time.

Q9 And still thinking about the last seven days: how often did I feel worried:
☐ never
☐ occasionally
☐ sometimes
☐ often
☐ all the time.

Q10 How often do I feel sad?
☐ never
☐ rarely
☐ some of the time
☐ usually
☐ nearly all the time.

Q11 When I think about whether I am calm and tranquil or agitated:
☐ always calm and tranquil
☐ usually calm and tranquil
☐ sometimes calm and tranquil, sometimes agitated
☐ usually agitated
☐ always agitated.

Q12 Thinking about how much energy I have to do the things I want to do, I am:
☐ always full of energy
☐ usually full of energy
☐ occasionally energetic
☐ usually tired and lacking energy
☐ always tired and lacking energy.

Q13 How often do I feel in control of my life?
☐ always
☐ mostly
☐ sometimes
☐ only occasionally
☐ never.

Q14 How much do I feel I can cope with life’s problems?
☐ completely
☐ mostly
☐ partly
☐ very little
☐ not at all.
Q15 Thinking about how often I experience serious pain. I experience it:
- very rarely
- less than once a week
- three to four times a week
- most of the time.

Q16 How much pain or discomfort do I experience:
- none at all
- I have moderate pain
- I suffer from severe pain
- I suffer unbearable pain.

Q17 How often does pain interfere with my usual activities?
- never
- rarely
- sometimes
- often
- always

Q18 Thinking about my vision (using my glasses or contact lenses if needed):
- I have excellent sight
- I see normally
- I have some difficulty focusing on things, or I do not see them sharply. E.g. smallprint, a newspaper or seeing objects in the distance.
- I have a lot of difficulty seeing things. My vision is blurred. I can see just enough to get by with.
- I only see general shapes. I need a guide to move around
- I am completely blind.

Q19 Thinking about my hearing (using my hearing aid if needed):
- I have excellent hearing
- I hear normally
- I have some difficulty hearing or I do not hear clearly. I have trouble hearing softly spoken people or when there is background noise.
- I have difficulty hearing things clearly. Often I do not understand what is said. I usually do not take part in conversations because I cannot hear what is said.
- I hear very little indeed. I cannot fully understand loud voices speaking directly to me.
- I am completely deaf.

Q20 When I communicate with others, e.g. by talking, listening, writing or signing:
- I have no trouble speaking to them or understanding what they are saying
- I have some difficulty being understood by people who do not know me. I have no trouble understanding what others are saying to me.
- I am understood only by people who know me well. I have great trouble understanding what others are saying to me.
- I cannot adequately communicate with others.

Thank you for your time.
Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ☐ in the one box that best describes your answer.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a  Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>b  Climbing several flights of stairs</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
</tbody>
</table>
3. **During the past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Accomplished less than you would like</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b Were limited in the kind of work or other activities</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. **During the past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Accomplished less than you would like</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b Did work or other activities less carefully than usual</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. **During the past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
</table>
7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Have you felt calm and peaceful?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>b. Did you have a lot of energy?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>c. Have you felt downhearted and depressed?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
Cost-Effectiveness of Adult Circumcision in a Resource-Rich Setting for HIV Prevention among Men Who Have Sex with Men

Jonathan Anderson, David Wilson, David J. Templeton, Andrew Grulich, Robert Carter, and John Kaldor

1National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Darlinghurst, 2Sexual Health Department, Royal Prince Alfred Hospital, Sydney, and 3Deakin Health Economics, Deakin University, Melbourne, Australia

Background. We examined the effects and cost-effectiveness of 4 strategies of circumcision in a resource-rich setting (Australia) in a population of men who have sex with men (MSM).

Method. We created a dynamic mathematical transmission model and performed an economic analysis to estimate the costs, outcomes, and cost-effectiveness of different strategies, compared with those of the status quo. Strategies included circumcision of all MSM at age 18 years, circumcision of all MSM aged 35–44 years, circumcision of all insertive MSM aged ≥18 years, and circumcision of all MSM aged ≥18 years. All costs are reported in US dollars, with a cost-effectiveness threshold of $42,000 per quality-adjusted life-year.

Results. We find that 2%–5% of human immunodeficiency virus (HIV) infections would be averted per year, with initial costs ranging from $3.6 million to $95.1 million, depending on the strategy. The number of circumcisions needed to prevent 1 HIV infection would range from 118 through 338. Circumcision of predominately insertive MSM would save $21.7 million over 25 years with a $62.2 million investment. Strategies to circumcise 100% of all MSM and to circumcise MSM aged 35–44 years would be cost-effective; the latter would require a smaller investment. The least cost-effective approach is circumcision of young MSM close to their sexual debut. Results are very sensitive to assumptions about the cost of circumcision, the efficacy of circumcision, sexual preferences, and behavioral disinhibition.

Conclusions. Circumcision of adult MSM may be cost-effective in this resource-rich setting. However, the intervention costs are high relative to the costs spent on other HIV prevention programs.

The incidence of human immunodeficiency virus (HIV) infection among men who have sex with men (MSM) has been increasing in many high-income countries, including Australia, over the past decade [1]. The increase in HIV infections has prompted interest in new prevention technologies, along with renewed interest in prevention and education programs.

Adult male circumcision has been shown to be effective for the prevention of HIV acquisition in 3 randomized trials among heterosexual men in Southern and Eastern Africa [2–4]. A meta-analysis of observational data on the effect of circumcision among MSM revealed insufficient recent evidence that male circumcision protects against HIV infection or other sexually transmitted infections, but this meta-analysis did report an association between circumcision and protection against HIV infection in studies of MSM that were conducted before the introduction of highly active antiretroviral therapy [5]. In 2008, a study of a large Australian community-based cohort reported a statistically significantly reduced risk of HIV seroconversion among circumcised MSM who predominantly took the insertive role in anal intercourse, with an 85% reduction in the acquisition of HIV among predominately insertive MSM and a 95% certainty that the true value was between 20% and 97% [6].

Cost-effectiveness models for Southern and Eastern
Africa have suggested that circumcision is cost-effective [7–9]. However, there have been no economic evaluations of the value of adult male circumcision for the prevention of HIV infection in resource-rich countries that have a relatively high baseline prevalence of circumcision and an HIV epidemic affecting mainly MSM. On the other hand, the popularity of pediatric circumcision has been steadily declining in Australia, from rates of 80% in the 1960s to <10% in the past decade, and hence the prevalence of circumcision among adults has also been decreasing [10].

This study aimed to model the potential costs and benefits, compared with the status quo, of implementing an adult male circumcision program for the prevention of HIV infection among Australian MSM. We also aim to consider the efficiency of targeting intervention to different groups of MSM in the event of budgetary constraints. Finally, we explored the impacts of potential changes in behavior on these estimates.

**METHODS**

Four main strategies of coverage are considered for implementation of circumcision; these are compared with the status quo or no specific intervention, which is defined as neonatal circumcision that continues at the current rate. The strategies are labeled as follows: (1) sexual debut, which is defined as circumcision of all uncircumcised MSM at age 18, because this approach is being adopted in African circumcision programs; (2) 35–44-year-olds, which is defined as circumcision of all uncircumcised MSM aged 35–44 years in the first year of the program and on entry to the age range thereafter, because this group has the highest incidence of HIV infection in Australia [1] (their baseline circumcision prevalence is 70% [10]); (3) insertive, which is defined as circumcision of all MSM aged ≥18 years who are predominately insertive in their sexual behavior, because circumcision is likely to have the greatest effect in this group; and (4) all MSM, which is defined as circumcision of all MSM aged ≥18 years. Each strategy is assumed to start with an intensive phase during the first year in which all men in the target group are circumcised and then to continue with an ongoing program to maintain circumcision rates for individuals entering the targeted age group each year.

We used a dynamic population-level mathematical transmission model composed of mathematical differential equations developed, implemented, and solved with Matlab software (MathWorks) to estimate the number of new HIV infections over a 25-year period starting in 2008 for each strategy in a hypothetical population of 180,000 MSM in Australia [11] (Figure 1). The data on the number of new infections and circumcisions are included in an economic analysis of costs and benefits that was performed from the perspective of the government as a third-party payer. The discounting of costs and outcomes (3%) is consistent with the policy set by the Panel on Cost-Effectiveness in Health and Medicine [12]. Costs are reported in US dollars (2007 prices) with purchasing power parity of 1.43 Australian dollars equal to 1 US dollar [13].

Our model includes data from previous studies of MSM in Australia on age-specific circumcision status (range, 50% for MSM aged 18–25 years to 83% for MSM aged ≥45 years) [10, 14–16] and HIV prevalence (range, 0.5% for MSM aged 18–25 years to 18% for MSM aged ≥45 years) [11]; probability of HIV acquisition and transmission for different sexual acts (0.008 for receptive anal sex and 0.0008 for insertive anal sex) [17–19]; frequency of sexual acts (125 acts per man per year)
Table 1. Parameters and Values Used in the Mathematical Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Sensitivity, %</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>180,000</td>
<td>...</td>
<td>[11]</td>
</tr>
<tr>
<td>Effectiveness of circumcision in prevention of HIV acquisition among insertive men, %</td>
<td>60</td>
<td>43–80</td>
<td>[2–4, 32]</td>
</tr>
<tr>
<td>Age-specific baseline circumcision status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25-Year-olds</td>
<td>50.3</td>
<td>...</td>
<td>[10, 14–16]</td>
</tr>
<tr>
<td>25–34-Year-olds</td>
<td>59.3</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>35–44-Year-olds</td>
<td>69.5</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>≥45-Year-olds</td>
<td>82.6</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>HIV infection prevalence, %</td>
<td></td>
<td></td>
<td>[11]</td>
</tr>
<tr>
<td>&lt;25-Year-olds</td>
<td>0.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>25–34-Year-olds</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>35–44-Year-olds</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>≥45-Year-olds</td>
<td>18</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Probability of acquisition</td>
<td></td>
<td></td>
<td>[17–19]</td>
</tr>
<tr>
<td>Insertive anal</td>
<td>0.0008</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Receptive anal</td>
<td>0.008</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Frequency of sexual acts, acts/man/year</td>
<td>125</td>
<td>...</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>Condom usage, %</td>
<td>65</td>
<td>70</td>
<td>[22, 23]</td>
</tr>
<tr>
<td>Condom efficacy, %</td>
<td>90</td>
<td>95</td>
<td>[24, 25]</td>
</tr>
<tr>
<td>Use and impact of ART on infectiousness, %</td>
<td></td>
<td></td>
<td>[22, 26–29]</td>
</tr>
<tr>
<td>HIV-infected MSM on ART</td>
<td>70–75</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>MSM on ART who achieve viral suppression</td>
<td>80</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Reduction in infectiousness if viral suppression is achieved</td>
<td>95</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Strategic positioning and role preference, %</td>
<td></td>
<td></td>
<td>[6, 30]</td>
</tr>
<tr>
<td>Insertive only</td>
<td>33</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Receptive only</td>
<td>10</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Insertive and receptive</td>
<td>57</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Cost of HIV management (discounted)</td>
<td>$342,916</td>
<td>$171,328–$513,986</td>
<td>[38]</td>
</tr>
<tr>
<td>Cost of intervention circumcision</td>
<td>$1,767</td>
<td>$883–$2,365</td>
<td>[36–38]</td>
</tr>
<tr>
<td>Utility loss due to HIV, QALYs (discounted)</td>
<td>7.5</td>
<td>...</td>
<td>[40]</td>
</tr>
<tr>
<td>Discount rate, %</td>
<td>3</td>
<td>0–5</td>
<td>[12]</td>
</tr>
</tbody>
</table>

**NOTE.** Results of the sensitivity analyses are given as percentages except where otherwise indicated. Costs are given in US dollars. QALY, quality-adjusted life-year.

Circumcision is assumed to have an effectiveness of 60%, on the basis of data from 3 randomized controlled trials among heterosexual men in Southern and Eastern Africa [2–4], with sensitivity analyses for a range from 40% to 80% to illustrate the impact of our assumption and the results of a published meta-analysis [32]. The putative direct benefit of circumcision would be only to men practicing insertive sex. In the Health in Men cohort, reported sexual behaviors correlated well with the initial declared preference [6]. Input values, ranges, and sources are reported in Table 1. Costs are reported in Table 2.
then \( \beta_i = (1 - \varepsilon_i) \beta^\alpha_i \). We define the probability of HIV acquisition per unprotected penetrative receptive penile-anal act to be \( \beta_p \), for both circumcised and uncircumcised men. We assume that condoms have a protective effectiveness of \( \varepsilon_i \) for both insertive and receptive penile-anal sex and for both circumcised and uncircumcised men, which leads to a probability of transmission of \((1 - \varepsilon_p) \beta_p \) if a condom is used. If HIV-negative MSM have an average of \( n \) penetrative penile-anal acts per year, and if condoms are used in a proportion \( p^\prime \) of receptive acts and \( p^\prime\prime \) of receptive acts, then the probability that a circumcised man (in age group \( k \)) who practices both insertive and receptive penile-anal sex will acquire HIV each year is

\[
\lambda^c_k = \sum_j p^\prime \left[ 1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p \right] \\
\times (1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p),
\]

where \( p^\prime \) represents the proportion of all acts that are receptive. The probability that an uncircumcised man (in age group \( k \)) who practices both insertive and receptive penile-anal sex will acquire HIV each year is

\[
\lambda^u_k = \sum_j p^\prime \left[ 1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p \right] \\
\times (1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p),
\]

In both cases, \( p_j \) denotes the prevalence of HIV infection in sexual partners of age group \( j \), and we use the standard binomial modeling formula [33, 34], adjusted to include the different protection options. For men who practice only receptive sex, the probability of HIV acquisition each year is

\[
\lambda^c_k = \sum_j p^\prime \left[ 1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p \right] \\
\times (1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p),
\]

and the probability of HIV acquisition per year for men who practice only insertive sex is

\[
\lambda^u_k = \sum_j p^\prime\prime \left[ 1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p \right] \\
\times (1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p),
\]

for circumcised men and

\[
\lambda^u_k = \sum_j p^\prime \left[ 1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p \right] \\
\times (1 - \beta_{ij}^\alpha (1 - \varepsilon_p) \beta_p (1 - \varepsilon_i) \beta^\alpha_p),
\]

for uncircumcised men.

If \( \alpha_k \) is the proportion of men in age group \( k \) who are circumcised and \( N_k \) is the number of men in age group \( k \), then the expected average number of HIV infections in year \( t \) is

\[
I(t) = \sum_k \alpha_k N_k (1 - p_j) \lambda_k^c + q_j \lambda_k^u + (1 - q_j \lambda_k^u) \\
+ | 1 - \alpha_k N_k (1 - p_j) \lambda_k^c + q_j \lambda_k^u + (1 - q_j \lambda_k^u) |
\]

where \( q_j \) is the proportion of men who engage only in insertive
Circumcision for HIV Prevention in MSM

Figure 2. Expected number of human immunodeficiency virus (HIV) infections per year among Australian men who have sex with men (MSM), according to our population-level mathematical transmission model, for the status quo (no intervention) and for strategies of circumcising 100% of MSM prior to sexual debut, circumcising 100% of 35–44-year-old (yo) MSM, circumcising 100% of MSM who practice only insertive penile-anal sex, and circumcising all MSM. Curves show mean trajectories of 1000 model simulations.

Figure 3. Number of circumcisions needed to prevent 1 human immunodeficiency virus infection for the strategies targeting men who have sex with men (MSM) prior to sexual debut, 35–44-year-old (yo) MSM, MSM who practice insertive penile-anal sex, and all MSM.

sex and $q_k$ is the proportion of men who engage only in receptive sex (thus, $1 - q_i - q_k$ is the proportion of MSM who practice both insertive and receptive sex).

The prevalence of circumcision among Australian men is nonuniformly distributed across age groups, as presented in Table 1 [16]. Because the distribution of circumcision rates is age dependent, the distribution of circumcision with age will change each year. The proportion of men in age group $k$ who are circumcised is adjusted each year according to the formula:

$$\alpha_i(t + 1) = \frac{\Delta t_k - 1}{\Delta t_k} \alpha_i(t) + \frac{N_i - 1}{N_i \Delta t_k - 1} \alpha_i(t) + \alpha_i(t)$$

where $\Delta t_k$ is the “length” in years of age group $k$ and $\alpha_i(t)$ represents specific intervention circumcisions in year $t$ to age group $k$. All parameter values used in our mathematical model are presented in Table 1.

Interventions based on focused circumcisions are simulated, and the outputs from the model include the number of HIV infections over time for each strategy. A detailed uncertainty analysis is performed for each strategy, whereby all input parameters are specified over a plausible range, and 1000 sets of parameter values are sampled and used in 1000 model simulations, producing a range of possible values for all outcome variables.

The population model was developed using inputs relevant to the Australian setting. To assess the outputs of the model, we compare the number of HIV infections in the first year of the model with Australian national surveillance data of HIV infection diagnoses in the year 2007. Although diagnosis may lag infection by a number of years, MSM in Australia have good access to free testing, so this assumption is likely to be reasonable, especially because the proportion of undiagnosed HIV infections has been estimated to be relatively low [35].

The economic analyses are performed using Excel software (Microsoft). Inputs include the number of circumcisions; the number of HIV infections for each strategy (from the transmission model); the cost of circumcision, including the cost of the operation [36] and the cost of medical visits for adverse-effect management and prevention counseling [37, 38], which are all derived from published cost estimates; the lifetime cost of management of HIV infection (discounted at 3%) [39]; and the lifetime loss of quality-adjusted life-years (QALYs) due to HIV infection (discounted at 3%) [40]. In the analysis, each incident HIV infection accrued a QALY loss and the cost of...
HIV care; both cost and QALY loss are discounted amounts that are discounted again at the time in the model that the infection is assumed to occur. The time horizon of the economic analysis is 25 years in 1-year cycles.

The costs (intervention and disease-related costs) and outcomes (HIV infections and QALYs) are estimated and the incremental cost-effectiveness ratios (ICER) are calculated by comparing the net costs and net outcomes of each strategy with the status quo. We assume that a strategy is cost-effective compared with the status quo when the ICER is <\$42,000 (equivalent to A$60,000) per QALY gained, which is a shadow price used in a government-published economic analysis of public-sector interventions, including HIV-related interventions [41].

For each strategy, we entered the 95% CIs for the number of HIV infections from the results of the population model into the Excel spreadsheet used for the economic analyses and then ran 2000 simulations and compared them with the status quo by means of the @Risk software program (Palisade). We report 95% CIs and probabilities that the ICER will be less than the cost-effectiveness threshold of \$42,000 per QALY or <0, and simulations with a loss of QALYs counted as dominated.

We performed 1-way sensitivity analyses to account for other important model assumptions and uncertainties in the input parameters, including the impact of risk disinhibition. For variables without a range of published estimates, the ranges for the sensitivity analyses represent our judgement of the variations likely to be encountered in the implementation of the intervention. In the baseline analysis, we included the costs of the management of postoperative complications of circumcision; in a sensitivity analysis, we also included a 10% loss of quality of life in a 4-week postoperative period, which was extrapolated from the literature on quality of life in men with erectile dysfunction [42]. We also explored the inclusion of program costs such as marketing, administration, monitoring, and evaluation.

RESULTS

Over the 25-year period of the population model and compared with the status quo, there were 241 (1.4%) fewer infections with the strategy of ensuring that all MSM are circumcised prior to sexual debut (sexual debut strategy), 318 (1.8%) fewer infections with the strategy of circumcising all men in the 35–44-year-old age group (35–44-year-olds), 363 (2.0%) fewer infections in the strategy of circumcising men who practice predominantly insertive penile-anal sex (insertive strategy), and 655 (3.7%) fewer infections in the strategy of circumcising all MSM (all MSM strategy). Our model indicates that, after 25 years, 3%–5% of HIV infections per year would be averted (Figure 2). In the insertive strategy, 118 circumcisions would be required to prevent 1 HIV infection, and in the all MSM strategy, 338 of the circumcisions would prevent 1 HIV infection (Figure 3). We found that 10–27 quality-adjusted days (undiscounted) would be gained per circumcision performed, depending on the strategy. The expected change in incidence due to any of the intervention circumcisions is relatively modest, and thus the overall prevalence was not found to change substantially over 25 years as a result of circumcision (a maximum change of 0.15% in absolute prevalence).

Circumcision and medical costs for the first year of the intervention would be \$3.6 million for the sexual debut strategy, \$20.6 million for the strategy targeting 35–44-year-old MSM, \$33.3 million for the strategy targeting insertive MSM, and \$95.1 million for the all MSM strategy. Once the initial startup phase had passed, the yearly costs would range from \$2.0 million to \$5.5 million.

The insertive strategy would save \$21.7 million over 25 years, compared with the status quo, for an overall investment of \$62.2 million (discounted), with 2% likelihood that it would not be cost-saving and a 0.4% likelihood of not being cost-effective. All other strategies would be cost-effective with an ICER of <\$42,000 (A$60,000) per QALY gained (Table 3), with 1% likelihood that the all MSM strategy would not be cost-effective, but with a 3.6% and 25% likelihood that the 35–44 year old and sexual debut strategies, respectively, would not be cost-effective. The insertive strategy was cost-effective after 7 years of the model, whereas the sexual debut strategy proceeded for 21 years until becoming cost-effective. The total investment over 25 years for the 35–44 year old strategy would be \$83.9

<table>
<thead>
<tr>
<th>Strategy</th>
<th>HIV infections averted(a)</th>
<th>QALYs gained(a)</th>
<th>Incremental cost, US$(a)</th>
<th>Incremental cost per QALY gained, US$</th>
<th>Upper 95% confidence limit, US$/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual debut</td>
<td>146</td>
<td>1093</td>
<td>29,332,093</td>
<td>26,841</td>
<td>94,991</td>
</tr>
<tr>
<td>35–44-Year-olds</td>
<td>204</td>
<td>1527</td>
<td>14,335,127</td>
<td>9,390</td>
<td>44,332</td>
</tr>
<tr>
<td>Insertive</td>
<td>246</td>
<td>1845</td>
<td>21,761,545</td>
<td>Cost-saving</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>All MSM</td>
<td>444</td>
<td>3328</td>
<td>25,760,458</td>
<td>7,741</td>
<td>18,224</td>
</tr>
</tbody>
</table>

NOTE. Costs are given in US dollars. HIV, human immunodeficiency virus; MSM, men who have sex with men; QALY, quality-adjusted life-year.

\(a\) Discounted.
million (discounted), and that for the all MSM strategy would be $177.6 million.

If men who have been circumcised as part of the intervention reduce their use of condoms by 10%, then none of the interventions are effective, and therefore, none could be cost-effective. If only 80% of all MSM are circumcised, the intervention costs $14,700 per QALY, and if 90% of all MSM are circumcised, the intervention costs $9,000 per QALY.

The results of sensitivity analyses of cost and discounting are presented in Figure 4 for the all MSM strategy. The results are similar for the other strategies (not shown). The model is most sensitive to the effectiveness of circumcision, the proportion of predominately insertive men, and the costs of circumcision and of the management of HIV infection: the intervention is cost-saving for all strategies if circumcision is 50% cheaper, it remains cost-effective for 3 of the 4 strategies if the cost doubles due to program and marketing costs, and it would remain cost-effective in most scenarios if HIV infection in Australia cost 50% less than the baseline assumption. The ICER is less affected by the discount rate. If men being circumcised have a temporary loss of quality of life, then there is little effect on cost-effectiveness (Figure 4).

DISCUSSION

This study explores the cost-effectiveness of circumcision as a technology to prevent HIV infection in MSM in a resource-rich setting. Our model suggests that a range of different strategies to implement circumcision could be cost-effective or cost-saving as an intervention to prevent the spread of HIV among MSM. The investment required for a circumcision program would be considerable for its limited impact on the epidemic.

However, the effectiveness of circumcision could be nullified if it leads to increases in risk behavior, which is a plausible outcome.

An estimated one-third of the MSM in Sydney predominantly take the insertive role in anal intercourse [6]. Circumcision of predominately insertive MSM would save $21.7 million over 25 years with a $62.2 million investment. However, our model assumes that the sexual preferences of MSM would remain stable over 25 years. This assumption is contestable, because sexual behavior and preference may depend on emotions, setting, partnership dynamics, age, and culture and hence be fluid in the long run.

Globally, circumcision programs to prevent HIV infection are being targeted at young men, on the basis of data from randomized controlled trials in Africa on effectiveness [2–4, 32] and cost-effectiveness [7, 8]. In our model, circumcision of young men close to sexual debut was the least cost-effective strategy. The implementation of the sexual debut strategy could also pose significant challenges because of difficulties in identifying large numbers of young MSM early in their sexual lives. Circumcision of men in the age group with the highest incidence of HIV infection in Australia (35–44 years old) [1] was almost as cost-effective as circumcision of all MSM, but the former strategy involved a much smaller initial investment. If circumcision were to be adopted as a public health intervention in Australia, our study suggests that the intervention would be best targeted at this age group.

The scale and effectiveness of a circumcision program could be limited by resource constraints and fiscal burden [43]. In Australia, adult male circumcision is currently usually performed by a surgeon as a day case or with an overnight hospital stay.
stay. Hospitals have significantly long waiting lists because of limited human and other resources, especially in regional and remote settings. Primary care practitioners would require extra training to perform the procedure and funding for higher levels of indemnity insurance. Australian federal and state governments spend different amounts of money on HIV prevention and education campaigns, but none exceed $7 million per year [44]. The likelihood that governments would decide to invest a large amount of money in a single prevention technology is low.

One could argue that a focus on circumcision might also reduce the funding and attention that is available to other cost-effective programs to prevent the spread both of HIV and of other diseases [45] and might have other negative externalities. For example, our model showed that a 10% decrease in the level of condom use would render the intervention ineffective. However, there was no evidence of disinhibition among participants in the African randomized trials [46].

Circumcision is a unique prevention intervention: it is delivered only once; requires no further adherence, cognition, or purchases; and is present at every sexual encounter for the lifetime of the individual. But the impact of circumcision was estimated to be low in the population of MSM; circumcision averted only 2%–5% of HIV infections in our model. Prevention of 1 HIV infection would require 118–338 circumcisions, a substantially higher number than the estimated 72 circumcisions required to prevent 1 HIV infection among African heterosexual men [32].

In our model, we assumed that all members of the population would accept circumcision and would have equal access to health services. However, acceptance of circumcision may be reduced by personal and cultural beliefs. Although there are no data on Australian MSM, a study from the United States suggested that MSM would consider adult circumcision if it reduced sexual transmission of HIV [47]. Men may believe that sexual pleasure is reduced without a foreskin, despite evidence to the contrary from the African setting.

The analyses of the uncertainty related to the population model inputs suggest that there is only a 75% likelihood that a strategy of circumcising young MSM would be cost-effective, although there was less uncertainty about the cost-effectiveness of a strategy of circumcising all MSM. Lower levels of coverage for the all MSM strategy would still be cost-effective and would have smaller initial budget impacts. The 1-way sensitivity analyses also demonstrate that the results are very sensitive to assumptions about the effectiveness of circumcision, the proportion of men who are predominately insertive, and the costs of circumcision and HIV-related health care.

Our study had a number of limitations. First, models are only approximations of the real world, and simplifying assumptions must be made. For example, there are no data available on the degree of assortative-disassortive mixing across age groups; we used estimates consistent with a recent modeling study that estimated mixing patterns across age groups of Australian MSM [31]. Second, we used the efficacy of circumcision that was determined from the randomized controlled trials involving heterosexual men in Southern and Eastern Africa [2–4]. However, this estimate fell within the CIs of the estimated reduction of HIV risk that was conferred by circumcision in a large prospective study involving MSM [6]. Third, we used estimates of the discounted QALYs lost and of the costs associated with a lifetime of HIV infection, but these were derived and valued in the United States, which has a health system that is very different from the health system in Australia [40]. However, the cost estimates used in our model were consistent with the costs of HIV-related health care that were derived using an activity-based approach with local costs and data in an Australian economic evaluation of needle and syringe programs [48]. Finally, we did not consider the potential additional benefits associated with circumcision in the reduction of other sexually transmitted infections, which may have underestimated the potential benefits.

In conclusion, our study is the first cost-effectiveness analysis of adult male circumcision among MSM and uses data from rigorously conducted studies in the population. We showed that circumcision could be cost-effective and even cost-saving for a range of implementation strategies. However, the investment required would be considerable, and the impact on the overall epidemic would be limited. In addition, if a perception of being protected from HIV led to increased HIV risk behavior, then the effectiveness of the intervention could easily be overcome. In such a setting, it is not inconceivable that the intervention could lead to an increase rather than a decrease in new HIV infections. A single technology such as circumcision is unlikely to be effective in a complex epidemic; combinations of new and classical health promotion actions are likely to be needed [49].

Acknowledgments
The National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, is funded by the Australian Government Department of Health and Ageing.

References


25. Begley E, Jafa K, Voetsch A, Heffelfinger J, Sullivan P. Willingness of


1. MAIN MESSAGES
   • Needle syringe programs should continue and could be increased.
   • Continuation of funding of non-occupational post-exposure prophylaxis could be considered if targeted to men having sex with men (MSM) after receptive anal sex, rather than all potential exposures.
   • Circumcision of MSM is recommended but could lead to large upfront costs if all eligible men are circumcised and there may be significant cultural and social barriers to overcome.
   • Pre-exposure prophylaxis taken intermittently is recommended for implementation subject to evidence from studies.
   • Early use of antiretrovirals (ARVs) would not be recommended at current prices and uncertainty exists surrounding their effect on infectiousness.
   • Anal cytology screening is cost-ineffective compared to annual digital rectal screening for anal cancers.

2. BACKGROUND

Huge improvements in the outlook for people living with HIV have taken place since the introduction of highly active antiretroviral medications with most people expected to live a near-normal lifespan. Previous estimates have suggested that HIV prevention was cost-saving and treatment of HIV, cost-effective. But rising rates of HIV infection have brought into question the effectiveness and cost-effectiveness of current prevention programs and new biomedical approaches for prevention have been studied.

3. INTERVENTIONS

We reviewed the literature on prevention and treatment. An expert panel of stakeholders including community, government, medical, and academic representatives chose six interventions for evaluation from the 17 options presented on the basis that they were on the policy agenda; represented a mix of classic and new prevention technologies and healthcare; had data to inform the modelling; and could be brought together into a doctoral research program. Unless otherwise stated, the interventions were targeted at MSM in Australia.
DESCRIPTION OF INTERVENTIONS

a) **Needle Syringe Programs**: sterile needles and syringes are provided through needle syringe programs (NSP) at no or low cost as well as advice on injection behaviour, safe sex and referral to other services. Injection drug users were the target population.

b) **Adult male circumcision**: would be a program to circumcise men having sex with men (MSM) to prevent HIV acquisition. Four target groups were compared: young MSM; MSM aged 35-44 years (highest incidence of HIV acquisition); insertive MSM; and all MSM.

c) **Non-occupational post-exposure prophylaxis**: provision of one month supply of 2-3 antiretroviral medicines to MSM with a recent potential high-risk sexual exposure to HIV.

d) **Pre-exposure prophylaxis**: two antiretrovirals taken by HIV negative MSM with high sexual risk behaviour as well as prevention counselling and medical monitoring. Pre-exposure prophylaxis could be taken continuously or intermittently.

e) **Early use of antiretrovirals for treatment and/or prevention**: initiation of ARVs in all patients with HIV regardless of CD4 T-cell count.

f) **Anal cytology screening for anal intraepithelial neoplasia**: annual anal cytology in HIV+ MSM using liquid based cytology and follow-up of high grade cytology by high resolution anoscopy with biopsy and treatment of lesions with topical therapies. We also considered a program of annual digital rectal examination (DRE) to detect early anal cancers.

4. **COMPARATOR**

   The status-quo was the comparator for all interventions except the NSP where a hypothetical situation where no program was in place applied.

5. **RESULTS**

   Needle-syringe programs were cost-saving at current levels (Table 1) and there would be increased healthcare cost-savings if the funding and provision of sterile injection equipment were increased by 50-75% compared to current levels of funding. Decreased funding would be associated with greater decreases in health care cost-offsets than would be saved in program costs.

   Adult male circumcision would be cost-saving if targeted to men who predominantly are the insertive partner in anal sex; it is likely to be cost-effective if implemented for all men but there would be high program costs, especially initially; programs for young men would have a significant likelihood of not being cost-effective.

   Pre-exposure prophylaxis could have a big impact on incidence and prevalence of HIV in men having sex with men but at high budget costs at current antiretroviral prices and uncertain cost-effectiveness.

   Post-exposure prophylaxis, as currently provided in Australia, is not cost-effective, with a very limited impact on HIV incidence. If targeted to HIV negative men having unprotected receptive anal sex only, the incremental cost-effectiveness ratio is below $50,000/ DALY.

   Early use of antiretrovirals as treatment alone would not be cost-effective but the inclusion of the benefits of prevention would have an impact on the incremental cost-effectiveness ratio, mainly by additional healthcare cost-offsets related to fewer HIV infections.

   Anal cytology screening may be cost-effective compared to no program but has very significant uncertainty surrounding the incremental cost-effectiveness ratio. However digital rectal examination is cost-saving and/or cost-effective compared to no program.
Table 1: Health impact, costs and incremental cost-effectiveness ratios for six HIV interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Health impact (95% CI or interquartile range-IQR)</th>
<th>Annual budget</th>
<th>ICER</th>
<th>ICER (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle Syringe Programs</td>
<td>75,000 HIV infections (IQR 41,000-84,000) 190,000 HCV infections (IQR 185,000-206,000) prevented</td>
<td>$24m</td>
<td>Cost-saving</td>
<td>$2.3bn (IQR $1.7-$4.0bn)</td>
</tr>
<tr>
<td>Circumcision</td>
<td>240 to 650 HIV infections prevented 1.4%-3.7% of expected incidence 1,800 to 4,900 DALYs</td>
<td>Initial $5m to $140m Ongoing $3m to $5m</td>
<td>$8,900/DALY</td>
<td>cost-saving to $45,000 to $22,000</td>
</tr>
<tr>
<td>Pre-exposure prophylaxis</td>
<td>HIV prevalence could fall to 6.8% over 20 years vs rise to 14% with no program. 95,000 DALYs (55,000 to 160,000)</td>
<td>$420m</td>
<td>$46,000/DALY</td>
<td>$24,000 to $69,000</td>
</tr>
<tr>
<td>Post-exposure prophylaxis</td>
<td>3 HIV infections prevented per year 540 DALYs (430 to 660)</td>
<td>$3m-$5m</td>
<td>$190,000/DALY</td>
<td>$170,000 to $210,000</td>
</tr>
<tr>
<td>Early Rx alone</td>
<td>11,000 DALYs (3,600 to 20,000)</td>
<td>$40m</td>
<td>$140,000/DALY</td>
<td>$65,000 to $350,000</td>
</tr>
<tr>
<td>Early Rx with prevention effect</td>
<td>12,000 DALYs ($400-14,000) including Rx and prevention</td>
<td>$40m</td>
<td>$59,000/DALY</td>
<td>cost-saving to $143,000</td>
</tr>
<tr>
<td>Anal cytology</td>
<td>2000 (0 to 14,000 )</td>
<td>Cytology $5m</td>
<td>Cost-saving to $37,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology $5m</td>
<td>Cost-saving to $330,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology $5m</td>
<td>Cost-saving to $700,000</td>
<td></td>
</tr>
</tbody>
</table>

In addition to the technical economic evaluation (cost-effectiveness analysis) the steering committee discussed and evaluated other considerations that effect implementation of options for change. These are presented in Tables 2 and 3 demonstrating the reasons often provided for changes to decisions when setting priorities in health. Acceptability to stakeholders is often paramount in these discussions.

Table 2: The stakeholders ranked the interventions after the economic analyses.

<table>
<thead>
<tr>
<th>Decision</th>
<th>Intervention</th>
<th>Main reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should fund</td>
<td>Needle Syringe Programs Pre-exposure prophylaxis</td>
<td>Cost-saving Impact on epidemic</td>
</tr>
<tr>
<td>Could fund</td>
<td>Circumcision Early use of treatment as prevention</td>
<td>Potentially cost-saving May be cost-effective if prevention effect within plausible limits</td>
</tr>
<tr>
<td>Don’t fund</td>
<td>Early use of treatment Non-occupational post-exposure prophylaxis</td>
<td>Not likely to be cost-effective Not good value for money Lack of evidence</td>
</tr>
</tbody>
</table>
6. **ABOUT ACE-PREVENTION**

To aid priority setting in prevention, the Assessing Cost-Effectiveness in Prevention Project (ACE-Prevention) applies standardised evaluation methods to assess the cost-effectiveness of 100 to 150 preventive interventions, taking a health sector perspective. This information is intended to help decision makers move resources from less efficient current practices to more efficient preventive action resulting in greater health gain for the same outlay.

For more information on this topic area, please visit website [www.sph.uq.edu.au/bodce-ace-prevention](http://www.sph.uq.edu.au/bodce-ace-prevention)

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### PAMPHLETS IN THIS SERIES

**Methods:**
A. The ACE-Prevention project  
B. ACE approach to priority setting  
C. Key assumptions underlying the economic analysis  
D. Interpretation of ACE-Prevention cost-effectiveness results  
E. Indigenous Health Service Delivery

**Overall results**
1. League table  
2. Combined effects

**Indigenous population results**
1. Cardiovascular disease prevention  
2. Diabetes prevention  
3. Screening and early treatment of chronic kidney disease

**General population results**
1. Adult depression  
2. Alcohol  
3. Blood pressure and cholesterol lowering  
4. Cannabis  
5. Cervical cancer screening, Sunsmart and PSA screening  
6. Childhood mental disorders  
7. Fruit and vegetables  
8. HIV  
9. Obesity  
10. Osteoporosis  
11. Physical activity  
12. Pre diabetes screening  
13. Psychosis  
14. Renal replacement therapy, screening and early treatment of chronic kidney disease  
15. Salt  
16. Suicide prevention  
17. Tobacco
<table>
<thead>
<tr>
<th>Acronyms and abbreviations</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-HIV</td>
<td>Assessing Cost-Effectiveness in HIV Project</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>AIN</td>
<td>Anal Intraepithelial Neoplasia</td>
</tr>
<tr>
<td>AQoL</td>
<td>Assessing Quality of Life Instrument</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>CD4</td>
<td>Cluster of Differentiation #4 T-cells</td>
</tr>
<tr>
<td>CEPAC</td>
<td>Cost-effectiveness of Preventing AIDS Complications</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-Adjusted Life Years</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
</tr>
<tr>
<td>EURONHEED</td>
<td>European Network of Health Economics Evaluation Database</td>
</tr>
<tr>
<td>GART</td>
<td>Genotype assisted resistance testing</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HPTN052</td>
<td>HIV Prevention Treatment Network study 52</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papilloma Virus</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost-Effectiveness Ratio</td>
</tr>
<tr>
<td>IDU</td>
<td>Injection Drug Users</td>
</tr>
<tr>
<td>IPrEx</td>
<td>Pre-exposure Prophylaxis Initiative</td>
</tr>
<tr>
<td>LYG</td>
<td>Life Years Gained</td>
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<td>MBS</td>
<td>Medicare Benefits Schedule</td>
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<tr>
<td>MSAC</td>
<td>Medical Services Advisory Committee</td>
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<tr>
<td>MSM</td>
<td>Men Having sex with men</td>
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<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside Reverse Transcription Inhibitors</td>
</tr>
<tr>
<td>NPEP</td>
<td>Non-occupational post-exposure prophylaxis</td>
</tr>
<tr>
<td>NPV</td>
<td>Net Present Value</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcription Inhibitors</td>
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<td>NSP</td>
<td>Needle-syringe programs</td>
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<td>p24</td>
<td>Protein #24</td>
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<td>PBAC</td>
<td>Pharmaceutical Benefits Advisory Committee</td>
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<td>PEP</td>
<td>Post-exposure prophylaxis</td>
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<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
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<tr>
<td>PrEP</td>
<td>Pre-exposure prophylaxis</td>
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<td>QALY</td>
<td>Quality-Adjusted Life Years</td>
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<tr>
<td>SF-12</td>
<td>Medical Outcomes Survey Short-form 12</td>
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<tr>
<td>SF-36</td>
<td>Medical Outcomes Survey Short-form 36</td>
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<tr>
<td>SF6D</td>
<td>Utility score derived from Short-Form 12</td>
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