Human Immunodeficiency Virus Testing and Linkage-to-Care in South Africa: an Epidemiological and Economic Evaluation of Expansion

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by
Michael D. April

St. Edmund Hall

Department of Public Health
University of Oxford
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Disclaimers

This thesis cites a previous review of the literature on human immunodeficiency virus (HIV) testing in sub-Saharan Africa. I wrote and submitted this review as my dissertation for the MSc in Global Health Science at Oxford University in 2006. These citations are made to justify various claims made in Chapter 2 of this thesis regarding previous research on HIV testing in Africa. Additionally, although the specifics have since evolved, the terminology used in the dissertation served as the basis for the testing policy definitions in this thesis. Finally, although again much evolved, the analytic framework used in this thesis to conceive of HIV testing as a series of steps (the 'HIV testing cascade') was first presented in the MSc dissertation.

This thesis also uses the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) simulation model. This model was constructed by the CEPAC collaborators primarily based at Massachusetts General Hospital in Boston. I made no contribution to the model's structure, which is discussed in detail in Appendix A. I also made no contribution to the collection or analysis of the data I use to inform its parameters unrelated to HIV testing, a summary of which is presented in Appendix B. Rather, the original contribution of this thesis presented in its main text is the use of CEPAC to evaluate the cost-effectiveness of expanded HIV testing in South Africa. I specifically collected testing data to serve as inputs for those CEPAC parameters describing the HIV testing process. I also constructed a supplementary model to simplify conversion of these data into CEPAC parameter inputs for evaluation of policies including test protocols designed to detect acute HIV infection (AHI).

Abstract

This thesis evaluates the cost-effectiveness of eight policies expanding human immunodeficiency virus (HIV) testing in South Africa. All policies entail provider-initiated test offers for primary healthcare users and one of two options across three policy components: (i) consent method, opt-in or opt-out; (ii) test protocol, rapid only or rapid plus acute infection testing; and (iii) linkage-to-care, standard or enhanced.

This thesis highlights four methodological issues. First is the challenge of conducting a population-level analysis, projecting the cost-effectiveness of expanded testing for each member of South Africa's adult African population. To this end, I conducted a retrospective, descriptive study to measure current population-level testing rates and epidemic descriptors in an African community near Cape Town, South Africa. Second, the effects of testing expansion on current testing uptake were estimated by distinguishing testing in the study community likely to cease after testing expansion (baseline testing) from that likely to continue (background testing). Third, because testing alone is an outcome of less interest than health benefits following treatment, study community linkage-to-care probabilities were estimated and models utilized to estimate the efficacy of treatment. Fourth, the methods to convert the study community testing data into inputs for these models' parameters are outlined.

The enhanced linkage-to-care policies proved the most cost-effective, with opt-in testing and a rapid-only test protocol the least expensive cost-effective option at $848 per life year gained (LYG). Adding an opt-out consent method or acute infection test protocol to this policy increased the LYGs, but at higher cost-effectiveness ratios.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

3TC: lamivudine

AHI: acute HIV infection

AHIT: Acute HIV Infection Testing (computer model)

AIDS: acquired immune deficiency syndrome

ANC: antenatal care

ART: antiretroviral treatment

ASSA: Actuarial Society of South Africa

AZT: zidovudine

CBA: cost-benefit analysis

CDC: Centers for Disease Control and Prevention

CEA: cost-effectiveness analysis

CEPAC: Cost-Effectiveness of Preventing AIDS Complications (computer model)

CMA: cost-minimization analysis

CTAC: Cape Town AIDS Cohort

CUA: cost-utility analysis

DALY: disability-adjusted life year

DTHF: Desmond Tutu HIV Foundation

ELISA: enzyme-linked immunosorbent assay

GDP: gross domestic product

GNI: gross national income

HCW: healthcare worker

HIV: human immunodeficiency virus

HSRC: Human Sciences Research Council

ICER: incremental cost-effectiveness ratio

ISPOR: International Society of Pharmacoeconomics and Outcomes Research

IVDU: intravenous drug user

LPV/r: lopinavir/ritonavir

LYG: life year gained

MAC: mycobacterium avium complex

MSF: Medicins Sans Frontieres

MSM: men who have sex with men

NGO: non-governmental organization

NICE: National Institute of Clinical Excellence

NNRTI: non-nucleoside reverse transcriptase inhibitor

NRTI: nucleoside reverse transcriptase inhibitor

NVP: nevirapine

OI: opportunistic infection

PCP: pneumnocystis carinii pneumonia

PCR: polymerase chain reaction

PEPFAR: President's Emergency Plan for AIDS Relief

PI: protease inhibitor

PMTCT: prevention of mother-to-child transmission of HIV

PPP: purchasing power parity

PSA: probabilistic sensitivity analysis

QALY: quality-adjusted life year

RCT: randomized controlled trial

SADoH: South Africa Department of Health

UK: United Kingdom

UNAIDS: Joint United Nations Programme on HIV/AIDS

USA: United States of America

USD: United States Dollar

VCT: voluntary counselling and testing

VL: viral load

WB: Western blot

WHO: World Health Organization

ZAR: South African Rand

Chapter 1: Introduction

1.1 Background

1.1.1 HIV testing policy

Human immunodeficiency virus (HIV) testing policy worldwide has traditionally required most patients to request testing. This passive approach to case detection is a legacy of the initial public health response to HIV in low-prevalence Western settings during the 1980s when no treatment options existed.[1] However, recent years have seen the advent of effective treatments for HIV-infected persons, namely antiretroviral treatment (ART),[2-4] together with global campaigns to increase the availability of these treatments in resource-poor settings.[5-7] As a result, the HIV testing policy discourse has transitioned to address how best to identify HIV-infected individuals and link them to treatment and care.

In May 2007, years of calls for more aggressive HIV testing policies[1,8-10] culminated in the release of the World Health Organization's (WHO) new screening guidelines. The WHO guidelines specifically support routine test offers for all adult healthcare users in high-prevalence (antenatal prevalence >1%) settings, and testing all test offer recipients unless they explicitly opt-out.[11] These guidelines are especially relevant for South Africa, now believed to be the country with the largest number of HIV infections in the world.[12] However, there is as yet no evidence base quantifying the effects of expanded screening policies on the cost-effectiveness of HIV testing programs in resource-poor, high-prevalence settings.

This thesis examines the cost-effectiveness of implementing in South Africa eight variations of provider-initiated testing policies for the adult African population.[*] Each of these policies adopts one of two approaches across three policy decisions: (i) consent method, (ii) test protocol, and (iii) approach to linkage-to-care. To this end, this thesis first presents a retrospective, descriptive study of current testing rates among an adult African population in the absence of expanded screening. Next, it uses a combination of secondary sources and empirical data to project the impact of each of the expanded screening policies on this current uptake. Finally, it uses these projections combined with secondary data on costs, natural history, and treatment efficacy to inform a previously published microsimulation model. This modelling approach then estimates the incremental cost-effectiveness of the eight provider-initiated testing programs compared to current testing practice.

1.1.2 Methodological issues

This thesis also focuses on four specific methodological issues related to evaluating the cost-effectiveness of expanded HIV testing. The first issue concerns the fact that testing alone is an outcome of limited interest. More interesting is the extent to which testing reduces medical costs, prevents disease transmission, or increases health benefits through earlier case detection. Of course, not all cases identified through screening subsequently receive linkage-to-care. Therefore, this thesis adopts an analytic framework conceiving of HIV testing as a cascade of steps through which patients must pass to realize treatment benefits.

[*] South Africa's government categorizes its citizens into four races as a matter of convention: (i) Whites: descendents of Dutch or British settlers or other European ancestors; (ii) Asians: descendents of Indians and other Asians imported to Natal during the 1860s as indentured laborers; (iii) Coloureds: persons of mixed ancestry, most commonly that of Whites and Khoikhoi Africans; and (iv) Africans or blacks: descendents of the original Bantu-speaking inhabitants of the territory comprising modern-day South Africa.[13] This thesis uses the term 'African' to refer to this latter group. The focus on this group is primiarly due to its especially high HIV prevalence and incidence (see Subsection 2.2).

The second issue relates to the first, the decision to focus on ultimate health outcomes of testing necessitating simulation of disease progression and care. Such simulation is complicated given the explosion of HIV research in recent years.[14] Indeed, increasingly complex and sophisticated models are necessary to reflect the current body of knowledge on HIV pathogenesis and treatment. This thesis circumvents the need to build such a model by using the previously-constructed Cost-Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation. CEPAC's extensive data demands raise the issue of how best to convert empirical data into model parameter inputs. This thesis simplifies these conversions through various assumptions and an Excel-based CEPAC supplement I constructed, the Acute HIV Infection Testing (AHIT) model.

The third methodological issue concerns the treatment of current testing. This issue is salient in estimating the incremental costs and effects of expanded testing policies compared to current practice. Current testing and linkage-to-care rates are approximated in this thesis through the aforementioned retrospective, descriptive study. However, because some of this testing would likely cease to occur if testing were expanded, the empirical testing observations are further distinguished between baseline and background tests. Baseline tests are assumed no longer to occur if expanded testing policies are implemented. Conversely, background tests are assumed to remain regardless of the overarching testing policy in effect.

The final major methodological issue addressed concerns the estimation of the costs and effects of expanded testing for each member of South Africa's adult African population. This population-level approach to economic evaluation provides more information than the more common practice of measuring intervention costs and

effects for solely those individuals utilizing the program. However, conducting such an analysis also requires estimating population-level testing and clinical outcome data. These measurements were also obtained through the retrospective descriptive study of a relatively enclosed and well-defined adult African population.

1.2 Thesis overview

1.2.1 Research questions

This thesis uses the results of the aforementioned epidemiological and economic evaluations to address the following research questions:

1. What are the current rates of HIV testing and linkage-to-care among South Africa's adult African population in the absence of expanded screening?
2. How effective would alternative policies expanding testing and linkage-to-care among primary healthcare users be in increasing these rates?
3. How cost-effective would these alternative policies be for the adult African population of South Africa compared to current testing practice?

In answering these questions, this thesis will also explore the four methodological issues outlined above.

1.2.2 Thesis structure

The thesis begins by providing background information on HIV testing in *Chapter 2*. It summarizes the testing technologies currently available and the history of HIV testing policy both worldwide and in South Africa. It then describes current testing practice, providing definitions to distinguish background from baseline testing, and

the eight expanded testing policies considered in this thesis. Finally, it presents the HIV testing cascade, the analytic framework used by this thesis to portray testing as a series of steps for the entire population. The discussion focuses on the application of the policy definitions and cascade framework to the economic evaluation conducted and to the methodological issues addressed in this thesis.

Chapter 3 then outlines the role of economic evaluation in medical decision making. It introduces the concepts and guidelines for conducting economic evaluations, with emphasis on those guidelines most relevant to an evaluation of HIV testing in a developing country (e.g., South Africa). Particular attention is paid to guidelines for choosing (i) health outcomes of interest; (ii) modelling approaches; (iii) comparators representing current practice; and (iv) study populations. The chapter concludes by discussing how the guidelines considered informed the methodological decisions made in this thesis regarding these four issues.

Next, *Chapter 4* reviews the economic literature on HIV testing, including studies from both low- and high-prevalence settings. It provides an overview of the methodologies and findings of this literature. This overview summarizes previous approaches to selecting testing outcomes of interest; modelling screening interventions; accounting for current testing; and choosing study populations. The chapter concludes by discussing how the literature influenced selection of both the research questions and methodological approaches adopted in this thesis.

Chapter 5 addresses the first thesis research question, reporting the results of the retrospective descriptive epidemiological study of HIV testing in an adult African community near Cape Town, South Africa. The population's enclosure makes it

possible to derive from the study results population-level statistics. These include current population rates of passage through the HIV testing cascade steps and distributions for selected clinical outcomes. Trends in these rates and outcomes are examined as is the extent to which current population testing is occurring through baseline versus background mechanisms.

In *Chapter 6*, the second thesis research question is addressed. The population impact of the eight expanded testing policies on adult Africans' throughput for the HIV testing cascade are estimated using data from the epidemiological study and from secondary sources. These projections account for both baseline and background testing. The methods underlying these projections were further designed to simplify their subsequent use with the CEPAC model.

The third research question is addressed in *Chapter 7*. It explains in greater detail the specific modelling approach adopted. It also outlines the methods used to convert the empirical and secondary testing data cited in Chapters 5-6 into CEPAC parameter inputs, facilitated by use of the AHIT model. CEPAC's simulation of testing, treatment, and disease progression then translates these data describing testing and linkage-to-care throughput into a more final health outcome measure, life years gained (LYGs). Given the use of population-level data inputs, the evaluation results are therefore expressed as costs and LYGs per member of South Africa's adult African population for each of the eight expanded testing policies. The chapter concludes with a discussion of the differential impact of various testing policy decisions on cost-effectiveness, results of sensitivity analyses, and implications of the findings for testing policy in South Africa.

Finally, *Chapter 8* summarizes the findings of the thesis. It reconsiders the three research questions and discusses the extent to which they have been answered. It further considers the implications of the four major methodological issues encountered for the study results. Based upon the thesis findings, it makes recommendations for HIV testing policy in South Africa. It concludes by discussing remaining gaps in knowledge regarding the economics of expanded HIV testing and the role for future research to inform further testing policy in South Africa.

Chapter 2:
HIV testing background, policy options, and analytic framework

The aims of this chapter are threefold. The first is to provide a background to human immunodeficiency virus (HIV) testing. The second is to describe and justify focusing upon those eight policies compared in this thesis for expanding testing among South Africa's adult African population. These descriptions encompass a discussion of current testing practice, to include the distinction drawn in this thesis between baseline and background testing. The third aim is to present the 'HIV testing cascade' analytic framework I constructed. The cascade portrays testing as a series of steps through which clients must pass to achieve health gains from linkage-to-care. The discussion considers further the reasoning behind the cascade structure, including focus on population final testing outcomes and converting empirical testing data into screening model parameter inputs.

2.1 Background to HIV testing

The objective of this section is to provide a general background to HIV testing. It begins with an overview of the current scope of the HIV pandemic, with focus on South Africa's epidemic. It then outlines the basics of HIV pathogenesis. Next, it describes the most commonly available HIV testing technologies. Finally, it summarizes the histories of testing policies in industrialized nations, where most testing policies were first implemented, and in South Africa.

2.1.1 The HIV pandemic

Clinical manifestations of HIV infection were first recognized among men who have sex with men (MSM) in Los Angeles during 1981.[15] Since then, the epidemic has expanded ceaselessly. In 2007, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that 33.2 million people worldwide were living with HIV, 2.5 million became newly infected, and 2.1 million died of HIV-related causes. These numbers are substantially lower than those from recent years due to changes in the methodologies underlying UNAIDS's estimates. Nevertheless, these estimates reflect a public health disaster, particularly in sub-Saharan Africa where an estimated 68% of all HIV-infected individuals worldwide lived and 76% of HIV-associated deaths occurred in 2007.[12]

South Africa's epidemic is especially alarming. UNAIDS now believes this country to have the largest number of HIV infections in the world.[12] Although recent seroprevalence surveys among South African antenatal care (ANC) users suggests HIV prevalence may be levelling off,[16] 10.8% of the country's entire population are still believed to be infected. The majority of these infections afflict the country's adult African population: Africans aged 14-49 years have an estimated prevalence of 19.9%.[17] These statistics attest to the importance of an effective public health response to the HIV epidemic in this group.

2.1.2 HIV pathogenesis

HIV is a retrovirus[18] spread through exposure to infected blood or through sexual activity with an infected person.[19] HIV targets hosts' CD4 lymphocytes, cells responsible for coordinating immune response.[20,21] Acute HIV infection (AHI), or primary HIV infection, is the stage of infection lasting the first several weeks

following exposure to HIV. AHI is characterized by high levels of virus in the blood or 'viral load' (VL); heightened infectiousness; and low levels of CD4 lymphocytes and HIV-specific antibodies generated by the immune system. AHI ends when VL falls while CD4 lymphocyte and HIV-specific antibody levels increase, all eventually stabilizing as infected persons enter a state of chronic infection.[22]

During chronic infection, HIV remains confined to latent reservoirs in lymphoid tissue, generally leaving infected persons asymptomatic.[23] The length of chronic infection is variable, but in the absence of anti-retroviral treatment (ART) has been found in both industrialized[24] and resource-poor settings[25] to last 7-13 years. When chronic infection ends, VL again climbs while CD4 counts fall. As a result, patients' immune systems become increasingly compromised, leaving them susceptible to a range of opportunistic infections (OIs). Common OIs include tuberculosis (TB); pneumocystis carinii pneumonia (PCP); and mycobacterium avium complex (MAC).[26] Once patients become severely immunosuppressed (CD4<200 cells/mL) or develop severe OIs, they are said to have entered the final stage of illness: acquired immune deficiency syndrome (AIDS).[27]

2.1.3 HIV testing technologies

Enzyme-linked immunosorbent assays and Western Blot tests

HIV's pathogenesis has important implications for the technology used to diagnose infection. The first HIV tests developed during the early 1980s detected HIV antibodies.[28] These tests, known as enzyme-linked immunosorbent assays (ELISAs),[*] accomplish this through applying serum samples to plates with attached HIV antigens.

[*] Strictly speaking, there are ELISAs capable of detecting antigen instead of, or in addition to, antibodies.[29] However, the term is more traditionally used to refer to antibody tests and it is in this manner that the term is used in this thesis.

The extent to which antibodies in the blood attach to the antigens on these plates is then measured to determine the serostatus of the blood samples.

The Western Blot (WB) test was a later development commonly used as a confirmatory test for samples testing positive by ELISA. WBs detect antibodies by inserting a HIV lysate into a gel and applying an electrical charge to separate HIV proteins, a technique known as electrophoresis. The proteins are then transferred to filter paper and incubated with the serum to be tested.[30] Finally, the paper is stained to detect specific viral bands indicating the presence of HIV antibody.

Although ELISAs and WBs are still used widely today, these tests have three major disadvantages. First, the length of time needed to process samples can span from hours to days. Second, the use of these tests often requires trained laboratory personnel and facilities. Third, they cannot reliably diagnose AHIs given that acutely-infected individuals have not yet produced sufficient amounts of antibodies for detection.[29]

Rapid tests

One development which revolutionized HIV diagnostics by addressing these first two disadvantages was the rapid HIV test. Like ELISAs and WBs, rapid tests also detect HIV antibodies. However, the results are usually ready in less than one half hour. Furthermore, these tests may be used in resource-poor settings with little infrastructure and by healthcare personnel who lack substantial training. Rapid tests also generally require smaller blood samples than ELISAs and WBs, the amount acquired from a finger-prick usually being sufficient.[29] Some rapid tests have even been modified for use on oral fluid samples.[31]

First developed in the late 1980s, rapid tests have garnered increasing acceptance as the primary means of screening for HIV. This is particularly so in sub-Saharan Africa[32] where resource and infrastructure constraints make the advantages of rapid tests particularly attractive. ELISAs or WBs can be used to check the quality of rapid screening programs. However, some rapid tests have been configured to maximize specificity, therefore making them suitable for use as confirmatory tests when used in serial with other rapid tests.[29] These rapid confirmatory tests have led to screening protocols comprised entirely of rapid tests, making possible the delivery of serostatus determination to clients within minutes of sample collection. Serial rapid testing is examined in this thesis as the default protocol (see Subsection 2.2.4).

Polymerase chain reactions and antigen tests

The third disadvantage of ELISAs and WBs, the inability to detect AHI, was addressed by the development of tests capable of detecting the presence of HIV directly. This can be done by testing for the presence of HIV nucleic acids, namely proviral DNA in cells or viral RNA in plasma, with a polymerase chain reaction (PCR). A less expensive and more common alternative is to detect HIV antigen, usually the p24 protein. Both the HIV nucleic acid and antigens are present in the blood before antibodies can be detected. Therefore, PCRs and antigen tests can detect AHI as early as 3 days after exposure.[29]

However, these tests have two major disadvantages of their own. First, while they are highly sensitive, this sensitivity often comes at the expense of specificity. Consequently, they are generally not used as confirmatory tests. Second, these tests frequently require substantial infrastructure, laboratory expertise, and time to administer.[29]

Fortunately, technological developments continue to lessen these drawbacks. For example, the AxSYM immunochemical automated analyser (Abbott Diagnostics, Abbott Park, IL, USA), can test for antibodies and antigen simultaneously. This combination test thus makes it possible to detect AHI while maintaining high specificity. Moreover, the AxSYM apparatus can process samples in 20 minutes and requires no laboratory facilities beyond a standard power source and supply of distilled water.[33-37] Technology advances such as the AxSYM test raise the possibility of routine AHI screening in resource-constrained settings becoming cost effective. Consequently, AxSYM antibody-antigen combination testing for all clients seronegative by standard rapid testing is considered as a test protocol option for the expanded testing policies examined in this thesis (see Subsection 2.2.4).

2.1.4 History of HIV testing policy in industrialized countries

The first HIV tests were licensed by the United States of America (USA) Food and Drug Administration in 1985, four years after the epidemic's first recognition. By this time, associations between homosexual lifestyles and HIV/AIDS had become firmly entrenched in the public consciousness in many industrialized countries due to extensive media coverage of known AIDS patients, most of whom at that time were MSM. This already-stigmatized group suffered further discrimination and suspicion as hysteria accompanied media portrayals of the suffering of late-stage AIDS patients.[28] Concerns over increased societal backlash and the lack of effective treatment options for seropositive patients compelled many in the gay community to initially discourage use of the test.

Eventually, decision makers accepted a HIV testing paradigm which came to be known as "HIV exceptionalism." This paradigm did not focus as much upon the

public health goal of protecting the uninfected as with testing policies for most infectious diseases. Instead, it prioritized patient rights to confidentiality and informed consent.[38] In practical terms, HIV exceptionalism required patients rather than healthcare providers to initiate most testing encounters.[†] Furthermore, such encounters resulted in testing only if clients explicitly 'opted in' (see Subsection 2.2.3 for definition of opt-in testing), usually by signing consent forms.

The greatest support for HIV exceptionalism came from the gay community and other advocates for patients' rights. However, the paradigm became more widely accepted (e.g., by the USA government) due to concerns that a more aggressive policy might drive persons at risk underground.[28] The perception that the disease would remain confined to specific minority groups such as MSM probably also contributed to the acceptance of HIV exceptionalism.[39]

Yet, the norm of client-initiated, opt-in HIV testing very gradually changed to more aggressive policies. This transition was driven by increasing knowledge regarding HIV pathogenesis and the availability of treatment options, most especially antiretroviral treatment (ART)[2-4] and OI prophylaxes.[40-43] Recommendations by the Centers for Disease Control and Prevention (CDC) in 1986 advised providers to initiate test offers to groups at high risk for HIV – e.g., MSM, haemophiliacs, and intravenous drug users (IVDUs) – rather than requiring such clients to initiate testing.[44] Similar recommendations were made in 1995 for all tests offered to pregnant women.[45] In 2002, the CDC expanded the group of patients who should routinely receive provider-initiated test offers to all individuals living in communities

[†] Exceptions to this general rule included tests for patients presenting with potentially HIV-related symptoms, or "diagnostic testing," which have usually been provider initiated. Another exception is blood donor testing which in most countries has long been mandatory albeit anonymous.[1,28]

with HIV prevalence >1%.[46] Most recently, in 2006 the CDC supported making these offers opt-out (see Subsection 2.2.3). This final recommendation marked the most definitive departure from HIV exceptionalism as it removed the requirement for clients to consent explicitly to receive testing.[10]

2.1.5 HIV testing policy in South Africa

Throughout the 1980s and 1990s, client-initiated, opt-in HIV testing was exported from industrialized countries to the rest of the world in a "striking example of modern globalization."[39] Worldwide acceptance of HIV exceptionalism was largely due to the view of the global epidemic by influential Western AIDS activists through a "domestic lens," placing paramount importance on patients' rights. For example, the American director of the United Nations's first HIV program, Jonathon Mann, did much to emphasize the importance of patient rights in devising a global response to the HIV pandemic.[47]

South Africa's acceptance of this paradigm was probably also driven by the political upheaval ongoing during the early years of the pandemic. The outgoing apartheid government was disinclined to address a disease associated with homosexuality. Meanwhile, the incoming African National Congress's preoccupation with challenging issues of reconciliation and governing following its transition into power precluded an effective response to the epidemic.[48] Consequently, South Africa, along with most sub-Saharan African countries, broadly accepted the worldwide testing paradigm and also frequently depended upon Western non-governmental organizations (NGOs) to provide testing venues and services.[39] By the time South African leaders began to address the epidemic exceptionalism had already become an international norm.

Rethinking HIV exceptionalism in South Africa

There have been moves in recent years toward more aggressive testing policies throughout sub-Saharan Africa. These typically came on the heels of implementation of similar policies in the West.[‡] South Africa, like most African nations, has implemented a prevention of mother-to-child transmission (PMTCT) program, begun in 2002 (see Subsection 5.1.1). As part of this program, test offers are provider-initiated for all antenatal care (ANC) users, although those test offers remain opt-in (see Subsection 2.2.3).[50] Moreover, a similar routine testing policy for TB patients has been increasingly implemented throughout the country since the late 1990s.[51]

Historically, decisions such as these to expand HIV testing have usually followed increases in availability of ART and OI prophylaxes.[52-54] For example, South Africa's expansion of testing among pregnant women came shortly after negotiations with pharmaceutical companies markedly lowered the cost of nevirapine, an antiretroviral drug often used for PMTCT.[50] This is because while testing itself is of little value to patients, these drugs are known to yield a substantial health benefit for patients.[§] Consequently, as receipt of effective treatment and counselling becomes an expected outcome of testing positive, decision makers presumably come to believe that the biomedical benefits increasingly outweigh the negative social consequences of the testing process.

Recent initiatives have further expanded access to lifesaving HIV treatment in South Africa. These have included the WHO's "three by five" program to place three

[‡] A notable exception is Botswana, where President Festus Mogae spearheaded legislation requiring provider-initiated, opt-out test offers to all citizens accessing public healthcare facilities in 2004,[49] two years before the CDC made its recommendations for a similar policy in the USA.

[§] Hence the need for an analytic framework in evaluating any testing program which accounts for the 'downstream' costs and effects of the screening process (see Section 2.3).

million HIV-positive persons on ART by 2005[6] and the Clinton Foundation's negotiations to lower ART prices.[5] As initiatives such as these continue to improve treatment availability, it is becoming increasingly important to consider implementation in South Africa of policies expanding HIV testing further still. Indeed, the WHO has already recommended that all countries such as South Africa with antenatal prevalence >1% offer provider-initiated, opt-out testing to all individuals accessing healthcare facilities (see Subsection 1.1.1).[11]

Economic evaluation of HIV testing

South Africa's government has not been particularly helpful in pushing forward the discourse on HIV testing policy. President Thabo Mbeki has famously consorted with HIV denialism, a paradigm of thought rejecting much of the otherwise widely accepted scientific work on HIV, including its role in causing AIDS.[55] Years of international and domestic pressure have compelled Mbeki's administration to support in principle the goal of providing ART to all infected South Africans. However, the government has continued to drag its feet on implementing any large-scale rollout. This resistance has frequently been couched as concern over cost-effectiveness.[48,50]

Some analyses have already evaluated the cost-effectiveness of provision of ART and other treatments for HIV-positive patients in South Africa.[50,56,57] However, no such analyses have yet included the costs and effects of an expanded testing program to accelerate treatment rollout (see Subsection 4.3.1). Therefore, determining the cost-effectiveness of expanded case detection with linkage-to-care for seropositive clients will be an important contribution of this thesis.

2.2 HIV testing policies

This section's objective is to describe the HIV testing policies considered in this thesis, including current practice in South Africa. It is assumed that for all of the policies considered the South African government will pay for all direct medical costs (e.g., medical personnel wages, tests, treatment). Also, this thesis conducts a population-level analysis, estimating the costs, effects, and cost-effectiveness of the alternative screening strategies for each member of South Africa's adult African population. To this end, this entire population is simulated using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model (see Appendix A).

I decided to focus on the implications of expanded screening for the adult African population because this group is suffering the most severe epidemic within South Africa.[17] Moreover, the risk factors, epidemiological context, and even HIV genetic subtypes afflicting each of South Africa's major demographic populations stratified by age and race are very different. Consequently, any analysis using summary data for South Africa's entire population risks glazing over important differences in the costs and effects per member of each specific group. Obviously, I am not advocating the differential delivery of these testing policies on the basis of race or age. Nevertheless, while I conceive of these policies as being implemented for all of South Africa's citizens, the scope of this thesis is confined to examining the implications of this implementation for adult Africans only.

The policies considered by this thesis include current testing practice and eight policies which expand testing by making test offers provider-initiated to primary healthcare users. Current testing policy is further divided between baseline and

background testing. 'Baseline testing' refers to current screening by primary healthcare users through voluntary counselling and testing (VCT). All baseline testing is assumed to decrease to zero when any of the eight policies expanding primary healthcare user testing are implemented. 'Background testing' refers to all other current screening unrelated to the expanded primary healthcare user testing policies under evaluation (e.g., antenatal testing). All background testing is assumed to continue regardless of the testing policy for primary healthcare users.

Each policy will be described by a combination of variations for five program components. These include (i) target population; (ii) initiation method; (iii) consent method; (iv) test protocol; and (v) linkage-to-care method. This section begins by defining and discussing each of these components and their respective variations. It concludes by summarizing the testing policies considered in this thesis, including current practice, as combinations of these component variations. The creation of these specific components and variations thereof used to describe HIV testing policies was based on the foregoing summary of testing technologies (Subsection 2.1.3) and policies (Subsections 2.1.4-2.1.5). An earlier review of the literature on HIV testing programs in sub-Saharan Africa also informed the component and variation definitions.[32]

2.2.1 Target population

While this thesis examines the effects of various HIV screening policies on testing throughput for the entire adult African population, none of these policies targets this entire population.[**] Instead, as with most HIV testing programs,[32] each of the policies

[**] The only policy option of which I am aware that targets an entire demographic population is home-based testing. For such policies, mobile testing centres deliver testing services directly to the

targets various groups accessing healthcare facilities. Healthcare users in general are common targets for testing programs because healthcare facilities are pre-established venues through which testing services can be readily offered (e.g., see Subsection 4.2.1 and Figure 4.3).

Background testing in this thesis comprises current screening of non-primary healthcare users. Such testing conceivably encompasses a range of groups likely to receive HIV testing in South Africa to include government personnel, soldiers, or private sector employees. However, this thesis considers only those two groups which I believe receive the vast majority of background testing among the adult African population: ANC users and TB patients.

Conversely, baseline testing refers to VCT initiated by primary healthcare users. Similarly, the eight expanded testing policies all entail provider-initiated test offers to primary healthcare users. This group was chosen as the target for the expanded testing policies because it comprises the largest segment of the population regularly accessing health facilities and so the surest target for increasing population testing.

2.2.2 Initiation methods

In this thesis, a testing policy's initiation method refers to the means by which test offers are made. Client-initiated programs require patients to request testing from providers. In contrast, provider-initiated programs require providers routinely to offer patients testing as part of the course of standard medical care. In this thesis, baseline testing targeting primary healthcare users is client initiated. Background testing of TB

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population of interest (see Subsection 8.2.2). I know of no research on any home-based testing program in sub-Saharan Africa.[32]

patients and ANC users and the eight policies expanding primary health user testing, are all provider initiated.[††]

2.2.3 Consent methods

Consent method refers to a testing policy's means of determining whether test offers will be accepted. Opt-in testing requires clients receiving offers to accept explicitly those offers to be tested. This explicit consent usually entails signing a consent form. In theory, opt-out testing requires providers to test all clients receiving test offers unless those clients explicitly refuse testing. Nevertheless, the practical legacy of HIV exceptionalism is that recommendations for opt-out testing often still require some form of expressed consent by the client, usually verbal.[11] Finally, mandatory testing is an option requiring all clients to accept testing, although its use is generally confined to blood screening and entry into select organizations (e.g., armed services)[1] and so is not considered in this thesis. Current testing through both baseline and background testing is opt-in. Among the eight expanded testing policies, four are opt-in and half are opt-out.

2.2.4 Test protocols

Test protocol is defined by this thesis as the algorithm and types of tests used to screen patients for HIV. There are many possible test protocols but this thesis considers only two. The first is the rapid test protocol used by the healthcare providers in the study community examined in Chapter 5 (see Subsection 5.1.1). I

[††] This thesis considers provider-initiated testing to be synonymous with the term 'routine testing.' This is because all the provider-initiated testing policies considered in this thesis require providers to initiate test encounters for all individuals accessing primary healthcare services. However, this commonly-used phrase is generally avoided in this thesis given its ambiguous uses and meanings in the HIV testing literature.[58] Moreover, there are conceivable scenarios of non-routine, provider-initiated testing, such as providers initiating test offers for only those clients presenting with potentially HIV-related symptoms, an approach to testing referred to by some as "diagnostic testing."[1]

chose this protocol because I believed it to be broadly representative of standard practice for many HIV testing programs in sub-Saharan Africa.[59] It entails two rapid tests in serial. First, all patients are screened with an Abbott Determine test.[60] Those testing positive from this first test then receive confirmatory testing to minimize the possibility of false positives. The confirmatory tests used in the study community have changed over time, but are assumed in this thesis always to be a Uni-Gold rapid test (Trinity Biotech PLC, Bray, Ireland). While never actually used in the study community, this test was chosen because a WHO report indicates that its cost and high specificity make it representative of those that might be used in South Africa.[60]

The second test protocol considered in this thesis includes AHI testing. Specifically, all patients first receive the same rapid test protocol as outlined above. In addition, those individuals testing negative by this protocol subsequently receive an antibody-antigen combination test. The specific combination test considered is that run by the AxSYM apparatus, as described in Subsection 2.1.3. This test was chosen due to its relative ease of use in resource-poor settings, availability in South Africa, and quick sample turn-around time.[33-37]

In this thesis, the rapid test protocol serves as the default option representing current practice. Thus, both baseline and background testing services in the study community used the rapid test protocol. Among the expanded testing policies, four use the same rapid test protocol while four include AHI testing for clients testing negative.

Details regarding the types of tests or algorithm in which the tests are used may differ in practice in South African settings from those outlined here. However, the goal here is not to account for every protocol possibility. Rather, I chose these protocols given

that I believe their costs and sensitivities/specificities to be representative of those for feasible rapid test protocols in South Africa with and without AHI testing. Non-rapid tests (e.g., conventional ELISAs) were not considered here given the already-common use of rapid tests by HIV screening programs throughout sub-Saharan Africa.[32] PCRs or other nucleic acid amplification techniques were also not considered as I did not believe them to be practical options for use in resource-poor settings.

2.2.5 Linkage-to-care methods

Evaluating testing programs is complicated by the fact that testing alone is an outcome of limited interest. Indeed, testing programs only deliver sizeable health benefits to their clients insofar as they successfully link individuals testing positive to treatment and care. This requires effective mechanisms for referring seropositive clients to treatment and prevention services and linking referred clients to drugs and education interventions (see Subsection 2.3.6). Therefore, it is important to consider the implications of alternative approaches to achieving this linkage-to-care.

A recent review of the testing literature did not indicate that different linkage-to-care strategies in sub-Saharan Africa have been studied or even defined such that they can be separated into discrete categories. This contrasts with the previously discussed policy components, all of whose options outlined above are based on terminology used in the literature (see Subsections 2.2.1-2.2.4).[32] To my knowledge, no extensive research on linkage-to-care for HIV-related interventions has been conducted in industrialized settings either. This lack of research is evidenced by the inclusion of only a single paragraph related to linkage-to-care in the CDC's 2006 guidelines for provider-initiated testing in the USA.[10] Consequently, there is currently no empirical basis for comparing the cost or effectiveness of different linkage-to-care methods.

However, it is possible to conceive of a testing policy in which all seropositive clients not receiving treatment or referral are sought by healthcare providers to return them to the treatment pipeline. This thesis examines such a scenario, referred to as 'enhanced linkage-to-care.' In this scenario, additional costs are incurred for each seropositive client not linked to care, presenting time spent by healthcare providers to contact those individuals via phone-calls or a household visit. Enhanced linkage-to-care is arbitrarily assumed to lead to referrals for half of HIV-positive patients otherwise not receiving referral. Similarly, enhanced linkage-to-care is assumed to lead to treatment for half of referred clients otherwise not receiving treatment.

Clients receiving baseline testing receive only standard linkage-to-care. Four of the expanded testing policies for primary healthcare users adopt a standard approach to linkage-to-care while the other four use enhanced linkage-to-care. The linkage-to-care method for background testing is always assumed to be identical to that for the primary healthcare user testing policy under evaluation.[‡‡]

2.2.6 Summary of HIV testing policies

This thesis compares the effectiveness, cost, and cost-effectiveness of alternative HIV testing policies for the adult African population in South Africa. This thesis considers current practice, as distinguished between baseline and background testing, and eight expanded testing policies (Table 2.1). Baseline testing targets primary healthcare users and is assumed to decrease to zero when any alternative screening program for primary healthcare users is implemented. Background screening targets non-primary

[‡‡] In other words, if an enhanced linkage-to-care program is implemented for primary health users, then it is assumed that all clients receiving background testing are similarly linked to care using an enhanced program. This was a necessary assumption for fitting the empirical data from Chapter 5 to the CEPAC parameters given the model's structure (see Subsection 7.1.3).

healthcare users and is assumed to remain constant for all policy alternative examined. As outlined in this section, all eight expanded testing policies entail provider-initiated test offers for primary healthcare users and one of the two variations across the three program components: consent method, test protocol, and linkage-to-care method. Since the evaluation in this thesis compares all eight of these policies, it will be possible to isolate the impact of each of these three components on the population costs and effects of HIV testing.

Table 2.1. Summary of HIV testing policies. Policies considered include current practice, encompassing both baseline (BL) and background (BG) testing policy, and eight variations of provider-initiated policies targeting primary healthcare users (IRS, IRE, IAS, IAE, ORS, ORE, OAS, and OAE). Test codes are provided for ease of reference and are comprised of three letters: the first indicates consent method ('I' for opt-in, 'O' for opt-out), the second indicates test protocol ('R' for rapid, 'A for rapid with acute HIV infection testing), and the third indicates linkage-to-care method ('S' for standard linkage-to-care, 'E' for enhanced linkage-to-care).

Code	Target population	Initiator	Consent	Protocol	Linkage-to-care
Current testing practice					
BL	Primary care users	Client	Opt-in	Rapid-only	Standard
BG	ANC, TB patients	Provider	Opt-in	Rapid-only	Standard*
Expanded testing policies					
IRS	Primary care users	Provider	Opt-in	Rapid-only	Standard
IRE	Primary care users	Provider	Opt-in	Rapid-only	Enhanced
IAS	Primary care users	Provider	Opt-in	Rapid & AHIT	Standard
IAE	Primary care users	Provider	Opt-in	Rapid & AHIT	Enhanced
ORS	Primary care users	Provider	Opt-out	Rapid-only	Standard
ORE	Primary care users	Provider	Opt-out	Rapid-only	Enhanced
OAS	Primary care users	Provider	Opt-out	Rapid & AHIT	Standard
OAE	Primary care users	Provider	Opt-out	Rapid & AHIT	Enhanced

* Linkage-to-care method for background is assumed always to be identical to that for primary healthcare users; in the baseline scenario, this is standard linkage-to-care
AHIT-acute HIV infection testing

The policies examined were defined to represent current practice and feasible strategies for increasing population testing in South Africa. Only expanded testing policies targeting primary healthcare users were examined as this group is the largest segment of the population regularly accessing venues where testing can be offered

(see Subsection 2.2.1). Client-initiated, opt-out policies were not considered because they are unlikely policy alternatives since the decision to make testing opt-out has historically been more controversial than making test provider-initiated.[§§]

Policies identical to baseline testing except for the use of alternative test protocols or linkage-to-care methods were also not examined. This is because, strictly speaking, neither increasing test protocol accuracy nor implementing an enhanced linkage-to-care effort would expand HIV testing. Instead, these policy options would increase the proportion of tested clients whose tests yield accurate results (see Subsection 2.3.4) and seropositive clients receiving linkage-to-care (see Subsection 2.3.6), respectively. Therefore, these policies fall outside of the scope of this thesis. The impact of protocol accuracy and linkage-to-care rates on the cost-effectiveness of HIV testing were examined only as part of expanded testing policies.

2.3 HIV testing cascade

Having described the various expanded HIV testing policies considered in this thesis, this section's objective is to outline an analytic framework for comparing the effects of these programs. As is argued throughout this thesis, testing alone is an outcome of limited interest. Rather, health benefits achieved following linkage-to-care and prevention education following diagnosis provide the greater incentive for expanded testing. To this end, it was useful to conceive of HIV testing as a series of steps through which patients must pass to realize these ultimate health benefits.

[§§] It also strikes me as probably unnecessary to adopt a consent method designed to increase acceptance rates among individuals already expressing interest in screening by initiating test encounters. Indeed, I have identified no examples in the HIV testing literature of programs using an opt-out method of consent prior to making test offers provider-initiated.[32]

For this purpose, I constructed the 'HIV testing cascade' (Figure 2.1). The cascade consists of four steps representing the testing process: (i) test venue attendance; (ii) test offer receipt; (iii) test offer acceptance; and (iv) post-test counselling. For those clients testing HIV-positive, two additional steps follow. These include (v) referral – namely for HIV-related care and monitoring to determine treatment eligibility – and (vi) treatment for eligible patients. This section discusses each of these steps in turn. It concludes with a brief summary and discussion of the analytic framework, its limitations, and its use in subsequent chapters.

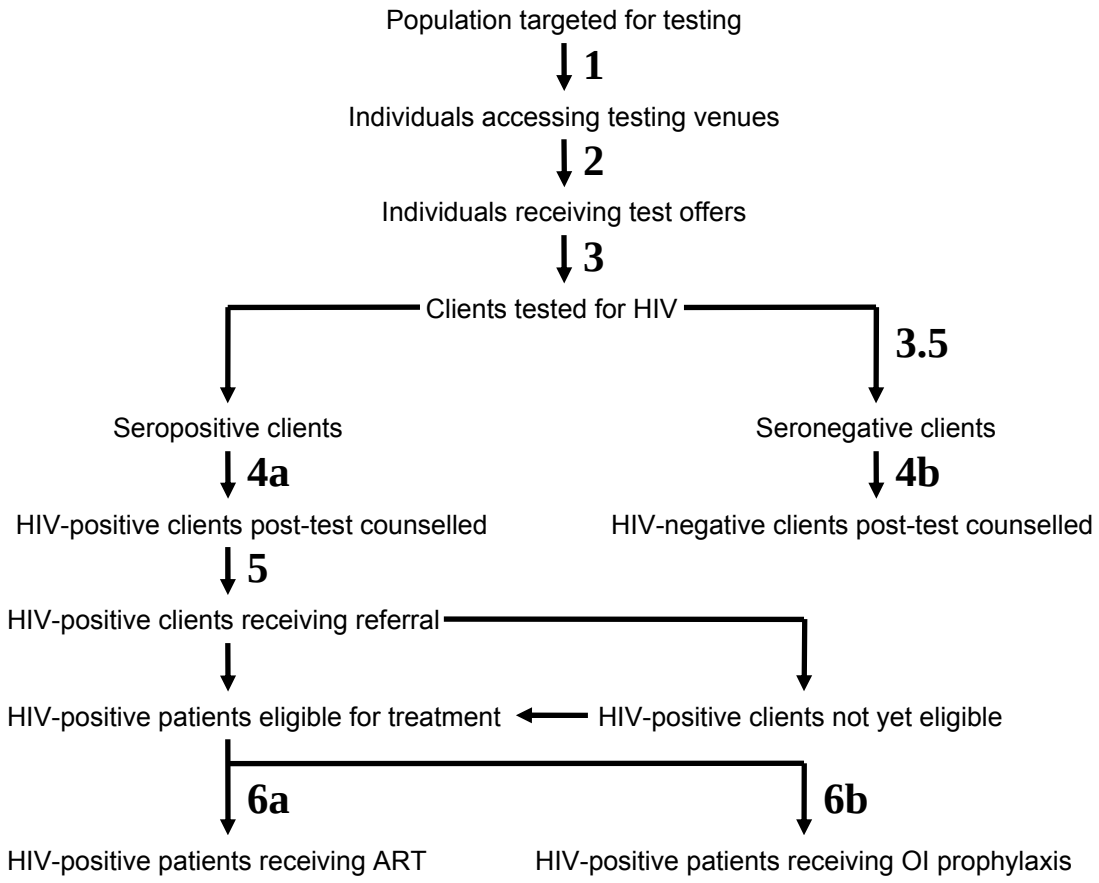

Figure 2.1. Schematic of the HIV testing cascade.

2.3.1 Step 1: test venue attendance

The first required step of HIV testing is for a client to access a venue providing testing services. During the 1980s and 1990s, sub-Saharan African countries frequently relied on NGOs to deliver testing services (see Subsection 2.1.5), many of which set up their own testing centres.[39] However, as these governments began acknowledging the importance of testing, they committed to increasing access to testing venues. Increasingly, it has become a common goal in sub-Saharan Africa (including South Africa) to offer testing at all public healthcare facilities.[61] These facilities are potentially useful testing venues since they generally possess the equipment, facilities, and personnel necessary for offering testing services. Moreover, government-run healthcare centres are often used regularly by large segments of the general population, even in resource-poor settings.

As mentioned in Subsection 2.1.4, there exist concerns that more aggressive testing policies may compel potentially infected individuals to avoid testing venues altogether.[28] Alternatively, others believe that expanding testing policies could encourage more individuals to access healthcare facilities specifically for the purpose of testing as screening becomes increasingly normalized.[62] No empirical data have been generated to validate either of these arguments. Consequently, it is assumed that the rate of throughput for this step is constant for all policies.

2.3.2 Step 2: test offer

The second step of the HIV testing cascade is the offering of a test to the client. It is assumed in this thesis that the only test policy component affecting client throughput for this step will be initiation method. It is expected that provider-initiated policies will lead to higher offer rates than client-initiated approaches. Indeed, making testing

provider- rather than client-initiated among pregnant women in Western Kenya significantly increased the proportion of clients accessing a testing venue who received test offers from 55% to 68%.[63] This thesis relies on its own data collected through a retrospective descriptive design to quantify this expected increase for South Africa (see Subsection 6.1.1).

2.3.3 Step 3: test offer acceptance

Following an HIV test offer, the next step in the testing cascade is the client's decision whether to accept that offer. It is assumed that the only test policy component affecting acceptance probability is the consent method. A comparison of acceptance probabilities in Botswana among pregnant women receiving provider-initiated tests with different consent methods found these probabilities higher using opt-out versus opt-in testing. Specifically, acceptance probabilities rose from 75.3% for opt-in testing to 90.5% for opt-out testing, an odds ratio (OR) of 3.1.[64] This thesis applies this OR from Botswana to empirical data collected in South Africa to estimate the acceptance probability using opt-out testing.

It is reasonable to question whether initiation method might also affect acceptance rates. Under a client-initiated testing policy, test offers will probably be accepted by most clients since they have already expressed interest in testing simply by virtue of initiating the test encounter. In contrast, a provider-initiated testing program may offer testing to additional clients less amenable to accepting those offers. However, this effect has not been observed in research comparing acceptance rates for provider-initiated, opt-in programs to those for client-initiated, opt-in programs.[63,65] Moreover, many studies of *provider-initiated*, opt-in testing programs in sub-Saharan Africa have reported acceptance probabilities comparable to that observed among individuals

receiving client-initiated, opt-in testing in the study community in this thesis (see Subsection 5.2.3).[66-70]

It is also possible that test protocol would affect acceptance rates. Clients inclined to accept rapid testing may be less amenable to ELISA testing given the requirement to return for the results. However, acceptance rates are unlikely to differ across the protocols considered in this thesis, all of which are rapid. The prospect of AHI testing for all those testing negative may deter some clients from accepting due to the extra waiting time required. Yet, this effect also seems improbable as testing for AHI using the AxSYM platform generally requires <30 additional minutes (see Subsection 2.1.3). Of course, if clients had to incur additional costs to receive AHI testing, this too might serve as a disincentive, but in none of the testing scenarios do clients incur any testing costs (see Section 2.2). Consequently, clients accepting rapid testing are assumed in this thesis also to accept AHI testing if they initially test negative.

2.3.4 Step 3.5: test results

As mentioned above, the actual testing of clients is not considered a separate step in the HIV testing cascade. Rather, clients' progression through this process is determined by their passage through Step 3 (accepting testing). Once clients accept testing, allowing a blood sample to be collected, the process of generating test results is considered automatic. Yet, it is important to consider the comparative likelihoods that alternative test protocols may fail to diagnose HIV-positive individuals correctly. It is assumed that the only test policy component affecting this likelihood is test protocol. Methods used in this thesis to estimate the accuracy of rapid testing with AHI screening compared to rapid-only testing are described in Section 6.1.3.

2.3.5 Step 4: post-test counselling

After being tested, clients must be notified of the results of their tests. Research in sub-Saharan Africa has demonstrated the effectiveness of rapid tests in elevating rates of post-test counselling compared to tests requiring clients to return for results.[71,72] However, all test protocols considered in this thesis have fast turn-around for results; even the AHI protocol is believed sufficiently fast to provide same-visit results for clients (see Subsection 2.2.3). Therefore, like throughput for Step 1 (see Subsection 2.3.1), post-test counselling rates are believed to remain constant for all policies considered in this thesis.

Post-test counselling can be divided into two parallel steps: one for HIV-positive clients and another for HIV-negative clients. It is possible that clients testing negative would experience lower post-test counselling probabilities than those testing positive. This is due to the likely desire of counsellors to focus on those clients most at need for education regarding prevention and other HIV-related interventions. Since data on post-test counselling were not collected for seronegative clients in this thesis (see Subsection 5.1.2), it was necessary to assume these probabilities equivalent. However, because this thesis does not consider secondary transmission, post-test counselling probabilities for seronegative clients have no substantive impact on the cost-effectiveness of HIV testing.

2.3.6 Steps 5-6: referral for treatment and treatment receipt

Following receipt of test results, HIV-positive clients must be referred for care and subsequently receive treatment once eligible (see Subsection 5.1.1 for eligibility criteria). The final step of treatment receipt for eligible patients in South Africa can be divided into two parallel steps: one for ART and another for cotrimoxazole, an OI

prophylaxis generally prescribed to HIV-positive clients in South Africa. It is assumed that only a policy's linkage-to-care method (standard or enhanced, as discussed in Subsection 2.2.5) will affect probabilities of referral and treatment.

It is possible that more aggressive variations of initiation method and consent method would depress rates of linkage-to-care. Provider-initiated and opt-out testing are both expected ultimately to expand the numbers of clients tested for HIV (see Subsections 2.2.2 and 2.2.3). It has been argued by some that these additional clients may have less motivation than those initiating their own testing encounters to seek appropriate treatment and care following a positive result.[73] However, this has not been observed in sub-Saharan African studies comparing either provider-initiated to client-initiated[63,65] or opt-in to opt-out programs.[64] Indeed, all of these studies observed expanded testing to have little effect on linkage-to-care rates, so justifying the default assumption of no effect in this thesis. Nevertheless, the possibility of depressed linkage-to-care for expanded testing policies is considered in the sensitivity analyses for the CEA in this thesis (Table 7.5).

2.4 Discussion

This section discusses further the application of the policy definitions and analytic framework outlined in this chapter to the subsequent analyses presented in this thesis. These analytic tools were largely designed to circumvent the methodological challenges first presented in Subsection 1.1.2. Thus, the discussion here is structured to address each of these four issues in turn.

2.4.1 HIV testing cascade outcomes

The HIV testing cascade framework makes explicit the acknowledgement in this thesis that testing is a necessary but insufficient condition for attaining health benefits from HIV-related treatment. Thus, this framework makes possible the depiction of clients' failure to pass through certain steps. Throughput losses are a vital consideration when evaluating any screening program, but commonly neglected in the HIV testing economic literature. The clearest manifestation of this neglect is the focus of many studies on intermediate outcomes representing only completion of the testing process rather than on subsequent final health gains (see Subsection 4.2.1).

The cascade framework defines six outcomes, representing passage through each of the cascade steps. None of these serve as the outcome of interest in this thesis. Instead, they serve as a tool for organizing and summarizing testing and linkage-to-care throughput data (see Subsection 2.4.2). These data are then linked to the CEPAC model to simulate life years gained (LYGs) as a final health outcome (see Subsection 3.3.1). However, this thesis does consider the effects on the costs and LYGs for HIV testing of focusing on increasing throughput for different steps of HIV testing cascade. This comparative analysis is achieved by comparing expanded testing policies identical in all else save for consent method, test protocol, and linkage-to-care. Since each of these policy components is assumed to affect throughput for only select steps, this thesis therefore examines the relative cost-effectiveness of increasing throughput for cascade Steps 3, 3.5 and 5-6, respectively.

2.4.2 HIV testing data

This thesis uses this analytic framework to describe empirical observations of testing from an adult African study community in South Africa (reported in Chapter 5). In so

doing, this thesis captures the throughput losses occurring in the HIV testing process, describing throughput for each of the cascade steps. Chapter 6 then applies assumptions and secondary data to these current throughput estimates to project the impact of the eight expanded testing policies (Table 2.1). These throughput estimates, configured as model parameter inputs, are then inserted into CEPAC in Chapter 7. Based upon these throughput data and additional secondary sources describing treatment costs and efficacy (see Appendix B), CEPAC then simulates the effects of treatment for clients linked to care (see Appendix A). CEPAC thus generates cost-effectiveness estimates for the expanded HIV testing policies (see Chapter 7).

Fitting the empirical testing observations from Chapter 5 to the cascade framework for use as CEPAC parameter inputs is complicated by the natures of some of the cascade steps. Steps 3, 3.5, and 4 as conceived here all occur within the span of a single healthcare visit. Consequently, the time span for passage through these steps is negligible compared to the month-long intervals over which CEPAC operates (see Appendix A). Therefore, throughput for these steps may be expressed as probabilities of occurrence of nearly-instantaneous events.

In contrast, the other cascade steps are best conceived as rates. To be sure, receipt of a test offer (Step 2) qualifies as a near-instantaneous event experienced by individuals accessing health facilities. However, the empirical data gathered for this thesis combine Steps 1-2, reporting population rates of testing (empirical data describing healthcare attendance rates were not available, see Chapter 5). CEPAC's parameter defining passage through Steps 1-2 similarly combines the two, soliciting rates of test offers. Consequently, the empirical data reported in Chapter 5 were inserted into CEPAC with minimal adjustment.

Conversion of data describing throughput for the referral and treatment steps is less straightforward. As with Steps 1-2, throughputs for Steps 5-6 are also best treated as rates because often many months transpire between diagnosis and referral or treatment. Yet, while CEPAC's parameters describing test offers accommodated data in the form of rates, its linkage-to-care parameters are defined as probabilities. Thus, a judgement was necessary concerning the length of time from diagnosis or treatment eligibility beyond which a client should be considered to not have received treatment. I chose a span of six months, as discussed in Subsection 5.1.3.

2.4.3 Current testing practice

The definition of current testing practice has important implications for the results of the economic evaluation presented in this thesis. All cost-effectiveness estimates of expanded testing policies presented in Chapter 7 are incremental to current practice. Incremental analysis is an important approach in economic evaluation which avoids overestimating the effectiveness of a policy by accounting for the amount of intervention already occurring. For this thesis, a traditional incremental analysis would prescribe assuming all current testing decreases to zero upon implementation of expanded testing. Consequently, expanded testing policies would incur costs for tests which were otherwise already being achieved at zero (incremental) cost. To the extent that some current testing continues to occur following testing expansion, this traditional approach would underestimate the effectiveness of expanding testing (see Subsection 3.1.4).

The distinction drawn between baseline and background testing in this thesis is designed to address this issue. Baseline testing is assumed to decrease to zero once an expanded policy is implemented. In this thesis, all current tests by primary healthcare

users observed in the study community are treated as baseline tests. This is because I believe these tests are most likely to cease following implementation of the expanded testing policies, all of which target primary healthcare users. In contrast, background tests are assumed to continue at the same rate regardless of other testing policy decisions. In the study community, background tests comprise all those by patients other than primary healthcare users. I believe testing by these groups (ANC users and TB patients) will continue regardless of primary healthcare user testing policy.

2.4.4 Population access to testing venues

The HIV testing cascade includes a step describing the rate at which the underlying population accesses testing venues. This is a difficult statistic to measure, and few attempts have been made in the literature to do so (see Chapter 5).[32] However, quantifying this access through population-level analyses permits projection of an entire population's receipt of testing and treatment. I believe this to be very important information for decision makers considering expansion of testing.

As noted above (see Subsection 2.4.2), the epidemiological study presented in Chapter 5 was not able to estimate throughput for this step. However, Chapter 5 does report an estimate of throughput for Steps 1-2 together (i.e., population rates of testing). This testing rate estimate was further validated by using a South African healthcare utilization survey as a reality check (see Subsection 6.1.1). The use of these data to estimate the cost and effectiveness of expanded testing for each member of South Africa's adult African population is an important contribution of this thesis.

Chapter 3:
Overview of economic evaluation in medical decision making: concepts and guidelines

This chapter provides an overview of the use of economic evaluation in medical decision making. To this end, its first aim is to outline basic economic concepts, including the rationale and theory underlying economic evaluations. The second aim is to outline guidelines for good practice in conducting economic evaluations and for using the results in medical decision making. In describing these guidelines, I outline the methodological approaches I adopted for the economic evaluation presented in Chapter 7. In the discussion, I consider in greater detail those methodological decisions with implications for the salient issues of this thesis. These include choice of health outcome of interest; selection of a modelling approach compatible with the data I collected and scenarios I wanted to simulate; definition of current testing practice; and choosing to conduct a population-level analysis.

3.1 Introduction to economic evaluation concepts

The objective of this section is to outline the concepts underlying economic evaluation in medical decision making. It describes relevant health economics concepts; rationales for conducting economic evaluations of healthcare programs; types of economic evaluations; decision rules for economic evaluations; and economic evaluation designs (with emphasis on modelling approaches).

3.1.1 Health economics concepts

Economics is the study of how resources are allocated. Health economics is a subset of economics which studies the allocation of resources (e.g., land, labour, capital) within the health economy. Both economics and health economics feature the premise that societal resources are scarce, meaning resources are insufficient to produce enough goods and services to meet demand. Given this scarcity, society must make choices concerning how goods and services should be allocated.[74]

The premise of scarcity establishes the importance of evaluating alternative mechanisms of resource allocation. Broadly speaking, such alternative mechanisms range from planned economies, with resource allocation managed in some form by a sovereign government (e.g., socialism), to free markets, with resource allocation driven by the mutual consent of buyers and sellers (e.g., capitalism). Various hybrid options, or mixed economies, comprise other possible economic systems.[75]

Free market economies theoretically optimize resource allocation* when operating under a hypothetical scenario known as *perfect competition*. The conditions of this scenario include free entry into and exit from the market for producers; perfect information regarding product prices for all producers and consumers; homogeneous products which may be substituted for one another; sufficiently large numbers of producers and consumers such that no single one of either can affect market prices; no public goods; no natural monopolies; no significant externalities, defined as "uncompensated direct effect[s] of the production or consumption of a good on

* Optimal resource allocation is here defined as *Pareto efficiency*, a state in which no resource allocation can improve any one person's situation without making another person worse off.[74]

persons other than the producers or consumers;" and behaviour by consumers and producers to maximize utility and profits, respectively.[74]

Thus, if real world markets actually functioned as theoretical free markets, economic evaluation would likely be unnecessary. However, the conditions for perfect competition are never entirely satisfied and may be especially questionable in the field of healthcare. The inherent uncertainty regarding the incidence of disease and efficacy of treatment[76] may make the expectation of perfect information unreasonable, particularly for healthcare consumers.[77,78] Moreover, externalities may accompany medical decisions, such as the failure to treat infectious patients generating costs incurred by others in the forms of spreading epidemics.[79]

Given the many ways in which free healthcare markets can become distorted, most governments have accepted in principle the value of some form of intervention as evidenced by their adoption of the World Health Organization (WHO) constitution. The constitution includes a statement that "governments have a responsibility for the health of their peoples which can be fulfilled only by the provision of adequate health and social measures."[80] There are many means by which a government body might intervene in a healthcare market, including insurance provision, private market regulation, or even direct healthcare provision for its citizens.[77]

3.1.2 Rationales for economic evaluation

To the extent that governments provide healthcare for their citizens, they can further disrupt the process by which free markets theoretically direct resource allocation: establishing equilibrium prices and production quantities through the mutual consent of producers and consumers. In the absence of this market pricing mechanism, other

methods are needed to direct resource allocation. Economic evaluation is one such tool for guiding optimal healthcare resource allocation.

Economic evaluation can help lead to efficiency in healthcare resource allocation, as defined in several ways. First, evaluations can inform *technical efficiency*, the maximization of output for a given input.[74,81] Evaluations can also facilitate realization of *productive efficiency*, a broader state of efficiency in which there is maximization of output for a given cost.[81] Achievement of productive efficiency requires valuing or assigning costs to potential inputs to determine the ideal combination of inputs to maximize production while minimizing cost. Figure 3.1 illustrates the differences between technical and productive efficiency.

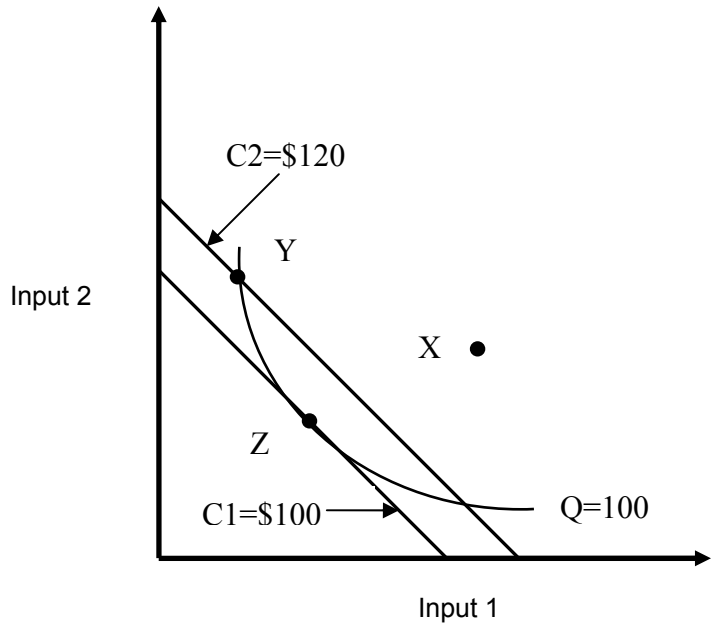

Figure 3.1. Schematic comparing technical and productive efficiency. Points X, Y, and Z represent input combinations for programs resulting in 100 units of output. Q is an isoquant, a line along which all input combinations result in 100 units of output. Lines C1 and C2 are isocosts, lines along which all input combinations cost the same amount. Point X is neither technically nor productively efficient, Y is technically but not productively efficient, and Z is both technically and productively efficient. (Figure adapted from Figure 5.7 in Folland et al.[74])

Finally, the still broader concept of *allocative efficiency* is the allocation of resources such that each is put to its most rewarding use in society. This form of efficiency results in the most desirable overall output possible and a state of Pareto efficiency (see Subsection 3.1.1).[74,81] In addition to the valuation of inputs, achieving allocative efficiency requires the valuation of various program outputs such that they can be compared to facilitate selection of the mixture of programs optimizing output.[82] Allocative efficiency implies productive efficiency, which in turn implies technical efficiency, but the converse implications are not necessarily true.[81] Figure 3.2 illustrates the differences between productive and allocative efficiency.

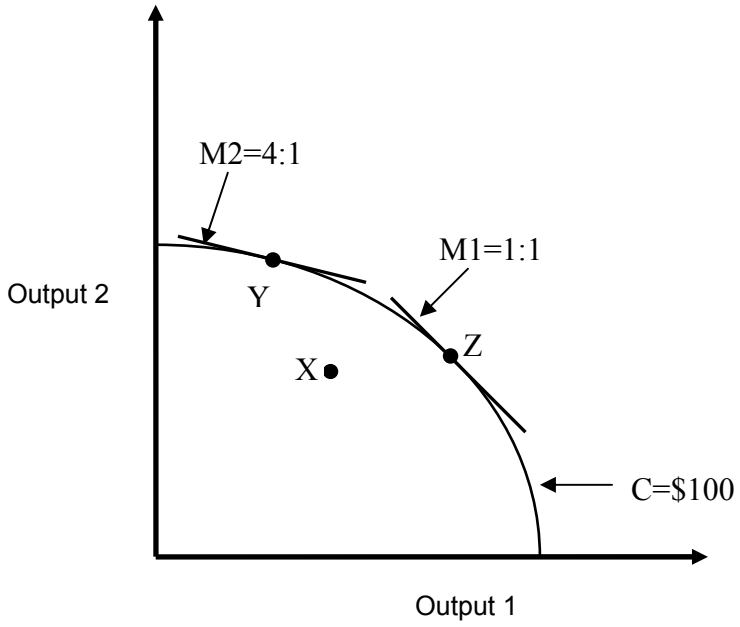

Figure 3.2. Schematic comparing productive and allocative efficiency. It is here assumed that the value of outputs 1 and 2 to society are equivalent, thus making it desirable to maximize production of both. Points X, Y, and Z represent output combinations for multiple programs requiring a total of $100 worth of inputs; all points on this line are by definition productively efficient. C is an isocost and is the production possibilities frontier, a line representing the output combinations possible for $100 worth of input. M1 and M2 are marginal rates of transformation, or lines the slopes of which correspond to the rates of exchange between the two outputs, here expressed as units of output 1 which must given up to produce an additional unit of output 2. Since the outputs are here assumed to be equal in value, allocative efficiency is achieved when the marginal rate of transformation between these outputs is 1:1 (line M1). Point X is neither productively nor allocatively efficient. Point Y is productively but not allocatively efficient. Point Z is productively and allocatively efficient. (Figure adapted from Figure 1.5 in Jacobs et al.[83])

3.1.3 Types of economic evaluation

Economic evaluation is defined by Drummond et al. as "the comparative analysis of [at least two] alternative courses of action in terms of both their costs and consequences."[82] There are five broadly recognized types of economic evaluations: (i) cost analysis – only a partial economic evaluation, as outlined below; (ii) cost-minimization analysis (CMA); (iii) cost-effectiveness analysis (CEA); (iv) cost-utility analysis (CUA); and (v) cost-benefit analysis (CBA). While all of these five approaches measure costs in the same manner, they each use a different approach for measuring consequences of healthcare programs, as outlined in Table 3.1. The remainder of this subsection discusses each of these types in turn.

Table 3.1. Types of economic evaluation. (Table adapted from Table 1.1 in Drummond et al.[82])

Study Type	Cost measurements	Consequence measurements
Cost analysis	Monetary units	None
Cost-minimization analysis	Monetary units	Various – determined equivalent across all programs considered
Cost-effectiveness analysis	Monetary units	Natural units of health (e.g. life years)
Cost-utility analysis	Monetary units	Healthy years (e.g. quality-adjusted life years)
Cost-benefit analysis	Monetary units	Monetary units

Cost analysis

Cost analyses make no attempt to measure the health consequences of programs, instead only measuring the costs. Therefore, costing analyses can only be considered partial economic evaluations. Because they do not provide any information on output, they cannot by themselves inform how best to achieve any form of efficiency.

Cost-minimization analysis

CMAs compare the costs of competing interventions the health consequences of which are believed to be equivalent. Thus, these studies inform productive efficiency by determining the least expensive means of achieving a given health outcome.[82,84] However, CMAs cannot speak to achieving allocative efficiency.

Cost-effectiveness analysis

CEAs, the analysis type conducted in this thesis, measure the monetary costs of interventions per natural unit (e.g., infections prevented). Typically, an intervention's performance is summarized with one such measure. However, a variety of outcomes may be listed separately and the costs of each calculated in turn. This is known as a cost-consequence analysis, considered a subset of CEA by some[82] and a separate form of analysis altogether by others.[84] Such analyses can be much easier to construct than standard CEAs because they remove the need to combine outcomes into a single measure. However, cost-consequence analyses can also be more difficult to compare across studies since they do not report the costs per unit of a single outcome measure.

Many different natural units may be used to measure health consequences. These outcomes may be intermediate (e.g., tests administered), or final (e.g., deaths prevented). Generally speaking, intermediate outcomes tend to be easier to measure but also more narrowly defined, disease-specific, and valuable only insofar as they serve as surrogates for final outcomes of arguably greater interest. In contrast, final outcomes tend to be intrinsically valuable and can generally be used in evaluating a broader range of programs.[82,85] For example, the intermediate outcome of human immunodeficiency virus (HIV) infections detected is only desirable to the extent that

it enables the infected individual to receive treatment resulting in the final health outcomes like life years gained (LYGs).

The selection of outcome has important ramifications for a study's ability to inform questions of efficiency. All CEAs can inform productive efficiency as they can determine the lowest cost per health outcome achievable by the programs under evaluation. However, they can inform allocative efficiency only insofar as the health outcome used is generic and used outside that particular evaluation. In other words, CEAs can inform allocative efficiency *among only those programs whose cost-effectiveness has also been measured using the same outcome measure.*

Thus, returning to the HIV testing example, CEAs determining costs per HIV infection detected can potentially inform allocative efficiency among interventions detecting HIV cases (i.e., HIV testing programs). However, CEAs measuring cost per LYG can theoretically inform allocative efficiency among the broader set of interventions yielding LYG.[†] To improve its capacity to inform allocative efficiency, the CEA in this thesis uses LYG as the outcome measure (see Subsection 3.3.1). Subsection 3.1.4 will focus in greater detail on the decision rules for interpreting the results of CEAs to inform efficiency.

[†] This encompasses a huge range of programs both within and outside the health sector which could potentially increase the life years lived by individual. However, one important caveat is the fact that LYG by a program extending the life of a suffering terminally ill patient is arguably less desirable than that by an intervention preventing the onset of cancer altogether. As such, life years may be more or less desirable based upon whether their gain also prevents some form of morbidity. Quantifying this differential desirability requires accounting for the quality of life experienced by patients during years that would not otherwise have been lived (see discussion on CUAs).

Cost-utility analysis

CUAs are similar to CEAs but differ in their use of special outcomes which quantify the desirability of various health states.[84‡] These outcomes permit CUAs to account for effects related to both morbidity and mortality, making them equally desirable regardless of how they are obtained (in contrast to LYGs, for example, see footnote in discussion of CEAs).[82] Consequently, CUAs are as capable as CEAs for informing productive efficiency, and better suited for informing allocative efficiency. Of course, CUAs are more complex to conduct than CEAs; deciding which utility-based measures to use and how best to convert effectiveness data into these measures is particularly challenging. Utility-based outcome weights are generally solicited from experts, patients, or members of the broader population using methods such as rating scales, standard gambles, or time trade-off questions.[93] The same decision rules for interpreting the results of CEAs apply to CUAs (see Subsection 3.1.4).

Cost-benefit analysis

CBAs assign monetary values to health outcomes. CBAs are ideal for informing allocative efficiency as their results may be compared to any program whose outcomes may be assigned monetary value. Since virtually any outcome can be valued in terms of money, CBAs can theoretically inform how best for society to allocate all of its resources.[82,94] However, the process of assigning monetary value to health outcomes is considered by many to be difficult and even unethical.[95] Decision rules for interpreting the results of CBAs are simple, with net social benefit calculated

‡ These outcomes are adjusted for the utility or value that individuals or society have for various health states.[82] For example, quality-adjusted life years (QALYs) are interval-scaled such that death is equal to 0 and a year of perfect health equal to 1.[86-89] Conversely, disability-adjusted life years (DALYs) – commonly used for evaluations in developing countries given their adoption by the World Bank[90] and the WHO[91] – are interval-scaled such that death is equal to 1 and perfect health is equal to 0 and therefore measured as averted outcomes.[92]

by subtracting a program's cost from its benefit: interventions with net social benefit >0 should be implemented and all others rejected.[82,84]

3.1.4 Decision rules for cost-effectiveness analyses

This subsection expounds upon the decision rules for interpreting the results of CEAs (or CUAs) such as that conducted by this thesis. These rules relate to the incremental cost-effectiveness ratios (ICERs) – the incremental costs per additional units of effectiveness relative to a comparator – associated with the healthcare interventions under evaluation. ICERs may be depicted graphically as coordinate pairs on a "cost-effectiveness plane" (Figure 3.3).[96] The y-axis of the plane represents cost, the x-axis represents effectiveness, and the origin is set as the cost and effectiveness of the comparator. Therefore, the slope of the line from the origin to a coordinate pair results in the ICER of the intervention depicted by that pair.

Policy recommendations for healthcare interventions are based on the following rules regarding those interventions' ICERs. First, if an ICER is in the north-west quadrant, the intervention will always be rejected as it is both more expensive and less effective than the comparator. Conversely, an ICER passing through the south-east quadrant will always be accepted as it is both less expensive and more effective than the comparator. Determining the best course of action is less simple when interventions' ICERs pass through the north-east or south-west quadrants. Such interventions are simultaneously more costly *and* more effective or less costly *and* less effective compared to the baseline program, respectively.[96]

The concept of a threshold ICER can further guide the decision of whether to adopt these programs. Depicted by the symbol λ, threshold ICERs represent the maximum

amount that a decision-maker or society is willing to pay for a unit of effectiveness (e.g., LYG). Threshold ICERs can be depicted on cost-effectiveness planes as lines passing through the origin (Figure 3.3). Any intervention whose ICER slope is less than λ should be implemented. Thus, on a cost-effectiveness plane, ICERs in the north-east or south-west quadrants below and to the right of λ will be accepted while all others in these two quadrants will be rejected.

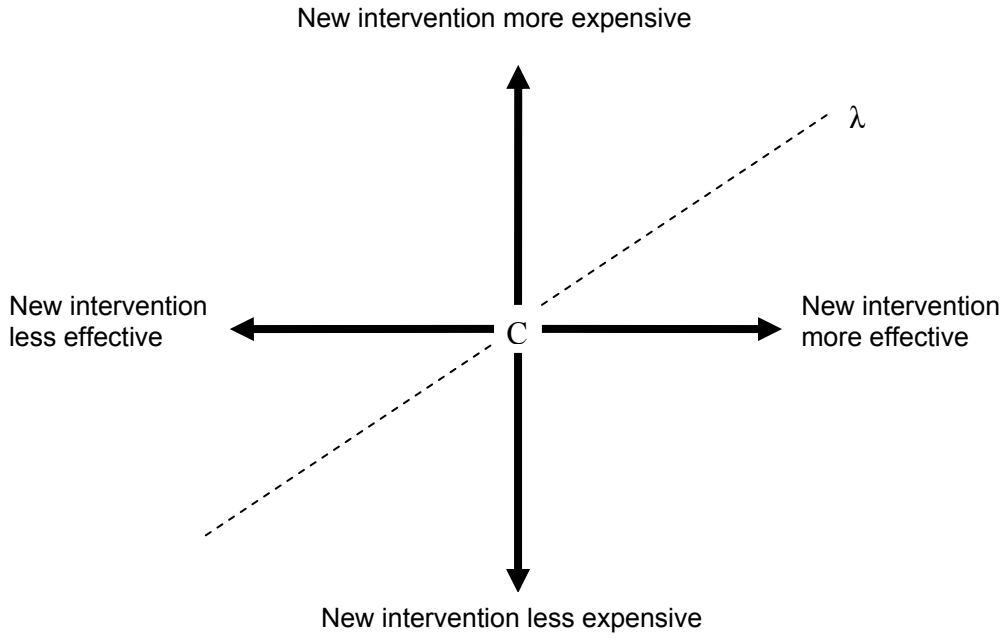

Figure 3.3. The cost-effectiveness plane.

Determining λ

The value of λ can be determined by a variety of methods. First, program options could be prioritized from lowest to highest ICERs and resources allocated accordingly. Under this scheme, the ICER of the final program for which sufficient resources remain to implement equals λ.[91,97] However, this approach requires estimates of the ICERs for all conceivable healthcare intervention options.[98] Each of

these estimates would further need to be of consistent quality and transferable to settings outside of those in which they were measured.[99]

Alternatively, λ could be set equal to the highest ICERs observed among programs already accepted as cost effective.[82] Of course, this approach effectively side-steps the dilemma of determining what value for λ would be consistent with allocative efficiency in the health sector, instead only highlighting what decision-makers have historically been willing to pay per unit of effectiveness. In other words, this approach determines what λ is rather than what it ought to be.

A third option is to use the values for λ recommended by published economic evaluation guidelines. For example, the National Institute for Clinical Excellence (NICE) in the United Kingdom (UK) recommends a general threshold ICER of £20,000 (US$39,400)/QALY.[§] NICE further recommends that programs with ICERs up to £30,000 (US$59,100) be considered possibly acceptable on grounds other than cost-effectiveness alone. Finally, NICE advises that programs with ICERs higher still will require special reasons and justification for their adoption.[100] Literature from the United States of America (USA) suggests that the lower-bound threshold ICER value in North America is comparable at US$50,000/QALY.[101]

Guidelines generally recommend a lower threshold ICER for developing countries. To my knowledge, country-specific guidance on λ values is rare and does not exist for South Africa. However, the WHO advocates the guidelines of the Commission on Macroeconomics and Health in all resource-poor settings. These guidelines stipulate

[§] Note that the NICE guidelines cited in this thesis are those published in 2004. These were superseded by new draft guidelines in early 2008 which have since been formalized.

that interventions yielding DALYs at a cost less than a country's per capita gross national income (GNI) – approximately US$5,390 in 2006 for South Africa, as measured in 2006 dollars[102] – are highly cost effective. The guidelines consider interventions yielding DALYs at a cost of less than three times a country's per capita GNI to be moderately cost effective.[103]

There is an absence of robust research methodologies for empirically measuring λ.[98] Therefore, this thesis accepts the WHO recommendations as an approximation of South Africans' current willingness to pay for HIV screening. However, applying these recommendations to the results of this thesis requires using the outcome measure examined in this thesis (LYG) as a proxy for DALYs. Because LYGs are not adjusted for utility, the costs per LYG deemed cost-effective by the WHO must be considered lower than those reported here. This fact is acknowledged and discussed further in the discussion of the CEA results (see Subsection 7.3.3).

Evaluating multiple interventions

In many instances, as in this thesis, more than one intervention is compared to current practice. If all options are plotted on a cost-effectiveness plane, the slopes of the lines drawn between the coordinate pairs constitute the ICERs of those policies compared to one another. For example, in Figure 3.4, the slope of the line between the origin and point A is the ICER for intervention A compared to the program which the origin depicts (e.g., current practice). Similarly, that of the line connecting points A and B is the ICER for intervention B compared to intervention A.

The decision rules for interpreting the results of these ICERs between program options are similar to that when considering only a single intervention. Intervention

options which are both more expensive and less effective than any others are said to be dominated (e.g., point C) and not cost-effective. Additionally, interventions with ICERs larger than those of the next most expensive cost-effective options are said to be extended dominated (e.g., point D).[82] The lines connecting the cost-effective policies together thus comprise a 'cost-effectiveness frontier,' any programs to the left of which are considered not cost-effective.

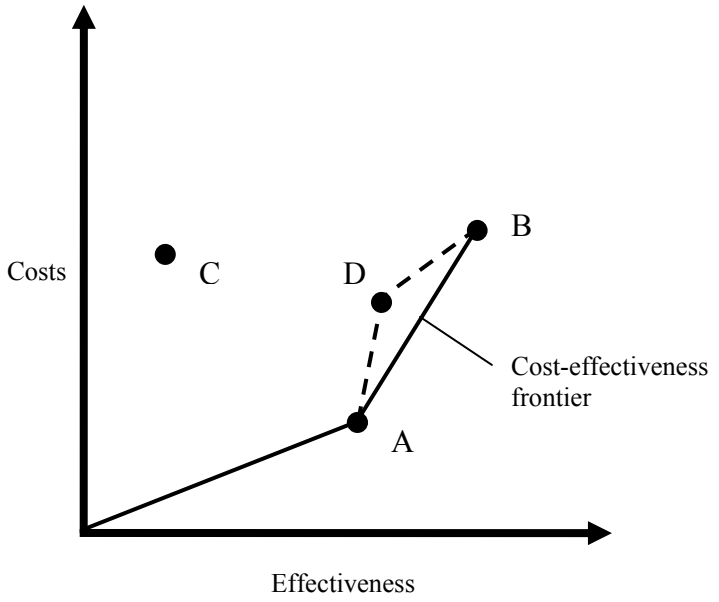

Figure 3.4. The cost-effectiveness plane with multiple interventions. The bold line running from the origin to points A and B represents the cost-effectiveness frontier.

Figure 3.4 highlights the importance of incremental analysis. When intervention A is an option, it cannot be said that the line between the origin and point B accurately depicts the ICER for point B compared to baseline practice. This is because some of that effectiveness can be achieved at a lower cost with intervention A. Thus, implementation of intervention B must ultimately result from an acceptance of its ICER compared to the next least expensive cost-effective option, in this case

intervention A. (See Subsections 2.4.3 and 3.3.3 for a further discussion of the complexity of incremental analysis of HIV testing programs.)

Using these decision rules for evaluating multiple interventions requires several important assumptions. First, all of the interventions under evaluation are mutually exclusive: if patients receive one of the interventions, they cannot receive any of the others. Second, the interventions are perfectly divisible and so deliverable to smaller groups of patients than those depicted in the cost-effectiveness plane. Finally, there are constant returns to scale, such that delivering these interventions to smaller groups of patients would not reduce cost-effectiveness. This thesis assumes all of these conditions hold for the CEA presented in Chapter 7.

3.1.5 Economic evaluation designs

Economic evaluation research designs may be broadly categorized as either primary or secondary. Primary designs focus on collecting primary data through research trials. These include *piggyback studies*, which collect economic data alongside ongoing efficacy studies,[82,84] and *cost-effectiveness trials*, designed specifically for detecting both economic and effectiveness data.[82,104,105] Alternatively, secondary designs focus on the use of models to synthesize data from various sources and simulate the costs and outcomes of interventions under evaluation. Hybrid designs are also possible, combining trial-based data collection with modelling to project outcomes that cannot be observed directly.

For the economic evaluation presented in Chapter 7, it would have been impractical to implement all eight expanded testing policies listed in Table 2.1. Furthermore, observing health effects over the entire lifetimes of the testing clients would have

been similarly implausible. Therefore, I adopted a modelling approach, using the previously-published Cost-Effectiveness of Preventing AIDS Complications (CEPAC) simulation model (see Appendix A). To better facilitate the application of this model to the research questions in this thesis, I also constructed the Acute HIV Infection Testing (AHIT) supplementary model for use with CEPAC (see Subsection 3.3.2). The next subsection provides background to this modelling approach by focusing in greater detail on modelling methodologies.

3.1.6 Methodological decisions for models

A health economics model is here defined as "any mathematical structure that represents the health and economic outcomes of patients or populations under a variety of scenarios."[106] Models have been described by some to be an "unavoidable fact of life" in economic evaluation.[104] They are useful for synthesizing evidence from various sources and simulating hypothetical scenarios, so facilitating analysis of more comparators than is practical for primary designs. Furthermore, the costs and effects of modelled interventions can be observed over long time horizons without limitations related to study time or resources. Finally, model parameter inputs may be easily adjusted, thereby making sensitivity analyses much simpler.[104,106]

However, there are drawbacks to using models. Models generally require a range of assumptions and must fit data from empirical observations to a range of parameters (see Subsection 3.3.2). These problems are exacerbated by the fact that models are often not transparent to individuals not conducting the evaluation, a particular problem for more complex models. These issues require investigators using models to outline carefully the methodological approaches underlying any model.[106]

This subsection explores some of these modelling approaches. Since the modelling terminology in the literature is often used inconsistently,[107] I make explicit my use of all terms. Given the wide variety of model options, I focus only on common options for three major components of any model often addressed in the health economics literature: (i) model type, (ii) evaluation method, and (iii) treatment of infectiousness.

Model types

Model type here refers to models' underlying analytic methodologies and structures. The most common model type is the decision tree (see Subsection 4.2.2), comprising an initial decision node representing a choice of interventions. The results of these choices are then modelled by 'branches' consisting of sequences of chance nodes representing probabilities of occurrence, defined by the investigator, for various events. All events are further assigned costs and health outcomes. Expected total costs and outcomes for a hypothetical cohort for each of the interventions possibilities are then summed and weighted according to the probabilities of occurrence. The expected costs and outcomes are then compared across the different intervention options to determine which is most cost-effective.[82,105-108]

Although conceptually simple, decision trees struggle with modelling recurring events. Examples of such events relevant to HIV testing include repeat screening and the recurring possibility of HIV-positive individuals experiencing opportunistic infections (OIs). Decision trees can theoretically model recurring events through the use of extensive tree structures with numerous branches. However, the complexity of such structures generally makes the use of alternative models preferable.[107]

The second common model type, a state-transition model, is better suited for modelling repeat events. In state-transition models, hypothetical patients assume one health 'state' at a time and may transition to other states according to user-defined probabilities. Such transitions occur at regular intervals (e.g., monthly) representing the passage of real time.[82,105-108] Many state-transition models feature the Markovian assumption that the probabilities of transition between states depend only on the current state and not the pathway by which the patient reached that state.[109]

The Markovian assumption greatly simplifies state-transition models but complicates portraying disease progression when patients' prognoses are dependent upon their clinical histories. Markov models can circumvent this limitation by expanding the state space to encompass "tunnel states." Such states represent both patients' current health states and the pathways by which they transitioned into those states. However, the addition of large numbers of tunnel states can make Markov models unwieldy.[106-108] Alternatively, non-Markovian state-transition models known as microsimulations (also known as discrete event simulations) are sometimes used to model situations when patient prognoses are highly dependent upon clinical history.

Evaluation methods

Decision trees and Markov models both use cohort evaluation methods, modelling entire groups of patients at once. However, they go about these cohort analyses in slightly different ways. A decision tree calculates expected costs and outcomes over the model's entire time horizon for a cohort under alternative programs. Conversely, Markov models assess cohorts in time cross-sections, measuring cohort costs and health outcomes at the end of cycles (e.g., each month); the costs and outcomes for all

cycles are then aggregated and compared across all program alternatives.** Advantages of cohort evaluation methods include their speed and simplicity.

Conversely, microsimulations use patient-level evaluation methods, considering one simulated individual at a time. These models are capable of incorporating patients' histories to determine state transition probabilities.[106-108] However, this approach is more complex, can require substantial computing power,[106,108,110] impose greater data demands, and make it difficult to account for second-order uncertainty (see Subsection 3.2.3 on handling uncertainty).[108] Moreover, one study comparing microsimulation and Markov models of breast cancer treatment found no substantial differences in results.[110] Nevertheless, the author predictably highlighted microsimulations' greater flexibility in modelling data describing patients' clinical histories. Ultimately, the ideal choice of model is likely to be disease-specific, with microsimulation likely superior for diseases like HIV for which progression is dependent upon past clinical events (see Subsection 3.3.2).

Treatment of infectiousness

Models of infectious diseases such as HIV can account for infectiousness by accounting for the probability of disease transmission. Models incorporating infectiousness may be either static or dynamic. Static models assume fixed rates of new infections and often consider only secondary transmission events (i.e., those originating with patients receiving the intervention under evaluation). In contrast, incidence rates in dynamic models are dependent upon the proportion of the total population which is infected, so making it possible to account for phenomena such as 'herd immunity.'[108,111] Moreover, dynamic models generally account for chains of

** This cross-sectional approach is similar to that used by many population demographic models.[105]

infection extending beyond secondary transmission. An evaluation's results can be highly dependent upon its treatment of infectiousness. For example, Brisson and Edmunds found very different cost-effectiveness ratios when evaluating the same vaccination programs using static versus dynamic models.[111]

Many models of infectious diseases used for economic evaluations, including the CEPAC model used in this thesis (see Appendix A and Subsection 3.3.2), do not account for infectiousness. Among those that do, most – including all decision trees and Markov models – adopt a static approach.[111] Yet, dynamic non-Markovian state-transition models do exist.[108] Such models may adopt either patient-level (e.g., microsimulations)[112] or cohort evaluation methods (e.g., system dynamics models).[107]

3.2 Economic Evaluation Guidelines

There are two key rationales for establishing and using guidelines for economic evaluations. The first is to ensure good practice within studies (internal validity). The second is to homogenize methodological approaches among studies, thus making them more readily comparable with one another (external validity).[113] This section outlines various guidelines for structuring, conducting, and interpreting economic evaluations. Throughout this section, I briefly describe how these guidelines informed the methodological decisions for my own evaluation presented in Chapter 7.

Many different economic evaluation guidelines exist. This section focuses on those particularly informative for the CEA of expanded HIV testing in South Africa presented in this thesis. Economic evaluation guidelines for developing countries are usually disease- rather than country-specific. Furthermore, the target audience for

guidelines most relevant to developing countries are typically program managers with limited economics training.[114] Thus, it is unsurprising that while I was unable to identify any South Africa-specific guidelines, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has published sets of HIV-specific guidelines aimed at non-economists. These include guidelines for conducting costing analyses[115,116] and CEAs[117] in developing countries, all of which are considered in this section.

Since the CEPAC model used in this analysis was originally constructed for use in the USA, prominent guidelines developed in affluent settings are also considered. These include the recommendations by the USA Panel on Cost-Effectiveness in Health and Medicine;[118] the economic evaluation text by Drummond et al.;[82] and the NICE guidelines from the UK.[100] Finally, two reports on good modelling practice are also considered: the National Health Service Health Technology Assessment (HTA)[119] and International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices.[120]

3.2.1 Guidelines for structuring economic evaluations

Objective and target audience

There guidelines broadly agree that the objective and target audience of all economic evaluations should be clearly defined.[82,84,100,116,117,119] The objectives of this thesis are embodied by its research questions (see Subsection 1.2.1). Regarding target audience, it is believed the results of this thesis will be of particular relevance to policy-makers in the South African Department of Health (SADoH) and other organizations funding HIV-related interventions in sub-Saharan Africa (e.g., the Global Fund).

Evaluation type

Investigators must specify and choose carefully methods for measuring costs and health consequences. The USA Panel[121] and NICE[100] both recommend CUAs using QALYs with value weights solicited from communities using standardized and validated instruments. The WHO similarly advocates CUAs, but supports using DALYs[91] instead of QALYs for outcome measures, with value weights solicited from experts.[92] The UNAIDS HIV-specific guidelines advocate CEAs,[117] possibly not advocating utility-based outcome measures due to a preference for simpler methodologies.[††] None of the considered guidelines actively espouses CBA, likely also because of the methodological difficulties in assigning monetary values to health outcomes (see Subsection 3.1.3). For this thesis, I conducted a CEA using LYG as the outcome measure (see Subsection 3.3.1).

Perspective

An evaluation's perspective refers to the means by which relevant costs are identified. There is agreement across all guidelines considered here that the perspective of any economic evaluation must be explicitly stated.[82,84,91,100,115-117,119] All of these guidelines also recommend adopting a societal perspective in which *all* costs, whether incurred by patients or providers, are included. This contrasts with a payer perspective in which only those costs incurred by a particular entity (e.g., hospital, government) are included. An example of a societal cost neglected if adopting a payer perspective is patient productivity lost due to a healthcare intervention (e.g., waiting for test results). A societal perspective also requires exclusion of costs which are in fact transfer payments (resource transfers from one party to another without

[††] Indeed, utility data can be particularly difficult to collect when non-economists are conducting evaluations in resource-poor settings, the scenario of focus for the UNAIDS guidelines.

resource consumption).[82,84,91,115] I follow these guidelines in this thesis, adopting a societal perspective for measuring the costs of HIV screening (see Subsection 7.1.2).

Intervention definition

All of the guidelines considered here agree upon the need for economic evaluations to define carefully the interventions being studied, including relevant comparators.[82,84,91,100,115-117,119] The USA Panel argues that relevant comparators include any existing programs related to the intervention in question.[84] In contrast, the WHO argues that the principal comparator should be the "counterfactual of the null set of the related interventions." In this counterfactual scenario, no programs related to the interventions under evaluation are available to the target population.[91] This thesis follows the recommendations of the USA panel (see Subsection 3.3.3).

Target population

There is similarly broad agreement across economic evaluation guidelines that the populations targeted by the interventions under evaluation must be explicitly defined.[82,84,91,100,115,119] Some guidelines further recommend estimating the cost-effectiveness of the intervention if applied to relevant subgroups.[84,100,115] All analyses in this thesis are confined to adults (see Section 2.2). Current testing practice targets both primary healthcare users (baseline testing), and antenatal care (ANC) users and tuberculosis (TB) patients (background testing). The expanded testing policies all target primary healthcare users. Yet, while these are the groups targeted for HIV testing, this thesis presents a population-level analysis, evaluating the impact of these policies for South Africa's entire adult African population (see Subsection 3.3.4).

Boundaries

The USA Panel,[84] Drummond text,[82] and HTA modelling guidelines[119] note that the effects of healthcare interventions may extend beyond their target populations.[‡‡] Therefore, it is important to state explicitly the boundaries of a study. Doing so makes clear whether such 'downstream' effects of an intervention are being considered.[82,118,119] The CEA reported in this thesis accounts only for the health benefits and costs for those individuals receiving HIV testing and linkage-to-care. I divided these benefits and costs by the size of South Africa's entire adult African population to determine the population-level impact (see Subsection 3.3.4).

Time Horizon

Most of the economic evaluation guidelines also recommend explicitly stating the study time horizon. Furthermore, they each advocate that this horizon be sufficiently long to capture all costs and outcomes attributable to the interventions evaluated.[82,84,91,100,116,119] The time horizon for the CEPAC microsimulation model used by this thesis spans the lifetime of each simulated patient (see Appendix A).

Design

Economic evaluations may adopt primary or secondary designs (see Subsection 3.1.5). The USA Panel states that robust primary data should be used for economic evaluation whenever possible.[84] However, primary research designs are often impractical, particularly for evaluations of multiple programs or interventions whose health effects span over many years. Given the limitations of primary research

[‡‡] For example, beyond linking clients diagnosed with HIV to care, expanded testing policies may also prevent infection of their future sex partners by encouraging safer sex.[122-127]

designs, many guidelines have acknowledged the potential value of model-based designs using primary data for parameter inputs.[82,84,91,100,117]

The HTA modelling guidelines note the importance of rigorously defending the methodologies underlying any model.[119] For new model construction, the HTA,[119] ISPOR,[120] and NICE[100] guidelines recommend carefully outlining all structural relationships and assumptions; ensuring these relationships are not dictacted by data availability; justifying use of all data used to populate parameters; and making models as transparent as possible. For state-transition models, the HTA[119] and ISPOR[120] guidelines further recommend using cycle lengths equal to the minimal interval over which clinically relevant disease progression is expected to occur.

Building new models adhereing to good practice requires a great deal of time and effort. Recognizing this, the WHO[91] and UNAIDS[115] have offered their own models for use by investigators. For this thesis, I used the CEPAC model previously constructed by investigators in the USA (see Appendix A) and collected primary data to fit to its parameters (see Subsection 3.3.2).

3.2.2 Guidelines for conducting economic evaluations

Identifying relevant costs

All of the guidelines considered here agree upon the importance of identifying all relevant costs for any interventions evaluated.[82,91,100,115-117,128] However, these guidelines also advise that the unavailability of such data should not preclude conducting evaluations. Indeed, the guidelines note that modelling approaches using imperfect information still provide more useful information than no evaluation.[119,120]

Perhaps the most obvious expenses are direct medical costs. These include costs for tests; drugs; personnel wages; facility maintenance; and administration, including overhead costs.[82] Also important are direct non-medical costs such as transportation to healthcare facilities and day care delivered to family members.[128] The methods used in this thesis for estimating direct costs related to HIV testing are outlined in Subsection 7.1.2 while those related to treatment are reported in Appendix B.

This thesis also estimates the costs of patient time (and hence productivity) lost due to HIV testing. This was done to capture all societal costs attributable to the testing process (see Subsection 3.2.1). However, there is no consensus regarding how best to incorporate these indirect costs into ICERs. The USA Panel argues that they should be captured as decreases in the ratio denominator, measured in terms of detriments to health outcomes (e.g., reductions in QALYs).[128] Others have argued for the inclusion of these costs into the ratio numerators, measured in terms of monetary expenses.[129] Finally, the WHO supports the exclusion of indirect costs entirely, believing the methodological difficulties too great to account for such costs appropriately.[91] Since I did not use utility-based health outcomes, I included these costs in the numerators of my cost-effectiveness ratios (see Subsection 7.1.2).

Guidelines also differ in their recommendations regarding which future costs to include. No guidelines contest the inclusion of future costs directly associated with an intervention in calculating its cost-effectiveness. It is less clear whether unrelated expenses incurred during life years gained by an intervention (e.g., costs of living). Some argue for including these costs as they would not have been incurred had it not been for the intervention.[130] Others retort that as long as all evaluations exclude these costs they will remain comparable to one another.[94] CEPAC lacked the parameters

necessary to account for these future costs. However, their exclusion likely makes my results more comparable to those of previous economic evaluations of HIV testing programs, none of which have accounted for these costs (see Subsection 4.2.2).

Measuring resource use

A spectrum of methods exists for quantifying resource use for identified relevant costs. On one end of the spectrum is micro-costing, the procurement of a detailed inventory of all resources consumed. On the other end, gross-costing uses approximations of resources consumed for entire units of input (e.g., days of hospitalisation). The USA Panel[128] and WHO[91] both support the use of micro-costing whenever possible. That said, the ISPOR[120] and HTA[119] modelling guidelines note it is appropriate to use less robust methods to approximate inputs for cost parameters to which a model is insensitive. I adopted a gross-costing approach with use of secondary data sources for measuring testing costs (see Subsection 7.1.2).

Valuing resources

There is widespread agreement that all costs should be valued using a single, constant currency.[91,100,115,116,128] Thus, costs measured in different time periods must be adjusted such that they are all expressed as monetary units for the same year. The WHO recommends using countries' gross domestic product (GDP) deflators to make these conversions.[91] The WHO[91] and UNAIDS[116] also recommend accounting for depreciation of capital expenditures (e.g., buildings in which HIV testing is offered) by using annuitization methods. Finally, the WHO[91] recommends applying a purchasing power parity (PPP) conversion rate to all final costs. A PPP rate reflects the fact that US$1 worth of South African Rand, for example, may buy more or fewer goods and services within South Africa than what US$1 can purchase in the USA.

This thesis follows all of these recommendations except for the use of a PPP exchange rate (see Subsection 7.1.2). This final recommendation was not followed as many of the medical supplies required for the testing policies examined in this thesis must be purchased abroad. I also used a standard exchange rate to make my results more comparable to previous economic evaluations of screening programs identified in Chapter 4, none of which used a PPP exchange rate (see Subsection 4.2.2).

Measuring effectiveness

Many of the guidelines considered here discuss good practice for collecting effectiveness data using primary research designs.[82,91,100,105§§] Many of the guidelines considering primary designs in economic evaluation focus on the use of randomized control trials (RCTs).[132] RCTs are considered the highest standard evidence by NICE[100] and the USA Panel[105] guidelines given their capacity to isolate the effects of single variables from external influences (confounders). Yet, the guidelines also note that RCT effectiveness data can have low generalizability, a particular problem when seeking parameter inputs for models projecting the cost-effectiveness of related interventions to broader populations.[82,91,100,105]

The NICE[100] and USA Panel[105] guidelines acknowledge the potential value of alternative epidemiological designs (e.g., cohort, case-control, descriptive studies) to provide more generalizable data describing intervention effectiveness. Such alternative designs are also likely to be less expensive than RCTs. However, these designs are less able to control for confounders and can be more prone to study biases (e.g., self-selection bias, recall bias).[100,105] While acknowledging these limitations,

[§§] See Hennekens and Buring[131] for a more comprehensive treatment.

this thesis uses a retrospective descriptive study to measure population testing rates in South Africa (see Subsection 3.3.4).

The guidelines on measuring effectiveness also touch on two of the methodological issues examined in greater detail in this thesis. First, regarding comparators, most of the guidelines recommend measuring incremental effectiveness compared to current practice.[82,100,105] However, as noted in Subsection 3.2.1, the WHO advocates evaluating the cost-effectiveness of interventions compared to the "counterfactual null set of interventions." Consequently, the WHO recommends measuring effectiveness compared to a 'do nothing' scenario. Current practice serves as the comparator in this thesis, although somewhat unconventional methods are used to quantify its influence on the incremental cost-effectiveness of expanded testing (see Subsection 3.3.3).[91]

Second, the guidelines also consider the issue of choosing outcomes of interest. Drummond et al.[82] caution against measuring effectiveness with solely intermediate health outcomes while acknowledging the difficulties of trials collecting generic final health outcomes (see Subsection 3.1.3). Also, the USA Panel guidelines recommend using outcome measures which are less open to interpretation by those measuring effectiveness to limit observer bias.[105] Subsection 3.3.1 discusses in greater detail the outcomes examined in this thesis.

Regardless of methods used to measure effectiveness, the guidelines all acknowledge that, particularly in modelling studies, secondary data will often be required to supplement primary effectiveness data. The USA Panel[105] and NICE[100] both highlight the importance of critical appraisal of such secondary sources to ensure the data retrieved are robust and appropriate for use in a model. The majority of secondary

data sources used in this thesis relate to the costs and effects of HIV-related treatment and were collated and appraised by the CEPAC collaborators (see Appendix B).

Discounting

It is common practice in economics to discount costs over time, reflecting the time preference of individuals. It has been argued that discounting health outcomes at the same rate as monetary costs is important for maintaining a steady-state relation between the two since health outcomes are being measured *relative to* monetary costs.[130] Using the same discount rate for health outcomes and costs remains a subject of controversy[133,134] but has nevertheless become the norm in economic evaluation guidelines. Indeed, a systematic review published in 2001 found only one jurisdiction, the UK, supporting different discount rates.[135] (Since then, NICE, a UK agency, has also begun recommending using the same discount rate, 3.5%, for effects as used for costs.[100]) The Drummond text[82] and UNAIDS costing guidelines[116] espouse using the same rate for each at whatever discount rate prevails in the study setting. The USA Panel[136] and WHO[91] recommend using a 3% rate ranging from 0% to 6% and 7% in sensitivity analyses, respectively. In the CEA presented in Chapter 7, I use a 3% discount rate in the baseline scenario with sensitivity analyses adjusting this from 0% to 7%.

3.2.3 Guidelines on economic evaluation analysis

Beyond the use of the decision rules outlined in Subsection 3.1.4 for CEAs, the principal issue related to the analysis of economic evaluation results is handling uncertainty. Uncertainty is a particular issue for models. There are four major types of uncertainty in modelling studies: (i) methodological, (ii) parameter, (iii) modelling,

and (iv) generalizability.[137] This subsection considers guidelines for handling each of these types of uncertainty. It concludes with a discussion of model validation.

Methodological uncertainty

Methodological uncertainty stems from the controversy on the range of methodological decisions outlined in Subsection 3.2.2 (e.g., choice of discount rate, methods for handling future costs).[137] The HTA modelling guidelines,[119] WHO,[91] and the USA Panel[138] all highlight the importance of addressing this uncertainty. These guidelines advocate assessing the effects on study results of adjusting parameter inputs whose values depend upon these methodological decisions one at a time (univariate sensitivity analyses). They further advocate adjusting multiple inputs simultaneously (multivariate sensitivity analyses) for parameters to which the study results are especially dependent.

The widespread use of guidelines in itself also minimizes methodological uncertainty across studies by homogenizing these methodological decisions: if all studies adopt the same methodological approaches, their results are more comparable to one another.[137] I attempted to minimize methodological uncertainty by basing the methodological decisions for this thesis on the guidelines for good practice outlined in Subsections 3.2.1-3.2.2. For those decisions for which no consensus exists among the guidelines, I attempted to adopt the approaches used by the previous evaluations of HIV testing programs I identified in the literature. Furthermore, I conducted limited sensitivity analyses of the effects of changing parameters inputs related to these methodological decisions (e.g., discount rate).

Parameter uncertainty

There are two broad forms of parameter uncertainty. First-order uncertainty refers to variability or chance.[139] For example, although data may demonstrate that the likelihood of a flipped coin landing on one side is 50%, it remains uncertain which side it will land on each time it is flipped. Models evaluating entire cohorts simultaneously (e.g., Markov models or decision trees, see Subsection 3.1.6) generally do not account for this uncertainty. Such models instead use "deterministic" calculations which, to continue the example, assume that exactly 50% of coins flipped will land on a particular side. Conversely, models simulating individual patients one at a time (e.g., microsimulations) do account for this uncertainty with "stochastic" calculations. These calculations compare generated random numbers with defined probabilities to determine if individuals experience events.[82,105,106,108]

Second-order uncertainty refers to uncertainty in the parameter input values.[139] Thus, using the same example above, second-order uncertainty refers to the possibility that the acceptance rate for HIV testing may not be 90%. Instead, 90% represents the best point estimate for a range of plausible values (e.g., 85%-95%). Models which are first-order deterministic as described above (e.g., decision trees and Markov models) can be easily made second-order stochastic. Second-order stochastic models run multiple iterations, each time drawing samples from defined data distributions informing parameters inputs. This process is known as probabilistic sensitivity analysis (PSA).[82,105,106,108] Conducting PSA with first-order stochastic models without imposing prohibitive computation demands is still an area of ongoing research.[108]

To my knowledge, no guidelines advocate a particular approach to accounting for first-order uncertainty. However, most advocate specific strategies for capturing

second-order uncertainty. The USA Panel recommends simple univariate and multivariate sensitivity analyses by estimating confidence intervals for each parameter input and adjusting the inputs according to those intervals. The USA Panel cautions evaluators to avoid max-min analyses, in which all variables are simultaneously given their lowest or highest values, unless such scenarios are believed to be realistic possibilities.[138] Conversely, the WHO,[91] HTA,[119] and NICE[100] recommend PSA to capture second-order uncertainty. Given that CEPAC is first-order stochastic and not currently readily capable of PSA, I attempt to capture parameter uncertainty through the definition of plausible ranges for input values (see Subsection 3.3.2) and subsequent univariate and multivariate sensitivity analyses.

Modelling uncertainty

Uncertainty regarding model structures (e.g., relationships between parameters) and the overall modelling process by which the economic evaluation was conducted together comprise modelling uncertainty. The USA Panel[138] and HTA[119] argue that sensitivity analyses may be used to address the former. However, both guidelines assert that the latter can only be addressed insofar as the results may be compared to those for separate studies and models. In the case of this thesis, I was not given access to CEPAC's underlying computer code. Consequently, while CEPAC's extensive record of publication and validation in the peer-reviewed literature suggests limited modelling uncertainty (see Subsection 3.3.2), I was otherwise unable to address this issue in this thesis.

Generalizability uncertainty

Finally, generalizability uncertainty concerns the extent to which economic evaluation results are transferable to contexts outside that in which the study was conducted.

Strictly speaking, this is an issue of variability rather than uncertainty.[82] Therefore, approaches addressing this uncertainty are amenable to the same methods as used to address parameter uncertainty. Indeed, for addressing generalizability, the USA Panel[138] guidelines again recommend univariate and multivariate sensitivity analyses while the WHO[91] and HTA[119] guidelines again recommend PSA. For the reasons outlined above, this thesis follows the USA Panel recommendations.

Validation

Establishing the validity of economic evaluations, particularly those using modelling approaches, verifies that their results are robust and meaningful. According to the HTA guidelines, there are two forms of validity for models. First, internal validity requires that model results are intuitive and reasonable given the inputs used. Second, external or predictive validity requires that results are comparable to those observed from similar modelling studies or empirical data.[119] Achieving external validation is equivalent to minimizing generalizability uncertainty. See Subsection 3.3.2 for more on validation efforts in this thesis.

3.3 Discussion

This section discusses in greater detail some of the issues raised in this chapter which became salient in answering the research questions posed by this thesis. First, I discuss my choice of health outcome for the CEA in Chapter 7, recognizing that throughput for the HIV testing cascade is by itself an outcome of limited value. Second, I outline my modelling approaches for this thesis and the challenges arising from fitting empirical data to the models used. Third, I consider the implications of current testing practice in South Africa for defining the interventions under evaluation

and conducting an incremental analysis. Finally, I conclude by discussing how the need for data appropriate for a population-level evaluation affected the design chosen for the epidemiological study presented in Chapter 5.

3.3.1 HIV testing outcomes

As argued throughout this thesis, an important issue concerning evaluations of any screening programs is the relative unimportance of testing alone compared to the health gains following linkage-to-care. As discussed in Subsection 3.1.3, the outcome used to evaluate programs has important implications for an evaluation's capacity to inform various types of efficiency (see Subsection 3.1.2 for definitions of efficiency). Yet, there is a balance to be struck as those outcomes with the greatest capacity for informing productive and allocative efficiency are also the most difficult to measure.

It would perhaps be ideal to conduct a CBA, measuring the health benefits of expanded HIV testing in South Africa in monetary terms. Such an analysis could best inform the arguments by some that South Africa's health budget should be increased to accommodate the costs of antiretroviral treatment (ART).[50] The next option most informative for allocative efficiency would have been a CUA, measuring gains in an outcome adjusted for patient values or utilities. Yet, as mentioned in Subsection 3.1.3, the methods of soliciting from patients the data necessary to derive either monetary valuations (for CBAs) or utility-based outcomes (for CUAs) for health states is complex.[82] Doing so in South Africa would have been especially difficult given that the first language of many members of the study community examined in Chapter 5 is Xhosa. Therefore, it would have been necessary to translate the instruments commonly used to solicit from individual patients the value they might place on a year of life health into this language.

To avoid these difficulties of soliciting preferences directly from patients, I instead conduct a CEA. For the interventions outcome, I examine LYGs. I believed this outcome to be more clearly relevant to patient health and applicable to a broader range of programs than passage through particular steps of the HIV testing cascade. Moreover, I also believed LYG to be a broad outcome measure of interest, as evidenced by its common use in the current HIV testing economic literature (see Subsection 4.2.1). Thus, my study potentially has relevance for informing allocative efficiency within the health sector in South Africa.

However, the choice of LYG as an outcome measure came with its own challenges. The epidemiological study presented in Chapter 5 did not directly observe the life spans of those clients receiving HIV testing. Indeed, doing so would have required a lengthy and expensive cohort trial. Instead, it was necessary to project the expected LYGs for HIV-infected persons receiving testing and linkage-to-care. These projections were facilitated through the use of modelling, as discussed in the next subsection.

3.3.2 Modelling approaches

This thesis adopts a modelling approach, relying on the CEPAC model to simulate the costs and health effects of HIV screening and treatment. This was necessary to project the LYGs by the various screening programs examined in this thesis. As noted in Subsection 3.1.5, this was also necessary given the impracticality of implementing and observing the lifelong health effects of all the eight expanded testing policies examined in this thesis (see Section 2.2 and Table 2.1). Moreover, a primary research design examining the effects of various policies with varying efforts to link seropositive clients to treatment would be unethical given the availability of

life-saving ART[2-4] and OI prophylaxes.[40-43] This subsection discusses further the specific modelling approaches I used and the accompanying challenges.

CEPAC

I chose the CEPAC state-transition microsimulation model for use in the evaluation of expanded HIV testing programs reported in Chapter 7. This model is programed in C++ programming language (Microsoft, Seattle, WA, USA). It models a series of complex relationships between HIV disease progression and a wide range of variables including patients' treatments, immune system states, and viral loads (VLs).[26,140-142] Furthermore, because CEPAC simulates single patients at a time, it can reflect empirical findings that patients' likelihoods of suffering HIV-related acute events can be affected by past events. The most important of these past events include previous opportunistic infections (OIs) or other complications.[141] Chapter 7 and Appendix A provide further details regarding CEPAC's structure.

The building of CEPAC by collaborators affiliated with Massachusetts General Hospital in the USA broadly followed the USA Panel guidelines for good practice in modelling outlined in this chapter. CEPAC's construction has been iterative since its first publication, leading to a modular structure.[143] The model initially comprised only a disease progression component and a module simulating the costs and effects of OI prophylaxes.[143-146] Soon after, a module was added to simulate the costs and effects of ART.[147-149] Goldie et al.[150] recently applied the model to a resource-poor setting, conducting a CEA of ART provision in Côte d'Ivoire. Most recently, a module simulating screening has been developed[151-154] which has yet to be applied

outside of the USA. A module simulating secondary transmission is also now in development, but was not finished in time for use in this thesis.[153,154***]

While CEPAC's complexity affords users substantial flexibility in modelling various interventions and scenarios, it also creates challenges for investigators. First, the model is not transparent. Second, it requires substantial computing power. Indeed, the computational demands have thus far proven the greatest barrier to making the model capable of conducting PSA and accounting for secondary transmission. The lack of secondary transmission modelling in particular has important implications for the CEA presented in Chapter 7. Given findings that HIV counselling and testing decreases risky sexual behaviour, the cost-effectiveness estimates presented in this thesis are conservative (see Subsection 7.3.4).[125]

Another challenge for investigators using CEPAC is its huge array of parameters, which require substantial data to inform. Fitting data describing empirical observations to these many parameters is oftentimes unintuitive. Chapter 6 focuses on adjusting the testing throughput data reported in Chapter 5 for eventual use as CEPAC parameters inputs. Subsections 7.1.2-7.1.3 outline the methods used to fit empirical and secondary testing data unrelated to cascade throughput to CEPAC's parameters. Finally, Appendix B discusses the values and data sources used for those parameters unrelated to HIV testing.

*** Nevertheless, some CEPAC studies have approximated the costs and health detriments averted due to prevention of secondary transmission. However, these approximations required simplifying assumptions and external supplementary models which were not attempted in this thesis (see Subsection 4.3.2).

AHIT

Another major limitation of the CEPAC model is its lack of parameters to describe simply the process of testing for acute HIV infection (AHI). AHI testing as conceived in this thesis consists of two 'rounds' of testing. First, all tested clients receive an initial screen for HIV antibodies by a rapid test protocol. For those testing negative by this initial protocol, an additional antibody-antigen combination test is administered (see Subsection 2.2.4).

However, CEPAC includes only a single set of parameters describing an HIV test (e.g., cost, sensitivity, and specificity). Thus, fitting data describing individual test characteristics to the CEPAC model was complicated by the need to 'compress' those data into a single set of test descriptors for the overall testing process. This is a relatively simple process when considering multiple tests as part of an antibody screening protocol (see Subsection 6.1.3). However, the process is more complex for protocols including AHI testing because the calculations depend upon not only test characteristics but also on epidemic characteristics (e.g., HIV incidence).

I constructed the AHI Testing (AHIT) supplementary model for use with CEPAC to simplify and make explicit my methods for translating data describing individual tests into a single set of summary test characteristics. AHIT's only function is to generate expected test characteristic values. As a result, it requires no definition of a time variable, making it possible to adopt a decision tree structure for the sake of simplicity. Thus, the model uses a cohort method of evaluation, taking no account of first-order uncertainty.

AHIT solicits inputs describing a population epidemic and characteristics (including costs) for both standard antibody rapid and AHI test protocols. From these inputs, it summarizes the testing costs incurred for a population of a defined size receiving both standard antibody and AHI testing. It also distributes patients completing the testing process according to their test results and actual serostatus (i.e., all clients are described as true positives, true negatives, false positives, and false negatives). These total expected costs and patient distributions are determined by 'rolling back' the decision tree: weighting each pathway by its respective probabilities and then summing across all pathways. Finally, it uses algebraic relationships (see Appendix C) to generate expected values for a single set of test characteristics which would lead to the same costs and patient distributions when used with CEPAC.

Because AHIT's function is to generate input for use with CEPAC, its other model components are bound by CEPAC's structure. AHIT does not make adjustments to its incidence estimates to account for secondary transmission as CEPAC does not directly incorporate consideration of infectiousness. Moreover, although AHIT could be configured to conduct PSA as it is first-order deterministic, this was not done due to the inability to incorporate CEPAC into any such analysis.[†††] Finally, the variabilities associated with AHIT's testing parameters are accounted for given that CEPAC runs using AHIT-generated inputs account for first-order uncertainty (see Subsection 7.1.1 for a further discussion of AHIT).

[†††] Each set of inputs generated by AHIT would have to run on CEPAC individually, requiring enormous amounts of time and computer power.

3.3.3 HIV testing interventions evaluated

In accordance with the economic evaluation guidelines considered in this chapter (see Subsection 3.2.1) the HIV testing policies evaluated in this thesis are carefully defined (see Section 2.2 and Table 2.1). The CEA in Chapter 7 further follows the USA Panel guidelines by conducting incremental analyses (see Subsections 3.1.4 and 3.2.1). Specifically, the effectiveness of each of the eight expanded testing policies is compared to current testing practice. Therefore, the cost-effectiveness estimates account for case detection and treatment occuring in the absence of expanded testing.

Current testing practice

However, I found the USA Panel recommendations for comparing interventions to current practice to belie the complexities of defining current HIV testing in South Africa. First, the current rate of HIV testing in South Africa is clearly a moving target (see Subsection 5.2.2). Indeed, testing rates have been increasing dramatically as treatment availability improves and HIV testing policy evolves (see Subsection 2.1.5). Choosing a cross-section of the testing rate data for use as a point estimate in a CEA therefore required important assumptions and judgements (see Subsections 6.1.1 and 6.1.6). The implications of these judgements were explored using extensive sensitivity analyses (see Subsection 7.2.2).

I also found current HIV testing to be a complex mixture of various testing programs. The majority of testing comprised client-initiated voluntary counselling and testing (VCT) encounters by primary healthcare users. However, current testing also included provider-initiated testing for ANC users and TB patients (see Subsection 5.1.1). Current VCT uptake among primary healthcare users (baseline testing) is likely to decrease following implementation of policies expanding primary healthcare

user testing. However, screening among ANC users and TB patients (background testing) is likely to undergo relatively little change.

This thesis recognizes both baseline and background testing and uses different methods to account for each. Baseline testing is assumed to decrease to zero upon implementation of any of the expanded testing policies. Meanwhile, background testing is assumed to remain constant (see Section 2.2). Accounting for background testing in this manner acknowledges that some current case detection in South Africa is unlikely to change following expansion of testing for primary healthcare users. In so doing, I ensure the cost-effectiveness ratios reported in this thesis are not inflated.

Counterfactual of the null set of interventions

Given the focus of this thesis on describing current testing practice, it is important to consider the WHO's unique recommendation regarding comparators. The WHO advocates comparing all evaluated programs to a "null set of interventions" instead of current practice (see Subsection 3.2.1). This approach is theoretically useful for identifying pre-existing inefficiencies in a country's healthcare sector.[91]

The WHO's recommendation was not followed in this thesis for two reasons. First, the domestic pressures on the South African government for expanding its citizens' access to HIV testing and treatment are increasingly gaining strength (see Subsection 2.1.5).[55] Thus, any scenario in which all HIV-related services would be suspended seems to me unrealistic. Second, removing all forms of the evaluated intervention could drastically change the epidemiological landscape in ways that could not be empirically measured.[91] Indeed, if South Africans had no access to HIV testing or education, risky behaviour conducive to transmission could be expected to

increase.[122-127] Adjusting empirical measurements of current HIV prevalence and incidence to reflect such hypothetical effects would be very challenging.

3.3.4 Population-level evaluation

The CEA reported in Chapter 7 estimates the costs and effects of policies expanding testing among primary healthcare users for South Africa's entire national adult African population. The decision to evaluate policies targeting primary healthcare users was made because this group comprises the largest segment of the adult African population regularly accessing venues offering HIV testing (see Section 2.2). By conducting a population-level analysis, this thesis estimates the broader impact of expanded screening. Moreover, a population-level analysis further acknowledges the important relationship between population access to testing venues and the effectiveness of efforts to increase testing uptake.

Epidemiological study

The lack of population-level testing data in the literature to inform the CEPAC testing parameters (see Subsection 2.3.1) drove my decision to collect new data describing these rates. My choice of epidemiological design (retrospective, descriptive study) was similarly driven by the challenges associated with collecting population-level testing data. Chapter 5 presents this work, reporting rates of baseline and background testing and passage through the HIV testing cascade steps for a small adult African population during 2001-2006. Beyond providing CEPAC parameter inputs to describe current testing practice (see Subsection 7.1.2), these data facilitate projecting the effects of expanding HIV testing (see Section 6.1). These data are also used to construct plausible input ranges for CEPAC's testing rate parameters for sensitivity analyses (see Subsection 7.1.3). The study design has limitations due to incomplete

data and generalizability. Nevertheless, I believe it to be the only plausible approach to measuring an entire population's testing behaviour (see Subsection 5.3.3).

Subgroup analyses

Several of the economic evaluation guidelines advocate subgroup analyses (see Subsection 3.2.1). However, no such analyses are undertaken in this thesis. I acknowledge that such analyses would potentially provide useful information for decision-makers. For example, since certain subgroups are more likely to be test seropositive (e.g., TB patients, see Table 5.4), testing programs targeting those groups would possibly be more cost-effective. However, this thesis seeks more to examine policies expanding testing beyond high-risk groups. Moreover, the sample sizes for the empirical data reported in Chapter 5 were too small to accomodate meaningful stratification by risk groups within the adult African population.

Chapter 4:
Review of the economic literature on HIV testing

This chapter presents a systematic review of the economic literature on human immunodeficiency virus (HIV) testing. The first aim of this review is to provide an overview of this literature. The second aim is to consider the methodological approaches adopted by previous evaluations of HIV testing programs, with particular focus on those decisions most relevant to the methodological issues explored in this thesis. Finally, this review aims to summarize the findings of the current HIV testing economic literature most relevant to this thesis. Specifically, I focus on the findings of studies which compared provider-initiated to client-initiated testing; opt-in versus opt-out consent methods; rapid-only versus rapid with acute HIV infection (AHI) testing protocols; and various approaches to linkage-to-care.

In the discussion, I consider the implications of this review for my own work. I first discuss the major gaps in the current HIV testing literature which my thesis seeks to fill. I next outline how the various modelling strategies used in previous economic evaluations of HIV testing programs informed the methodological approach adopted in this thesis. Finally, I consider how the methodologies of the studies identified in this review informed my approaches for addressing the key challenges explored in this thesis: selecting an appropriate outcome of interest; fitting testing data to models; defining and accounting for current testing practice; and conducting a population-level analysis.

4.1 Methods

4.1.1 Search strategies

Two databases were searched from their inception to 15 June, 2008 for economic articles related to HIV testing (see Appendix D for specific search terms): Ovid MEDLINE – including in-process and other non-indexed citations – and EMBASE. (Econlit was not searched.) The titles and abstracts of all articles identified through these searches were then scanned. Articles were retrieved based upon defined inclusion and exclusion criteria (Table 4.1). These criteria were designed to capture all economic studies of HIV testing programs in the literature. While many of these studies evaluated programs very different from those explored in this thesis, all presented methodological approaches for examining steps of the HIV testing cascade (see Section 2.3).

The titles of articles cited in the bibliographies of all retrieved studies were similarly scanned. The abstracts of those with titles suggesting relevance for this literature review were then accessed. These articles were then retrieved again based on the inclusion and exclusion criteria. I subsequently refer to this process of retrieving articles cited in the bibliographies of other identified studies as 'snowballing.'

Table 4.1. Literature review inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Sources	
-Peer-reviewed journal articles	-Independent reports
Article types	
-Original research articles -Reviews of original research articles	-News articles -Editorials -Non-English language articles
Study types	
-Economic evaluation -Cost-minimization analyses -Costing studies	-Correlation studies -Comparative studies w/out monetary valuation -Resource utilization studies w/out monetary valuation
Programs studied	
-HIV testing programs	-Surveillance programs -Opportunistic infection screening policies for HIV-positive patients -ART resistance testing programs

ART: antiretroviral treatment

4.1.2 Analysis

Retrieved articles were appraised in accordance with the guidelines provided by Drummond et al.[82] Data were then extracted from each study including general information such as publication year and study country. Data were also gathered on policies evaluated, including descriptions of the target populations and comparators. Details on study methodologies were recorded, including perspective adopted; outcomes examined; and model structures adopted. Finally, summaries of the results for each study were also gathered.

4.2 Results

4.2.1 Overview of studies

In total, 123 relevant articles were retrieved (Figure 4.1). Of these, 95 were economic evaluations,[151-245] 21 were studies providing cost data for HIV testing programs,[246-266] and 7 were reviews of economic literature related to HIV testing.[267-273] The reviews included one examining approaches for modelling HIV screening programs;[267] two of economic evaluations of programs screening pregnant women;[268,269] two comprising overviews of the economic literature examining a range of HIV-related interventions in developing countries;[270,272] one of cost analyses;[273] and one of economic evaluations of HIV testing in the United States of America (USA).[271]

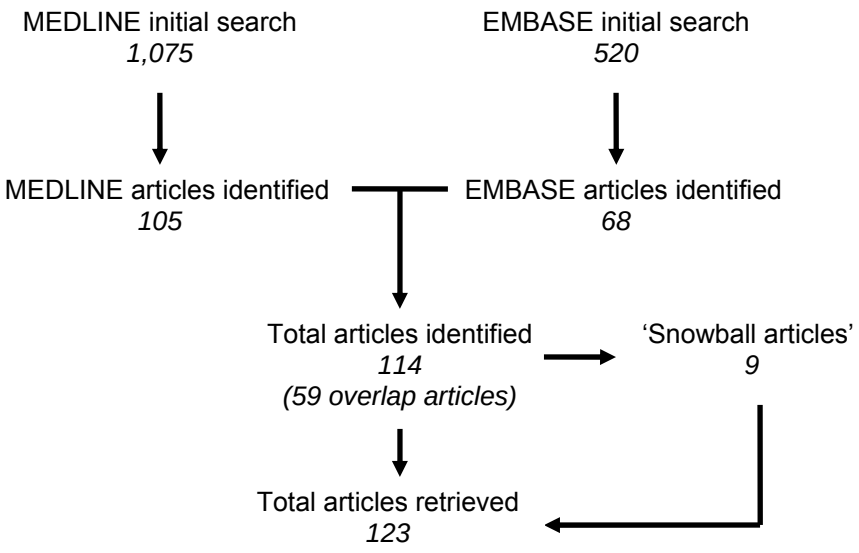

Figure 4.1. Summary of literature review results.

Study settings and types

Most studies were conducted in the USA[151-154,156,157,161,162,164,165,168,169,172-174,176-181,183,185-188,190,193,195,201,202,204-211,213,214,218-224,226,229,232,234,235,242,243,247,251,255,259,265,266] and

other North American countries (Figure 4.2).[167,212,217] The region with the second greatest number of studies was Africa, in which most studies were conducted in South Africa,[225,227,238-240,250] and Tanzania or Kenya;[184,231,233,246,252] all other African studies identified were conducted in other sub-Saharan African countries.[163,170,182,197-199,203,228,230,237,241,249,254,256,258,261,263] Comparatively few studies were conducted in Europe,[155,158,159,166,171,191,200,215,216,236,253,257,260,262,264] Asia,[189,192,194,223,244,245,248] Oceana,[160,175] or South America.[196]

The majority of economic evaluations were cost-effectiveness analyses (CEAs, see Subsection 3.1.3).[155,157-163,165-177,179-184,186-189,191-193,195,197,200-205,207-209,211-213,215-220,222,224-230,234-239,241-245] A small number of cost-minimization analyses (CMAs) were conducted in North America,[185,223] Asia,[194,223] and South America.[196] The only regions in which cost-utility analyses (CUAs) were conducted were North America[151-154,156,164,206,209,210,214,221,232] and Africa.[198,199,231,233,240] All three identified cost-benefit analyses (CBAs) were conducted in the USA.[178,181,190] Cost analyses were conducted in most regions.[246-266] No cost-consequence analyses were identified.

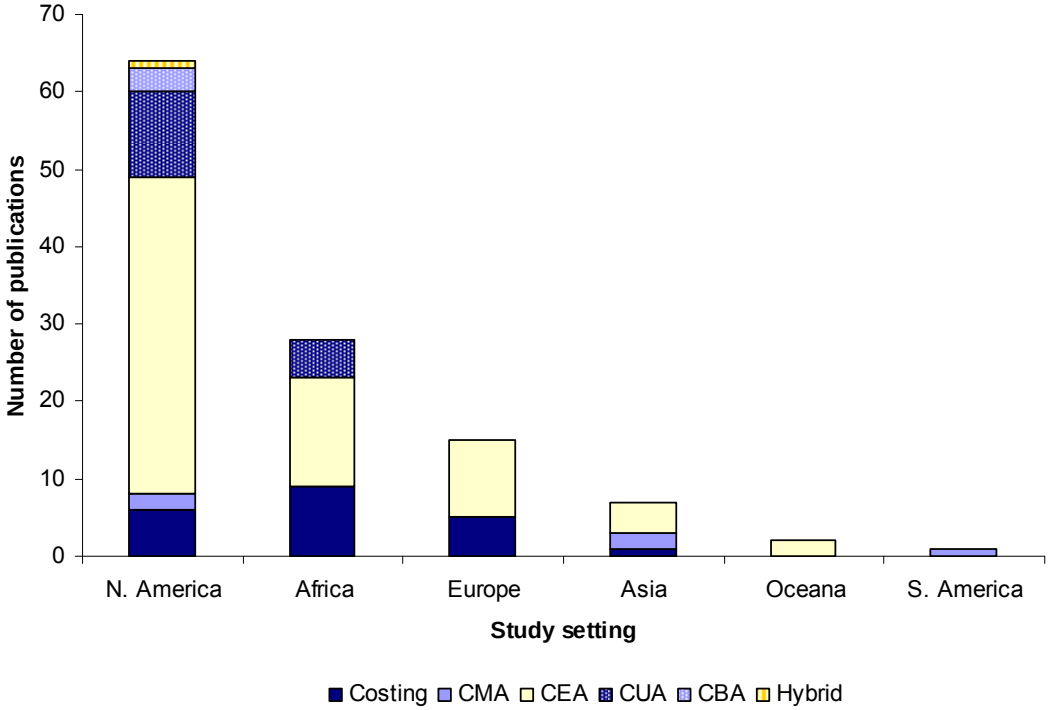

Figure 4.2. Study settings and types for HIV testing economic studies. Settings are stratified by continent, with Asia encompassing the Middle East and Oceana including Australia and the Pacific islands. Study types include cost-effectiveness analyses (CEA), cost-utility analyses (CUA), cost-benefit analyses (CBA), cost-minimization analyses (CMA), hybrid studies comprising two or more types, and costing studies. This figure includes several studies conducted over multiple regions[172,223,273] and combining multiple evaluation types.[204,209] All reviews are exluded in this figure.

Target populations studied

The annual numbers of economic studies of HIV testing have fluctuated (Figure 4.3). Up until 2005, the fluctuations were largely driven by the numbers of evaluations of screening programs for pregnant women published. Many such evaluations based in low-prevalence,* industrialized settings were conducted during the early 1990s.[168,174,181,191,193,201,257,265] However, the annual numbers of these studies spiked higher in the late 1990s.[155,160,165,171,175,176,183,206,208,212,215,216,218,220,222,229,243] The

* The terms low- and high-prevalence are here used as defined by the World Health Organization (WHO): low-prevalence refers to settings with HIV prevalence <1% while high-prevalence refers to settings with HIV prevalence >1% (as detected by antenatal surveillance).[11]

majority of evaluations of testing programs for pregnant women in developing countries came later, in the subsequent decade.[163,167,189,192,197-199,217,227,230,239,240,245]

Fewer studies evaluated testing programs for any single group apart from pregnant women. Among these, evaluations of blood screening programs, in both industrialized[156,228,237,264] and resource-poor settings,[170,182,184,203,248,249,258] were most common. Many studies examined testing programs in industrialized settings for specific groups of healthcare users, including healthcare workers (HCWs);[162,185,196,224,251,253] inpatients;[151,177,190,195,200,207,209,238,259] intravenous drug users (IVDUs);[173,187,219,236] and STD patients;[158,159,234,255] ob/gyn patients;[166] Other studies examined testing programs in industrialized settings for other specific populations, including couples applying for marriage licenses;[204,213] men who have sex with men (MSM);[172,232] private sector employees;[157] commercial sex workers and soldiers;[186] prisoners,[235] and contacts of tuberculosis (TB) patients.[247] Finally, two studies evaluated testing for infants exposed to HIV via infected mothers.[206,225]

Studies have also increasingly examined HIV testing programs targeting primary healthcare users, as done in this thesis (see Subsection 2.2.1). During 1990-1997, only six evaluations in low-prevalence settings[169,178,202,209,211,242] and one cost analysis in a high-prevalence setting[254] considered such program. After this period, the number of these studies has increased in both low-[152-154,164,179,180,188,214,221,226,233,266] and high-prevalence settings.[225,231,233,241,245,250,252]

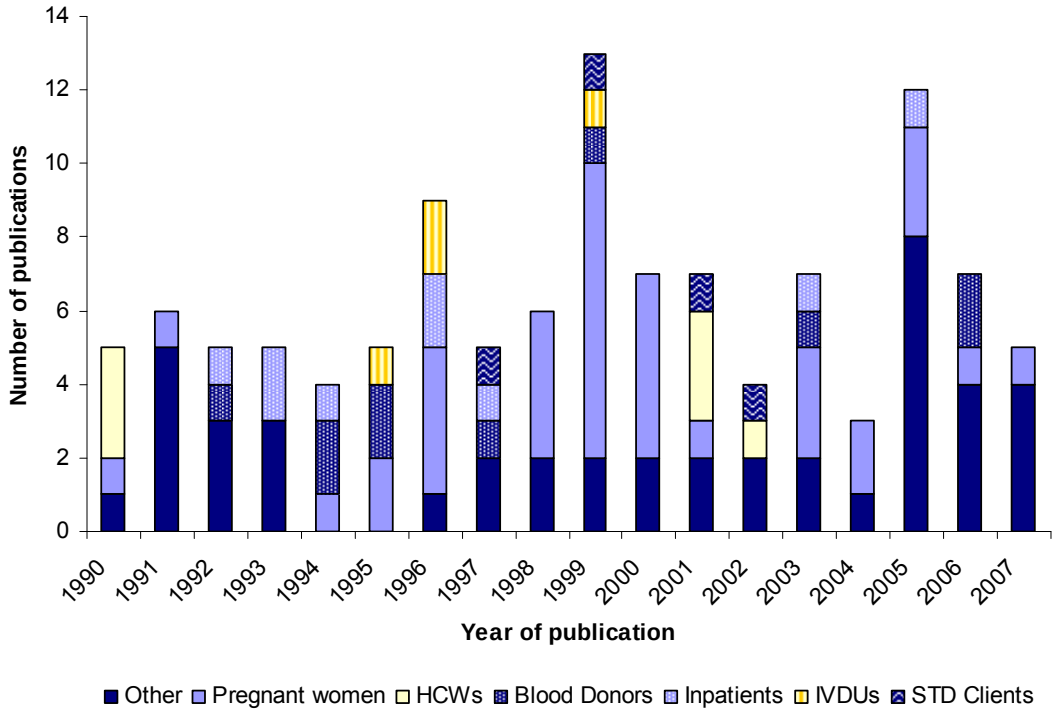

Figure 4.3. Publication years and populations for HIV testing economic studies. Target populations include pregnant women, healthcare workers (HCWs), blood donors and recipients, inpatients, intravenous drug users (IVDUs), sexually transmitted disease (STD) clients. The 'other' category includes couples applying for marriage licenses, men who have sex with men (MSM), commercial employees, commercial sex workers, soldiers, prisoners, ob/gyn patients, female healthcare users of child-bearing age, contacts of tuberculosis (TB) patients, and infants exposed to HIV via infected mothers.

Policy comparators

Most of the studies compared multiple HIV testing programs as done in this thesis. Many of these comparisons were between policies identical except for initiation methods. All of these studies compared initiation methods broadly equivalent to provider-initiated testing to client initiated programs in low-prevalence settings (see Subsection 2.2.2).[153-155,158-160,171,175,186,191,210,214,216-218,221,243,247] One of these studies was a cost analysis.[247]

None of the identified studies compared policies identical except for consent method (see Subsection 2.2.3) as done in this thesis. However, studies did compare programs

different in multiple testing policy components, including consent method. One such evaluation compared client-initiated, opt-in testing to provider-initiated, opt-out testing for primary healthcare users in the USA.[179] Three additional evaluations compared client-initiated, opt-in testing to provider-initiated, mandatory screening for pregnant women,[208] HCWs,[224,242] and inpatients,[242] all conducted in the USA.

Many comparisons of alternative test protocols (see Subsection 2.2.4) conducted in low-prevalence, industrialized settings were identified in the literature. These included cost analyses[248,264] and evaluations[156,200] comparing alternative blood screening protocols. Additionally, two cost analyses[260] and one evaluation[194] compared alternative enzyme-linked immunosorbent assay (ELISA) test protocols. A single evaluation compared the use of pooled-sera testing to conventional single-sera testing.[223] Finally, two studies compared acute HIV infection (AHI) testing protocols to the current practice of antibody testing for primary healthcare users[164] and infants newly born to HIV-infected mothers.[205]

Four studies compared test protocols in high-prevalence, resource-poor settings. Of these, only one was an economic evaluation, comparing blood screening protocols.[228] One of the three cost analyses compared rapid to ELISA test protocols.[263] The other cost analyses compared various ELISA-based protocols.[256,261] No studies conducted in high-prevalence settings considered AHI testing protocols, as done in this thesis (see Chapter 7).

Only two studies compared HIV testing programs adopting alternative linkage-to-care processes.[152,239] As is done in this thesis, both of these studies relied on assumptions

and hypothetical scenarios rather than on empirical data to define linkage-to-care throughput for enhanced linkage-to-care scenarios.

Finally, a substantial number of studies examined only one testing policy. These studies compared testing policies either to non-testing programs,[186,198,199,203,227,229,230,253,259] or no intervention.[151,157,161-163,166,168,170,173,174,176-178,180-182,184,187,189,190,192,193,195,197,201,202,204,206,207,212,213,215,219,220,226,231,232,234-237,240,244-246,250-252,254,257,258,265]

4.2.2 Study methodologies

This subsection outlines the methodologies adopted in the studies identified. It focuses upon the approaches regarding the four methodological issues explored in this thesis including choosing a health outcome; using modelling; defining relevant comparators; and conducting a population-level analysis. It concludes by briefly outlining approaches used in the literature to measure costs, a summary informing my own cost measurements in this thesis (see Subsections 7.1.2-7.1.3).

Outcome measures

Many studies identified acknowledged the limited value of testing alone as an outcome by measuring throughput for the HIV testing cascade (Figure 2.1). Most of these studies did not measure the rate at which the target population accessed testing venues (Step 1 of the HIV testing cascade). However, many others estimated throughput for Steps 2,[151-155,166,172,173,179,180,187-189,191,192,212,221,226,233,234,239,244] 3;[151-155,160,161,163,166,169,172-176,183,187-189,191-193,206,208,211,212,214,218,220,222,226,230,233,235,239,242,244] 3.5;[151-155,160,161,163,166,169,172-176,183,187-189,191-193,198,206,208,212,218,221,222,226,230,233,235,242-244] 4;[151-154,166,169,172,173,179,180,187,188,191-193,212,221,226,233,234,239] and 5-6.[151,152,163,226,233] Studies

not considering throughput for any cascade step either implicitly assumed perfect follow-up for all clients or measured effectiveness with intermediate outcomes.

Such intermediate outcomes were frequently used by the CEAs identified. One frequently-used intermediate outcome was cases identified,[157,160,161,166,169,172,175,177,186-188,191,195,200,205,207,211,213,214,220,225,226,228,237,242,244] particularly common among trial-based analyses.[165,166,172,177,187,188,191,207,225,237,244,245] Two other more informative intermediate outcomes commonly used included HIV-positive clients receiving linkage-to-care[163,165,226] and HIV infections prevented.[158,160-162,167,168,174-176,179,180,182,183,189,192,193,195,197,201,203,204,208,212,217-219,224,227,229-231,233-235,239,240,243]

Use of more final outcomes has become more frequent since the late 1990s. Life years gained (LYGs), as used in this thesis, were the most common of these final outcomes.[155,158-160,170,171,175,184,189,192,202,209,215,216,222,227,236,239,243] Comparatively few studies used outcome measures adjusted for patient utilities or values (i.e., CUAs, see Subsection 3.1.3). Five CUAs conducted in sub-Saharan Africa used disability-adjusted life years (DALYs)[198,199,231,233,240†] and twelve CUAs conducted in the USA used quality-adjusted life years (QALYs).[151-154,156,164,206,209,210,214,221,232]

A salient divide exists regarding the inclusion of treatment costs and effects between those studies using intermediate versus final outcomes. Of those studies excluding costs and effects due to HIV-related treatment and care,[162,163,165,166,169,170,172,177,181,182,184,185,187,188,191,194,196,200,205,207,213,219,223,225,226,228,230,231,237-242,244,245,266] The majority adopted intermediate outcomes such as cases

† All five of these studies obtained the necessary data to calculate DALYs by using the disability weights reported by the Global Burden of Disease Project.[274]

identified,[166,169,172,177,187,188,191,200,205,207,213,225,226,228,237,242,244] HIV-positive persons identified and receiving linkage-to-care,[163,165,226,245] and infections prevented.[162,182,219,230,231,239,240] Far fewer of the CUAs[231,240] or studies measuring benefits in LYGs[170,184,239] omitted these costs and benefits.

As the use of more final outcomes has become common for evaluations of testing programs in recent years, so has the inclusion of treatment and care costs by these studies. Indeed, many studies conducted in industrialized countries since 1999 explicitly accounted for the costs and benefits of antiretroviral treatment (ART) for seropositive clients.[152-154,158,159,164,179,180,186,214,221,234,235] However, many evaluations of testing programs in developing countries continue to neglect treatment-related costs and benefits.[‡] Indeed, to date only one study has incorporated these costs and effects into an evaluation of testing for a high-prevalence general population: a CEA of voluntary counselling and testing (VCT) in Tanzania.[233]

Study designs

Many identified studies used primary, or trial-based, designs (see Subsection 3.1.4). These included most of the identified cost analyses[246-250,252-258,260-265] and many of the economic evaluations conducted in resource-poor settings.[172,194,196,225,228,237,238,244,245] Among those conducted in industrialized nations, most were published during the 1990s,[165,166,173,177,187,188,191,193,207,212] with only three published after 1999.[172,185,226] Many used intermediate outcomes such as HIV-positive cases identified,[166,172,187,188,191,207,225,226,228,237,244] and only one accounted for treatment.[193]

[‡] While there are no other examples I identified of evaluation of *testing* programs incorporating these costs, there is a sizeable literature of economic evaluations which have considered the costs and effects of treatment and care (namely ART) in isolation from the testing and linkage-to-care processes in high-prevalence, resource-poor settings countries.[56,57,150]

Alternatively, many of other identified economic evaluations used modelling designs (see Subsection 3.1.6). The majority of these studies used decision trees.[155,157,160,162-164,167-170,174-176,178-184,189,190,195,197-201,203-206,208,211,213,214,217,218,220,222,223,229,230,234,235,239-243,251,259,266] Decision trees were particularly common among studies comparing test protocols,[169,205,222,223,241,266] blood screening programs[170,182,184,203] or programs testing pregnant women.[160,163,167,168,174-176,181,183,189,197-199,201,206,208,217,218,220,222,229,230,239,240,243] Like the trial-based studies, many of the economic evaluations using decision trees did not account for the costs of care or treatment for seropositive clients. This omission again generally reflected the use of intermediate outcome measures, as outlined above.[162,163,169,170,181,182,184,200,205,213,223,230,239-242,251,259,266]

Markovian state-transition models comprised the second most common model type used in the identified studies. These models were rarely used in the early 1990s, with only two such studies published before 1996.[202,224] However, the use of Markov models for economic evaluations of HIV testing programs became much more common in later years.[156,158,159,171,215,216,221,227,236] In contrast to those studies using decision trees, all of these Markov modelling studies incorporated treatment and care costs for seropositive clients.

Relatively few identified studies used models other than decision trees or Markov models. Three studies used system dynamics models (see Subsection 3.1.6) to depict the effects of HIV testing on population transmission dynamics.[161,219,232] A pair of studies used a decision tree modelling HIV testing linked to Markov structures modelling disease progression,[209,210] an approach somewhat analogous to that used by this thesis (see Chapter 7). Finally, three studies explicitly combined primary data collection in developing countries with modelling projections using decision

trees.[192,231,233] Four evaluations of USA HIV testing programs in recent years used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation model, as used in this thesis (see Appendix A).[151-154]

Defining comparators

As outlined in Subsection 4.2.1, many of the identified studies compared the testing interventions under evaluation to current practice. However, none of these studies drew any distinction between baseline and background testing as done in this thesis (see Section 2.2).[§] Instead, these studies treated all current testing as baseline testing, decreasing it to zero when modelling implementation of the testing programs under evaluation.

Population-level analyses

Few of the identified studies conducted population-level economic evaluations (see Subsection 2.3.1), considering the cost-effectiveness of HIV testing for every member of a target population. Instead, most of the studies assessed screening programs' costs and effects for only those individuals utilizing these programs. Some USA-based studies conducted population-level analyses by circumventing the difficulties of measuring population testing rates (including passage through cascade Step 1). This circumvention was accomplished by using assumptions rather than empirical data to inform population rates of testing uptake for both current practice and the

[§] As defined in Section 2.2, baseline testing refers to testing related to the intervention under evaluation whereas background testing refers to testing unrelated to the intervention under evaluation. Since the expanded testing policies examined in this thesis target primary healthcare users in the adult African population, baseline testing refers to current testing among adult African primary healthcare users while background testing refers to all other testing by adult Africans (namely, antenatal testing or screening tuberculosis patients, see Subsection 2.2.1). However, in the example of an evaluation of ANC testing targeting all pregnant women, baseline testing as defined in this thesis would comprise current antenatal testing while background testing would comprise any other testing received by pregnant women (e.g., VCT).

interventions under evaluation.[153,154,160,161,240] To date, only one study has used empirical data to project the costs and effects of a HIV testing program for every member of an entire population, as done in this thesis. This study comprised a CEA of provider-initiated, opt-out testing offered through healthcare facilities for all people living in the USA.[179]

Other studies have conducted 'subpopulation-level' evaluations for testing programs targeting specific risk groups. These studies used decision trees models to assess the cost-effectiveness of PMTCT interventions for pregnant women in India, South Africa,[239,240] and the USA.[243] Each used demographic data to project the size of the pregnant population being targeted for testing and ANC utilization data to estimate the proportion of those women accessing testing venues. Other studies used dynamic state-transition models (system dynamics models, see Subsection 3.1.6) to estimate the cost-effectiveness of testing programs targeting MSM,[232] IVDUs.,[219] and women of child-bearing age.[161]**

Other methodologies – cost measurements

Generally speaking, the trial-based analyses identified used original cost data[165,166,172,173,177,185,187,188,191-194,196,207,212,225,226,228,231,233,237,238,244-250,252-258,260-265] while the modelling studies relied instead on secondary cost data.[151-164,167-171,174-176,178-184,186,189,190,195,197-206,208-211,213-224,227,229,230,232,234-236,239-243,251,259,266] Regarding perspectives used to measure these costs, both payer[155,156,158-160,162,163,165,166,168,170-172,176,177,179,182,184-189,191-196,198-205,207-213,215-217,219,220,223,224,226-231,233,236-242,244-249,251-265] and societal perspectives were common (see Subsection 3.2.1).[151-

** Beyond incorporating estimates of patient throughput for the first step of the HIV testing cascade, these models also considered the effects of behaviour change due to HIV testing on population HIV transmission dynamics.

[154,157,161,164,167,169,173-175,178,181,183,190,206,214,218,221,222,225,232,235,243] Furthermore, five studies compared results when using either perspective.[180,197,234,250,266] None of the identified studies counted future costs unrelated to HIV treatment or care, converted monetary costs to USA dollars using a purchasing power parity (PPP) exchange rate, or discounted monetary costs at a different rate than health benefits.

4.2.3 Study findings

Determinants of the cost-effectiveness of HIV testing

Numerous evaluations found the cost-effectiveness of HIV testing programs to be sensitive to inputs related to several of the methodological issues focused upon in this thesis. First, two of the few population-level analyses conducted found the cost-effectiveness of HIV testing to be sensitive to the rates of testing venue access (cascade Step 1) in low-prevalence settings.[189,243] This result therefore justifies a population-level analysis to quantify this access.

Many modelling studies similarly found the cost-effectiveness of HIV testing to improve as client throughput for other cascade steps increases. Specifically, the cost-effectiveness of HIV testing was found to improve in low-prevalence settings as throughput increased for cascade Steps 2;[192] 3;[160,175,176,183,206,214,243] 3.5;[176] 4;[266] and 5-6.[152,208,215] These results highlight the importance of analyzing outcomes subsequent to the testing process to account for throughput losses. However, less evidence exists suggesting that this is as important a consideration for studies conducted in high-prevalence settings. One such study found that the cost-effectiveness of testing improved as acceptance probabilities increased.[227] Two other studies in high-prevalence settings found improved linkage-to-care to correspond to higher overall costs and benefits but little impact on the cost-effectiveness ratio.[153,233]

There is also evidence to suggest that the quantification of testing already occuring (i.e., definition of the comparator) has important implications for study results. Specifically, two studies in the USA examined the effects of adjusting estimates of the current rate of testing. Both determined that the cost-effectiveness of screening programs decreases as current testing rates rise.[153,154]

But the parameter input on which the cost-effectiveness of HIV screening has most consistently been found to be dependent is undiagnosed HIV prevalence.[152-155,160-162,164,168,173-175,177,179,180,183,190,192,195,198,199,201,202,205,207-209,214,215,221,227,229-231,233,236,240,242]

The lower the undiagnosed prevalence, the more tests must be administered (and so more testing costs incurred) for the detection of each new case of HIV infection. Consequently, high undiagnosed prevalence corresponds to greater cost-effectiveness for HIV testing.[198,199,227,230,231,233,240] However, Paltiel et al. demonstrated that there is a threshold undiagnosed prevalence – approximately 1.0% – above which this effect diminishes.[154] Paltiel et al.'s findings demonstrate the caution necessary in extrapolating cost-effectiveness relationships observed in low-prevalence settings to high-prevalence settings.

Initiation method comparisons

Numerous studies in low-prevalence settings compared policies identical except for test initiation method (see Subsection 2.2.2). These studies generally found provider-initiated testing to be more cost-effective than client-initiated policies. This was true both for programs targeting primary healthcare users[153,154,214] and pregnant women believed to be at high risk for infection.[217,218,243] Studies in low-prevalence settings also found provider-initiated testing to be more cost-effective than diagnostic testing (see Subsection 2.1.4) for pregnant women[155,160,171,175,216] and STD clients.[158,159] Thus

far, no studies have compared policies identical except for initiation method in high-prevalence, resource-poor settings.

Consent method comparisons

The results of evaluations comparing testing policies adopting different consent methods (see Subsection 2.2.3) were more varied. No studies compared policies identical except for consent method (see Subsection 4.2.1). Therefore, it is difficult to project the effect of consent method alone on the cost-effectiveness of screening from the current literature. That said, two CEAs of mandatory versus provider-initiated, opt-in testing for pregnant women in the USA concluded mandatory testing to be cost-effective.[183,208] These results seemingly support implementation of more aggressive consent methods.

However, other similar studies concluded policies adopting more aggressive consent methods to be insufficiently cost-effective for implementation. These studies include comparisons of provider-initiated, opt-out versus client-initiated testing for all healthcare users[179] and mandatory versus provider-initiated, opt-in testing for HCWs in the USA.[224] Also, an evaluation of mandatory versus client-initiated, opt-in testing for pregnant women and inpatients found incremental cost-effectiveness ratios (ICERs) for the two policies were highly sensitive to study assumptions and inputs.[242]

Test protocol comparisons

Many studies compared the costs and effects of testing policies using various test protocols (see Subsections 2.1.3 and 2.2.4). Some of these studies compared protocols for blood testing.[156,223,228,264] However, more relevant to this thesis are those studies which examined various protocols used for diagnostic purposes. Most of the

evaluations examining protocols compared rapid tests to ELISAs in low-prevalence settings.[165,167,169,185,188,196,238] Of these, all but two concluded that rapid tests were more cost-effective; the two exceptions assumed very high costs for rapid test kits relative to ELISAs.[165,188††] Finally, a study comparing rapid test algorithms in African settings concluded that while parallel testing offered the most accuracy, the lower cost of serial testing may justify its preferential use in resource-poor settings.[241] This latter finding supports my decision to consider serial rapid testing as the default option for the analysis presented in this thesis (see Subsection 2.2.4).

To date, only a single evaluation has compared test protocols designed to detect AHI with conventional protocols. This study, conducted in the USA, determined antigen testing to be more cost-effective in detecting AHI than either RNA tests or ELISAs.[164] This finding supports my selection of an antigen test for the protocol designed to detect AHI evaluated in this thesis (see Subsection 2.2.4).

Linkage-to-care method comparisons

Two studies examined the effects of linkage-to-care improvements (see Subsection 2.2.5) on the cost-effectiveness of testing programs. One of these studies, a CEA of antenatal testing in South Africa, compared a hypothetical scenario representing improved linkage-to-care to current practice. The study concluded the improved linkage-to-care scenario to be both much more expensive and effective.[239] A second USA-based study shed more light on the effects of improving linkage-to-care on the ratio between costs and effects. Rather than comparing a handful of defined programs to one another, this study considered a wide range of scenarios representing

†† In making this assumption, these studies represent something of an anomaly. In fact, cost analyses examining rapid and ELISA tests have consistently found rapid tests to be far less expensive in both resource-poor[263] and industrialized settings.[253,255,266]

differential allocation of resources into the testing process (HIV testing cascade Steps 2-4) versus linkage-to-care (cascade Steps 5-6) process. The study concluded that investments in linkage-to-care improved the cost-effectiveness of testing, but further noted that this effect diminishes at higher prevalence.[152]

4.3 Discussion

This section further discusses how the findings of this literature review shaped the original work presented in this thesis (see Chapters 5-7). First, the gaps in the existing literature are highlighted to explain my decision to evaluate expanded HIV testing policies for the adult African population in South Africa. Second, modelling approaches presented in the literature are discussed and the use of the CEPAC model in this thesis is justified. Finally, a brief overview is provided of the implications of the current HIV testing literature for the major methodological issues examined in this thesis (see Subsection 1.1.2).

4.3.1 Gaps in the HIV testing literature

As discussed in Subsection 4.2.1, the majority of identified studies examined testing programs in low-prevalence settings in North America. Most CUAs and all CBAs, complex forms of economic evaluation requiring greater research resources and expertise than CEAs (see Subsection 3.1.3),[82] were conducted in low-prevalence industrialized countries. Moreover, the effects of new developments (e.g., PMTCT interventions) on the cost-effectiveness of HIV testing programs have invariably been evaluated first in high-income countries (see Subsection 4.2.1). Evaluations of such new developments in resource-poor settings, such as sub-Saharan Africa, have historically come only in subsequent years.

This disparity in research has been especially glaring following the advent of data describing the lifetime benefits and costs of ART in the mid 1990s.[147,275] As mentioned in Subsection 4.2.2, several evaluations of HIV testing in low-prevalence settings have incorporated the costs and benefits of ART. Yet, to date only one evaluation of a testing program for a high-prevalence general population has incorporated the potential benefits of ART.[233] Moreover, this Tanzania-based evaluation of VCT study assumed very low rates of linkage-to-care, reflecting the low availability of treatment in the country.

There have not yet been any evaluations of expanded testing programs in sub-Saharan Africa with widespread treatment availability. This is probably again due to the lack of widespread treatment availability in this region until recent years. However, now that treatment is become widely available in resource-poor settings, there is a need to evaluate the cost-effectiveness of various strategies for identifying HIV-positive persons and linking them to this treatment. While many studies have evaluated expanded testing policies in industrialized settings (see Subsections 4.2.1-4.2.2), much of this research is probably not transferable to sub-Saharan African settings (see Subsection 4.2.3). By examining expanded testing policies in South Africa with widespread treatment availability, this thesis seeks to fill a critical gap in the HIV testing economic literature.

4.3.2 HIV testing modelling approaches

HIV infection is chronic, the time from initial exposure to developing acquired immune deficiency syndrome (AIDS) and eventual death lasting years or even decades (see Subsection 2.1.2). The advent of ART has lengthened further still the time over which the health consequences of HIV infection occur. The resulting long

timeframes make it impractical for studies with primary designs to account for lifetime costs and benefits of HIV-related interventions. Consequently, most trial-based studies of HIV testing identified used simple outcome measures which did not capture the full benefits of testing and linkage-to-care (see Subsection 4.2.2). Predictably, the numbers of trial-based evaluations declined as more data became available regarding natural history and treatment efficacy, particularly in industrialized countries.

Instead, models have increasingly been used by evaluations of HIV testing programs. As discussed in Subsection 4.2.2, most of the modelling studies identified used simple decision trees. However, the simplicity of these models comes at the expense of the ability to model easily recurring processes over long stretches of time (see Subsection 3.1.6). For instance, those decision tree studies which accounted for the effects of treatment and care did so by abbreviating treatment data into crude summary estimates of lifetime costs and benefits. Moreover, none of the decision trees identified were capable of examining the interplay between risks of infection for clients over time (incidence) and the possible benefits of earlier diagnosis achieved by repeat screening. This is an important limitation given that repeat screening features in both the CDC[10] and WHO[11] recommendations for expanded testing.

Conversely, state-transition models can readily portray recurring processes over time. Indeed, all such studies identified explicitly accounted for the long-term effects and costs of treatment and care. However, all but one of these models featured the Markovian assumption. Complex adjustments must be made to Markovian models if they are to be capable of incorporating patient history into transition probabilities between health states (see Subsection 3.1.5). This fact is problematic for models of

HIV disease progression given empirical findings that the probabilities of AIDS death are affected by clients' histories of opportunistic infections (OIs).[141]

CEPAC

The one identified non-Markovian state-transition model, CEPAC, was selected for use in this thesis (see Chapter 7). Beyond its capability to reflect the complexities of HIV disease transmission, it was also chosen for its large numbers of inputs which afford users enormous flexibility. These parameters include those describing all steps of the HIV testing cascade (Figure 2.1). Consequently, the model facilitates analysis of the differential impact of allocating resources to various steps of the testing cascade, as done in this thesis. Its parameters modelling the first steps of the HIV testing cascade further allow users to conduct population-level analyses. Finally, it also includes a specific parameter for 'background testing,' making it possible to distinguish baseline from background testing in evaluating the incremental effectiveness of screening programs.

Upon approaching Dr. Ken Freedberg of the CEPAC collaboration, it was agreed that I would be provided training support and a copy of the model for my analysis. I did not have training or authorization to manipulate the model's structure. However, I was provided a trace program with which to scrutinize the model's simulations, facilitiating checks to ensure the correct operation of individual parameters. I was also able to construct a supplementary model based in Excel (Microsoft, Redmond, WA), referred to as the AHI Testing (AHIT) model, for use with CEPAC. AHIT facilitates the depiction by CEPAC of test protocols capable of detecting AHI (see Subsection 7.1.1).

One notable drawback to the use of CEPAC was the inability to model secondary transmission. Some CEPAC studies have provided crude estimates of the effects of testing programs on secondary transmission with Excel add-ons (analogous to AHIT). However, these estimates assumed static transmission rates (see Subsection 3.1.6) and were compelled to use very rough approximations of the lifetime costs of HIV infection.[153,154] Unfortunately, this limitation seemingly reflects a broader neglect within the field of health economics to incorporate sophisticated models of disease transmission.[111] Indeed, only three identified studies used system dynamics models to capture these effects of HIV testing (see Subsection 4.2.2).[161,219,232]

4.3.3 Implications of research findings for selected HIV testing issues

HIV testing throughput and outcomes

Studies accounting for throughput losses in the HIV testing process generally found the cost-effectivess of screening to be sensitive to client throughput for the HIV testing cascade. This result is to be expected insofar as the costs of screening are constant and incurred regardless of client throughput and to the extent that linkage-to-care leads to treatment, so serving as a surrogate for effectiveness. The higher the client throughput, the more effective screening becomes because more clients are linked to interventions yielding health benefits and so cost-effectiveness improves.

This result highlights the importance of selecting final outcomes in evaluating the cost-effectiveness of HIV testing programs. As noted in Subsection 4.2.2, many of the identified studies chose outcomes related to completion of only portions of the testing process. Analyses using such intermediate outcomes are less meaningful than those using more generic final outcomes because testing by itself is of little value if

those diagnosed HIV-positive do not receive effective treatment.[‡‡] As stated in Subsection 3.3.1, this thesis uses LYGs as the outcome of interest. As a result, this thesis seeks to inform efficiency in achieving client throughput for the *entire* HIV testing cascade, as opposed to individual steps.

To this end, this thesis examines multiple scenarios representing alternative means of expanding the numbers of undetected HIV-infected persons receiving both testing and linkage-to-care. These policies are defined by a number of programmatic decisions. Specifically, eight provider-initiated policies adopting one of two options across three programmatic decisions (consent method, test protocol, and linkage-to-care method) are considered (see Section 2.2). Each of these programmatic decisions is then assumed only to increase throughput for particular steps of the HIV testing cascade (see Section 2.3). Therefore, by comparing these eight policies to one another, this thesis determines the differential cost-effectiveness of testing strategies prioritizing resource allocation to increase client throughput for different cascade steps.

Strictly speaking, if considering the costs and effects of treatment only (ignoring transmission effects), the choice of step upon which to focus efforts to increase throughput should be irrelevant. In the words of Walensky et al., "failure of any one [step] results in overall system failure."[152] In this sense, no one step is more important than any other. However, it may in fact be more efficient to increase the total proportions of a population receiving linkage-to-care by improving throughput for specific cascade steps for two reasons. First, testing costs are incurred by patients

[‡‡] It is important to emphasize that this statement is predicated on this thesis's exclusion of the effects of screening on secondary transmission. In truth, if testing achieves the important goal of educating clients to practice safer sex, there may in fact be a substantial benefit for the target population even if no one is linked to treatment and care.[231]

simply by passing through some of the cascade steps, regardless of whether they ultimately receive linkage-to-care. To the extent that these costs are 'frontloaded' it may be more cost-effective to focus on increasing throughput for clients who have already entered the testing cascade. Second, throughput for the different steps may vary such that some have greater potential for improvement than others.

To my knowledge, only one study (Walensky et al.[152]) has attempted a similar comparison of the cost-effectiveness of resource allocation to increase throughput for alternative HIV testing cascade steps (see Subsection 4.2.3). I attempt to build on their USA-based analysis in two important ways. First, Walensky et al. examined dozens of scenarios defined by different rates of client passage through the testing steps, many of which may not be practical policy options. I instead define a smaller number of scenarios whose client throughput values are based on my estimates of what is practically achievable for specific testing approaches (Table 2.1). Second, I explore further Walensky et al.'s finding in the USA that improvements in cost-effectiveness for programs focusing on linkage-to-care diminish with increased prevalence. Since this thesis examines testing in South Africa, its results will verify whether this improvement becomes negligible in a high-prevalence setting.

Background screening

It is common for economic evaluations to compare interventions to current practice. Doing so reflects the fact that some of the effectiveness yielded by an intervention under evaluation is already being obtained (see Subsection 3.1.4). Failing to account for such baseline effectiveness overestimates the cost-effectiveness of interventions under evaluation. However, it is less common to account for effectiveness achieved by current practice believed to continue beyond that achieved by an intervention.

Indeed, as highlighted in Subsection 4.2.2, none of the identified studies distinguished and treated differently baseline versus background testing as in this thesis (see Section 2.2). This thesis is unique in that it accounts for both. To this end, it relies on data describing testing encounters in a small African community differentiated between those for primary healthcare users versus all others (e.g., ANC users and TB patients, see Subsection 5.1.2).

Population-level analyses

A population-level analysis as defined in this thesis calculates the costs and effects for an intervention for each member of the targeted population, regardless of whether she actually receives the intervention. This approach contrasts with most of the studies identified by this review which determined the costs and effects of interventions only for those clients offered or accepting testing (see Subsection 4.2.2) Non-population-level economic evaluations inflate client throughput for the HIV testing cascade by confining the analysis to individuals who have already progressed through part of the testing process. For example, an analysis of costs and effects for test offer recipients makes throughput losses due to lack of testing venue access impossible.

Ultimately, such analyses inflate both the costs *and* the effectiveness of interventions, and may also skew the ratio between the two. This inflation is exacerbated when evaluating testing programs targeting a general population for whom testing coverage is less than universal, as done in this thesis. Of course, knowing the costs and effects for subpopulations is itself useful information. However, I believe the costs and effects per population member comprise more useful information for decision-makers considering widespread implementation of expanded testing.

Conducting population-level analyses is complicated by the need for denominator data. Most population-level analyses identified in this review either evaluated HIV testing programs targeting well-defined subpopulations (e.g., pregnant women) or estimated population testing rates using assumptions rather than empirical data (including two previous CEPAC studies,[153,154] see Subsection 4.2.2). I obtained denominator data for an enclosed general population living in an African community (see Chapter 5) whose testing behaviour could be measured. Thus, the CEA presented in Chapter 7 is unique in estimating for the first time population-level costs and effects of expanded HIV testing in South Africa.

Fitting empirical data to model parameters

The final methodological issue examined in this thesis relates to the translation of empirical testing data into model parameter inputs. Given my desire to consider client throughput for all testing cascade steps, distinguish baseline from background testing, and examine the population-level impact of testing, a flexible modelling approach was of paramount importance to my analysis. The CEPAC model is unique among the models identified in this review in possessing parameters necessary to accommodate all of these needs. However, a drawback associated with this flexibility is substantial data demands. Fortunately, I had access to a unique study community from which to gather the necessary testing data (see Chapter 5) and to the CEPAC collaboration's collection of work informing the model's non-testing parameters (see Appendix B).

However, a related challenge was the fitting of these data to CEPAC's parameters which were designed to simplify portrayal of the testing process rather than to accommodate testing data. Specific issues related to this difficulty included converting testing rates as observed in the study community to probabilities as defined

in the model; choosing when to censor observations of referral and treatment outcomes; and defining plausible ranges for all parameter inputs. Chapters 5-7 will discuss in greater detail the specific methods used to address these challenges.

Chapter 5:
Measuring population rates of HIV testing and linkage-to-care in an African community in South Africa, 2001-2006

Expanding human immunodeficiency virus (HIV) testing can increase case detection and the numbers of HIV-infected persons linked to life-saving treatment. The magnitude of this increase will depend upon the extent to which testing and linkage-to-care occur in the absence of these policies. Thus, estimating current rates of HIV testing and linkage-to-care in South Africa is critical for estimating the potential effectiveness and cost-effectiveness of the expanded HIV testing policies considered in this thesis (Table 2.1). If current testing and linkage-to-care rates are already high, then additional uptake achieved by expanding testing may be insufficient to justify the additional costs incurred.

Many studies have measured testing and linkage-to-care rates for HIV-testing programs in sub-Saharan Africa.[63,65-70] However, none of these studies measured rates of client passage for all of the steps of the HIV testing cascade (Figure 2.1). For the purposes of this thesis, estimates of rates of passage for all steps were necessary to examine the comparative cost-effectiveness of policies designed to increase throughput for particular steps.[*] Thus, this chapter reports estimates for client throughput for the entire HIV testing cascade, using testing registers and medial records to quantify testing and linkage-to-care rates, respectively.

[*] Such an exercise has heretofore only been undertaken in the United States of America (USA) by a single study (see Subsection 4.3.3).[152]

Data describing rates at which the underlying populations targeted for testing access testing venues (Step 1 of the testing cascade) is conspicuously absent from the current literature. Instead, these studies measured testing rates only among clients presenting to testing venues. These studies therefore provide an incomplete picture of the effectiveness of these testing programs as increasing testing rates for program clients is by itself a goal secondary to increasing population testing rates.

The paucity of population-level HIV testing analyses in the literature (see Subsection 4.2.2) is likely due in part to the lack of data describing population testing rates. Most population-level analyses in South Africa[17,276] and elsewhere in sub-Saharan Africa[61] have been cross-sectional surveys only measuring the proportions of individuals reporting previous utilization of testing services. Indeed, to my knowledge only one study, done in Botswana, attempted to approximate population testing rates by using aggregate statistics from healthcare facility reports. However, low levels of reporting and the lack of patient-specific data precluded calculation of the annual rates at which unique individuals not previously diagnosed with HIV received testing and linkage-to-care.[277]

This study takes advantage of the unique characteristics of a small African community near Cape Town, South Africa to measure rates of testing and linkage-to-care for an adult population. Due to its small size and well-defined borders, previous censuses have been able to quantify its population, providing denominator data. Moreover, the high levels of poverty in the community make it unlikely that travel expenses were incurred by many population members to obtain testing outside of two local healthcare facilities. This combination of near-complete capture of population testing

and denominator data makes it possible to calculate the population test offer rates (cascade Steps 1-2) reported in this chapter.

Furthermore, this thesis measures test offer rates for baseline and background testing separately. As discussed in Section 2.2, baseline testing rates are here defined as the current rates at which the general population accesses primary healthcare facilities and uses voluntary counselling and testing (VCT) services (client-initiated, opt-in testing). Background testing rates are defined as the rates at which the general population receives provider-initiated tests as a result of infection with tuberculosis (TB) or attending antenatal care (ANC) services. This differentiation of current screening into baseline and background testing enables the impact of both on the cost-effectiveness of expanding HIV testing among adult African primary healthcare users to be examined in Chapter 7.

The data reported in the results section of this chapter are used to estimate the effectiveness of expanded testing policies in increasing client throughput for the HIV testing cascade in Chapter 6. They are then fitted to the parameters of the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model in Chapter 7 to estimate the cost-effectiveness of these expanded testing policies. I will also discuss implications of my findings for HIV testing policy in South Africa in the discussion of this chapter. To this end, there will be some further consideration of the various trends observed during the study period (2001-2006) in the population's rates of testing and linkage-to-care.

5.1 Methods

This section discusses methods adopted in conducting a retrospective descriptive study of testing rates in an African community under current testing practices during 2001-2006. First, the study setting is described. Next, the data collection process used to measure the community population's size and demographics, testing encounters, and linkage-to-care is described. Finally, the specific methods by which these data were used to generate testing and linkage-to-care rates and test for linear trends over time are outlined. This research was formally approved by the Partners Human Subjects Committee (protocols 2003-P-001019 and 2005-P-002197) and University of Cape Town Research Ethics Committee (protocol 402/2006).

5.1.1 Study setting

The study was conducted in a peri-urban African community located near Cape Town (<20 km) previously described elsewhere.[278] The settlement has a well-demarcated border facilitating definition of its population. A 2006 census found 13,180 individuals living in 2,099 households – predominantly informal dwellings such as shacks – with unemployment exceeding 50%. A 2005 anonymous unlinked seroprevalence survey detected 23% HIV prevalence among the adult (>14 years) population using simple random sampling.[279]

A government-run primary healthcare facility within the community provides basic outpatient care free of charge to all patients. A nearby hospital (<5 km) provides all secondary care for the population, including inpatient and antenatal services. Hospital services are charged to patients according to a progressive fee schedule: patients

earning a single annual income <R72,000 (2006 US$10,600) or household income <R100,000 (2006 US$14,700) receive all hospital care free of charge.[280]

HIV-related interventions, 2001-2006

Client-initiated, opt-in VCT services were available to all individuals accessing either the local clinic or the hospital during 2001-2006. In addition to patients who requested testing, provider-initiated, opt-in testing was routinely offered to TB patients throughout the study period. Starting in 2002, all pregnant women accessing the hospital or clinic were similarly offered provider-initiated, opt-in testing. Acceptance of all tests required signed consent. Given the closed nature of the community and high levels of poverty precluding travel, the tests offered through these two healthcare facilities are believed to comprise virtually all of the population's tests. A serial testing protocol was used for all encounters with the Abbott Determine test (Abbott Diagnostics, Abbott Park, IL, USA) serving as the initial test. Various confirmatory tests were used over the study period, with the Pareekshak rapid test (Bhat Bio-tech India (P) Ltd, Bangalore, India) being the most recent.

The standard of HIV-related care in the community evolved substantially over the study period, largely due to the unique provision of resources and expertise by the Desmond Tutu HIV Foundation (DTHF). Since 2001, HIV-related care consisted of a "positive living" clinic meeting twice weekly[281] and prescription of cotrimoxazole prophylaxis for eligible clients according to World Health Organization (WHO) guidelines (CD4<200 cells/mm^3 or WHO stage 3/4).[282] Seropositive pregnant women started receiving single-dose nevirapine in 2001 and dual therapy (zidovudine and nevirapine) in 2006 for prevention of mother-to-child transmission (PMTCT),

predominantly delivered through the hospital where the formal ANC program was based.

Three-drug combination antiretroviral treatment (ART) first became available for eligible clients in 2003 with international funding provided to DTHF by a Doris Duke grant. The ART roll-out accelerated in January 2004 with funding from the National Institutes of Allergy and Infectious Diseases (grant number 1U19AI0533217). Eligibility criteria throughout the study period were again based on WHO guidelines (CD4<200 cells/mm^3 or WHO stage 4).[283]

5.1.2 Data collection

Census data

The numbers of individuals living in the settlement each year were estimated from census data collected in 2002, 2004, and 2006 by community health workers affiliated with DTHF.[284] Questionnaires administered to one member of every dwelling solicited data on the number, age, and sex of the inhabitants of each household. Stripped of individual identification information, these numbers were then made available to me for reanalysis.

Testing data

With assistance from members of DTHF (Dr. Jennifer Pitt and Ms. Ntombizodwa Mzongwana), I accessed the hardcopy HIV testing registers from the primary healthcare clinic and the hospital to retrieve data on the number of HIV tests offered to adult community residents during 2001-2006. These registers included entries reporting repeat tests. For each test offer entry in the testing registers, data were retrieved on client identification characteristics including first name; surname; date of

birth; and medical record number. Data were also retrieved on each client's place of residence; sex; offer acceptance; and test result. Lastly, the site (clinic or hospital) and service (VCT, ANC, or TB care) in which each offer was made were also recorded.

I then compared client identification variables across all testing observations. Observations in which at least three of the four identification variable values were identical were assumed to represent repeat testing by a single person. In instances where ambiguity remained following this decision rule, the client's medical record was retrieved for clarification. Upon identifying all unique individuals in the dataset, each was assigned a unique identification number. The dataset was then stripped of all identification variables except dates of birth to preserve patient anonymity.

Clinical indicators and linkage-to-care data

I retrieved the medical records of all adults who tested seropositive according to the testing registers. For those clients post-test counselled, clinical indicators including WHO stage at diagnosis;[27] dates and results of all CD4 counts and HIV viral load measurements to date; and dates of death were collected. Finally, dates of eligibility for and initiation of cotrimoxazole and ART were also recorded.

5.1.3 Statistical analyses

All analyses excluded observations of testing by individuals with previously recorded HIV-positive diagnoses (n=579). Observations of testing by individuals known to be less than 15 years of age (n=290) were also excluded.

Census data

A small number of observations from the censuses were missing data on adult respondent age (n=38) and sex (n=2). These census numbers served as denominators in the testing rate calculations (see discussion below), so deletion of these observations would have inflated these rates. Proportions of census observations missing data on respondent age and sex were compared across all age (15-19, 20-29, 30-39, 40-49, and >49) and sex (male and female) categories by calculating exact confidence intervals using the binomial distribution. The missing data were thus found to be missing completely at random,[285] so justifying their imputation using regression based on the distribution of non-missing data. The representativeness of the adult community population was explored by comparing its population pyramid to that for the national adult African population in 2006.[286]

To estimate testing rates for all years of the study period, it was necessary to estimate the size and demographic distribution of the community population in non-census years. The numbers of adults belonging to each sex-specific age category were estimated using linear extrapolation for 2001 and linear interpolation for 2003 and 2005. Finally, to facilitate calculations of sex-specific test rates to include those for pregnant women, the proportion of females within each age stratum who were pregnant each year was estimated using the ASSA2003 demographic model (Actuarial Society of South Africa, Cape Town, South Africa).[287] Specifically, the projections for Africans living in the Western Cape Province were used. All of these pregnancies are assumed by the model to be contained within each calendar year.

Testing rate calculations

To examine the extent to which testing occurred in the study community through background versus baseline testing, annual rates of test offer receipt (testing cascade Steps 1-2) through each service (VCT, ANC, and TB care) were calculated for the adult population residing in the study community. To examine demographic trends in testing, sex- (males, non-pregnant females, and pregnant females) and age-specific (as per the age categories outlined in Subsection 5.1.2) rates of test offer receipt through any service were also calculated. The numerators for these rates were the numbers of test offers made each year to unique adult residents not previously diagnosed with HIV. As discussed above, the denominators for these rates were based on the community census data. Clients receiving HIV-positive diagnoses were removed from the pool of patients eligible for testing in subsequent years to ensure the testing rate calculations reflected the cumulative effect of case detection.

No special treatment was given to the denominators for pregnant women. Consequently, the annual pregnant women testing rates reported in this chapter are in fact rates of testing among all women experiencing pregnancies each calendar year. Since the ASSA2003 model assumes that all pregnancies are contained within each calendar year,[287] no woman contributes a year of person time to two separate calendar years as a result of a single pregnancy. This calculation method avoided the complications associated with allocating observation time for these women to the pregnant versus non-pregnant cohorts. However, it must be emphasized that the testing rates among this group are therefore lower than would be expected among women strictly observed during pregnancy.

Beyond the premise that virtually all test offers received by the population were recorded in the registers that I accessed (see Subsection 5.1.2), these testing rate calculations required four assumptions. First, those testing clients whose ages were unknown (n=121) were assumed to be younger than 15 years, so requiring their exclusion from the numerator. Second, those testing clients whose places of residence were unknown (n=1,269) were assumed to live outside the study community, similarly requiring their exclusion from the numerator. Third, it was assumed that only those 36 clients known to be HIV-infected by 2001 had received positive diagnoses prior to the study period start, so requiring their exclusion. Fourth, all diagnosed HIV-infected clients were assumed to remain in the community and survive through 2006 unless a date of death was indicated in their records, so requiring that all clients diagnosed with HIV be removed from all subsequent rate denominators.

To examine the level of certainty regarding my rate calculations, I considered the effects of extreme alterations to these four assumptions. High-bound rate estimates altered the assumptions to inflate numerators and deflate denominators. Regarding the first and second assumptions, all clients of unknown age and residence were assumed to be older than 14 years and community residents, respectively, so including them in the testing rate numerators. Also, the third assumption was changed to assume that all HIV-infected clients not diagnosed during the study period were diagnosed prior to 2001, thus excluding them from the testing rate denominators for all years of the study period. For this assumption, the size of the HIV-infected population was assumed to be constant and equal to the 2006 adult population multiplied by 23%, the prevalence as estimated by the aforementioned survey.[279] Conversely, the low-bound rate estimates altered the fourth assumption to inflate the

denominators. Specifically, all clients diagnosed HIV-positive were assumed either to emigrate or die prior to the start of the next calendar year and be replaced with individuals previously undiagnosed with HIV and eligible for testing.

HIV testing cascade rates

Rates of progression through the other steps of the HIV testing cascade were also calculated including test offer acceptance (Step 3), post-test counselling (Step 4), referral for treatment (Step 5) and receipt of ART and cotrimoxazole (Step 6). Referral was defined as receipt of a CD4 count or total lymphocyte count within six months of HIV diagnosis. Treatment with ART or cotrimoxazole prophylaxis was defined as receipt of first drugs within six months of CD4 or WHO stage-based eligibility, as determined using the eligibility criteria outlined in Subsection 5.1.1 with the additional requirement that clients receive referral. Since, unlike the test offer rate calculations, cascade rates do not depend upon population-based denominators, they were calculated using test observations for all adults, regardless of place of residence.

Statistical tests

Clients not known to be adults or community residents were excluded from groups compared using formal statistical tests to minimize confounders. All analyses other than those of repeat testing and clinical indicators considered only first-time tests during 2001-2006 to ensure comparisons between mutually exclusive groups.

Pearson's chi-squared test[288,289] was used to test for associations between year of first-time test offer and four sets of categorical outcomes (client distributions according to age, sex, test location, and test service categories) and between year of diagnosis and WHO clinical stage distribution. The chi-squared test for linear trend[290] was used to

test for linear associations between year of first-time testing and the binary outcome of test result for each age, sex, test location, and test service category. This test for was also used to test for linear trends between year of positive diagnosis and both availability of a CD4 count within six months of diagnosis and receipt of a CD4 count <200 cells/mm^3. Finally, a median regression (least-absolute values) model was used to test for linear trend between year of diagnosis and median CD4 count.[291]

Repeat testing was analyzed using Kaplan-Meier estimates,[292] measuring the time elapsed from first-time testing with first repeat testing the event of interest. This analysis excluded all individuals tested through ANC or TB services during the study period to minimize potential confounders which may have explained test-seeking behavior. Kaplan-Meier estimates were used because retesting rates were not constant over the study period, each individual was followed for a unique timeframe, and the probability of censoring was unrelated to the probability of retesting.[†] Differences in the Kaplan-Meier estimates stratified by sex (males and non-pregnant females), were tested for statistical significance using the log-rank test.[293]

These survival data were also used to estimate rates of new infections. Sex-specific incidence rates were estimated for repeat testers by dividing the numbers of newly-diagnosed cases by the number of months between first-time and last-time testing for all of these testers. Finally, sex-specific rates of new diagnosis for the entire group were calculated by dividing the number of newly-diagnosed cases by the total number of months between all first-time tests and the study period end. All analyses were conducted with Stata version 9.1 (StataCorp, College Station, TX, USA).

[†] No deaths were recorded among this group so all clients were followed from the time of first test to the end of the study period.

5.2 Results

5.2.1 Population characteristics

Census data indicate that the community's adult population increased steadily during the study period, from 6,723 in 2001 to 10,165 by 2006. The age and sex distributions of the adult population did not change markedly during 2001-2006. In 2006, the adult population's mean age was 29.8 years and 53% were male. These demographics contrast with those of the national African population which comprised proportionately fewer persons aged 20-39 years old and only 49% males (Figure 5.1). The ASSA2003 demographic model produced stable projections of the proportions of females pregnant each year, in 2006 estimating them to be 5.0% for the age group 15-19 years, 12.6% for 20-29 years, 9.9% for 30-39 years, and 2.4% for 40-49 years.

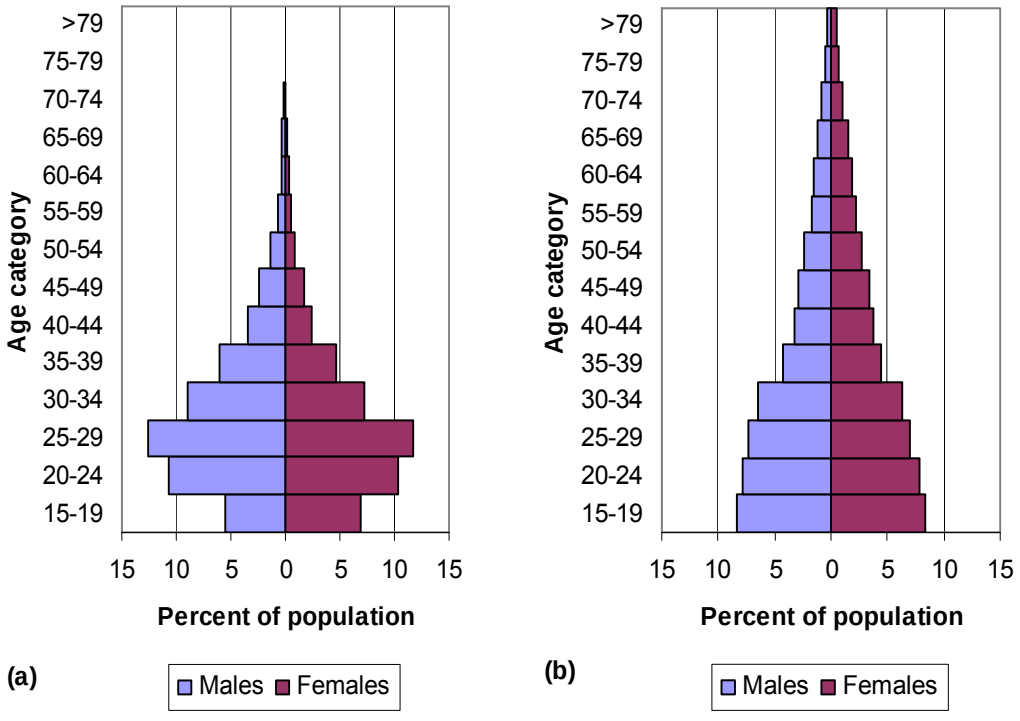

Figure 5.1. Adult African population pyramids, 2006. The community population (a) exhibited a 'youth bulge,' with greater proportions of members aged 20-39 years and fewer aged >49 years, and a greater proportion of males when compared to the national (b) population.

5.2.2 Test offers (Steps 1-2)

During the study period, 6,322 tests were offered to 5,006 individuals known to be adult community residents not previously diagnosed with HIV infection (Table 5.1). Males were consistently the recipients of proportionately fewer test offers than females, receiving only 29% of first-time test offers (39% when excluding ANC tests, data not shown). The proportion of offers made to males increased slightly as a proportion of all first-time test offers ($p<0.001$), but remained unchanged when excluding ANC tests ($p=0.363$, data not shown). Most first-time testers were young adults aged 20-29 (55%) or 30-39 (22%). Excluding 2001 tests, the age distribution for first-time testers changed slightly over time, skewing toward individuals aged 15-19 and away from individuals aged <39 ($p=0.01$). The proportion of first-time test offers made through VCT services decreased to 55% in 2002 when ANC testing became routine (see Subsection 5.1.1), but later increased to 76% in 2006 ($p<0.001$).

Table 5.1. Distributions of first-time test offers, 2001-2006.

	2001	2002	2003	2004	2005	2006	All	p*
No. first-time offers	285	529	644	1030	989	1529	5006	
% offers, by sex†‡								
Male	34	23	24	28	29	34	29	<0.001
Female, not pregnant	58	37	38	42	37	44	41	
% offers, by age†								
15-19	16	11	11	15	12	14	13	0.010
20-29	53	56	53	54	56	55	55	
30-39	21	22	25	21	22	22	22	
40-49	8	7	8	7	7	5	7	
>49	2	4	2	3	3	2	3	
% offers, by service†								
VCT	86	55	60	69	60	76	68	<0.001
ANC	8	40	38	30	33	22	29	
TB	6	5	2	2	6	2	3	

***** Chi-squared test for association between demographic, service, or venue category distributions and year during 2002-2006 (2001 data excluded) – test was applied to the numbers in each category and not the percentages as reported in this table
† Reported percentages within each year may not add to 100 due to rounding or missing data
‡ Percentages for pregnant women are synonymous with those for ANC testers
VCT: voluntary counselling and testing
ANC: antenatal care
TB: tuberculosis

Venue distributions for first-time test offers changed significantly over time (Table 5.2). The proportion of first-time test offers made at the clinic as opposed to the hospital similarly fell after 2001 but eventually increased from 34% in 2002 to 63% in 2006 ($p<0.001$). Also, while the proportion of first-time TB test offers ($p<0.001$) and ANC test offers ($p<0.001$) made at the clinic both changed significantly since 2002, the change in proportion of VCT offers made at the clinic was much greater, rising from 36% in 2002 to 80% in 2006 ($p<0.001$).

Table 5.2. Proportions of first-time test offers made at clinic, 2001-2006.

	2001	2002	2003	2004	2005	2006	All	p*
% total test offers	73	34	28	47	45	63	49	<0.001
% offers, by sex†‡								
Male	61	32	38	65	71	85	69	<0.001
Female, not pregnant	82	49	49	70	68	83	71	<0.001
% offers, by age†								
15-19	81	44	44	58	50	66	58	<0.001
20-29	75	41	31	50	47	66	53	<0.001
30-39	67	26	27	44	45	65	49	<0.001
40-49	65	21	31	43	63	81	55	<0.001
>49	67	17	18	36	56	61	43	0.001
% offers, by service†								
VCT	75	36	44	68	66	80	69	<0.001
ANC	67	25	9	0	1	0	6	<0.001
TB	63	89	68	78	100	100	89	<0.001

* Chi-squared test for linear trend between venue category and year of test offer during 2002-2006 (2001 data excluded) – test was applied to the numbers in each category and not the percentages as reported in this table
† Reported percentages within each year may not add to 100 due to rounding or missing data
‡ Percentages for pregnant women are synonymous with those for ANC testers
VCT: voluntary counselling and testing
ANC: antenatal care
TB: tuberculosis

Test offer rates

Annual population HIV test offer rates increased from 4.4% in 2001 to 24.1% in 2006. The rate at which population members initiated VCT encounters (baseline testing) increased from 3.8% in 2001 to 18.9% in 2006. This rate experienced most of its rise after 2003 when the ART roll-out began in the study community. The

population received background testing offers (i.e., testing through ANC and TB services) at much lower rates. The rate at which the population received ANC test offers increased sharply from 0.4% in 2001 to 3.0% in 2002, the year antenatal testing became provider-initiated as part of the provincial PMTCT program. The population TB test offer rate remained consistently low, never exceeding 0.9% (Figure 5.2).

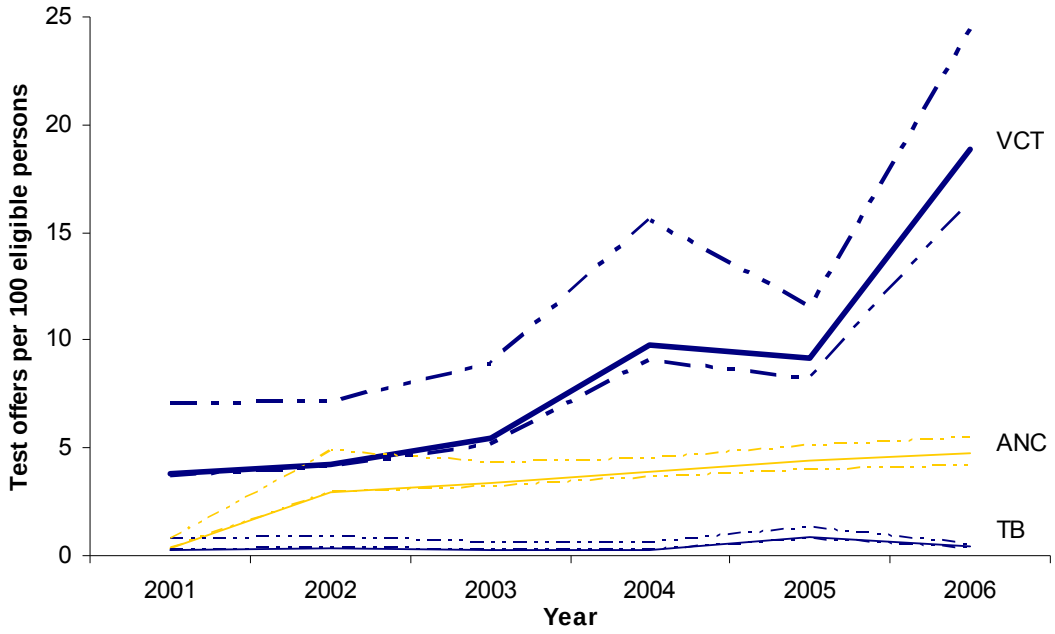

Figure 5.2. Service-specific eligible population test offer rates, 2001-2006. Eligibility is here defined as adult (>14 years) residents of the study community not previously diagnosed with HIV. Among the rates of test offer for the individual services, the rates for tests offered through tuberculosis (TB) care were consistently the lowest (dark solid line), followed by the antenatal care (ANC) user test offer rates (light solid line), with the voluntary counselling and testing (VCT) test offer rates the highest (dark bold line). The dashed lines represent the upper- and lower-bound rate estimates (see Subsection 5.1.3 for methods); in many instances, the lower-bound estimates are indistinguishable from the baseline estimates.

There were significant differences in the rates of test offers for the population stratified by sex. Test offer rates among pregnant females reflect the increase in testing which resulted from the implementation of provider-initiated ANC testing in 2002. Test offer rates among non-pregnant females and males also rose, albeit more moderately (Figure 5.3). These rates were higher among non-pregnant females than

males in all years. There were no substantial differences in test offer rates by age stratum (data not shown).

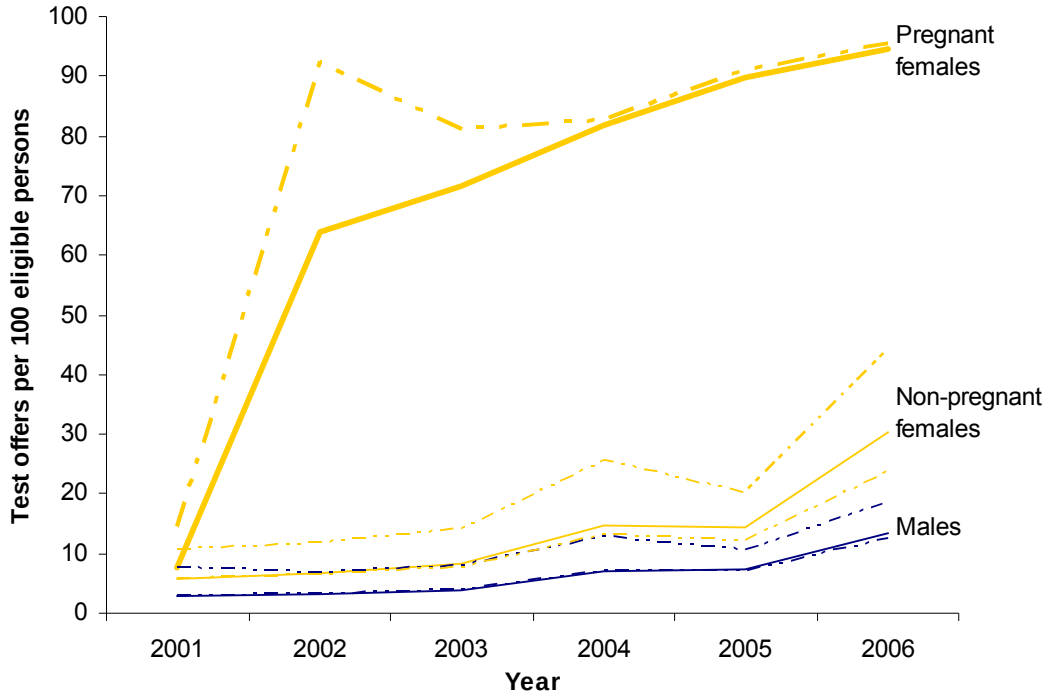

Figure 5.3. Sex-specific eligible population test offer rates, 2001-2006. Eligibility is here defined as adult (>14 years) residents of the study community not previously diagnosed with HIV. Rates were highest among pregnant females (light bold line), and increased sharply from 7.8% in 2001 to 63.8% in 2002 when ANC testing became provider-initiated. Non-pregnant females (light solid line) consistently received test offers at a higher rate than males (dark solid line). The dashed lines represent the upper- and lower-bound rate estimates (see Subsection 5.1.3 for methods); in many instances, the lower-bound estimates are indistinguishable from the baseline estimates.

5.2.3 Acceptance probabilities and test results (Steps 3-3.5)

There were few changes in annual probabilities of acceptance observed in the study community during 2001-2006 (Table 5.3). The majority of test offers were accepted. Indeed, 4,761 (95.1%) of the 5,006 first-time test offers made during the study period were accepted. Of all test offers, 93.8% (5,932 of 6,322) were accepted. There were no consistent trends over time or substantial differences between client age, sex, or

service in first-time test offer acceptance rates (the only tests for linear trend which were statistically significant were those for subgroups with high sample sizes).

Table 5.3. Proportion of first-time test offers accepted, 2001-2006.

	2001	2002	2003	2004	2005	2006	All	p*
% acceptance, by sex†								
Male	100	87	94	94	95	87	92	<0.001
Female, not pregnant	98	94	94	93	96	89	93	<0.001
% acceptance, by age								
15-19	93	89	97	97	98	95	96	0.072
20-29	99	90	92	92	95	89	92	<0.001
30-39	100	94	93	96	96	92	94	0.107
40-49	100	92	98	96	100	94	96	0.198
>49	100	96	93	100	100	97	98	0.598
% acceptance, by venue								
Clinic	98	97	96	93	97	88	93	<0.001
Hospital	100	88	93	95	96	97	94	<0.001
% acceptance, by service								
VCT	99	91	94	94	96	89	92	<0.001
ANC	91	91	93	96	97	99	96	<0.001
TB	100	100	100	94	97	91	96	0.347
% acceptance, total	98	91	94	94	96	91	93	<0.001

***** Chi-squared tests for linear trend between test acceptance and year of test over 2002-2006 (2001 data excluded) – test was applied to the numbers in each category and not the percentages as reported in this table
† Yield for pregnant females is synonymous with that for ANC testers
VCT: voluntary counselling and testing
ANC: antenatal care
TB: tuberculosis

The proportion of screened individuals testing positive for HIV, or yield, exceeded 25% in all years (Table 5.4). Ultimately, 1,721 (36.1%) of all 4,761 individuals accepting screening were seropositive. Yield among all age groups >19 years was nearly double that for clients aged 15-19. Yield for non-pregnant females (40%) exceeded that for males (32%) and pregnant females (26%), $p<0.001$. Finally, the yield for TB patients was the highest of the three services (51%) while that for antenatal care users was the lowest (26%). Yield among first-time testers decreased significantly for nearly all groups over time as testing rates rose ($p<0.001$ for all

groups save for those with small sample sizes, e.g., clients aged >39 years or testing through TB services).

Table 5.4. Yield for first-time tests, 2001-2006.

	2001	2002	2003	2004	2005	2006	All	p*
% seropositive, by sex†								
Male	38	44	47	32	26	26	32	<0.001
Female, not pregnant	48	52	54	38	37	33	40	<0.001
% seropositive, by age								
15-19	43	29	30	12	11	16	18	<0.001
20-29	47	46	42	33	31	28	35	<0.001
30-39	53	53	40	40	38	35	40	<0.001
40-49	45	47	47	37	27	35	38	0.043
>49	0	36	36	41	24	19	29	0.344
% seropositive, by venue								
Clinic	45	47	54	33	30	31	36	<0.001
Hospital	51	44	35	30	29	23	32	<0.001
% seropositive, by service								
VCT	43	48	50	36	32	29	36	<0.001
ANC	75	40	23	22	25	21	26	<0.001
TB	61	60	79	53	34	55	51	0.044
% seropositive, total	46	42	38	30	29	25	31	<0.001

***** Chi-squared tests for linear trend between test results and year of test over 2002-2006 (2001 data excluded) – test was applied to the numbers in each category and not the percentages as reported in this table
† Yield for pregnant females is synonymous with that for ANC testers
VCT: voluntary counselling and testing
ANC: antenatal care
TB: tuberculosis

Retesting

Substantial numbers of clients underwent retesting. Excluding all patients testing through ANC or TB services, 2,145 adult community residents were seronegative at first-time testing. Rates of retesting for these individuals were 15.9% within one year, 28.8% within two years, and 51.7% within five years. Non-pregnant females retested at higher rates than males ($p<0.0001$ by log-rank test, Figure 5.4).

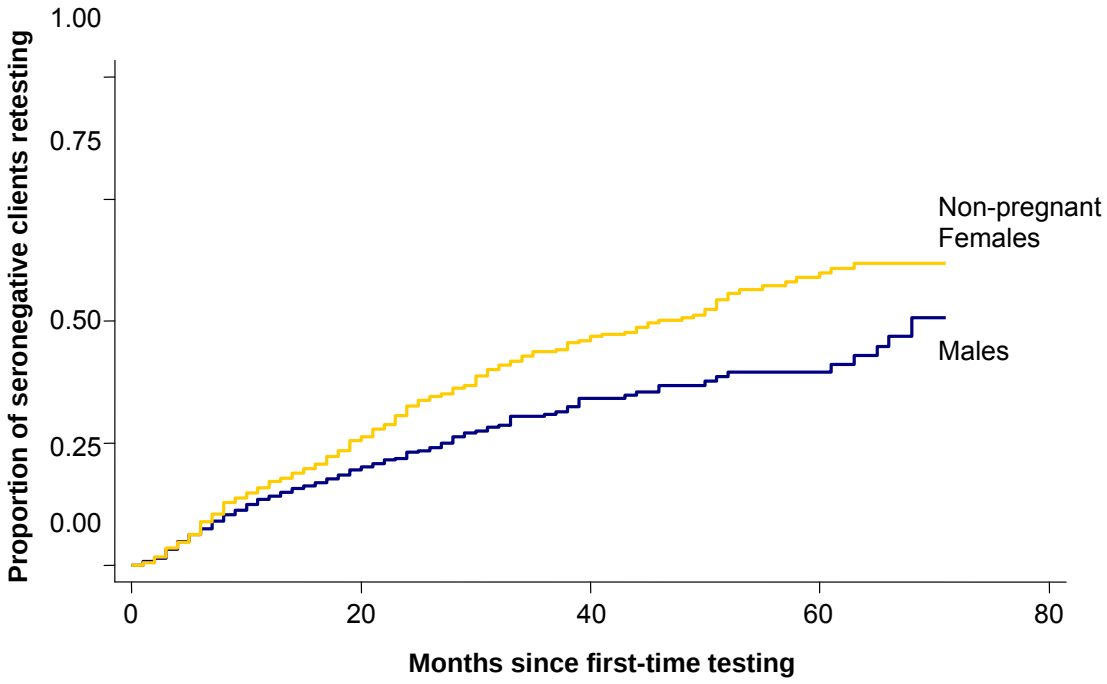

Figure 5.4. Kaplan-Meier estimates of time to retesting for seronegative clients. Estimate excludes all individuals tested through antenatal or tuberculosis services during 2001-2006. Men (dark solid line) retested at lower rates than women (light solid line), p<0.0001 by log-rank test.

Although lower than first-time tests, yield remained high for these repeat testers who were seronegative at first-time testing. Yield for second-time tests was 11.4% (62 of 542) while that for third-time testers was 6.3% (10 of 158). The observed incidence rate among only those clients returning for testing over the entire study period was 8.4 per 100 person-years (5.2 for males and 8.7 for non-pregnant females). The observed rate of diagnosis of infections among all 2,145 initially seronegative clients was 2.0 per 100 person-years (1.4 for males and 2.3 for non-pregnant females).

5.2.4 Clinical indicators and linkage-to-care for seropositive clients (Steps 4-6)

Clinical indicators for HIV-positive clients

While clinical indicators for seropositive clients did not change markedly over time, the proportions of HIV-infected clients receiving CD4 counts within six months of diagnosis increased substantially during the study period (p<0.001, Table 5.5). There was no linear trend in the annual medians of the first CD4 counts received (p=0.539), 36% of which were <200 cells/mm^3. There were small inconsistent fluctuations in the distributions of clients according to WHO stage at diagnosis (p<0.001, likely due to large sample size). The proportion of clients determined at diagnosis to be relatively asymptomatic (WHO stages 1-2) was generally twice that of patients clearly exhibiting HIV-related symptoms (WHO stages 3-4): 55% asymptomatic versus 22% symptomatic. Among the small subset of patients whose VLs were measured within six months of diagnosis (n=139), the median measurement was 206,000 copies/mL.

Table 5.5. Clinical indicators for seropositive clients, 2001-2006.

	2001	2002	2003	2004	2005	2006	All	p*
No. seropositive	132	225	259	340	310	455	1721	
CD4 counts†								
% cases with CD4	2	9	27	36	41	53	34	<0.001
Median, cells/mm3	265	232	263	299	219	292	275	0.539
% <200 cells/mm3	33	33	38	32	46	31	36	0.586
WHO stage‡								
% stage 1	46	35	39	51	33	53	44	<0.001
% stage 2	20	11	14	7	10	9	11	
% stage 3	18	18	17	17	22	16	18	
% stage 4	0	1	3	4	6	5	4	
% unknown	16	35	27	22	28	18	24	

* Chi-squared tests for linear trend between CD4 availability and year of diagnosis and between CD4 <200 cells/mm3 and year of diagnosis; median regression model for linear trend between median CD4 and year of diagnosis; chi-squared test for association between WHO stage distribution and year of diagnosis

†Table includes only CD4 counts received within six months of diagnosis

‡ Reported percentages within each year may not add to 100 due to rounding or missing data

WHO: World Health Organization

Client throughput for cascade Steps 4-6 increased (Figure 5.5). Among seropositive clients for whom information on post-test counselling was available (70%, including clients whose age or place of residence was unknown), post-test counselling rates exceeded 96% each year. Referral rates (receipt of CD4 or total lymphocyte counts within six months of diagnosis, see Subsection 5.1.3) increased from 27% of seropositive clients in 2001 to 64% in 2006. Seropositive clients determined to be eligible for ART before the end of the study period remained stable as a proportion of all seropositive clients but decreased as a proportion of referred clients (90% in 2001 versus 34% in 2006). Seropositive clients determined to be immediately eligible for ART at diagnosis remained unchanged (data not shown). ART initiation rates within six months of determination of eligibility increased dramatically from 0% in 2001 to 70% in 2006. Cotrimoxazole initiation ratio within six months of eligibility also increased, doubling from 26% in 2001 to 52% in 2006 (data not shown).

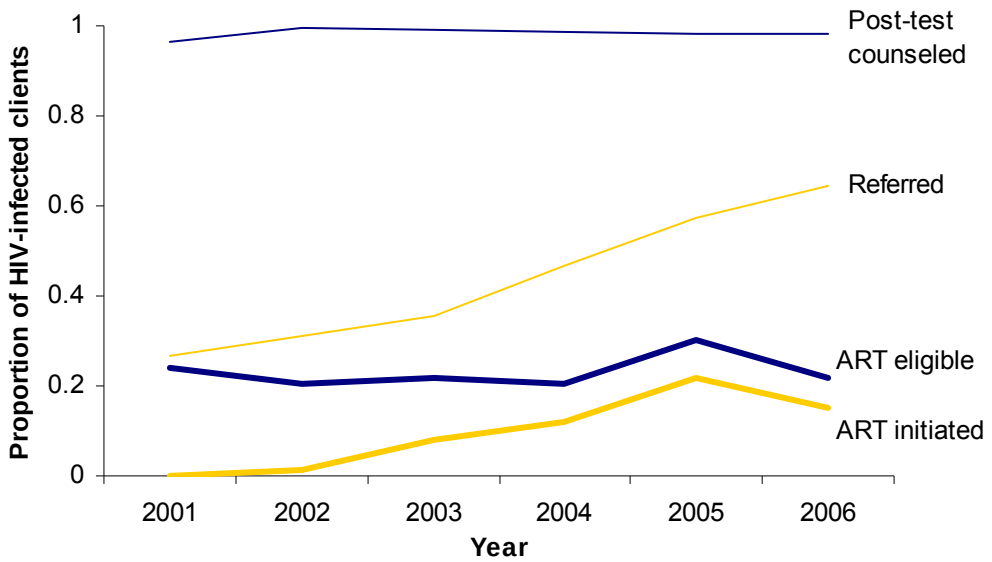

Figure 5.5. Rates of counselling and linkage-to-care for seropositive clients. Seropositive clients for whom information on post-test counselling was available comprise the denominators for these rates. Nearly all of these clients received post-test counselling (dark solid line). Referral is defined as receipt of a CD4 or total lymphocyte count within six months of diagnosis (light solid line). Antiretroviral treatment (ART) eligibility is defined as receipt of a CD4 count <200 cells/mm^3 or diagnosis with a World Health Organization stage 4 HIV-related illness[27] (dark bold line). Finally, ART receipt is defined as receipt of first drugs within six months of determination of eligibility (light bold line).

5.3 Discussion

This study found a clear rise in test offer rates for an adult African population in South Africa during 2001-2006, largely due to the rise in test offers made through VCT services (i.e., baseline testing). Sex-specific test offer rates were highest among pregnant females from 2002 onwards when antenatal testing became routine. Acceptance rates were high, with 93.8% of all offers accepted during the study period. Retesting accounted for much of the population's testing: 51.7% of seronegative first-time testers retested within five years. HIV-positive yield decreased but remained high, exceeding 25% in all years. The median of CD4 counts at diagnosis did not change significantly. The two principal gaps in linkage-to-care, referral for CD4 counts and receipt of ART, both closed markedly during the study period as the availability of these services expanded. The remainder of this section will discuss the implications of these findings for testing policy in South Africa.

5.3.1 Trends in test offer rates

The substantial growth in test offer rates observed by this study highlights the difficulty of defining baseline or background testing rates under current practice as these are moving targets. This growth complicates summarizing these data into a single rate estimate for input into CEPAC. The changing rates can be explained in part by test policy changes (i.e., making testing provider-initiated for pregnant women in 2002), the rates before implementation of which should not be considered indicative of current testing. However, after 2002 the background test offer rate (ANC and TB) increased only marginally while the baseline test offer rate (VCT) increased dramatically. Thus, it appears that in later years the rise in testing was primarily due to rising test-seeking behaviour among the population.

The particularly fast growth in the rates at which VCT offers were sought after 2003 suggests that the ART roll-out that commenced that year contributed to this increase. However, ART is only now becoming widely available elsewhere in South Africa.[61] Therefore, the 2003 test offer rates may be indicative of the current rate for the national adult African population and are used for the background and baseline test offer rate model parameter inputs in Chapters 6-7. These findings suggest that ongoing efforts to increase and advertise ART availability could contribute to the success of efforts to expand testing further.[294]

Of course, the sharp growth in test offer rates for pregnant females between 2001 and 2002 highlights the potential effectiveness of provider-initiated testing policies (as examined in this thesis, see section 2.2 and Table 2.1) for increasing these rates. Pregnant females may have tested at higher rates in part because they comprise a unique group likely to receive provider-initiated test offers through antenatal care[66,295,296] and to accept such offers out of concern for their unborn babies.[297] Yet, these explanations seem unlikely to account for the growth as testing rates among pregnant females were comparable to those for all other groups until 2002 when antenatal testing became routine. Thus, provider-initiated testing could potentially prove especially effective in increasing testing rates among groups receiving proportionately fewer tests under current practice (e.g., males, who consistently received test offers and retested at lower rates than females). In Chapters 6-7, the testing rate observed among pregnant females in 2003 is used as the estimate of that likely to occur for any population offered provider-initiated testing.

Implications for stigma

In recent years, a debate has emerged regarding the social effects of expanded testing policies. Some believe expanded screening will normalize the testing process so decreasing HIV-related stigma.[62] On the other hand, others have expressed concerns that expanded testing may compromise patient autonomy and expose HIV-infected clients to social backlash.[73] The modelling approach adopted in this thesis does not capture the effects of HIV-related stigma, but the data may be informative regarding its prevalence in South Africa society.

The increasing testing rates suggest that HIV testing has become increasingly acceptable to the community population under current practice over the past six years. This argument is more compelling when also considering the decline in proportion of client-initiated tests occurring at the hospital in later years. Use of the hospital's testing services required clients to travel farther and incur greater costs, with the major plausible benefit for testing at the hospital being preservation of anonymity. The fact that fewer clients seeking VCT did so at the hospital may imply decreasing concern among residents regarding stigma associated with testing.

Country-wide trends support this hypothesis: increasing proportions of national survey respondents are reporting previous testing and less prejudiced attitudes towards people living with HIV.[17,298] As these trends continue and HIV testing becomes increasingly normalized, there may be less concern that expanding HIV testing will exacerbate HIV-related stigma (see Subsections 2.1.4-2.1.5).

5.3.2 Trends in testing outcomes

Yield

The yield of HIV testing decreased as testing rates increased. This is an indication of testing program success in increasing case detection at the population level: as the prevalence of undiagnosed HIV falls, more tests will be required for each new case identified. However, annual yield never fell below 25% for first-time tests. Yield remained high even among antenatal care users and TB patients already receiving provider-initiated testing. These figures indicate the urgent need for expanding testing among the general population while continuing aggressive case detection for pregnant women and TB patients. The observation of 2.0 diagnoses with HIV per 100 person-years among initially seronegative adult community residents tested through VCT services highlights the importance of also sustaining any expanded testing efforts to achieve regular retesting of population members to identify new infections.

Clinical characteristics

Further evidence of the need for retesting comes from the lack of substantial change in the clinical characteristics of newly diagnosed HIV-infected patients. The median CD4 counts and proportions of seropositive clients presenting with HIV-related symptoms both remained unchanged. Thus, in spite of rising testing rates, current retest frequencies did not appear to have a material impact on the stage of HIV infection at which HIV-infected clients were diagnosed.

Linkage-to-care

As argued throughout this thesis, the most important outcome for testing is linking seropositive clients to effective treatment so that they might realize the benefits of expanded testing. The epidemiological study presented in this chapter did not attempt

to capture fully the health benefits of this treatment. However, it did measure rates of client passage through all steps of the HIV testing cascade (the effects of that treatment on disease progression for those linked to care will then be modelled in Chapter 7).

The dramatic rise in rates of referral and treatment observed in this study are undoubtedly due in large part to the international funding made available to the healthcare providers in this community. Nevertheless, these results are encouraging signs of the capacity of South Africa's healthcare facilities to absorb the increased caseload that will be identified through expanded testing. Indeed, these increases signal the success of healthcare providers in this setting in sorting through the logistical difficulties found in South Africa to be responsible for most throughput losses for HIV-infected patients (e.g., quickly linking patients testing positive to follow-up services).[299] Another important future task for this and other healthcare settings will be ensuring linkage of HIV-infected patients not yet eligible for treatment to support, positive living messages, monitoring and other pre-ART care.[300]

Indeed, a substantial proportion of the newly-diagnosed HIV-infected patients were not yet eligible for treatment upon diagnosis under current treatment guidelines.[282,283] This proportion will grow even larger if testing expands as HIV-infected persons will be identified at earlier stages of infection. Any expanded testing program will need to be accompanied by initiatives to track these individuals, and provide them with prevention education and ongoing clinical and laboratory monitoring. As growing numbers of HIV-infected individuals not yet eligible for treatment are identified, it may also become increasingly relevant to consider revising treatment guidelines to begin ART earlier.[301] That said, this decision should ultimately be driven by

assessments of the benefits to patients of earlier ART initiation and would raise issues of treatment capacity in any event.[302]

The large proportion of diagnosed HIV-infected clients not immediately identified as eligible for treatment also raises an important issue regarding how best to communicate these empirical data. This observation demonstrates how, in contrast to every other step of the HIV testing cascade, few patients immediately receive referral and treatment. The necessity for most newly-diagnosed clients to return for referral and care greatly compounds the difficulty of linking them to care. Fitting these data to conceptually simpler model parameter inputs defining probabilities of linkage-to-care required a judgement regarding the amount of time that should be allowed to transpire between diagnosis and receipt of a CD4 count or determination of eligibility before considering patients as throughput losses. As noted in section 5.1.3, I chose a six-month interval, believing it to balance the need for a span long enough to account the time needed by providers to link patients to care, but not so long as to encompass those clients falling out of the cascade but subsequently receiving linkage-to-care.

5.3.3 Study limitations

This study has several limitations. The community's unique small size and ready access to ART and other HIV-related services since 2003 may limit the generalizability of these findings to other African settings. Yet, the community's small size made possible the measurement of population-level testing rates. Similarly, while this study's retrospective design necessitated use of incomplete data from testing registers and clinical records, it was necessary for analyzing the entire population since prospectively following every population member would have been impractical. Since each member of the study population was not followed

prospectively, I also cannot account for immigration or emigration. However, the 2006 census found that only 1.0% of residents had immigrated and 0.4% planned to emigrate during that year, supporting the contention that the population was relatively closed during the latter years of the study period.

Thus, as argued at the outset of this chapter, this study's design is unique in providing estimates of population-level HIV testing rates and outcomes. It has further quantified the extent to which this screening has been offered through background versus baseline testing services (see Section 2.2). Chapters 6 and 7 will use these results together with the measured linkage-to-care rates to project the effects on client throughput for the HIV testing cascade and cost-effectiveness of policies expanding testing among South Africa's adult African population.

Chapter 6:
Projecting the effectiveness of expanded HIV testing policies in increasing testing and linkage-to-care in South Africa

This chapter considers the effectiveness of the eight expanded testing policies examined in this thesis in increasing client passage through the human immunodeficiency virus (HIV) testing cascade. Implementing all eight policies in different communities would have been impractical. Therefore, projections of the effects of these policies on client throughput for the HIV testing cascade steps (Figure 2.1) are made. These projections make use of secondary data sources identified in a previous literature review[32] and the empirical data gathered in Chapter 5.

Client throughput for the individual steps of the HIV testing cascade is the only outcome measure examined in this chapter. In Chapter 7, the projections produced here will be used as parameter inputs to estimate the cost-effectiveness of expanded HIV testing policies using life years gained (LYGs) as the final outcome. Since Chapter 5 measured population rates of test offers, this chapter has the data necessary to project population rates of throughput. Furthermore, these data distinguished the extent to which current screening is due to baseline versus background testing; the projections here account for both. Efforts are taken throughout this chapter to adjust the empirical testing data to make the results as generalizable as possible for South Africa's national adult African population and suitable as inputs for the CEPAC model's testing parameters. In the discussion, the implications for testing policy and limitations of these projections are discussed.

6.1 Methods

To conduct the analysis presented in Chapter 7, it was necessary to adjust the various empirical and secondary data used to describe testing throughput for inputs into the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model. To a certain extent this necessity dictated the methods adopted in this chapter for projecting client throughput for the alternative testing policies considered in this thesis (Table 2.1). Nevertheless, I also had to make a number of judgements in generating these estimates. By exploring these judgements, I further examined the certainty around the estimates, generating upper- and lower-bound potential values. These upper- and lower-bound estimates serve as the basis for the sensitivity analyses of both the results in this chapter and the cost-effectiveness estimates presented in Chapter 7.

This section reports the methods used to generate the point, lower-bound, and upper-bound throughput estimates reported in this chapter and is organized according to the HIV testing cascade steps (Figure 2.1). For each step, the methods adopted to estimate throughput for individuals tested through baseline tests are reported first. Then the methods for quantifying the expected changes in baseline throughput following implementation of each of the eight expanded testing policies (Table 2.1) are reported. As noted in Section 2.3, the simplifying assumption is made that, ceteris paribus, changes in policy for each of the four components of a testing program affect only select steps of the HIV testing cascade. Thus, it is assumed that the choice of initiation method affects only test offer rates (cascade Step 2); consent methods affect only probabilities of acceptance (Step 3); test protocols affect only the accuracy of test

results (Step 3.5); and linkage-to-care methods affect only the probabilities of referral and receipt of ART (Steps 5-6).*

Finally, the methods for estimating background testing throughput are reported separately (see Subsection 6.1.6). This is because CEPAC's background testing parameter is distinct in requiring specification of the monthly probability that clients learn their serostatus (equivalent to client passage through cascade Steps 1-4). This contrasts with the model's treatment of non-background testing in which clients are subject to defined probabilities of non-progression for each of the testing cascade steps. Thus, the background testing throughput estimates require unique methods.

6.1.1 Effects of initiation methods on test offer rates (cascade Steps 1-2)

Data describing rates of healthcare facility attendance in the study community were not available. However, the test offer rates reported in Subsection 5.2.2 were equivalent throughput for Steps 1-2 together as they are the products of population members' rates of healthcare facility attendance and healthcare users' rates of test offer receipt.† As CEPAC solicits input in the form of test rates combining Steps 1-2, there was no need to attempt to estimate healthcare utilization rates. Nevertheless, estimates of these rates from the 2006 general household survey were used as an internal validation measure to ensure that the estimates of test offer rates for the

* Note that the use of only observations of VCT test offer data for estimating probabilities of acceptance (see Subsection 6.1.2) and post-test counselling (see Subsection 6.1.4) are due to the belief that acceptance and counselling probabilities among clients offered testing through ANC and TB services may be different not because of the test strategy but rather because of the context of the test offer – pregnant women and tuberculosis patients may well progress through the cascade at higher rates due to greater health-seeking behaviour.

† For example, if the annual rate of healthcare attendance is 50% and the probability test offer for population members presenting to healthcare facilities is 80%, then the annual rate of test offer receipt for population members is 50% * 80% = 40%.

general population do not exceed the rates at which this population is believed to access healthcare facilities offering testing.

Although when used as CEPAC input these data will be described as rates, they are reported as monthly probabilities in this chapter for a more intuitive presentation. The conversion from rate to probability was achieved using the following equation:

$$p = 1 - \exp(-r * 1/12) \qquad (6.1)$$

In Equation 6.1, p is the monthly probability of occurrence and r represents the annual rate of occurrence. The remainder of this section discusses the calculations for translating the empirical data from Chapter 5 into CEPAC model input.

Baseline test offer rates

I believe the 2003 cascade test offer rate observed in the community is broadly representative of that currently prevailing among South Africa's national adult African population given current national antiretroviral treatment (ART) provision levels (see Subsection 5.3.1). Thus, the baseline population test offer rate used as CEPAC input was assumed to be equivalent to that for voluntary counselling and testing (VCT) offer receipt by the community in that year (see Figure 5.2). Sensitivity analyses of these values were conducted by using test offer rates for alternative years rather than the upper and lower bound estimates presented in Figure 5.2 as these generally provided broader ranges of values. The upper- and lower-bound baseline testing rates were taken from the highest and lowest annual rates of test offers made through VCT services.

Provider-initiated test offer rates

The effectiveness of provider-initiated testing in the general population was estimated by using the post-2002 test offer rates observed among pregnant females in the study community (Figure 5.3). As with the background and baseline test offer rate, the 2003 data were used for these estimates. The highest and lowest annual ANC test offer rates for pregnant women observed since 2002 when antenatal testing became provider-initiated were used for the upper- and lower-bound rates, respectively.

It is potentially problematic to assume that test offer rates among pregnant women receiving routine antenatal testing are broadly equivalent to those for general population members receiving provider-initiated testing without controlling for healthcare usage. The principal concern in this context is that higher test offer rates among pregnant women may in part reflect their higher rates of accessing healthcare facilities (cascade Step 1) compared to other population members. If this were the case, then the testing rate among pregnant women would likely overestimate that for general population receiving provider-initiated testing. However, it appears likely that the healthcare usage rates for the general population in the study community were comparable to those among pregnant women as test offer rates for the two groups were similar before antenatal testing became provider-initiated (Figure 5.3).[‡]

6.1.2 Effects of consent methods on acceptance probabilities (Step 3)

Baseline acceptance probabilities

Fluctuations in annual test acceptance probabilities for voluntary counselling and testing (VCT) services were observed in the study community during 2001-2006.

[‡] To my knowledge, there are no studies from South Africa which could have informed this assumption by comparing healthcare utilization rates between pregnant women and the general population.

However, these fluctuations were small and did not exhibit any consistent trend over the study period (see Subsection 5.2.3). Therefore, I used the average acceptance probability for all test offers made through VCT services (including clients whose ages or places of residence were unknown at the time of testing) for the CEPAC parameter's point estimate. Upper- and lower-bound acceptance probability estimates were taken from the highest and lowest annual acceptance probabilities.

Opt-out acceptance probability

Opt-out testing was not implemented as standard practice in the study community for any testing service during the observation period (see Subsection 5.1.1). Consequently, it was necessary to use secondary data to estimate the probability of test acceptance for opt-out testing policies. A single study has been identified in the HIV testing literature which compared testing policies identical in all else save for consent method (see Subsection 2.3.3). The odds ratio reported by this Botswana-based study for test acceptance under an opt-out versus opt-in screening program (3.1)[64] was then applied to the point estimate for the acceptance probability to estimate the opt-out acceptance probability. Upper- and lower-bound opt-out acceptance probabilities were estimated by applying this same odds ratio to the upper- and lower-bound baseline acceptance probabilities, estimated as described above.[§]

6.1.3 Effects of test protocol on test accuracy (Step 3.5)

None of the clients tested in the study community examined in Chapter 5 were tested with a 'gold standard' protocol following completion of their testing encounters.

[§] It would have been possible to apply to the upper- and lower-bound baseline acceptance probabilities the upper- and lower-bounds of the 95% confidence interval for the odds ratio reported in the Botswana-based study, respectively. Doing so would have simultaneously accounted for uncertainty in the acceptance probabilities and the odds ratio. However, I believed this to reflect the sort of max-min analyses which the United States of America (USA) Panel on Cost-Effectiveness advises against (see Subsection 3.2.3).

Thus, it was impossible to use the data from Chapter 5 to estimate the true sensitivity and specificity for the serial rapid protocol used (see Subsection 5.1.1 for details). Instead, these were estimated using secondary data sources. Moreover, as the AxSYM antibody-antigen combination test for acute HIV infection (AHI) evaluated in this thesis (see Subsection 2.2.4) was never administered in the community, its sensitivity and specificity were similarly derived from the literature.

In addition to the sensitivity and specificity estimates, the probabilities of correct diagnosis for tested HIV-infected clients will also be reported in the results section as a more intuitive representation of the accuracies of these test protocols. These probabilities will also serve as input for the CEPAC and AHI Testing (AHIT) models in Chapter 7. These probabilities depend upon the proportion of clients chronically versus acutely infected since the accuracy of tests depends upon stage of infection. For the purposes of these calculations, it was assumed that the point estimates of undiagnosed population prevalence of chronic infection (18.6%) and AHI (0.52%) used in Chapter 7 (a ratio of approximately 36 chronic infections to every AHI, see Subsection 7.1.2) reflected those among all testing clients.

Rapid-only test protocol

The standard rapid test protocol used in the study community comprised an Abbott Determine initial rapid test followed by various confirmatory tests (see Subsection 5.1.1), assumed by this thesis always to be a Uni-Gold rapid test (see Subsection 2.2.4). The sensitivities and specificities of both of these tests for chronic infections were estimated using a World Health Organization (WHO) sera panel evaluation.[60] The overall protocol sensitivity and specificity was then calculated by assuming independence between the tests, or that the likelihood of a false positive or negative

result by one test for a particular individual was unrelated to that for the second test. Thus, the formulas used were as follows:

$$s_{\text{rapid protocol}} = s_{\text{initial}} * s_{\text{confirmatory}} \quad (6.2)$$

$$sp_{\text{rapid protocol}} = sp_{\text{initial}} + sp_{\text{confirmatory}} - (sp_{\text{initial}} * sp_{\text{confirmatory}}) \quad (6.3)$$

In these equations, s represents sensitivity while sp represents specificity. The subscripts on the variables indicate the object of the sensitivities and specificities (i.e., those of the protocol, initial test, or confirmatory test).

Equation 6.2 was adjusted for determining the sensitivity of the rapid test protocol for detecting AHIs. Specifically, it was assumed that the probability of a HIV-positive result for acutely infected individuals would be the same as for HIV-negative individuals. This assumption is based on the premise that rapid tests are, by definition, unable to detect AHIs unless it is the result of a test error (i.e., low specificitiy resulting in a 'false' positive). Thus, the new equation for the protocol AHI sensitivity (abbreviated as sAHI) was as follows:

$$sAHI_{\text{rapid protocol}} = (1 - sp_{\text{initial}}) * (1 - sp_{\text{confirmatory}}) \quad (6.4)$$

Upper- and lower-bound estimates for the protocol sensitivities and specificities were also generated using Equations 6.2-6.4, but with different values for the individual test sensitivities and specificities. These alternative values were taken from the same WHO publication which provided the original values together with ranges for the sensitivities and specificities for each test.[60]

Rapid with AHI testing protocol

For the rapid with AHI testing protocol, clients testing HIV-negative from the rapid protocol subsequently received AHI testing with Abbott's AxSYM antibody-antigen combination test (see Subsection 2.2.4). The sensitivities and specificities for the initial rapid protocol were generated using the same methods as described above. The sensitivity of the AxSYM test for detecting chronic infections was taken from an evaluation of the test's performance in evaluating chronically infected clients.[33] The sensitivity of the AxSYM combination test for detecting AHIs was taken from the proportion of seroconversion panels (for which the presence of HIV RNA had been confirmed but had as yet tested negative for the presence of antibodies) correctly identified in two additional studies.[34,35] The specificity of the AxSYM combination test was that observed in all three of the aforementioned studies.

These sensitivities and specificities were then combined with those for the rapid protocol to calculate the overall sensitivity and specificity for the rapid with AHI testing protocol:

$$s_{\text{AHI protocol}} = s_{\text{rapid protocol}} + (1 - s_{\text{rapid protocol}}) * s_{\text{AxSYM}} \quad (6.5)$$

$$sp_{\text{AHI protocol}} = sp_{\text{rapid protocol}} * sp_{\text{AxSYM}} \quad (6.6)$$

$$sAHI_{\text{AHI protocol}} = (1 - sp_{\text{rapid protocol}}) + sp_{\text{rapid protocol}} * (1 - sp_{\text{AxSYM}}) \quad (6.7)$$

Upper- and lower-bound estimates for the sensitivity and specificity values for the rapid tests used as part of the AHI test protocol were taken from the same range of values reported in the WHO publication as outlined above. In contrast, the range of values for the combination test sensitivities and specificities were based on ranges I

defined. The sensitivity for detecting AHIs was decreased and increased by 10%. The sensitivity for detecting chronic infections was not adjusted as the data source used to estimate the baseline value determined it to be 100%[33] and it seems unlikely that appreciable numbers of chronically infected clients will fail to be detected by this test. Finally, the AHI test specificity was increased to 100% for the upper-bound value and decreased by the same proportion to 99.6% for the lower-bound value.

6.1.4 Probability of post-test counselling (Step 4)

None of the expanded testing policies examined in this thesis are focused on affecting client receipt of post-test counselling. Throughput for this step is likely dependent upon test type (see Subsection 2.3.5),[71,72] but all of the tests examined in this thesis were chosen for their ability to provide results within the span of a single healthcare visit. Thus, the probability of post-test counselling was assumed to be the same for all testing policies. As with the probability of acceptance, there were no consistent trends in annual probability of post-test counselling observed in the study community during 2001-2006 (see Subsection 5.2.3), so the baseline acceptance probability was that observed in the study community for all observed test offers made through VCT services. Upper- and lower-bound acceptance probability estimates were taken from the highest and lowest observed annual post-test counselling probabilities.

6.1.5 Effects of linkage-to-care method on referral and treatment (Steps 5-6)

This thesis assumes that the likelihood of a seropositive client receiving linkage-to-care is not related to the context in which the diagnosis was delivered (i.e., whether through VCT, ANC, or TB testing services). This assumption is necessary as it is currently not possible to define differential linkage-to-care rates in CEPAC. Nevertheless, it does not seem to me an entirely unreasonable assumption for the

study community examined in Chapter 5 as all community residents testing positive were ultimately linked to care via the same personnel and procedures at the clinic's ART facility.

The linkage-to-care data reported in Chapter 5 were fit to CEPAC's parameters defining probabilities of referral and treatment. However, estimates for these inputs were complicated by the fact that these linkage-to-care data were best described as rates given that most clients do not immediately receive referral or treatment upon diagnosis. It is for this reason that the threshold of six months was chosen as the timespan beyond which clients were determined to have not received linkage-to-care (see Subsection 5.1.3). The probability of referral for South Africa at large was thus estimated to be equal to the proportion of clients diagnosed during 2003 who received CD4 or total lymphocyte counts within six months of their diagnoses. Again, 2003 data were used since the ART roll-out began that year, making it broadly equivalent to the current treatment context of South Africa (see Subsections 6.1.1-6.1.2).

However, I adopted a different approach for estimating the probability of treatment for referred clients. The treatment probability during this first year of ART roll-out was still quite low (Figure 5.5), likely reflecting initial programmatic difficulties associated with treatment roll-out. Consequently, I instead used the 2006 probability, believing it a better representation of the linkage-to-care achievable by a program after overcoming initial logistical difficulties and a more meaningful estimate of the treatment likelihood to be expected by a comprehensive HIV testing program. Upper-bound estimates were again taken from years in which the referral and treatment probabilities observed in the study community (Figure 5.5) were highest while lower-bound estimates were taken from the years in which these probabilities were lowest.

Referral and treatment under enhanced linkage-to-care

Beyond exploring the economic implications of expanded testing alone, in this thesis I also sought to examine the impact of enhanced linkage-to-care on these results. To this end, I defined an 'enhanced' linkage-to-care scenario in which there are increases in linkage-to-care. The magnitudes of these increases are all based on assumptions rather than empirical data (Subsection 2.2.5). A testing program including enhanced linkage-to-care is assumed to refer 50% of post-test counselled clients not referred by a testing program with a standard approach to linkage-to-care. Similarly, an enhanced linkage-to-care program will link to treatment 50% of refered clients normally not receiving treatment. Sensitivity analyses adjusted these throughput values for cascade Steps 5 and 6 together. Due to the arbitrary nature of these probabilities, sensitivity analyses considered a broad range of values: 25% for the lower-bound value and 75% for the upper-bound value.

6.1.6 Background testing client throughput

As discussed at the outset of this section, CEPAC defines background screening as the monthly probability that clients will learn their serostatus through testing services unrelated to the testing program under evaluation. This probability was estimated by examining the annual rate at which population members living in the study community learned their serostatus through ANC or TB test offers (combination of client throughput for cascade Steps 1-4). This rate in 2003 was used for the point estimate while the upper- and lower-bound estimates used the highest and lowest rates observed since 2002 when ANC testing became provider-initiated. These annual rates were then converted to monthly probabilities using Equation 6.1 to make the input compatible for entry into CEPAC.

6.2 Results

6.2.1 Test offer rates (Steps 1-2)

Baseline testing

In 2003, 8,322 known adult community residents were believed eligible for testing (population size was estimated to be 8,721 minus 389 members previously diagnosed). During that year, this population received 453 VCT offers (5.4 per 100 persons). The lowest rate of test offers through VCT services occurred in 2001, when 6,691 eligible residents (estimated population size of 6,723 minus 32 members previously diagnosed) received 252 VCT offers (3.8 per 100 persons). The highest rate of VCT offers occurred in 2006, when 8,864 eligible residents (population size of 10,165 minus 1,301 members previously diagnosed) received 1,673 VCT offers (18.9 per 100 persons). Using Equation 6.1, these annual rates correspond to monthly probabilities of receipt of a baseline test offer of 0.45% in 2003, 0.31% in 2001, and 1.56% in 2006.

Provider-initiated testing

In 2003, 282 provider-initiated test offers were made to a population of 394 pregnant women (as estimated by the ASSA2003 demographic model, see Subsection 5.1.3), an annual rate of 71.6 per 100 persons. The lowest rate of test offers for pregnant women once antenatal testing became provider-initiated occurred in 2002 when 224 ANC test offers were made to 351 pregnant women (63.8 per 100 persons). The highest rate was observed in 2006 when 425 offers were made to 449 pregnant women (94.7 per 100 persons). Using Equation 6.1, these rates correspond to monthly probabilities of provider-initiated test offer receipt of 5.8% in 2003, 5.2% in 2001, and 7.6% in 2006.

Internal validation

All of these estimates, including the upper-bound test rate offer under provider-initiated testing, appear reasonable and plausible when considered alongside the estimates of healthcare utilization rates. South Africa's 2006 general household survey determined that the monthly rate of healthcare facility attendance for adult Africans was approximately 10 visits per 100 persons.[303] Even the upper-bound estimate of the test offer rate reported above for provider-initiated testing does not exceed 8 per 100 persons, suggesting that these rate estimates are reasonable as they are not greater than the estimated healthcare utilization rates. (This validation exercise assumes that individuals ineligible for testing access healthcare facilities at the same rate as eligible individuals.)

6.2.2 Test acceptance probabilities (Step 3)

Baseline test acceptance probabilities

During 2001-2006, 92.4% (5,211 of 5,640) of all VCT offers made to individuals not previously diagnosed with HIV (including those whose ages or residences were unknown at the time of testing) were accepted after pre-test counselling. The lowest probability of acceptance for VCT test offers was observed in 2004 when 92.1% (1,161 of 1,260) of these tests were accepted. The highest probability of acceptance for VCT offers was observed in 2001 when 96.4% (400 of 415) were accepted.

Opt-out test acceptance probabilities

Acceptance probability estimates for opt-out testing in the study community were only slightly higher than those observed under opt-in testing. This is because current acceptance rates were already quite high. The opt-out acceptance probabilities were

estimated to be 97.4% when using the VCT acceptance data for the study period entirety, 97.3% when using the 2004 data, and 98.8% when using the 2001 data.

6.2.3 Test protocol sensitivities and specificities (Step 3.5)

Table 6.1 reports the sensitivity and specificity values for the Abbott Determine and Uni-Gold rapid tests taken from a WHO publication[60] and for the AxSYM antigen-antibody combination test taken from the peer-reviewed literature.[33-35] Also, Table 6.1 reports the sensitivity and specificity estimates for these tests under high- and low-accuracy scenarios, based on the range of values reported in the aforementioned publications. The low-accuracy scenario reports the lowest specificity and chronic sensitivity values while the high-accuracy scenario reports the highest. Table 6.2 reports the sensitivities and specificities for the rapid-only and rapid-plus-AHI test protocols based on the numbers in Table 6.1 and the methods outlined earlier (see Subsection 6.1.3).[**]

[**] Since the rapid tests' AHI sensitivities are based on their specificity values, AHI sensitivity is actually maximized in the low-accuracy scenario and minimized in the high-accuracy scenario.

Table 6.1. Individual test sensitivity and specificity values. See section 6.1.3 for data sources.

Test	Baseline	Low accuracy	High accuracy
Determine rapid test			
Sensitivity, chronic	100	95.5	100
Sensitivity, AHI*	0.6	3.3	0
Specificity	99.4	96.7	100
Uni-Gold rapid test			
Sensitivity, chronic	100	95.5	100
Sensitivity, AHI*	0	2.1	0
Specificity	100	97.9	100
AxSYM			
Sensitivity, chronic	100	100	100
Sensitivity, AHI	57.3	51.6	63
Specificity	99.8	99.6	100

* Rapid test sensitivities for detecting acute HIV infections (AHIs) were calculated by subtracting test specificity from one; therefore, the upper-bound AHI sensitivities occur only in scenarios in which the specificity is at its lower-bound value and vice-versa

Table 6.2. Test protocol sensitivity and specificity values. See section 6.1.3 for methods.

Protocol	Baseline	Low accuracy*	High accuracy†
Rapid protocol			
Sensitivity, chronic	100	91.2	100
Sensitivity, AHI	0	0.1	0
Specificity	100	99.9	100
AHI protocol			
Sensitivity, chronic	100	100	100
Sensitivity, AHI	57.3	46.5	63.0
Specificity	99.8	99.5	100

* Low accuracy protocol sensitivity and specificity value estimates generated by using the low accuracy sensitivity for chronic infections and specificity values for individual tests reported in Table 6.1

† High accuracy protocol sensitivity and specificity value estimates generated by using the high accuracy sensitivity for chronic infections and specificity values for individual tests reported in Table 6.1

Based on the assumption that 18.6% of tested clients were chronically infected with HIV and 0.52% acutely infected with HIV, the likelihood of correct diagnosis for tested HIV-infected persons was 97.2% (100% for chronic infections and 0% for AHIs, Table 6.2) for the rapid-only protocol using point estimates. This rose to 98.8% (100% for chronic infections and 57.3% for AHIs) for the AHI test protocol. For the rapid-only protocol, this probability is unchanged in the high-accuracy

scenario and decreases to 88.7% (92.1% for chronic infections and 0.1% for AHIs) in the low-accuracy scenario. For the AHI protocol, this probability rises to 99.0% (100% for chronic infections and 63% for AHIs) in the high-accuracy scenario and drops to 98.6% (100% for chronic infections and 46.5% for AHIs) in the low-accuracy scenario.

6.2.4 Post-test counselling probabilities (Step 4)

Over the course of the study period entirety, 98.3% (1,038 of 1,056) of all clients testing HIV-positive from VCT offers were recorded as having received post-test counselling. The year in which this probability was lowest was 2001, when only 95.7% (89 of 93) seropositive VCT clients were post-test counselled. The highest rate occurred in 2003 when 100% of seropositive VCT clients received post-test counselling.

6.2.5 Referral and treatment probabilities (Steps 5-6)

Standard linkage-to-care

The probability of referral was taken from the proportion of study community residents diagnosed in 2003 who received a CD4 or total lymphocyte count within six months of diagnosis: 36.0% (71 of 197). The lower-bound probability was taken from 2001 when 27.7% of seropositive clients (31 of 112) received referral. The upper-bound probability was taken from 2006 when 65.7% (247 of 376) of seropositive clients received referral.

The probability of treatment was taken from the proportion of eligible seropositive community residents diagnosed in 2006 who received treatment within six months of eligibility: 69.9% (58 of 83). The lower-bound estimate was taken from 2003, the

first year of the ART roll-out, when 37.2% (16 of 43) of eligible clients received ART. The upper-bound estimate was taken from 2005 when 71.0% (49 of 69) of eligible clients received ART.

Enhanced linkage-to-care

Under a scenario of enhanced linkage-to-care as defined by this thesis (in which 50% of all clients normally not receiving treatment or referral are linked to care), the probability of referral is 68.0% and the probability of treatment with ART 84.9%. If the lower additional proportion were linked to care (25%), and the point estimate referral and treatment likelihoods prevailed, then enhanced linkage-to-care may lead to referral and treatment probabilities as low as 52.0% and 77.4%, respectively. Conversely, if the higher additional proportion were linked to care (75%), and the baseline referral and treatment likelihoods prevailed, then enhanced linkage-to-care would lead to referral and treatment probabilities of 84.0% and 92.5%, respectively.

6.2.6 Background testing

In 2003, 282 provider-initiated tests offered through ANC and TB services were accepted among the 8,332 eligible study community residents (population size was estimated to be 8,721 minus 389 members previously diagnosed). Data on post-test counselling were not collected for clients testing negative for HIV (see Subsection 5.1.2), but 96.1% (50 of 52) seropositive clients received counselling during this year. Applying this proportion to the 282 accepted tests yields an estimated annual rate of learning serostatus through provider-initiated testing of 3.3 per 100 persons. Using equation 6.1, this rate corresponds to a monthly probability of 0.27%.

The lowest rate of background testing occurred in 2002 when 7,758 eligible residents (estimated population size of 7,722 minus 164 previously diagnosed individuals) accepted 231 provider-initiated test offers. Among these individuals for whom post-test counselling information was known (n=64), all received post-test counselling. The highest rate of background testing occurred in 2005 when 8,947 eligible residents (estimated population size of 9,937 minus 990 previously diagnosed individuals) accepted 464 provider-initiated test offers. All of these individuals for whom post-test counselling information was known (n=55) also received post-test counselling. Thus, the rates of learning serostatus through provider-initiated testing per 100 persons were 3.0 in 2002 and 5.2 in 2006. Using equation 7.1, these rates correspond to monthly probabilities of 0.25% and 0.43%, respectively.

6.2.7 Summary

Figure 6.1 summarizes the projections reported in this chapter for the client HIV testing cascade throughput under the expanded testing policies examined by this thesis. Figure 6.1a presents throughput using point estimates. Figure 6.1b presents the lower throughput scenario in which all lower-bound throughput values are used. Finally, Figure 6.1c presents the higher throughput scenario in which all higher-bound throughput values are used.

The policies incorporating AHI test protocols have been omitted from this figure as the improvements in client throughput for cascade Step 3.5 (see Subsection 6.2.3) were so small as to be indistinguishable on the scale used here. The next smallest difference in the ultimate proportion of HIV-infected persons linked to ART comes from the consent method, or decision to make testing opt-out versus opt-in. The

choice of linkage-to-care method made a substantial impact on this proportion, but the greatest impact came from the choice of initiation method.

Provider-initiated, opt-out testing with an AHI test protocol and enhanced linkage-to care (policy code OAE, see Table 2.1) was projected to link the highest proportion of HIV-infected persons to ART, followed closely by the same policy except with a rapid-only test protocol (ORE). The policies linking the next greatest proportion of HIV-infected persons to ART were provider-initiated, opt-in testing with enhanced linkage-to-care and an AHI test protocol (IAE) followed by the same policy with a rapid-only test protocol (IRE). Finally, the policies using standard approaches to linkage-to-care followed the same ordering, but all linked substantially fewer HIV-infected persons to ART than their enhanced linkage-to-care counterparts.

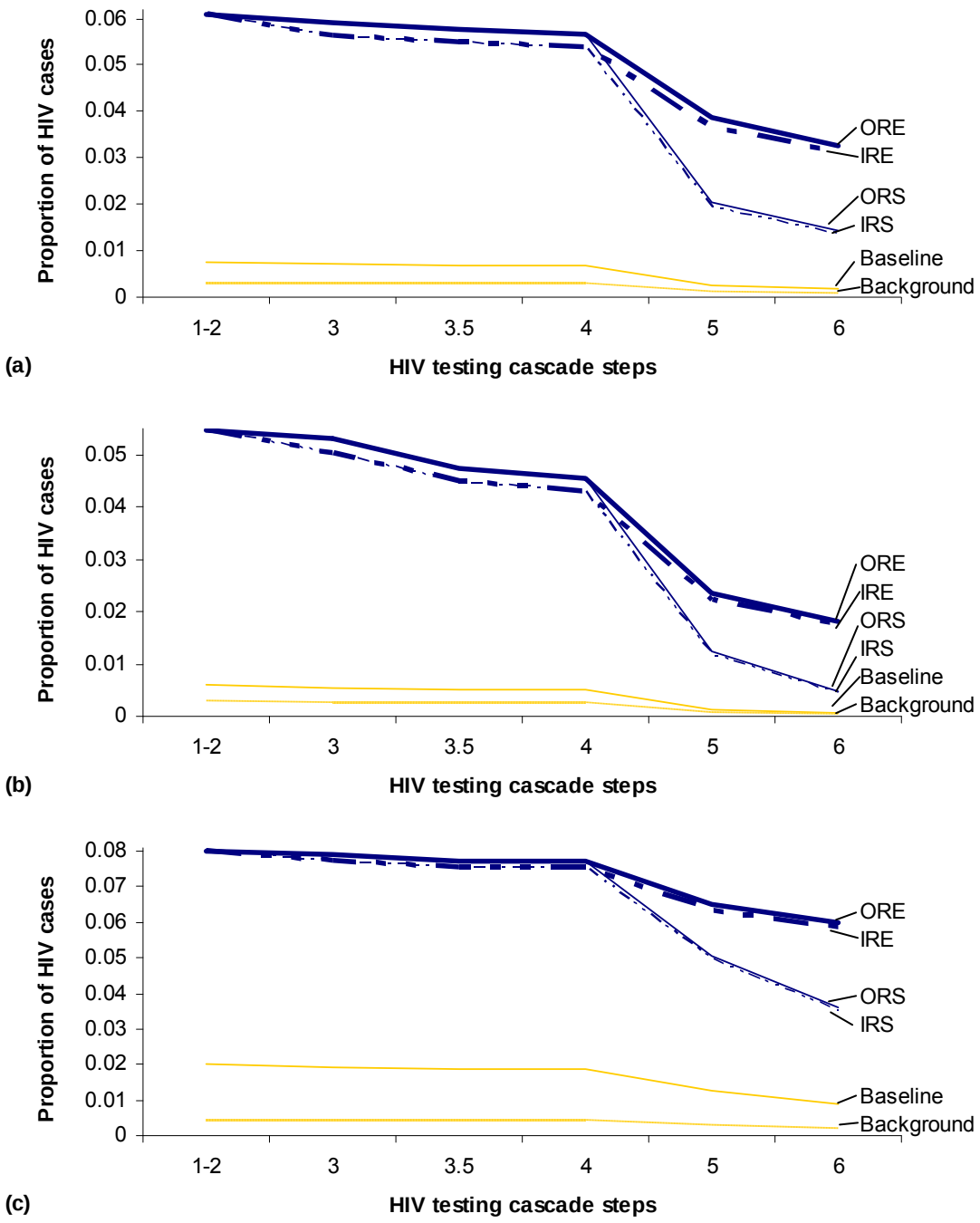

Figure 6.1. Monthly HIV testing throughput for HIV-infected persons. The orderings of client throughput for the HIV testing cascade are presented for the point estimate (a), lower throughput (b), and higher throughput (c) scenarios. All expanded testing policies adopting acute infection test protocols are excluded as the differences in throughput are indistinguishable on this scale. Provider-initiated, opt-out testing with enhanced linkage-to-care (ORE, dark bold line) linked the highest proportion of HIV-infected individuals to antiretroviral treatment (ART), followed by the same policy except with an opt-in consent method (IRE) dark bold dashed line). The strategies linked the next greatest proportions of HIV-infected individual to ART were provider-initiated, opt-out testing with standard linkage-to-care (ORS, dark solid line) and the same policy except with an opt-in consent method (IRS, dark dashed line). Baseline testing (light solid line) consistently linked substantially fewer HIV-infected persons to ART. The dotted line beneath baseline testing represents background testing assumed to remain constant across all testing policies considered.

6.3 Discussion

6.3.1 Testing policy impact on client throughput

Of the policy components considered in this thesis (see Section 2.2) the choice of initiation method clearly has the most impact on overall population throughput for the HIV testing cascade. Currently, the monthly rate of test offer (including both baseline and background testing) even under the higher throughput scenario is estimated to be well under 2 per 100 persons. The point estimate of the test rate offer for provider-initiated policies indicates that such policies could more than triple this rate to nearly 6 per 100 persons. Furthermore, if provider-initiated testing programs could be optimized to ensure that all healthcare users were offered testing, this rate could theoretically be increased to 10 per 100 persons, encompassing all individuals accessing healthcare facilities.[††]

The other programmatic decisions appeared to have less impact on population testing throughput. The choice of linkage-to-care method to increase probabilities of referral and treatment (Steps 5-6) with ART was found to be the next most important for client throughput. Finally, the choices of consent method on client acceptance (Step 3) and test protocol (Step 3.5) had comparatively little impact on overall cascade throughput. Controlling for background testing did not affect these results as, again, it was assumed to remain constant for all policy alternatives.

The projected impact of the various policy components was largely determined by the extent to which client throughput for the steps affected by those components was

[††] That being said, there are many reasons why such optimized delivery may be unrealistic (see Chapter 8). Indeed, data collected by researchers from the University of Pennsylvania based at Princess Marina Hospital in Gaborone, Botswana demonstrate that, even nearly two years after the formal adoption of provider-initiated, opt-out testing for all adults accessing healthcare facilities, many patients accessing this large facility in the country's capital remain untested.[32]

already maximized. There clearly appears to be great potential for increasing the proportion of healthcare users in the study community receiving test offers. Similarly, there is room for much improvement in the probabilities of referral and treatment with ART for counselled HIV-positive clients. By conducting a population-level analysis, it is also clear that were efforts made to increase client access to testing venues (e.g., through mobile home-based testing), the potential for increasing throughput would be greater still.

Conversely, throughput for subsequent steps was observed in the study community to be already quite high under current practice. Virtually all clients offered testing in the study community accepted even under an opt-in program (see Subsection 5.2.3). Similarly, the rapid test protocol in use already provides highly accurate results for clients chronically infected with HIV; moreover, while the current protocol has very poor sensitivity for detecting AHIs, the proportion of HIV infections which are acute is very small (see Subsection 6.2.3).

Current testing practice

The throughput achieved by both baseline and background testing appeared small in comparison to that for all of the provider-initiated testing policies. Consequently, it appears as though the effects of considering current testing practice has little material impact on incremental effectiveness of expanding testing. Chapter 7 will examine this issue further by using conducting sensitivity analyses of the parameters defining baseline and background testing to determine their importance for cost-effectiveness.

6.3.2 Projection limitations

The first limitation of the projections reported in this chapter is the questionable generalizability of the data on which they are based from Chapter 5. The unique nature of the community means that the baseline testing throughput values may not be comparable to that elsewhere in South Africa or sub-Saharan Africa. The unique features of this community which may influence cascade throughput are largely the same which made it possible to conduct a population-level study. These include the community's small size and access to HIV-related education and services (see Subsection 5.3.3).

Ideally, the generalizability of these data and projections could be established through comparisons to the literature. However, as discussed in Chapter 5, there are no other sources reporting rates of test offer receipt for eligible population members (cascade Steps 1-2). Moreover, few studies have measured the proportions of clients testing HIV-positive who have received ART.[163] Finally, while many studies have measured probabilities of test acceptance and post-test counselling, the majority examined testing programs very different from those considered in this thesis (e.g., programs targeting pregnant women who were offered no long-term treatment).[63,66-70,304-309]

Related to the issue of generalizability is the second limitation of uncertainty in the throughput estimates presented here. The estimated magnitude of the effect of provider-initiated testing on throughput for test offer rates (Step 2) was particularly uncertain. This uncertainty was largly due to the need to assume that the effects would be equivalent to those observed among pregnant women in the study community following implementation of provider-initiated antenatal testing. The estimated effects of enhanced linkage-to-care on referral and treatment probabilities

(Steps 5-6) were even more uncertain as these were based entirely on assumptions and speculation. This uncertainty as expressed in the confidence intervals reported in this chapter are not so large so as to bring into question the broader conclusions of this chapter regarding the comparative importance of different policy decisions for increasing testing uptake. Nevertheless, Chapter 7 will explore further the impact of this uncertainty on the cost-effectiveness of expanded testing (see Subsection 7.2.2).

A third limitation is the use of the simplifying assumptions outlined in Section 2.3 that changes in the various policy components affect throughput for only select steps of the HIV testing cascade. The possibility of policies improving throughput for some steps while simultaneously decreasing throughput in other steps warrants further attention in the future. For example, of concern to me is the possibility that increasing test offer rates by making tests provider-initiated would decrease probabilities of acceptance or post-test counselling. To my knowledge the current literature does not yet make a strong case against these assumptions (see Section 2.3). However, it bears emphasizing again that the target populations for the studies which have compared testing throughput under alternative programs are not representative of primary healthcare settings as examined in this thesis.[32]

Chapter 7 will take the analysis presented in this chapter a step further by considering the comparative *cost-effectiveness* of different policies focusing on increasing throughput for particular cascade steps. This analysis will mirror that conducted by Walensky et al. (see Subsection 4.3.3).[152] Moreover, by using the CEPAC model, it will be possible to project effectiveness in terms of the more informative outome of life years gained (LYGs). This modelling study will thus provide useful additional information to the projections outlined in this chapter.

Chapter 7:
Estimating the cost-effectiveness of policies expanding HIV testing and linkage-to-care in South Africa

This chapter reports a cost-effectiveness analysis (CEA) of the eight policies examined in this thesis expanding human immunodeficiency virus (HIV) testing among primary healthcare users (Table 2.1). This analysis assumes that each of these policies only affects client throughput for particular steps of the HIV testing cascade (see Section 2.3). Consequently, the comparative cost-effectiveness across these programs further indicates the cascade steps for which resource allocation to increase throughput should be prioritized.

This CEA is conducted using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model built and used by collaborators in the United States of America (USA) based at Massachusetts General Hospital (see Appendix A). The CEPAC component modelling HIV screening is not currently capable of modelling multiple diagnostic strategies used in concert. This was problematic since this thesis considers a policy in which clients testing negative from an initial rapid protocol are provided acute HIV infection (AHI) testing (see Subsection 2.2.4). Consequently, it was necessary to construct an additional model for use with CEPAC to circumvent this limitation. To this end, I constructed the AHI testing (AHIT) decision tree model, detailed in this chapter and in Appendix D.

I gathered all data used to inform those CEPAC parameters related to HIV testing. Testing effectiveness data, including estimates of client throughput for the HIV testing cascade and population characteristics, are based on the empirical data reported in Chapter 5 and adjusted for input into CEPAC as reported in Chapter 6. Because these data were collected as part of a population-level analysis, the cost-effectiveness estimates reported in this chapter are for South Africa's national adult African population rather than solely for that subpopulation accessing testing venues. The estimates account for both baseline and background screening (see Section 2.2). The methods for collecting cost data are reported in this chapter as part of the CEA (see Subsection 7.1.2). Inputs for parameters unrelated to HIV testing were taken from the work of the CEPAC collaborators (see Appendix B).

7.1 Methods

This section reports the methods used to evaluate the cost-effectiveness of eight policies expanding testing among primary healthcare users in South Africa. First, the modelling approach is presented, including a brief overview of the relationship between the AHIT and CEPAC models. The focus is on discussing the purpose, structure, and assumptions underlying the AHIT model I constructed for use with CEPAC.[*] Next, I discuss inputs for the AHIT and CEPAC model parameters related to HIV testing.[†] Finally, the methods of generating plausible ranges of values for parameter inputs for sensitivity analyses are outlined.

[*] Since I did not contribute to the construction of CEPAC, only a brief discussion of its function is provided here. More information on its technical details are presented in Appendix A.
[†] Again, since I did not contribute to the collection of these data, the discussion of inputs for parameters unrelated to HIV testing has been placed in Appendix B.

7.1.1 Modelling approach

CEPAC

CEPAC is a state-transition, first-order stochastic, static microsimulation model (see Subsection 3.1.6). CEPAC simulates disease progression for HIV-infected individuals. It consists of two principal components (Figure 7.1). First is the disease model simulating disease progression through the use of three main state categories: chronic-asymptomatic, chronic-symptomatic, and death. The state space for the two chronic categories includes states describing CD4 count, viral load (VL), treatment status, and history of opportunistic infection (OI). CEPAC permits users to define the costs and effectiveness of treatment and care options and the circumstances under which treatment is initiated for HIV-positive clients.

The second and newly added principal component of CEPAC is the screening model which adds a further dimension to each HIV-positive state by permitting differentiation between those cases which have been identified by screening versus those not yet detected.[151-154] To reflect the fact that not all clients testing will be infected, the screening model also defines a HIV-negative state and temporary AHI state for those clients newly infected. The CEPAC screening model permits users to define the costs, frequency, and sensitivity/specificity of the testing process. Appendix A provides further details regarding CEPAC's underlying structure and assumptions. The remainder of this section describes the AHIT model I constructed for use with CEPAC to model HIV testing programs including AHI testing.

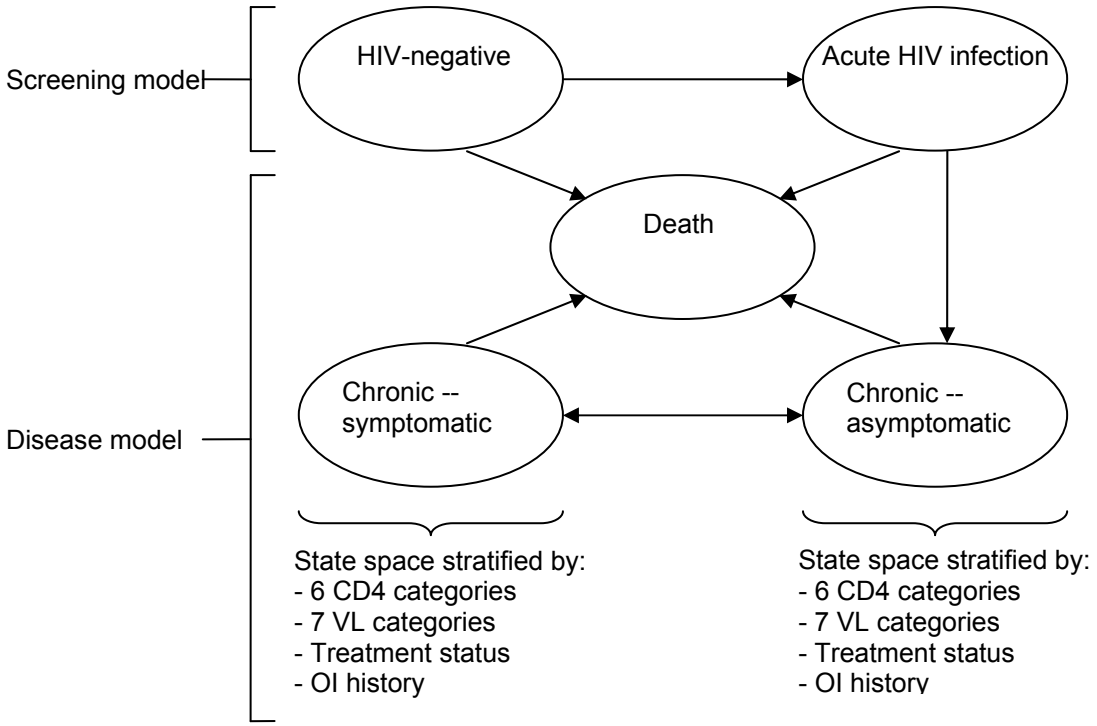

Figure 7.1. Schematic depicting the CEPAC state space.

AHIT purpose

AHIT is a supplementary model designed to circumvent the limitations due to CEPAC's definition of only a single set of parameters descriptive of a HIV test. This single set of parameters may be used to model a test protocol using multiple tests, but doing so requires the conversion of data describing a single test into 'summary test characteristics.' When modelling a simple protocol, this is a relatively straightforward process requiring simple calculations (e.g., Equations 6.2-6.4). Past applications of CEPAC to evaluate screening programs involving more than one test have made use of such calculations (personal communication, Professor David Paltiel). However, given the added complexity of adding yet another test configured specifically to detect those patients experiencing AHI, I believed it useful to construct a model to generate values for the summary test characteristics.

AHIT model structure

To this end, the AHIT model comprises two sets of deterministic decision trees (see Subsection 3.1.6). Each set includes a decision tree for each of the four major classifications of patients defined by CEPAC (see Appendix A): (i) HIV-negative clients; (ii) asymptomatic chronically infected clients; (iii) symptomatic chronically infected clients; and (iv) acutely infected clients. The first set of decision trees comprise the 'AHI testing' decision trees. These trees begin with the decision to offer testing and then follow client passage through Steps 3, 3.5, and 4 of the HIV testing cascade (Figure 2.1) for both initial rapid testing and subsequent AHI testing for clients testing negative by the rapid protocol (Figure 7.2). The second set of trees comprise the 'CEPAC imitation' decision trees. These trees depict the testing process as modelled by CEPAC, with all clients testing with only a single test (Figure 7.3).

AHIT solicits inputs defining the costs and probabilities associated with each of the branches on the AHI testing decision trees (Figure 7.2)[‡] using an Excel-based user interface mimicking that of CEPAC. AHIT then calculates the probabilities and costs associated with all of each decision trees' pathways from start to finish. As shown in Figures 7.1-7.2, there are only two possible health-related final outcomes of interest: receipt or no receipt of diagnosis with HIV. AHIT 'rolls back' the AHI testing decision trees (see Subsection 3.3.2) to generate estimates of the proportions of patients diagnosed with HIV and the testing costs per client for each of the four patient classifications.

[‡] The AHIT model still requires that users calculate summary characteristics for the rapid test protocol including costs and probabilities of accurate test results for each of the four classifications of patients.

AHIT then uses these results to generate 'summary test characteristics' for use with CEPAC. These characteristics include probabilities and costs for the branches of the CEPAC imitation decision trees (Figure 7.3) such that the final costs and proportions of clients receiving HIV-positive diagnoses are equal to those for the AHI testing decision trees. Appendix D outlines the specific equations used for these calculations.

For the purpose of internal validation, the ultimate costs per client and proportions of clients receiving HIV-positive diagnoses for each of the four patient categories are compared between the acute testing decision trees and the decision trees mimicking the CEPAC testing process to ensure identical results. Once the internal validation is complete, the summary characteristics are inserted as parameter input for CEPAC. CEPAC is then run with the new inputs to estimate the cost-effectiveness of the AHI testing program.

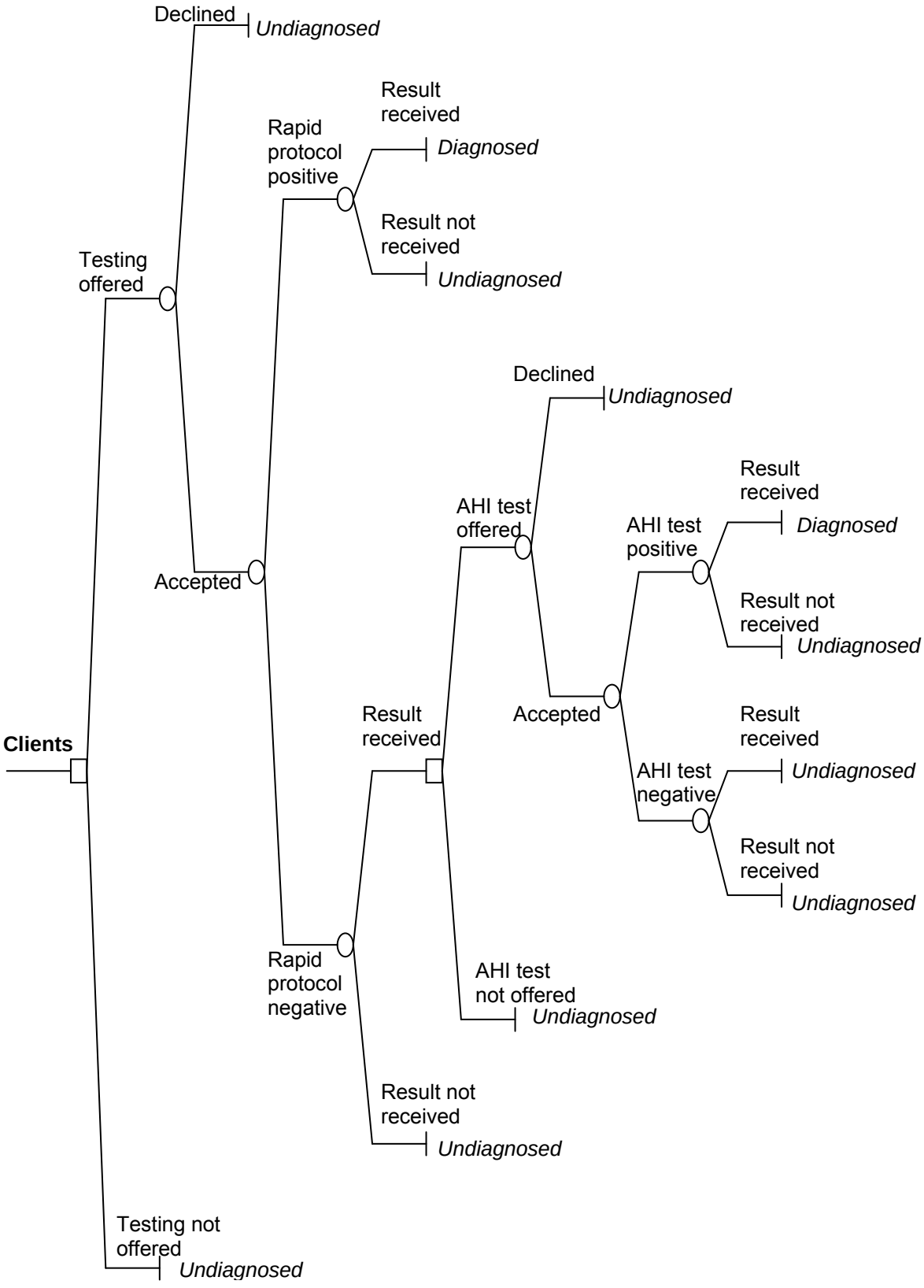

Figure 7.2. Generic AHIT model acute testing decision tree. AHIT comprises four decision trees like the generic tree depicted here, one each for HIV-negative clients, asymptomatic chronically infected clients, symptomatic chronically infected clients, and acutely infected clients. Tree structures are identical across all four trees although the branch probabilities and costs differ.

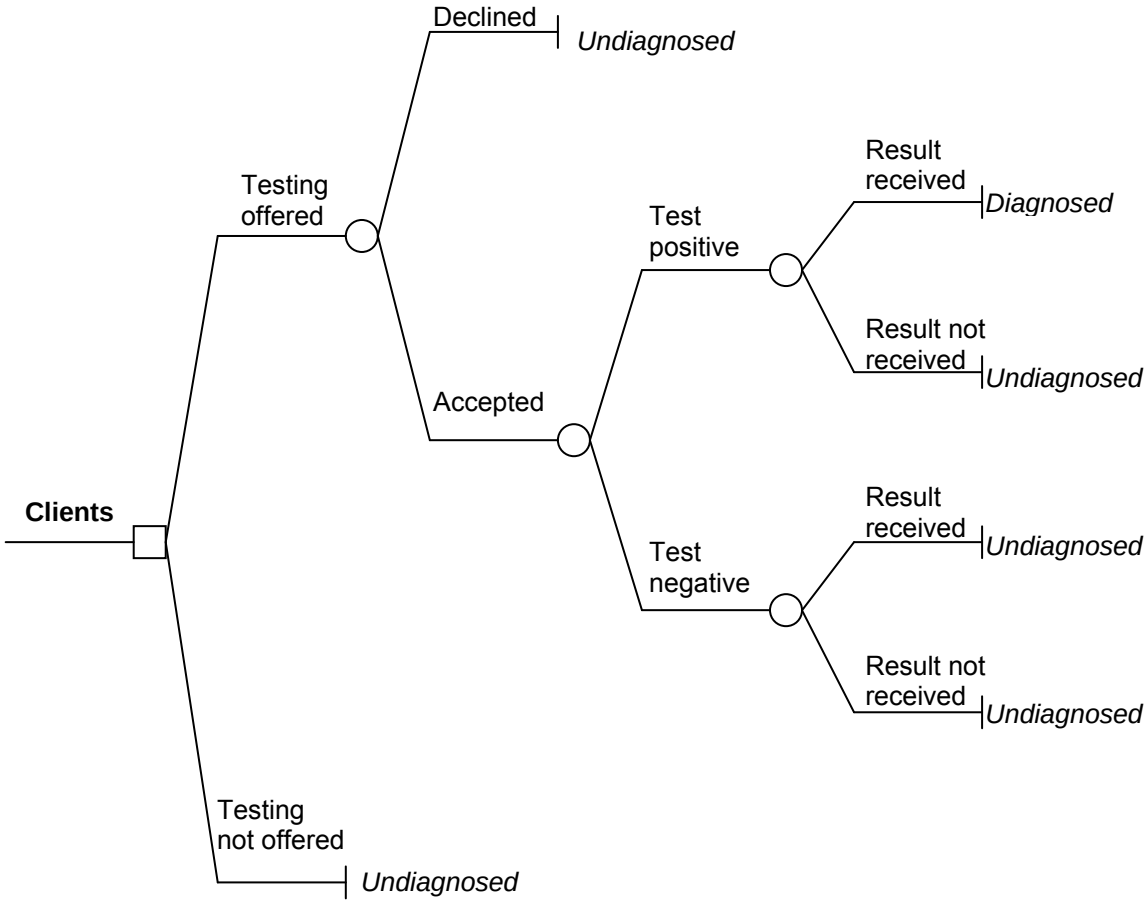

Figure 7.3. Generic AHIT model CEPAC testing decision tree. AHIT comprises four decision trees like the generic tree depicted here, one each for HIV-negative clients, asymptomatic chronically infected clients, symptomatic chronically infected clients, and acutely infected clients. Tree structures are identical across all four trees although the branch probabilities and costs differ.

Assumptions

A number of assumptions were made to simplify use of the AHIT model. First, because the output of the model is used to define test characteristics for clients tested in the CEPAC model, all clients were assumed to receive offers for rapid testing and, if negative by the rapid protocol, receive offers for AHI testing. Second, all clients accepting testing from the initial rapid test protocol were assumed also to accept AHI testing (see Subsection 2.3.3). Third, the probabilities of receiving results (i.e., receiving post-test counselling) were assumed to be identical for the rapid protocol

and AHI test (see Subsection 2.3.3). Fourth, independence was assumed between all tests, meaning that the likelihood of a false positive or negative result by one test for a particular individual was unrelated to that for any other test (see Subsection 6.1.3).

7.1.2 Point estimate model inputs

This section outlines the point estimates for the CEPAC and AHIT model inputs related to HIV testing.[§] First, inputs for parameters characterizing the target population are discussed. Next, inputs describing throughput for the HIV testing cascade are outlined. Finally, the HIV testing costs are presented. Table 7.1 at the end of this section summarizes all of these point estimates.

All costs were estimated using a societal as opposed to a payer (e.g., government) perspective, so attempting to capture all relevant costs (see Subsection 3.2.1). Furthermore, while costs were measured in South African Rand (ZAR) for various years, they were multiplied by the quotient of the 2006 South Africa gross domestic product (GDP) deflator divided by the deflator for the year in which the costs being converted were measured (see Subsection 3.2.2). The GDP deflators for South Africa were obtained from the International Monetary Fund's (IMF) 2007 World Economic Outlook report.[310] Costs were then converted to 2006 United States dollars (USD) using an average exchange rate for 2006 (1 USD = 6.79 ZAR).[311]

Undiagnosed prevalence and incidence

CEPAC describes undiagnosed prevalence as a distribution of the population targeted for testing among four categories: (i) HIV negative, (ii) asymptomatic chronic

[§] Note that the scenario in which the 'point estimates' are used for model inputs is equivalent to the 'baseline scenario' as that term is commonly used in the economic literature. However, this term has been avoided in this thesis given my unique and very specific use of the term 'baseline' to describe current testing by primary healthcare users in South Africa.

infections, (iii) symptomatic chronic infections, and (iv) AHIs. As argued previously (see Subsection 5.3.1 and Section 6.1), I believe the testing behaviour observed in the study community during 2003 to best represent that for South Africa's contemporary national adult African population. Therefore, values for the undiagnosed prevalence were based on estimates for that among the study community in 2003.

First, overall prevalence of chronic HIV infection was assumed to be 23.0%, as estimated by an anonymous unlinked seroprevalence survey conducted in the study community in 2005.[288] This estimate translates to 2,005 infections for a population of 8,721 (as estimated by linear interpolation based on census data, see Subsection 5.1.3). The number of infections already identified among study community residents by 2003 was estimated to be 473 when including individuals of unknown age or residence. These latter groups were included to lower the undiagnosed prevalence estimate. Given the association between higher undiagnosed prevalence and greater cost-effectiveness for testing programs (see Subsection 4.2.3), the inclusion of these groups therefore ensures the cost-effectiveness estimates presented in this chapter are conservative. These 473 individuals were then subtracted from both the population size and number of HIV-infected residents. The resulting estimate of the number of undiagnosed HIV-infected residents divided by the size of the population not previously diagnosed with HIV yielded an undiagnosed prevalence estimate of 18.6%.

Estimating the proportion of asymptomatic versus symptomatic cases for the entire HIV-positive population was complicated by the lack of any data on the World Health Organization (WHO) stage among those HIV-positive clients never diagnosed. Moreover, 24% (Table 5.5) of the medical records for diagnosed HIV-infected community residents were missing information on clinical symptoms at the time of

diagnosis. Finally, the clinical data that are available may suffer from inter-observer bias since the various healthcare providers may have interpreted both the WHO staging classification system[27] and individual patients' symptoms differently (personal communication, Professor Robin Wood).

Nevertheless, the data reported in Chapter 5 permit an approximation of this proportion (Table 5.5). The proportion's denominator comprised all known adult community residents receiving WHO stage classifications at diagnosis. Observations for the entire study period were used to increase sample size. Given the lack of consistent trend in WHO stage distributions for HIV-positive clients diagnosed as symptomatic over time (Table 5.5), the inclusion of these data is not likely biasing the estimate. Clients classified as WHO stage 1 were assumed to be asymptomatic (57.6% of clients with data on WHO stage at diagnosis). Clients receiving any other WHO stage classification were assumed to be symptomatic (42.4%). When multiplied by the total undiagnosed prevalence estimate above, these percentages correspond to estimated proportions of the entire population experiencing asymptomatic and symptomatic chronic infections of 10.7% and 7.9%, respectively.

The baseline estimate for the proportion of the population acutely infected with HIV was dependent upon the HIV incidence and AHI length parameters, the latter dictating the time in months that AHI lasts.[**] The baseline incidence rate chosen was that detected among all Africans >14 years responding to the Human Sciences Research Council's (HSRC) 2005 national prevalence and incidence survey for South Africa

[**] CEPAC treats the AHI length as equivalent to both the window period during which standard antibody tests cannot detect HIV infection (see Subsection 2.1.3) and the period of heightened viral load associated with recent infection (see Subsection 2.1.2). In fact, there may be significant differences in the lengths of the two periods.

survey[17] (unpublished subset provided via personal communication, Professor Thomas Rehle): 3.1%. This annual incidence rate was converted to a monthly probability using Equation 6.1, yielding 0.26%. The default value for the length of AHI in CEPAC is two months, so this probability was multiplied by two, resulting in an estimate of 0.52% for the initial proportion of the population acutely infected.

CD4 and viral load distributions

CD4 and viral load (VL) distributions for the entire HIV-positive population were estimated from the CD4 (Table 5.5) and VL counts (see Subsection 5.2.4) observed within six months of diagnosis for all known adult community residents diagnosed during 2001-2006, including pregnant women. As with the estimates of the proportions of HIV-infected clients experiencing symptoms, data from the study period entirety were used to increase sample size and generate more stable estimates as no consistent trend in median CD4 count was observed. CD4 and VL distributions were stratified by asymptomatic (WHO stage 1) and symptomatic patients (WHO stages 2-4). For acutely infected individuals, the VL distribution was assumed to comprise only the highest category (>100,000 copies/mL) and the CD4 distribution was set equal to that for asymptomatic patients.[††] While these data capture only a fraction of all infected residents, they provide a useful approximation of the entire HIV-positive population's CD4/VL distributions.

HIV testing cascade throughput

All estimates regarding client throughput for the individual steps of the HIV testing cascade were taken from those reported in Chapter 6. CEPAC defines rates of test

[††] CEPAC does not yet directly account for secondary transmission, and CD4 and VL during AHI have no impact on eventual disease progression in the model, so these distributions for acutely infected patients are of no consequence to the model's results in this analysis.

offer as a frequency in months rather than a monthly probability. Therefore, these were generated by dividing twelve by the annual rates reported in Subsection 6.2.1, yielding a baseline scenario frequency of testing of once every 221 months for client-initiated testing and 17 months for provider-initiated testing.

CEPAC defines distributions for patients related to linkage-to-care outcomes. The first distribution, analogous to referral outcomes, defines the probabilities that HIV-infected clients will access healthcare facilities (i) whenever scheduled to attend, including all visits for monitoring when not yet eligible for treatment, (ii) only when experiencing acute opportunistic infections (OI) or receiving antiretroviral treatment (ART) or OI prophylaxes, or (iii) only when receiving ART or OI prophylaxes. The probability of clients assumed to attend all scheduled clinic visits for standard linkage-to-care was set equal to the proportion of clients receiving CD4 counts within six months of diagnosis in the study community (see Subsection 5.2.4). All other clients were assumed to attend clinic visits only if experiencing acute OIs or receiving ART or OI prophylaxis. Under an enhanced linkage-to-care policy, the proportion of clients not attending all healthcare visits was halved (see Subsection 2.2.5).

Regarding treatment outcomes, clients are distributed to three possible outcomes: receipt of (i) no treatment, (ii) OI prophylaxis only, or (iii) ART and OI prophylaxis. As all clients comprising the denominator of treatment probability reported in Subsection 6.2.5 were eligible for both cotrimoxazole and ART, this probability was assumed equal to the proportion of clients receiving ART and OI prophylaxis in the model.[‡‡] The proportion of clients receiving only OI prophylaxis was set equal to that

[‡‡] In fact, 23 of these clients did not receive cotrimoxazole, but CEPAC does not permit receipt of ART without OI prophylaxis.

of these 83 clients who received only cotrimoxazole (9 individuals, or 10.8%). All remaining clients were assumed to receive neither ART nor OI prophylaxis under a standard linkage-to-care program. Under an enhanced linkage-to-care program, half of clients receiving no treatment or only OI prophylaxis received ART and OI prophylaxis and half of the remaining clients receiving no treatment received only OI prophylaxis (see Subsection 2.2.5).

All other cascade throughput probabilities were used as reported in Section 6.2, including that for background testing, also defined by CEPAC as the monthly probability of clients learning their serostatus. Table 7.1 reproduces these values.

Test kit costs

Cost data for the rapid and AHI tests were gathered separately. The initial and confirmatory rapid test costs were set to the prices paid by the Desmond Tutu HIV Foundation (DTHF) for these diagnostics from the Western Cape Province Department of Health (unpublished data provided by Ms. Colleen Herman, personal communication). These costs were nearly identical to those reported by the WHO for the Abbott Determine and Uni-Gold rapid tests, respectively.

The costs of Abbott's AxSYM antigen-antibody combination test were provided by Abbott representatives in South Africa (unpublished data provided by Mr. Tony Botes, personal communication). The AxSYM tests are usually provided to customers through a reagent agreement program. Under such a program, customers are provided the AxSYM apparatus, with a service agreement in the event of breakdown, at no cost. Customers then pay a fixed price per test encompassing all costs associated with the AxSYM tests (to include shipping, the tests themselves, and

repair and maintenance). The price depends upon the location to which the apparatus is shipped and approximations of annual client volume. The cost per test decreases as the numbers of tests performed each year rises.

Price estimates were solicited from Abbott for healthcare facilities based in Cape Town performing numbers of tests equal to those projected for the AHI screening strategies considered in this thesis (as reported in Chapter 6). Since all of the AHI screening policies are also provider-initiated, and the effects of making opt-in testing opt-out is minimal in this setting (see Subsection 6.2.7), there is little difference between client volumes between them. Consequently, differences in costs per AHI test across the eight expanded testing policies were assumed negligible and the analysis was simplified by using the same average cost per test provided by Abbott.

Healthcare personnel costs

The primary healthcare facilities offering testing to underprivileged communities in South Africa, such as that examined in Chapter 5, are generally government operated. Thus, the healthcare personnel costs associated with the testing and linkage-to-care processes were taken from a nation-wide survey administered to government healthcare providers soliciting information on their salaries and wages during 2007 (unpublished data provided by Ms. Trish Deas, personal communication). The survey provided ranges for the monthly salaries for various government healthcare providers. Hourly wages were derived from these monthly salaries by calculating the average number of monthly work hours for the providers based on work schedules at the study community's primary healthcare clinic (unpublished data provided by Colleen Hermann). It was assumed that all pre-test counselling and administration of rapid

tests was completed by social workers serving as AIDS counsellors. The AxSYM AHI tests were assumed to be performed by lab technicians.

These hourly wages were then multiplied by the amounts of time required for each portion of the HIV testing process. Estimates of the times for pre- and post-test counselling were taken from the rapid test session counsellor prompt cards for the RESPECT-2 trial run by the Centers for Disease Control and Prevention (CDC), the details and results of which have been reported elsewhere.[312] Although this study was conducted in the USA, I believe the amounts of time are unlikely to be substantially different in South Africa. Estimates of the times required for the tests themselves to run were taken from a WHO test assessment[60] and Abbott's AxSYM manual[313] for the rapid and AHI tests, respectively. These same time estimates for each portion of the testing process were used for all eight expanded HIV testing policy alternatives.

The AxSYM apparatus also requires regular monthly, weekly, and daily maintenance. To estimate the costs of this maintenance attributable to each test performed, monthly, weekly, and daily maintenance time ranges for the AxSYM apparatus were divided by the average monthly, weekly, and daily numbers of clients testing HIV-negative by the standard rapid protocol in the study community during 2006, respectively. These times were then summed for a composite estimate of total maintenance time expected per client. The simplifying assumption was made that these per capita maintenance times remained constant regardless of total numbers of clients tested and so increased rates of testing would simply correspond to more necessary maintenance time. Since the AxSYM manual implies no such increase in maintenance is required with greater use, this assumption further ensures conservative cost-effectiveness estimates.

Finally, estimates were generated for the provider time required to implement an enhanced linkage-to-care program. For the purposes of this hypothetical program option, it was assumed that AIDS counsellors would spend one hour contacting each diagnosed HIV-positive client not referred and referred clients not treated (note that it would be possible for this cost to be incurred twice for a single client). This estimate encompasses the time required to analyze treatment or referral records, identify the contact information for delinquent patients, and contact these patients to encourage them to return to the clinic. Beyond the healthcare personnel time, other related costs were not accounted for, namely travel costs. In the study community, travel costs would likely have been negligible given the small size of the community and high access to cell phones, permitting contact by phone or walking to patients' domiciles.

Productivity costs

The times required for testing and pre- and post-test counselling as outlined above may also incur productivity costs by consuming the time of clients. I estimated these costs using a human capital approach.[82] Thus, clients' time was valued at an amount equivalent to South Africa's official minimum wage across all labour sectors in urban settings during 2007 (adjusted to 2006 USD).[314] No additional productivity costs are incurred in this analysis for clients referred or treated as a result of enhanced linkage-to-care efforts. This is because these costs are not believed to differ significantly from those for clients referred and treated through standard linkage-to-care processes.

Overhead and capital outlay costs

Overhead costs were taken from the 2006 budget for the study community's primary healthcare clinic (unpublished data provided by Ms. Martina Traut, personal communication). These costs included expenses associated with administration;

cleaning; refuse removal; electricity and other power usage; water consumption; sewerage; telecommunication charges; insurance premiums; and stationary. These costs also included general healthcare-related materials and consumables such as latex gloves, syringes, and bandages. Finally, the costs of repairs and maintenance for both the clinic building and equipment used by all clinic attendees (e.g., benches in the waiting area) were also encompassed by these overhead expenses.

Overhead costs per client tested were estimated using direct allocation,[82] with floor space serving as the allocation basis. The proportion of floor space devoted to HIV testing and counselling was estimated by comparing the space of the clinic rooms used solely for HIV testing to that of the entire clinic. This proportion was multiplied by the total overhead costs which were then divided by the total number of tests administered at the clinic in the study community during 2006 to procure an estimate of the overhead cost attributable to each client tested. As with the AxSYM apparatus maintenance costs, it was assumed that these overhead costs would increase correspondingly as the numbers of clients testing increased.

Costs due to capital outlays were allocated using the same methods as with overhead costs. The primary healthcare clinic's 2006 budget provides data on the annual cost attributable to capital depreciation. The opportunity cost incurred due to the use of the land on which the clinic is situated (assumed to be the clinic's only non-depreciable asset) was estimated by using the amount of the interest paid during 2006 on the original internal government loan used for the land purchase (unpublished data provided by Ms. Martina Traut, personal communication). However, the resulting values could only be considered approximations of the true opportunity cost given that data were unavailable regarding the interest rates or history of loan payments.

Table 7.1. Summary of point estimates for model parameter inputs.

Parameters	Values	Sources
Target population		
Initial undiagnosed HIV prevalence distribution (%)		Wood et al.;[288] HSRC survey,[17] unpublished subset provided by T. Rehle to M. April on 12 Aug 2007; thesis Subsection 5.1.3; Table 5.5; assumed that AHI lasts 2 months
Negative	80.9	
Positive, asymptomatic	10.7	
Positive, symptomatic	7.9	
Positive, acutely infected	0.52	
Monthly HIV incidence (%)	0.26	HSRC survey;[17] unpublished subset provided by T. Rehle to M. April on 12 Aug 2007
Initial CD4 distribution (mean, standard deviation)		Table 5.5; adjusted for input into CEPAC by M. April on 3 Dec 2007; CD4 distribution for acutely infected patients assumed to equal that for asymptomatic patients
Asymptomatic chronic infections	438.0, 246.6	
Symptomatic chronic infections	224.1, 209.7	
Acute infections	438.0, 246.6	
Initial VL distribution (%)		Thesis Subsection 5.2.4; adjusted for input into CEPAC by M. April on 3 Dec 2007; all acutely infected clients assumed to have very high viral loads (>100,000 copies/mL)
Asymptomatic chronic infections		
HVL, very high	30.8	
HVL, high	53.8	
HVL, medium high	15.4	
HVL, medium	0	
HVL, medium low	0	
HVL, low	0	
HVL, very low	0	
Symptomatic chronic infections		
HVL, very high	70.6	
HVL, high	16.7	
HVL, medium high	9.5	
HVL, medium	0.8	
HVL, medium low	1.6	
HVL, low	0.8	
HVL, very low	0	
Acute infections		
HVL, very high	100	
HVL, high	0	
HVL, medium high	0	
HVL, medium	0	
HVL, medium low	0	
HVL, low	0	
HVL, very low	0	
Length of AHI (months)	2	Assumption; Puren[29]

Table 7.1 cont'd. Summary of baseline scenario model parameter inputs.

Parameters	Values	Sources
HIV testing cascade throughput		
Steps 1-2: average HIV test offer frequency (months)		Thesis Subsections 5.2.2 and 6.2.1; adjusted for input into CEPAC by M. April on 3 Dec 2007
Client-initiated	221	
Provider-initiated	17	
Step 3: test acceptance (%)		Thesis Subsections 5.2.3 and 6.2.2
Opt-in	92.4	
Opt-out	97.4	
Step 3.5		
Rapid test serial protocol		WHO;[60] Ly et al.;[34,35] Sickinger et al.;[33] thesis Subsections 5.2.3 and 6.2.3; Tables 6.1-6.2
Sensitivity (%)		
AHI	0	
Post AHI	100	
Specificity (%)	100	
AHI test		
Sensitivity (%)		
AHI	57.3	
Post AHI	1	
Specificity (%)	99.8	
Step 4: post-test counselling (%)	98.3	Thesis Subsections 5.2.4 and 6.2.4
Step 5: HIV-infected clients attending scheduled clinic visits (%)		Thesis Subsections 5.2.4 and 6.2.5
Standard linkage-to-care	36.0	
Enhanced linkage-to-care	68.0	
Step 6: distribution of treatment implementation (%):		Thesis Subsections 5.2.4 and 6.2.5; adjusted for input into CEPAC by M. April on 3 Dec 2007
Standard linkage-to-care		
None	19.3	
OI prophylaxis only	10.8	
ART & OI prophylaxis	69.9	
Enhanced linkage-to-care		
Neither	4.8	
OI prophylaxis only	10.3	
ART & OI prophylaxis	84.9	
Monthly probability (%) of learning serostatus through background testing (ANC and TB services)	0.27	Thesis Subsections 5.2.2-5.2.4 and 6.2.6; adjusted for input into CEPAC by M. April on 3 Dec 2007

Table 7.1 cont'd. Summary of baseline scenario model parameter inputs.

Parameters	Values	Sources
Costs		
Testing costs per person (2006 USD)		See thesis Subsection 7.1.2 for methods; adjusted for input into CEPAC by M. April on 3 Dec 2007
Test offer	1.02	
Initial rapid testing	1.87	
Confirmatory rapid testing	3.67	
AHI testing	5.86	
Post-test counselling costs (per person)		See thesis Subsection 7.1.2 for methods; adjusted for input into CEPAC by M. April on 3 Dec 2007
HIV-negative clients	0.56	
HIV-positive clients	0.81	
Enhanced linkage-to-care cost (per person)	2.48	See thesis Subsection 7.1.2 for methods; adjusted for input into CEPAC by M. April on 3 Dec 2007

HSRC: Human Sciences Research Council
CEPAC: Cost-Effectiveness of Preventing AIDS Complications
AHI: Acute HIV Infection
OI: opportunistic infection
ART: antiretroviral treatment
USD: United States Dollars

7.1.3 Sensitivity analyses for parameter inputs

Most of the point estimates for the parameter inputs (see Table 7.1) were adjusted to assess the sensitivity of the cost-effectiveness estimates to the values used. Univariate sensitivity analyses were first performed using ranges explained and justified in this section (summarized in Table 7.2). Subsequently, limited multivariate sensitivity analyses as outlined at the end of this section were performed to assess the effects of adjusting simultaneously those inputs likely to change in concert and to which the CEPAC results have historically been found most sensitive.

Undiagnosed prevalence and incidence

The high-bound undiagnosed prevalence distribution values maintained the aforementioned 23.0% prevalence estimate,[288] but assumed that no HIV cases had yet

been identified. The lower-bound distribution values assumed the same number of pre-diagnosed HIV-positive cases as in the point estimate but used a low-prevalence value, 17.7% as estimated by the HSRC's 2005 national seroprevalence survey.[17] The proportion of asymptomatic to symptomatic individuals among those infected was not altered.

Lower- and upper-bound estimates for the community incidence rate were drawn from the same data generated by the national 2005 survey in South Africa used for the baseline incidence estimate (unpublished subset provided by Professor Thomas Rehle, personal communication). Specifically, the lower- and upper-bounds of the 95% confidence interval for this survey's incidence estimate for South Africa's adult African population was used. Using Equation 6.1, these incidence rates, 2.1% and 4.1%, yielded monthly probabilities of HIV infection equal to 0.17% and 0.34%, respectively. The prevalence distribution parameter defining the proportion of the population acutely infected with HIV was adjusted in accordance with these values.

CD4 and viral load distributions

Alternative distributions for population CD4 and VL counts were not based on empirical data. Instead, all mean CD4 counts were halved and doubled for upper- and lower-bound estimates, respectively. The standard deviations for these means were not adjusted. For VL distributions, the upper-bound estimate allocated all HIV-positive individuals (regardless of health state category) to the highest VL bracket (>100,000 cells/mL). Conversely, the lower-bound estimate allocated all HIV-positive individuals to the lowest bracket (0-20 cells/mL).

HIV testing cascade throughput

Ranges for the rates and probabilities of client passage for the steps of the HIV testing cascade were based upon those reported in Section 6.2. To generate the range of test offer frequencies, twelve was divided by the upper- and lower-bound annual test rates reported in Subsection 6.2.1. These resulted in upper- and lower-bound estimates for client-initiated test offer rates of once every 64 and 319 months, respectively. Upper- and lower-bound provider-initiated test offer rates were once every 13 and 19 months.

Upper- and lower-bound probabilities of referral and treatment were taken from those reported in Subsection 6.2.5. Again, the probabilities of clients accessing all healthcare visits were based on the proportions of seropositive clients in the study community receiving a CD4 count within six months of diagnosis, with the remainder attending healthcare facilities only if receiving treatment or experiencing an acute OI. The lower-bound probability of eligible clients receiving ART under standard linkage-to-care was set to 37.2% (16 of 43) as observed in 2003 (see Subsection 6.2.5). The proportion of clients diagnosed that year eligible for both ART and cotrimoxazole but receiving only cotrimoxazole within six months of eligibility was 32.6% (14 of 43). The upper-bound probability of eligible clients receiving ART under standard linkage-to-care was set to 71.0% (49 of 69) as observed in 2006. The proportion of clients diagnosed that year eligible for both ART and cotrimoxazole but receiving only cotrimoxazole within six months of eligibility was 13.0% (9 of 69).

Treatment and referral probabilities under enhanced linkage-to-care programs for patients normally not receiving referral and treatment were also adjusted in sensitivity analyses. As outlined in Subsection 6.1.5, these were adjusted to 25% in the lower-bound scenario and 75% in the upper-bound scenario. In the case of treatment

probabilities, the same methods of adjustment were used as outlined in Subsection 7.1.2: half of all clients normally receiving no treatment or only OI prophylaxis were assumed to receive ART and half of the remaining clients still receiving no treatment were assumed to receive OI prophylaxis only.

All other cascade throughput probability ranges were taken from Section 6.2, including that for background testing, also defined by CEPAC as the monthly probability of clients learning their serostatus. Table 7.2 reproduces these ranges.

Costs

Plausible ranges for HIV testing costs were generated by using upper- and lower-bound estimates for each of the testing process components. These bounds for healthcare personnel costs were taken from the range of salaries reported in the aforementioned survey of government healthcare workers (Ms. Trish Deas, personal communication) and the range of times required for pre- and post-test counselling by the CDC's RESPECT-2 trial.[312] Ranges for the times required for the tests to operate were taken directly from Abbott's AxSYM manual for the antigen-antibody combination test.[313] Since such ranges were not reported by the WHO for the rapid tests,[60] the baseline time estimates were simply halved and doubled for the lower- and upper- bound estimates. Per capita costs for enhanced linkage-to-care and capital outlays were similarly halved and doubled for sensitivity analyses. No upper-bound productivity cost was estimated, but to reflect the likelihood that high unemployment may preclude significant productivity losses, these costs were set to zero for a lower-bound estimate. Finally, lower- and upper-bounds were not estimated for the test kit or AxSYM maintenance costs due to the precision of the estimates.

Table 7.2. Summary of upper- and lower-bound model parameter inputs.

Parameters	Lower-bound inputs	Upper-bound inputs
Target population		
Initial HIV prevalence distribution		
Negative	86.5	76.5
Positive, asymptomatic	7.5	13.2
Positive, symptomatic	5.5	9.7
Positive, acutely infected	0.52	0.52
Monthly HIV incidence	0.17	0.34
Initial CD4 distribution (mean, standard deviation)		
Asymptomatic chronic infections	217, 246	657, 246
Symptomatic chronic infections	112, 209	336, 209
Acute infections	217, 246	657, 246
Initial VL distribution		
Asymptomatic chronic infections		
HVL VHI	0	1
HVL HI	0	0
HVL MHI	0	0
HVL MED	0	0
HVL MLO	0	0
HVL LO	0	0
HVL VLO	1	0
Symptomatic chronic infections		
HVL VHI	0	1
HVL HI	0	0
HVL MHI	0	0
HVL MED	0	0
HVL MLO	0	0
HVL LO	0	0
HVL VLO	1	0
Acute infections		
HVL VHI	0	1
HVL HI	0	0
HVL MHI	0	0
HVL MED	0	0
HVL MLO	0	0
HVL LO	0	0
HVL VLO	1	0
Length of AHI (months)	1	6

Table 7.2 cont'd. Summary of upper- and lower-bound model parameter inputs.

Parameters	Lower-bound inputs	Upper-bound inputs
HIV testing cascade throughput		
Steps 1-2: average HIV test offer frequency (months)		
Client-initiated	319	64
Provider-initiated	19	13
Step 3: test acceptance (%)		
Opt-in	92.1	96.4
Opt-out	97.3	98.8
Step 3.5		
Rapid test protocol		
Sensitivity (%)		
AHI*	0	0.1
Post AHI	91.2	N/A
Specificity (%)	99.9	N/A
AHI test		
Sensitivity (%)		
AHI	46.5	63.0
Post AHI	N/A†	N/A†
Specificity (%)	99.5	100
Step 4: post-test counselling (%)	95.7	100
Step 5: probability of client attendance for scheduled clinic visits (%)		
Standard linkage-to-care	27.7	65.7
Enhanced linkage-to-care	52.0	84.0
Step 6: distribution of treatment implementation (%)		
Standard linkage-to-care		
Neither	30.2	16.0
OI prophylaxis only	32.6	13.0
ART & OI prophylaxis	37.2	71.0
Enhanced linkage-to-care		
Neither	10.9	1.2
OI prophylaxis only	11.7	6.3
ART & OI prophylaxis	77.4	92.5
Monthly probability (%) of learning serostatus through background testing (ANC and TB services)	0.25	0.43

Table 7.2 cont'd. Summary of upper- and lower-bound model parameter inputs.

Parameters	Lower-bound inputs	Upper-bound inputs
Costs		
Testing costs per person (2006 USD)		
Test offer	0.41	1.74
Initial rapid testing	1.19	3.26
Confirmatory rapid testing	2.99	5.06
AHI testing	3.52	8.76
Post-test counselling costs (per person)		
HIV-negative clients	0.22	0.88
HIV-positive clients	0.30	1.29
Enhanced linkage-to-care cost (per person)	1.24	4.96

* Pre AHI sensitivity for the rapid protocol is dependent upon the protocol specificity; therefore, the upper-bound AHI sensitivity value is achieved when the lower-bound specificity is used

† Sensitivity analyses were not performed on the AxSYM test's sensitivity in detected post-AHI cases (see Subsection 7.1.3)

HSRC: Human Sciences Research Council
CEPAC: Cost-Effectiveness of Preventing AIDS Complications
AHI: Acute HIV Infection
OI: opportunistic infection
ART: antiretroviral treatment
USD: United States Dollars

Parameters unrelated to HIV testing

Select parameters unrelated to HIV testing were also adjusted. These were selected based on the preliminary results of the sensitivity analyses outlined in Table 7.2 to explain better the factors underlying the cost-effectiveness of HIV screening in South Africa. These parameters included the discount rate which was changed from 3% in the baseline scenario to 0% for the lower-bound scenario and 7% for the upper-bound scenario. Also, the CD4 count below which, if detected, patients initiated ART was increased from 200 cells/mm^3 to 350 cells/mm^3 and 500 cells/mm^3. Finally, the monthly cost of ART was increased and decreased by 20% (see Appendix B for further discussion of the point estimates and data sources used for these parameters).

Multivariate sensitivity analyses

Limited multivariate sensitivity analyses were performed in addition to the univariate sensitivity analyses. These additional sensitivity analyses applied the upper- and lower-bound limits reported in Table 7.2 to multiple HIV testing parameters simultaneously. Since the CEPAC screening model has been found sensitive to prevalence and incidence estimates in analyses based on the United States population,[153] these variables were adjusted to their upper- and lower-bound limits together. The overall effects of testing costs on cost-effectiveness were assessed by using the lower- and upper-bound estimates for all cost variables simultaneously. Finally, given the consistently greater cost-effectiveness of policies including enhanced linkage-to-care components (see Subsection 7.2.1), a scenario unfavourable to enhanced linkage-to-care was generated using upper-bound estimates of current referral and treatment rates, lower-bound estimates of the effects of enhanced linkage-to-care, and upper-bound estimates for the per capita costs of enhanced linkage-to-care.

7.2 Results

7.2.1 Cost-effectiveness point estimates

Results for the point estimates of the cost-effectiveness of expanded HIV testing are presented in Figure 7.4 and Table 7.3. The use of enhanced versus standard linkage-to-care dramatically increased both the cost and life years gained (LYG) per population member (Figure 7.4a). Furthermore, all four standard linkage-to-care policies were extended dominated (see Subsection 3.1.4 and Figure 3.4 for more on economic evaluation terms and decision rules).

Figure 7.4b magnifies the area of the cost-effectiveness plane encompassing solely the four enhanced linkage-to-care policies. Among these, provider-initiated, opt-in testing with a rapid-only protocol (IRE) was the least expensive cost effective policy, yielding per population member approximately 0.8571 additional life years at a cost of $727 compared to current practice ($848/LYG). Making this policy's consent method opt-out rather than opt-in (ORE) was projected to gain for each population member another 0.0038 life years at a cost of $8 per population member ($2,087/LYG). Finally, when compared to provider-initiated, opt-out testing with a rapid-only test protocol, the same policy save with an AHI test protocol and the most expensive of the cost-effective options, was projected to gain another 0.0089 life years per population member for a per capita cost of $58 ($6,511/LYG).

The standard linkage-to-care policies exhibited a similar cost-effectiveness pattern (Figure 7.4a). The policies identical except for consent method were clustered closely together on the cost-effectiveness plane, with the opt-out policies yielding slightly greater health benefits compared to current practice at a slightly higher cost. The policies including an AHI test protocol similarly yielded slightly greater life years when compared to policies using rapid-only protocols, but did so only at a markedly greater cost. However, one difference among the two patterns is that if the standard policies were examined while excluding the enhanced linkage-to-care policies, provider-initiated, opt-in testing with a rapid-only protocol (IRS) was extended dominated, making provider-initiated, opt-out testing with a rapid-only protocol (ORS) the least expensive cost-effective option. Nevertheless, the difference in the cost-effectiveness ratios between these two options was small.

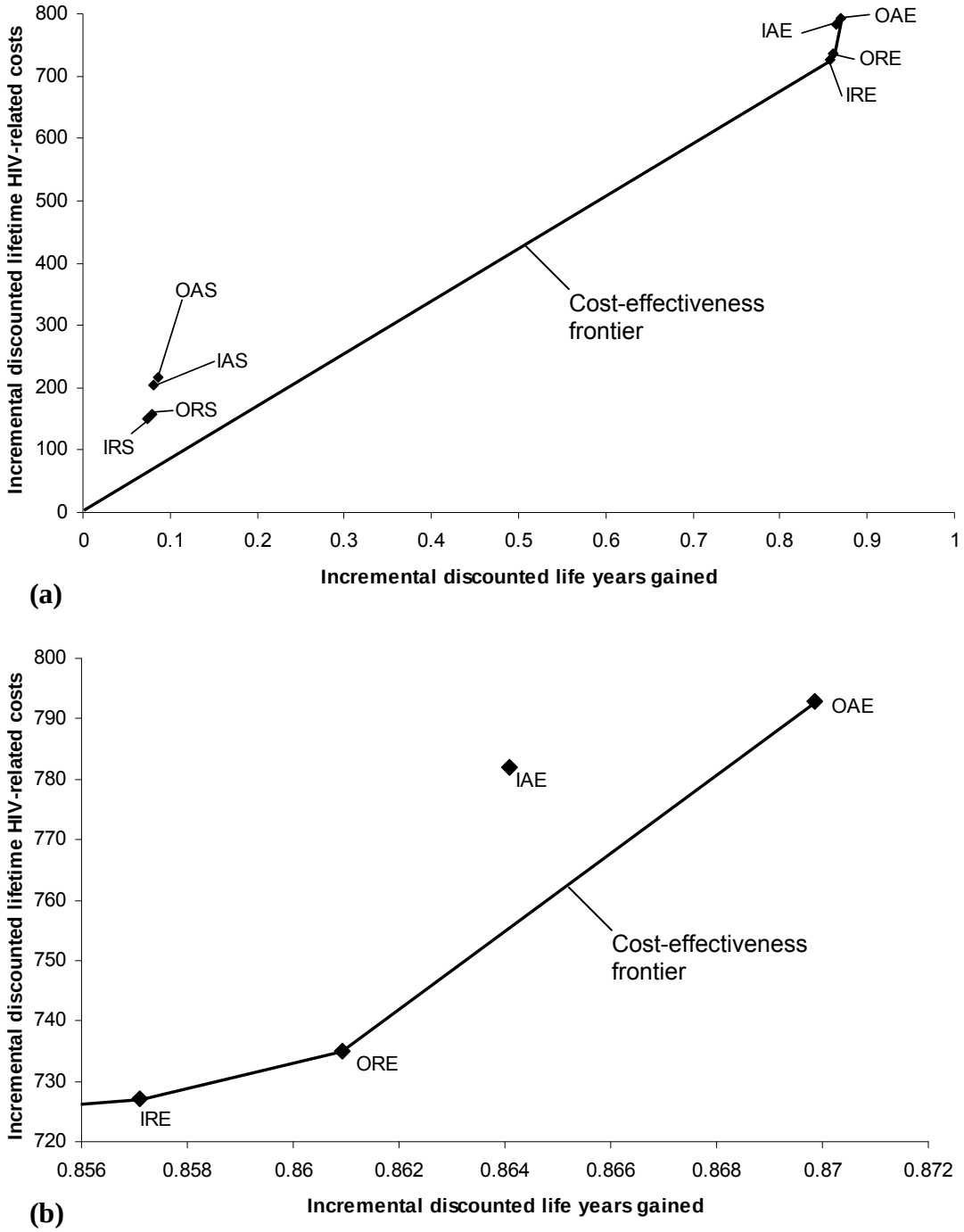

Figure 7.4. Cost-effectiveness estimates for expanded HIV testing policies. All cost-effectiveness frontiers intersect with the origin which is set to the cost and effectiveness of current testing practice. Comparing all eight provider-initiated policies (a), all of the standard-linkage-to-care policies are extended dominated. Among the enhanced linkage-to-care policies (b), opt-in testing with a rapid-only protocol (IRE) is the least expensive cost-effective strategy, followed by opt-out testing with a rapid-only protocol (ORE), and then opt-out testing with an acute HIV infection (AHI) testing protocol, with opt-in testing with an AHI protocol (IAE) extended dominated.

Table 7.3. Cost-effectiveness estimates for expanded HIV testing policies.

Policy*	Cost†	Effect†	ICER
IRE v. current practice	$727	0.8571	$848
ORE v. IRE	$8	0.0038	$2,087
OAE v. ORE	$58	0.0089	$6,511

* See Table 2.1 for policy acronym definitions
† Costs and effects are incremental and per member of the target population
ICER: incremental cost-effectiveness ratio

While overall costs increased, the breakdown of costs remained stable across current testing practice and each of the cost-effective HIV testing policies examined (Figure 7.5). Costs of care for HIV-positive individuals (e.g., routine care, treatment of infections, etc.) overwhelmingly comprised the largest cost component. ART and monitoring costs (including CD4 and VL testing) together comprised the next largest cost components. Screening costs (including costs of linkage-to-care) consistently comprised a small (<3%) proportion of overall costs, although this proportion did increase noticeably for provider-initiated policies with enhanced linkage-to-care versus current practice. This proportion also increased for policies adopting an AHI test protocol versus a rapid-only test protocol. Finally, costs of OI prophylaxis always comprised the smallest component of HIV testing policy costs.

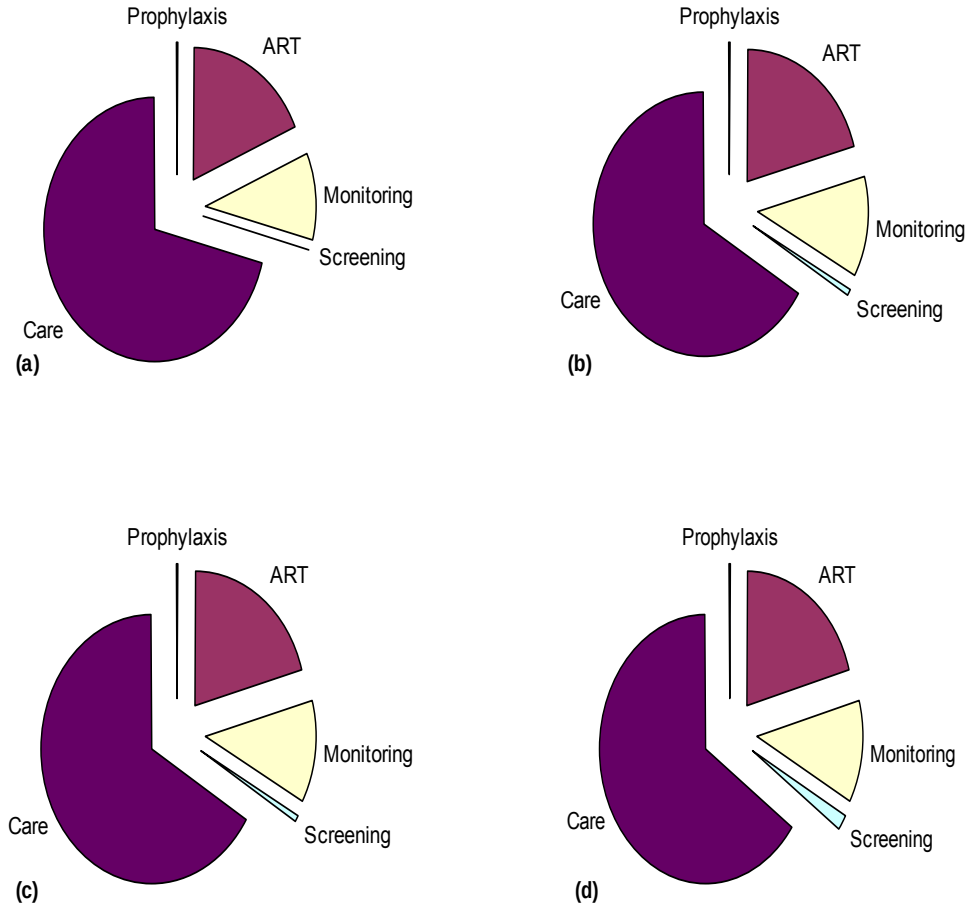

Figure 7.5. Breakdown of costs for HIV testing policies. Policies include current testing practice (a), provider-initiated, opt-in testing with a rapid-only protocol and enhanced linkage-to-care (b), provider-initiated, opt-out testing with a rapid-only protocol and enhanced linkage-to-care (c), and provider-initiated, opt-in testing with an acute HIV infection testing protocol and enhanced linkage-to-care (d).

7.2.2 Sensitivity analyses

The results of the sensitivity analyses demonstrated the main CEPAC results reported in Subsection 7.2.1 to be very robust. In only a handful of scenarios did the costs per LYG change considerably for the least expensive cost-effective policy. Moreover the ordering of policies by cost-effectiveness remained unchanged in all but one scenario. The remainder of this section will consider in greater detail the results of these sensitivity analyses.

Target population parameters

Few substantial differences were observed in costs per LYG in the sensitivity analyses of the inputs for those CEPAC and AHIT parameters describing the target population (Table 7.4). Ratios of incremental costs to incremental benefits (i.e., ICERs) between the cost-effective scenarios were also stable. The only exceptions include the scenarios of high-bound population CD4 distribution and low-bound AHI length in which the ICERs for provider-initiated, opt-out testing with an AHI test protocol and enhanced linkage-to-care (OAE) compared to provider-initiated, opt-out testing with a rapid-only test protocol and enhanced linkage-to-care (ORE) increased substantially.

Ordering of policies by cost-effectiveness change was stable. Enhanced linkage-to-care policies always extended dominated standard linkage-to-care policies. Provider-initiated, opt-in testing with rapid-only test protocol (IRE) was consistently the least expensive cost-effective option, followed by the same policy with opt-out testing (ORE) and then provider-initiated, opt-out testing with an AHI test protocol (OAE). More variation was observed in the incremental costs and benefits of these policies, particularly when adjusting inputs defining the population's incidence and CD4 distribution. As population CD4 dropped and HIV incidence rose and decreased, overall costs and benefits of expanded testing increased and decreased, respectively.

Table 7.4. Results of sensitivity analyses of target population parameter inputs. Costs, effects, and cost-effectiveness ratios reported by each row are incremental to those for the policy in the preceding row or, in the case of the first rows, incremental to current practice.

	Minimum parameter estimate				Maximum parameter estimate			
	Policy*	Cost†	Effect†	ICER	Policy*	Cost†	Effect†	ICER
HIV prevalence distribution	IRE	$693	0.8014	$865	IRE	$755	0.9001	$837
	ORE	$7	0.0033	$1,403	ORE	$9	0.0048	$1,830
	OAE	$65	0.0066	$9,844	OAE	$58	0.0109	$5,319
HIV incidence	IRE	$616	0.7217	$854	IRE	$811	0.9613	$844
	ORE	$8	0.0038	$2,150	ORE	$10	0.0068	$1,472
	OAE	$62	0.0077	$8,120	OAE	$57	0.0115	$4,999
CD4 distribution	IRE	$801	0.9248	$865	IRE	$655	0.7240	$905
	ORE	$12	0.0118	$1,017	ORE	$7	0.0012	$5,419
	OAE	$71	0.0199	$3,570	OAE	$54	0.0013	$41,538
Viral load distribution	IRE	$918	0.8765	$1,047	IRE	$727	0.8589	$846
	ORE	$10	0.0047	$2,128	ORE	$9	0.0055	$1,546
	OAE	$60	0.0075	$7,998	OAE	$60	0.0109	$5,505
AHI length	IRE	$732	0.8586	$852	IRE	$707	0.8465	$835
	ORE	$12	0.0071	$1,692	ORE	$8	0.0040	$1,999
	OAE	$56	0.0025	$22,379	OAE	$69	0.0259	$2,666

* See Table 2.1 for policy acronym definitions
† Costs and effects are per member of the target population
ICER: incremental cost-effectiveness ratio
AHI: acute HIV infection

HIV testing cascade throughput parameters

Sensitivity analyses also found the CEA results stable despite variations in inputs for the HIV testing cascade throughput CEPAC and AHIT parameters (Table 7.5). In all of these scenarios, ordering of policies by cost-effectiveness remained the same. The only scenarios for which noteworthy changes in incremental costs or effects occurred were those altering linkage-to-care probabilities. As standard linkage-to-care throughput for cascade Steps 5-6 (referral or treatment) rose or enhanced linkage-to-care throughput dropped, incremental costs and benefits for the enhanced linkage-to-care policies decreased and the ratio of costs to LYGs for these increased. Conversely, when standard linkage-to-care throughput fell or enhanced linkage-to-care throughput rose, incremental costs and benefits for the enhanced linkage-to-care policies increased and the ratio of costs to LYGs for these policies decreased.

Table 7.5. Results of sensitivity analyses of testing throughput parameters. Costs, effects, and cost-effectiveness ratios reported by each row are incremental to those for the policy in the preceding row or, in the case of the first rows, incremental to current practice.

	Minimum parameter estimate				Maximum parameter estimate			
	Policy*	Cost†	Effect†	ICER	Policy*	Cost†	Effect†	ICER
Test offer frequency, client-init.‡	IRE	$731	0.8587	$851	IRE	$682	0.8344	$817
	ORE	$8	0.0038	$2,087	ORE	$8	0.0038	$2,087
	OAE	$58	0.0089	$6,511	OAE	$58	0.0089	$6,511
Test offer frequency, provider-init.	IRE	$719	0.8457	$846	IRE	$752	0.8695	$865
	ORE	$8	0.0036	$2,221	ORE	$9	0.0047	$1,915
	OAE	$66	0.0079	$8,354	OAE	$69	0.0099	$6,970
Test acceptance, opt-in	IRE	$724	0.8566	$845	IRE	$729	0.8580	$850
	ORE	$14	0.0059	$2,373	ORE	$3	0.0020	$1,519
	OAE	$58	0.0089	$6,511	OAE	$58	0.0089	$6,511
Test acceptance, opt-out	IRE	$727	0.8571	$848	IRE	$727	0.8571	$848
	ORE	$8	0.0035	$2,286	ORE	$10	0.0071	$1,434
	OAE	$58	0.0089	$6,511	OAE	$58	0.0089	$6,511
Rapid sensitivity, chronic	IRE	$727	0.8562	$848				
	ORE	$8	0.0039	$2,079				
	OAE	$59	0.0091	$6,484				
Rapid protocol specificity	IRE	$727	0.8572	$848				
	ORE	$8	0.0040	$2,066				
	OAE	$58	0.0086	$6,602				
AHI test sensivitiy, AHI	IRE	$727	0.8571	$848	IRE	$727	0.8571	$848
	ORE	$8	0.0038	$2,087	ORE	$8	0.0038	$2,087
	OAE	$58	0.0089	$6,575	OAE	$58	0.0071	$8,219
AHI test, specificity	IRE	$727	0.8571	$848	IRE	$726	0.8584	$846
	ORE	$8	0.0038	$2,087	ORE	$9	0.0053	$1,690
	OAE	$58	0.0079	$7,342	OAE	$58	0.0088	$6,470
Post-test counselling probability	IRE	$725	0.8550	$848	IRE	$726	0.8578	$846
	ORE	$8	0.0035	$2,320	ORE	$8	0.0044	$1,821
	OAE	$56	0.0077	$7,273	OAE	$61	0.0101	$6,065
Referral probability, standard	IRE	$743	0.8693	$855	IRE	$672	0.8133	$827
	ORE	$9	0.0045	$2,050	ORE	$7	0.0037	$1,903
	OAE	$60	0.0088	$6,818	OAE	$57	0.0089	$6,400
Referral probability, enhanced	IRE	$655	0.7891	$830	IRE	$788	0.9293	$862
	ORE	$7	0.0033	$2,001	ORE	$11	0.0057	$1,932
	OAE	$56	0.0081	$6,914	OAE	$59	0.0101	$5,940
Treatment probability, standard	IRE	$998	1.2412	$804	IRE	$520	0.5641	$922
	ORE	$9	0.0069	$1,304	ORE	$8	0.0026	$3,054
	OAE	$56	0.0060	$9,333	OAE	$55	0.0085	$6,468
Treatment probability, enhanced	IRE	$504	0.5211	$967	IRE	$947	1.2003	$789
	ORE	$8	0.0031	$2,581	ORE	$10	0.0061	$1,648
	OAE	$57	0.0075	$7,605	OAE	$60	0.0097	$6,186
Background testing probability	IRE	$728	0.8591	$847	IRE	$727	0.8570	$848
	ORE	$9	0.0055	$1,636	ORE	$8	0.0030	$2,668
	OAE	$59	0.0099	$5,960	OAE	$57	0.0080	$7,128

* See Table 2.1 for policy acronym definitions; shaded areas denote scenarios for which no sensitivity analyses were conducted

† Costs and effects are per member of the target population

‡ This parameter is equivalent to baseline testing as defined by this thesis

ICER: incremental cost-effectiveness ratio

AHI: acute HIV infection

Testing cost parameters

The testing cost parameters had the least influence on incremental costs, effects, and costs per effects out of any of the parameter sets examined (Table 7.6). Indeed, none of the alternative testing cost scenarios yielded results which differed notably from those of the point estimate scenario.

Table 7.6. Results of sensitivity analyses of testing cost parameters. Costs, effects, and cost-effectiveness ratios reported by each row are incremental to those for the policy in the preceding row or, in the case of the first rows, incremental to current practice.

	Minimum parameter estimate				Maximum parameter estimate			
	Policy*	Cost†	Effect†	ICER	Policy*	Cost†	Effect†	ICER
Test offer cost	IRE	$724	0.8571	$844	IRE	$731	0.8571	$853
	ORE	$8	0.0038	$2,105	ORE	$11	0.0038	$2,895
	OAE	$58	0.0089	$6,517	OAE	$57	0.0089	$6,404
Initial rapid test cost	IRE	$723	0.8571	$844	IRE	$736	0.8571	$859
	ORE	$8	0.0038	$2,105	ORE	$9	0.0038	$2,368
	OAE	$58	0.0089	$6,517	OAE	$59	0.0089	$6,629
Confirmatory rapid test cost	IRE	$727	0.8571	$848	IRE	$729	0.8571	$851
	ORE	$8	0.0038	$2,105	ORE	$8	0.0038	$2,105
	OAE	$58	0.0089	$6,517	OAE	$58	0.0089	$6,517
AHI test cost	IRE	$726	0.8571	$847	IRE	$727	0.8571	$848
	ORE	$8	0.0038	$2,105	ORE	$8	0.0038	$2,105
	OAE	$39	0.0089	$4,382	OAE	$85	0.0089	$9,551
Counselling cost, neg. clients	IRE	$726	0.8571	$847	IRE	$730	0.8571	$852
	ORE	$8	0.0038	$2,105	ORE	$8	0.0038	$2,105
	OAE	$57	0.0089	$6,404	OAE	$59	0.0089	$6,629
Counselling cost, pos. clients	IRE	$726	0.8571	$847	IRE	$727	0.8571	$848
	ORE	$8	0.0038	$2,105	ORE	$9	0.0038	$2,368
	OAE	$57	0.0089	$6,404	OAE	$59	0.0089	$6,629
Enhanced linkage-to-care cost	IRE	$727	0.8571	$848	IRE	$728	0.8571	$849
	ORE	$8	0.0038	$2,105	ORE	$10	0.0038	$2,632
	OAE	$57	0.0089	$6,404	OAE	$59	0.0089	$6,629

* See Table 2.1 for policy acronym definitions
† Costs and effects are per member of the target population
ICER: incremental cost-effectiveness ratio
AHI: acute HIV infection

Parameters unrelated to HIV testing

In all scenarios adjusting the values of CEPAC parameters unrelated to HIV testing, the ordering of these policies by cost-effectiveness remained stable (Table 7.7). In the

case of increasing the CD4 count below which ART is initiated, the incremental costs and effects of expanded testing both increased. The ratio of the incremental costs per incremental LYG for the least expensive cost-effective option (opt-in testing with a rapid-only protocol and enhanced-linkage-to-care) compared to current practice decreased notably as this CD4 count threshold increased. However, the difference in this ratio between the ART initiation at 350 cells/mm^3 and 500 cells/mm^3 scenarios was negligible.

Sensitivity analyses of the discount rate similarly had a noticeable effect on the ICERs of the expanded testing policies and a substantial effect on the incremental costs and benefits of these policies. When the discount rate was decreased, the incremental costs and benefits of the policies both increased substantially although the ratio of costs to benefits decreased. Conversely, the incremental costs and benefits decreased when the discount rate increased and the ratio between the two rose.

Finally, the monthly cost of ART had the clearest effect on the expanded testing policies' ICERs when compared to current testing practice. Although this effect was small, this must be interpreted given the small range examined in sensitivity analyses (+/- 20%, see Subsection 7.1.3). As the monthly costs of ART decreased, the incremental cost of the expanded testing and linkage-to-care policies fell dramatically while LYG remained constant, so resulting in a drop in the costs per LYG. Conversely, as these costs rose, the incremental cost of the expanded testing policies rose while the LYG remained constant, so causing the costs per LYG to increase.

Table 7.7. Results of sensitivity analyses of parameters unrelated to testing. Costs, effects, and cost-effectiveness ratios reported by each row are incremental to those for the policy in the preceding row or, in the case of the first rows, incremental to current practice.

	Minimum parameter estimate				Maximum parameter estimate			
	Policy*	Cost†	Effect†	ICER	Policy*	Cost†	Effect†	ICER
CD4 criteria for ART initiation‡	IRE	$781	0.9780	$796	IRE	$830	1.0498	$791
	ORE	$12	0.0088	$1,215	ORE	$12	0.0111	$1,081
	OAE	$61	0.0119	$4,771	OAE	$63	0.0135	$4,668
Discount rate	IRE	$1,380	1.6960	$815	IRE	$380	0.4262	$891
	ORE	$14	0.0131	$1,071	ORE	$6	0.0032	$2,188
	OAE	$90	0.0145	$6,207	OAE	$38	0.0041	$9,268
Monthly ART cost	IRE	$682	0.8571	$795	IRE	$773	0.8571	$903
	ORE	$8	0.0038	$2,100	ORE	$9	0.0038	$2,370
	OAE	$58	0.0089	$6,501	OAE	$61	0.0089	$6,855

* See Table 2.1 for policy acronym definitions
† Costs and effects are per member of the target population
‡ Minimum parameter input for CD4 criteria for ART initiation was 350 and maximum 500 versus 200 for baseline
ICER: incremental cost-effectiveness ratio
AHI: acute HIV infection

Multivariate sensitivity analyses

Most of the multivariate sensitivity analyses had little impact on the overall results of the CEA (Table 7.8). Increasing undiagnosed prevalence and incidence together had the joint effect of increasing the incremental cost and LYG for the cost-effective expanded testing policies and decreasing the ICER for provider-initiated, opt-out testing with an AHI testing protocol and enhanced linkage-to-care (OAE) when compared to the same policy using a rapid-only protocol (ORE). Decreasing prevalence and incidence together decreased the incremental cost and LYG for the expanded testing policies while increasing the ICER for provider-initiated, opt-out testing with AHI testing and enhanced linkage-to-care (OAE).

Adjusting all testing costs simultaneously had little impact on the CEA results. These sensitivity analyses did increase the incremental costs of the cost-effective expanded

testing policies very slightly. However, these effects were insufficient to impact the ICERs for these policies.

Finally, the scenario in which all inputs related to linkage-to-care were adjusted to be unfavourable to enhanced linkage-to-care still resulted in all standard linkage-to-care policies being extended dominated by the enhanced linkage-to-care policies. This scenario was the only one among those examined in this chapter in which provider-initiated, opt-in testing with a rapid-only protocol and enhanced linkage-to-care (IRE) was extended dominated. Provider-initiated, opt-out testing with a rapid-only protocol and enhanced linkage-to-care (ORE) was the least expensive cost-effective policy, yielding 0.0940 LYG per population member at a cost of $1,756/LYG. The same policy except for use of an AHI instead of rapid-only protocol (OAE) remained the most expensive cost-effective option.

Table 7.8. Results of multivariate sensitivity analyses of selected parameters. Costs, effects, and cost-effectiveness ratios reported by each row are incremental to those for the policy in the preceding row or, in the case of the first rows, incremental to current practice.

	Minimum parameter estimate				**Maximum parameter estimate**			
	Policy*	Cost†	Effect†	ICER	Policy*	Cost†	Effect†	ICER
HIV prevalence & incidence	IRE	$573	0.6585	$870	IRE	$835	1.0015	$834
	ORE	$7	0.0056	$1,250	ORE	$10	0.0059	$1,694
	OAE	$66	0.0061	$10,820	OAE	$52	0.0095	$5,472
All testing costs	IRE	$715	0.8571	$834	IRE	$743	0.8571	$867
	ORE	$8	0.0038	$2,104	ORE	$10	0.0038	$2,633
	OAE	$39	0.0089	$4,382	OAE	$88	0.0089	$9,888
Enhanced linkage inputs‡	ORE	$165	0.0940	$1,756				
	OAE	$61	0.0075	$8,135				

* See Table 2.1 for policy acronym definitions; shaded areas denote scenarios for which no sensitivity analyses were conducted
† Costs and effects are per member of the target population
‡ The parameters whose inputs were adjusted for the scenario unfavourable to enhanced linkage-to-care are outlined in Section 7.1.3.
ICER: incremental cost-effectiveness ratio
AHI: acute HIV infection

7.3 Discussion

7.3.1 Determinants of cost-effectiveness

The results reported in this chapter were stable across nearly all sensitivity analyses conducted. This suggests that many of the methods outlined in Sections 6.1 and 7.1 to configure the empirical testing data from Chapter 5 for input into CEPAC and AHIT were of little consequence for the overall results. Indeed, in nearly every scenario examined, the ordering of policies by cost-effectiveness remained unchanged.

Provider-initiated, opt-in testing with a rapid-only test protocol and enhanced linkage-to-care (IRE) was in all but one case the least expensive cost-effective option. This policy generally yielded LYG at a cost of approximately $850 each. The next least expensive option was the same policy except for use of an opt-out consent method (ORE), usually yielding incremental LYG at approximately double the cost. Finally, provider-initiated, opt-out testing with an AHI test protocol and enhanced linkage-to-care (OAE) was always the most expensive cost-effective scenario. The incremental cost per LYG for this most expensive cost-effective policy was more variable than that for the aforementioned policy, but generally hovered around $6,500.

Undiagnosed prevalence

Notably, undiagnosed prevalence was among those many parameters with little impact on the cost-effectiveness of expanded HIV testing, a finding running contrary to the results of many cost-effectiveness analyses (CEAs) of HIV testing in low-prevalence settings (see Subsection 4.2.3). However, this finding echoes the argument by Paltiel et al.[154] that as undiagnosed prevalence increases, the costs of testing fall relative to treatment costs because fewer tests are required to identify new

HIV-infected persons who can then be linked to treatment. At 1.0% undiagnosed prevalence and above, Paltiel et al. found that the costs of case detection (i.e., counselling and testing) became negligible relative to treatment costs such that further increases in undiagnosed prevalence had little effect on the cost-effectiveness of HIV testing. Given that the prevalence values used in this analysis greatly exceeded 1.0%, it is not surprising that the results yielded by CEPAC were found insensitive to even wide fluctuations in this parameter.

Treatment costs

Of all the parameters whose inputs were adjusted in sensitivity analyses in this chapter, the cost of ART was among those with the clearest influence on the cost-effectiveness of expanded HIV testing. As these treatment costs increased even moderately (+/- 20%), so did the cost per LYG for the expanded testing policies. Similarly, as the cost of ART fell, it became less expensive to achieve additional LYG. These findings indicate that the CEA presented in this chapter essentially amounts to a CEA of the provision of treatment and care for HIV-positive clients. Indeed, in this setting, even simultaneously maximizing the inputs for all of the testing cost parameters had little impact on the cost-effectiveness of expanded testing.

Linkage-to-care

This phenomenon whereby testing costs become negligible compared to treatment costs in settings of high undiagnosed prevalence depends upon the availability of treatment and care. If only a small fraction of clients diagnosed with HIV are linked to care, then testing costs will again rise relative to treatment costs as more resources will need to be devoted to case detection for each client linked to treatment. In such a

scenario, greater testing costs would be added to constant treatment costs for each individual linked to treatment, so increasing the overall costs per LYG.

This effect is exemplified by the extended dominance of the enhanced linkage-to-care policies over the standard linkage-to-care policies observed in this setting. Indeed, as found by Walensky et al.,[152] the HIV testing cascade steps for which throughput had the greatest impact on cost-effectiveness were referral (Step 5) and most especially treatment (Step 6). Moreover, while enhanced linkage-to-care policies still extended dominated standard linkage-to-care in the multivariate sensitivity analysis unfavourable to enhanced linkage-to-care, the costs per LYG for the enhanced linkage-to-care policies became much higher in this scenario.

Parameters related to client eligibility for treatment similarly affected the cost-effectiveness of expanded testing. As the population's CD4 distribution rose, more cases had to be detected for each individual linked to care, so again increasing the costs of testing relative to treatment costs and increasing the costs per LYG for expanded testing. Decreasing the population's mean CD4 count had little effect on the results, likely because this mean was already so low that viritually all HIV-infected persons were eligible for treatment immediately upon diagnosis.

Similarly, increasing the CD4 threshold for ART initiation improved the cost-effectiveness of testing. This effect may indicate enhanced health benefits per dollar spent on treatment, as per the argument that earlier ART initiation yields better health outcomes.[301] However, this effect was observed only to the extent that it permitted additional clients to receive treatment immediately following diagnosis. Increasing this CD4 threshold above 350 cells/mm^3 had little effect on cost-effectiveness,

presumably because few clients had CD4 counts exceeding this value at diagnosis. Consequently, I believe the improvements in cost-effectiveness observed by increasing the CD4 threshold at which patients are eligible for ART instead reflects the need to test fewer individuals for each patient linked to care.

Baseline and background testing

Another noteworthy result was the insensitivity of the cost-effectiveness results to adjustments in the estimates of either baseline or background testing. Background testing had no material impact on the cost-effectiveness of any of the expanded testing policies. While baseline testing had a slightly larger effect, this was still minimal.

Discount rate

Finally, there was a strong positive correlation between the discount rate and the costs per LYG for the expanded testing policies. Since the same discount rate was applied to the costs as to the health benefits, this result reflects the fact that costs for HIV-infected patients are generally differentially incurred in later years as it becomes necessary to initiate treatment and care.

7.3.2 Determinants of costs and effects

Undiagnosed prevalence, CD4 distributions, and eligibility criteria

The magnitudes of the cost and health effects of expanded HIV testing were more sensitive to those parameters solely influencing the proportion of patients eligible for treatment. For example, increases in undiagnosed prevalence and incidence both served to increase the proportion of patients in the population who were HIV-infected

and potentially eligible for treatment upon diagnosis.[§§] Consequently, in scenarios in which these parameters were increased, the costs and benefits both rose proportionately as a result of more clients receiving treatment and care. Conversely, in those scenarios where these parameters were decreased, the costs and health benefits of expanded testing both decreased.

More HIV-infected clients became eligible for treatment when the population's CD4 distribution decreased. Consequently, as mean CD4 count decreased the costs and health effects of expanded testing increased. Conversely, when the population's mean CD4 increased, fewer individuals ever met the eligibility criteria before dying – whether of acquired immune deficiency syndrome (AIDS) or causes unrelated to HIV testing – and so these costs and effects both decreased. Of course, another means by which to increase the size of the pool of patients eligible for testing is to redefine the eligibility criteria. Indeed, as the CD4 count below which HIV-infected clients were eligible for ART increased, so did the costs and health benefits of expanded testing.

Linkage-to-care

Probabilities of linkage-to-care also impacted the size of the cost and health gains by expanded testing policies. As the proportion of identified HIV-infected clients linked to care under an enhanced linkage-to-care program decreased, so did the costs and health benefits of expanded screening (although costs at a slower rate than health benefits as testing costs were still incurred, see Subsection 7.3.1). Of course, as this proportion fell for standard linkage-to-care, the costs and health benefits of enhanced linkage-to-care both increased compared to current practice.

[§§] Again, this effect can also substantially influence cost-effectiveness ratios, but only when the undiagnosed prevalence <1%.

Baseline and background testing

Background testing had no notable impact on the incremental costs or incremental effects of any of the expanded testing policies. This was to be expected given that background testing is assumed to remain constant under all testing policy alternatives in this thesis. Thus, while it affects the total costs and LYGs by HIV testing, it has zero impact on the incremental costs and health effects of expanded testing policies compared to current practice.

Baseline testing estimates had a somewhat greater impact on the results of this analysis. Specifically, as these rates increased, the costs and benefits of expanded testing decreased slightly. Conversely, as baseline testing rates decreased, the costs and benefits of expanded testing increased slightly. These small effects had little effect on the ratio of costs to LYGs (see Subsection 7.3.1). These effects on costs and benefits may have been more substantial had the baseline testing rates been larger in comparison to those under expanded testing. Instead, the differences in testing throughput between current testing practice and the expanded testing policies examined in this thesis were considerable (see Figure 6.1).

Discount rate

Finally, the choice of discount rate also had a substantial impact on the estimates of the incremental costs and effects of expanded HIV testing. Lower rates resulted in greater costs and effects while higher rates resulted in fewer. This is simply an artefact of the method used to weight monetary and health costs (see Subsection 3.2.2). Nevertheless, it has a substantial impact on the estimates of the total costs and health benefits to be expected from expanding testing among South Africa's adult African population. When taken together with the sizeable impact of the discount rate

on the cost-effectiveness estimates (see Subsection 7.3.1), these results highlight the importance of homogenizing the choice of discount rate and other methodological decisions to make the results of CEAs comparable across studies (see Section 3.2).

7.3.3 Implications for HIV testing policy in South Africa

The results of this study indicated that provider-initiated, opt-in testing with a rapid-only protocol and enhanced linkage-to-care (IRE) was the least expensive cost-effective option for expanding HIV testing among South Africa's adult African population. This policy was projected to yield LYG at a cost of $848 each. This falls well below the World Health Organization (WHO) Commission on Macroeconomics and Health's threshold cost per disability-adjusted life year (DALY) of a highly cost-effective intervention ($5,390, see Subsection 3.1.4).[103] Indeed, life years lived by HIV-infected clients would have to be valued at less than one-sixth of a DALY for this policy to not be considered highly cost effective.

The more expensive cost-effective expanded testing policies were less clearly cost-effective by the WHO Commission's criteria. Changing a provider-initiated, opt-in testing policy with a rapid-only testing protocol and enhanced linkage-to-care (IRE) to an opt-out policy (ORE) would yield additional LYG at a cost of $2,087 each. The substantial increase in ICER between this policy and the least expensive cost-effective option is a product of the assumption that acceptance rates remain constant regardless of initiation method. Due to this assumption, the decision to adopt an opt-out instead of opt-in consent method leads to a very small additional testing uptake. While the incremental costs are also small, I believe they rise at a higher rate than the incremental effects because testing rates are already so high using opt-in testing that the majority of HIV cases with advanced disease progression have already been

detected. Thus, the few additional cases detected by opt-out testing are likely to be relatively new cases, incurring years of monitoring costs before receiving linkage-to-care. Nevertheless, while this ICER is less than half the value of the $5,390 threshold, the effect size for this opt-out program is small, projected to achieve only 0.0038 additional LYGs.

Implementing provider-initiated, opt-out testing with an AHI test protocol and enhanced linkage-to-care (OAE) would cost $6,511 per LYG. While the ICER for this final policy remains well below the WHO Commission's threshold for a moderately cost-effective policy ($16,170, see Subsection 3.1.4), it is sensitive to assumptions regarding the length of AHI and the population's CD4 distributions. Therefore it remains less clear whether AHI testing is sufficiently cost-effective to be included as part of South Africa's response to its HIV epidemic.

Nevertheless, these results should not be interpreted as an unqualified rejection of expanded testing policies including opt-out consent or AHI testing. The small incremental costs and effects of the opt-out policies are a product of the high acceptance probabilities observed among individuals receiving client-initiated testing in the study community. As argued at the outset of this thesis, I do not believe evidence yet exists exploring whether acceptance rates among the general population decrease following implementation of provider-initiated testing. Yet, it seems quite possible that these rates would decrease following the routinizing of test offers, decreasing throughput for cascade Step 3 even as that for Step 2 rises. If this were to occur, opt-out testing could become much more attractive as a policy alternative. Future research is needed to assess acceptance probabilities among primary healthcare users receiving provider-initiated testing using opt-out versus opt-in consent methods.

Similarly, the current results are insufficient to reject use of AHI testing on economic grounds. The inability of CEPAC to account for transmission dynamics undoubtedly led to an understatement of the effectiveness of policies including AHI testing. Future modelling studies considering AHI testing in South Africa would therefore provide useful additional information by modelling the effects of AHI detection on population transmission dynamics (see Subsection 7.3.4). Moreover, in spite of omitting these transmission effects in this analysis, the policies' ICERs policies were still much smaller than the incremental cost per quality-adjusted life year (QALY) observed by the only other study to compare AHI to rapid-only test protocols (US$30,800).[164]

Population-level impact

This chapter conducted a population-level CEA. Consequently, it is possible to describe these results more intuitively as the impact of these policies on South Africa's national adult African population (these projections are based on the South African government's projection of the size of this national population in 2006[286]). Implementing a provider-initiated, opt-in policy with a rapid-only protocol and enhanced linkage-to-care can be expected to save approximately 21 million life years at a cost of approximately $18 billion over the course of the lifetime[***] of the current adult African population. Changing this policy's consent method to opt-out would save nearly 95,000 additional life years at a cost of approximately $200 million. Finally, implementing provider-initiated, opt-out testing with an AHI test protocol and enhanced linkage-to-care would save yet another 220,000 life years at an incremental cost of $1.4 billion. These figures must be interpreted with a great deal of caution, particularly given that the costs and effects of enhanced linkage-to-care are not based

[***] In this context, the population lifetime is defined as by CEPAC: from the time of initial implementation of the policy until the death of the final member of this group.

on empirical data (see Subsection 2.2.5), but they nevertheless provide useful approximations.

These costs are substantial but are not necessarily unrealistic levels of expenditure for South Africa. Based on the year-specific CEPAC output for the scenarios presented in Table 7.3, the annual cost of the most expensive of these three cost effective policies over the first 10 years of implementation would amount to approximately 1.6% of South Africa's annual gross domestic product (GDP), as estimated by the World Bank in 2006.[102] This amount is comparable to an estimate of the size of GDP necessary for comprehensive ART provision by Nattrass.[50] While outside the scope of this discussion, see Nattrass also for a discussion of different plausible means by which South Africa may fund such comprehensive HIV policies, including increasing taxes, cutting expenditures such as defence spending, and seeking foreign aid.

HIV testing cascade throughput

The results of this study mirror those of Walensky et al.[152] insofar as it was determined that the approach taken to linkage-to-care is the most important in affecting the cost-effectiveness of an expanded testing policy. These results also mirror those of a South Africa-based study which found antenatal screening policies adopting enhanced linkage-to-care to be most cost-effective.[239] Even in the scenario unfavourable to enhanced linkage-to-care, the standard linkage-to-care policies all remained extended dominated. These results highlight the importance of accounting for throughput losses in evaluating screening programs. Clearly, the extent to which tested patients actually receive treatments improving final health outcomes such as LYG has an important impact on the cost-effectiveness of screening policies.

Baseline and background testing

As discussed in Subsections 7.3.1-7.3.2, neither background nor baseline testing had much impact on the results of this CEA. While sufficiently large increases in baseline testing could significantly diminish the incremental health gain achievable by expanded testing, it is currently so low so as to be of little consequence to the projected effects of provider-initiated testing. Such careful treatment of the quantification of current testing practice as done in this thesis is probably unnecessary for future evaluations unless current testing rates are larger relative to those under the policies being evaluated.

7.3.4 Study limitations

Linkage-to-care scenario

This study has several limitations, the foremost being the reliance on assumptions rather than empirical data to quantify the effects of enhanced linkage-to-care. Given that the parameters describing these effects were found to have such a substantial impact on the cost-effectiveness of expanded HIV testing, having empirical data to inform them would have been helpful. Given the lack of such data, the precise estimates of the costs and effects of these policies may be inaccurate. However, it is nevertheless clear that the general cost-effectiveness patterns remain the same even under a scenario highly unfavourable to enhanced linkage-to-care: those policies allocating additional resources to identifying and contacting post-test counselled HIV-infected persons not receiving referrals or referred HIV-infected persons not receiving treatment were always more cost-effective than those adopting a standard linkage-to-care approach; opt-out policies yielded a small additional health benefit at a small

additional cost compared to opt-in policies; and policies using AHI test protocols yielded a small additional health benefit at a significantly greater cost.

The research question

The research question addressed by this thesis resulted in its own limitations. The results from this chapter suggest that it may be important for future investigations to consider the cost-effectiveness of adjusting current testing practice only by enhancing linkage-to-care. This study did not do so as the central aim of this thesis was to examine the cost-effectiveness only of variations of provider-initiated policies (see Subsection 1.2.1). However, such analyses would serve two important functions.

First, it would indicate whether provider-initiated testing should be considered prior to to maximizing linkage-to-care for already-identified cases. Second, such analyses would make possible additional direct comparisons between policies identical except for initiation method, thus providing more insight into the effects of this policy decision on the cost-effectiveness of expanded testing. Based on the sensitivity analyses from this study, it seems reasonable to expect that making testing provider-initiated in this setting will substantially increase the costs and health benefits of any testing program but have little impact on the ratio between these costs and effects.

Data inputs

Many of the data sources used for this analysis were less than ideal. The population CD4 counts in particular represent largely incomplete data, capturing only the proportion of the HIV-infected population whose infections were diagnosed and subsequently received a CD4 count within six months of diagnosis (Table 5.5). Furthermore, while this study used the CEPAC model to derive more meaningful

health gains (LYGs) from the throughput projections reported in Chapter 6, the lack of quality-of-life data precludes incorporation of the effects of HIV-related morbidity on the cost-effectiveness estimates presented in this chapter. This latter shortcoming in particular highlights a potential pitfall of applying models originally built for use in industrialized countries to resource-poor settings: while secondary data could have been used to construct DALYs to describe HIV-related health states in South Africa, CEPAC is configured only for use of QALYs, the data for which was not available in this setting.

Also problematic given the findings of this thesis was my focus on examining data informing the CEPAC's testing parameters (see Sections 6.1 and 7.1). Ultimately, the model was far more sensitive to parameters unrelated to testing whose inputs I did not explore as extensively (see Appendix B). The costs of treatment and care especially may have warranted closer examination. For example, while estimating ART costs was not a central objective in this thesis, I used lower-bound estimates from secondary sources not specific to South Africa. Consequently, the cost-effectiveness estimates presented here may be skewed in favour of expanded testing.

The linkage-to-care statistics were the only data I collected and manipulated to which the results of this analysis were highly sensitive. As noted in Sections 5.1, 6.1, and 7.1, I converted the empirical observations of linkage-to-care into probabilities of referral and treatment for input into the models by counting only those clients receiving referral within six months of diagnosis as being referred and only those clients receiving treatment within six months of eligibility having initiated ART. These time frames were largely arbitrary judgements based on discussions with experts (personal communication, Dr. Rochelle Walensky). However, research could

be conducted to attempt to classify more closely the circumstances under which a patient can meaningfully be said to have passed through the HIV testing cascade and not represent a throughput loss.

Future economic evaluations of expanded HIV testing programs should perhaps attempt to focus less on those data informing the initial testing processes and more on those describing the subsequent treatment pathway. This chapter demonstrates that the cost-effectiveness of testing is more dependent on the probability of diagnosed HIV-infected persons receiving treatment and the costs of that treatment.

Model limitations

CEPAC is a complex program requiring substantial computing power. Moreover, the model is not yet capable of probabilistic sensitivity analysis (PSA). Consequently, for this analysis I was forced to rely on univariate and selected multivariate sensitivity analyses which probably failed to account comprehensively for the uncertainty in the cost-effectiveness estimates given the potential interactions between multiple variables. Compounding the problem of conducting extensive sensitivity analyses was CEPAC's requirement for enormous cohort sizes to reach statistical convergence. In this study, sample sizes of 100,000,000 were used but complete statistical convergence was still not reached (although stability up to three significant figures for absolute costs and benefits as measured in health months gained was achieved). Yet, these limitations are a necessary price for CEPAC's sophisticated disease progression model which accounts for patients' clinical histories, a uniquely powerful instrument specially suited for examining HIV disease progression (see Appendix A).

The lack of a component estimating transmission events prevented and incorporating the resulting health effects into CEPAC's cost-effectiveness estimates was another serious limitation to this study. The effects of HIV testing on risky behaviour[125] and effective treatment on infectiousness[315] are both important factors to consider in gauging the cost-effectiveness of any comprehensive response to HIV. Again, population transmission dynamics are a particularly important consideration for estimating the cost-effectiveness of testing policies including AHI test protocols given that individuals are especially infectious while acutely infected.[316] While recognizing the difficulties in modelling disease transmission, future work would benefit from attempting to capture the effects of expanded HIV testing on population transmission dynamics.

Chapter 8:
Summary and conclusions

This chapter presents the summary and conclusions for this thesis. It first recounts the research questions addressed by this thesis and the extent to which they have been answered. It then discusses the implications of these findings for HIV testing policy in South Africa. Finally, it concludes with a discussion of what I believe to be the priorities for future economic and epidemiological evaluations of HIV testing.

8.1 Summary

8.1.1 Current testing practice

The first research question of this thesis sought to determine the current rates of HIV testing and linkage-to-care among South Africa's adult African population in the absence of expanded screening policies. Answering this question required conducting a population-level analysis. The only precedent in the African HIV testing literature for a study analogous to that conducted in this thesis was an analysis of national-level testing data from Botswana. Since the data used in the Botswana study were not patient-specific, the investigators were unable to identify repeat tests by single individuals or exclude testing by individuals already diagnosed with HIV.[277]

I attempted to avoid these limitations in my own work by focusing on a small study community with a well-defined and enclosed population. Adopting a retrospective descriptive epidemiological study, I measured the rates of testing and linkage-to-care during 2001-2006 in this community. To this end, I accessed the testing registers and

medical records of HIV-infected persons at two facilities believed to offer virtually all HIV testing and treatment services for the study community. While required to use assumptions to control for issues of recall bias, self-selection bias, and generalizability, this approach permitted the estimation of population uptake of HIV testing and treatment under current screening practices.

Annual test offer rates among the adult African population living in the study community have risen dramatically in recent years from approximately 4.4% in 2001 to 24.1% in 2006. Most of these tests, particularly in later years, were offered through voluntary counselling and testing (VCT) services (baseline testing) as opposed to tuberculosis (TB) or antenatal care (ANC) services (background testing). The majority of tests were accepted and annual probabilities of post-test counselling were high. The two principal gaps in linkage-to-care, referral for CD4 counts and receipt of ART, both closed markedly during the study period as the availability of these services expanded.

However, despite rising rates of testing, the proportion of these tests resulting in positive diagnoses remained high. Moreover, population clinical indicators of HIV disease progression (e.g., WHO clinical stage distribution, median CD4) remained unchanged. Consequently, it is clear that there is an urgent need for testing to be expanded further to achieve more comprehensive case detection and identification of HIV-positive persons earlier in the course of their infection.

8.1.2 Projecting testing throughput for expanded screening policies

This thesis's second research question asked how effective the eight expanded testing policies would be in increasing rates of testing and linkage-to-care in South Africa. It

was impractical to implement and observe the effects on these rates of all eight expanded testing policies examined in this thesis. However, it was possible to project these effects by manipulating the empirical testing data gathered from the study community and using secondary data sources.

Several interesting issues arose in making these projections. First, it became necessary to define explicitly what constitutes passage through various steps of the HIV testing process. For the earlier steps occurring near-instantaneously in the course of a single visit (e.g., test offer, offer acceptance) this process was straightforward. However, for later steps where throughput losses depend in large part on the observation period (e.g., referral, treatment) these definitions were less obvious and had important ramifications for study results. Ultimately, the pragmatic requirement for data compatible for use as model parameter definitions guided these decisions. A second issue related to the need to differentiate between current primary healthcare user testing likely to decrease following expansion of testing among this group (background testing) versus that unrelated to primary care settings expected to remain constant (baseline testing). It was possible to distinguish from the empirical testing data as each test observation was classified by the service through which it was delivered (e.g., ANC, TB, VCT).

The projections indicated that the decision to make testing provider-initiated is the single most effective measure for increasing testing client throughput. The projections of these increases for primary healthcare users made in this thesis were not based directly on empirical data collected on testing among the general population. Nevertheless, testing rates among pregnant women and the general population were nearly identical before antenatal testing became provider-initiated; afterwards,

pregnant women tested at substantially higher rates. Even using broad sensitivity analyses, it remained clear that provider-initiated testing was likely to have the greatest impact on total throughput for the HIV testing cascade.

The second greatest impact on overall throughput came from implementing an enhanced linkage-to-care program, although the magnitude of this impact was entirely assumed. Making testing opt-out versus opt-in had little effect on throughput, likely due to the already-high acceptance probabilities observed in the study community. Finally, the additional throughput resulting from an acute HIV infection (AHI) test protocol versus rapid-only protocol was almost negligible in comparison to that achieved by the other policy decisions. The projections also demonstrated that testing throughput for current testing practice is sufficiently low so as to have a minimal impact on the incremental throughput achieved by expanded testing policies.

8.1.3 Cost-effectiveness of expanded HIV testing

The final research question addressed by this thesis explored the cost-effectiveness of the eight expanded testing policies examined. The use of population-level testing data made it possible to estimate the cost-effectiveness of these policies per member of the adult African population. This was a unique approach as I identified only one previous HIV testing program evaluation which conducted a population-level analysis with population uptake based on empirical data from the USA.[179] Moreover, use of the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) simulation model made it possible to translate the testing throughput projections made in Chapter 6 for the alternative testing policies into the true outcome of interest for HIV testing programs: lifespan increases achieved by linkage to treatment. Only one study identified in the literature review similarly evaluated a testing program in a high-

prevalence setting using a final outcome such as LYG. However, that Tanzania-based study assumed very low treatment availability and client-initiated rather than more aggressive case detection as examined in this thesis.[233] I also used the AHI Testing (AHIT) decision tree model which I constructed to facilitate the conversion of data describing tests serving as part of AHI test protocols into CEPAC parameter inputs.

Provider-initiated, opt-in testing with a rapid-only test protocol and enhanced linkage-to-care (IRE) was the least expensive cost-effective option, under most scenarios yielding life years gained (LYGs) at an approximate cost of US$850 each. The next least expensive option was the same policy except for use of an opt-out consent method (ORE), usually yielding slight incremental health gains at a cost of approximately US$2,000/LYG. Finally, provider-initiated, opt-out testing with an AHI test protocol and enhanced linkage-to-care (OAE) was always the most expensive cost-effective scenario, costing approximately US$6,500/LYG. Baseline and background testing rates were sufficiently low and the ranges for these values sufficiently narrow such that they had little impact on these results.

Those policies including an enhanced linkage-to-care component were overwhelmingly more cost-effective than those policies adopting a standard approach to linkage-to-care. These results must be interpreted with caution given that the costs and effects for enhanced linkage-to-care were based on assumptions rather than empirical data. Nevertheless, the enhanced linkage-to-care policies remained most cost-effective even when substantially varying model parameter inputs so as to make enhanced linkage-to-care less favourable. This result mirrors that found by the USA-based study by Walensky et al. using the CEPAC model in low-prevalence settings in the USA.[152]

The decision to make testing opt-in versus opt-out appeared to have little impact on overall costs and effects but an adverse impact on cost-effectiveness, with opt-out testing yielding slightly more LYGs, each of which at a notably greater cost than incurred for opt-in testing. Choosing an AHI test protocol as opposed to a rapid-only protocol appears the most controversial decision from an economic perspective, yielding few additional LYG at a significant cost. Because all of the expanded testing policies examined were provider-initiated, it was not possible to determine definitively the comparative impact on cost-effectiveness of making testing provider- versus client-initiated. Nevertheless, sensitivity analyses adjusting rates of test offers suggest that the transition from client-initiated to provider-initiated testing would probably increase total costs and health benefits, but not the ratio between the two.

Finally, the CEA results reported in Chapter 7 suggest that the careful descriptions of current testing practice were likely unnecessary. Provider-initiated testing policies are likely to achieve such great gains in testing throughput compared to client-initiated testing such that any changes in baseline and background testing rates have little impact on either the effects or costs of these expanded testing policies. This suggests that future investigators should not spend so much time on quantifying current testing practice unless the testing intervention under evaluation is projected to result in only small additional testing uptake.

8.2 Implications for HIV testing policy and research

8.2.1 Linkage-to-care

The clear importance of prioritizing resource allocation for linkage-to-care observed in this thesis highlights the value of the HIV testing cascade framework. By

conceiving HIV testing as a series of steps through which patients must pass and for which various policies can focus on increasing throughput, it was possible to maintain focus on the ultimate end goal: achieving health gains through linkage-to-care. Although the effectiveness of enhanced linkage-to-care was assumed, the broad sensitivity analyses in this thesis clearly demonstrate the importance of maximizing throughput for the linkage-to-care steps of the HIV testing cascade to optimize the cost-effectiveness of screening.

This is an important result given that the most prominent recent expanded testing guidelines have paid little attention to linkage-to-care methods. The Centers for Disease Control and Prevention's (CDC) 2006 guidelines supporting provider-initiated, opt-out testing in all healthcare settings devoted only a single paragraph to linkage-to-care. This paragraph mentioned the importance of linkage-to-care, but offered no specific strategies for achieving it.[10]

The World Health Organization (WHO) guidelines recommending provider-initiated, opt-out testing address this issue somewhat more comprehensively. These guidelines offer specific recommendations such as the need to establish local referral centres to prevent throughput losses attributable to patients' inability to incur extensive travel costs. They also advise healthcare providers to give patients thorough information about referral services and to increase the likelihood of referral appointments being kept by making them in the presence of patients. However, the WHO recommendations cite no research to support these linkage-to-care strategies, so implying they are based on common sense rather than any evidence base.[11]

The lack of such evidence is highlighted by the need in this thesis and other studies[152,164] to generate a hypothetical scenario to describe an alternative approach to linkage-to-care. Different approaches to the other components of a testing program (initiation method, consent method, etc.) can be conveniently fit into pre-defined and often extensively-researched discrete categories and thereby easily compared to one another. However, to my knowledge no such categories for linkage-to-care methods have yet been defined or studied. The future development of testing policy would therefore benefit from investigations defining and comparing policies according to their use of measures such as those proposed by the WHO for increasing the probability of referral and treatment (see Subsection 4.3.1).

The importance of linkage-to-care for a screening program is certainly not a new revelation. Indeed, this was noted as early as 1968 when Wilson and Junger highlighted the necessity of effective linkage-to-care mechanisms in their report for the WHO on the criteria for any screening program.[317] Again, as stated throughout this thesis, the outcome of interest for any screening program should ultimately be the health gains achieved due to linkage-to-care for identified cases. However, in the field of HIV testing, the focus on this outcome appears to have fallen by the wayside as more aggressive approaches to case detection have been proposed. This is evidenced by the large number of evaluations identified in this thesis which focused on intermediate outcomes (e.g., cases identified, see Subsection 4.2.2). Focus on the final health consequences for seropositive clients needs to be renewed as increasing numbers of HIV-infected persons are identified.

8.2.2 Provider-initiated testing

While linkage-to-care method probably has the greatest impact on the ratio of costs to health benefits for HIV testing programs, the decision to make test offers provider-initiated probably leads to the greatest increases in these costs and benefits from a population-level perspective. However, it is important to acknowledge that South Africa, along with many high-prevalence countries particularly in sub-Saharan Africa, may not have sufficient healthcare resources to cope with the increased caseload resulting from nation-wide implementation of provider-initiated testing. The healthcare setting examined in this thesis expanded the proportions of clients referred and linked to treatment even as the number of cases identified each year rose. However, as noted earlier, this setting is unique in its healthcare infrastructure and likely not representative of the broader South Africa.

The WHO HIV testing guidelines in particular warn of the need to consider the capacity to 'absorb' increased caseload upon implementing expanded HIV testing. This capacity depends not only on healthcare infrastructure but also on the availability of trained healthcare personnel and resources for drugs and other medical supplies.[11] Decision-makers considering provider-initiated testing in high-prevalence jurisdictions will need to consider these issues carefully prior to implementation.

Future HIV testing policy development would benefit from continued research on alternative initiation methods. One such method which has increasingly gained more attention in recent years for use in sub-Saharan Africa is home-based or mobile testing,[318] the aim of which is to increase client throughput for Step 1 of the HIV testing cascade (accessing testing venues). While the study in this thesis failed to capture client throughput for this initial step of the testing cascade, its measurements

of test offer rates together with secondary data sources suggest that client access to testing venues is sufficiently high such that substantial increases in testing rates could be achieved simply by routinely testing all individuals accessing healthcare facilities. However, in populations with lower rates of healthcare usage (e.g., rural populations) mobile HIV testing could be an effective albeit probably expensive means of achieving comparable increases in testing uptake.

Future studies should also explore the potential impact of initiation method on throughput for HIV testing cascade steps other than receipt of test offer. Indeed, research examining the validity of any of the assumptions outlined in Section 2.3 regarding whether the various policy components solely impact throughput for specific HIV testing cascade steps would be helpful. However, I believe such research to be of particular importance for initiation method given that making test offer provider-initiated is likely to achieve the greatest magnitude in increased testing uptake and throughput of any possible policy decision. Of particular concern for investigators should be determining whether sizeable proportions of new clients brought into the testing process by provider-initiated testing would lack the inclination to pass through the remaining steps of the HIV testing cascade.

8.2.3 Opt-out versus opt-in testing

This thesis has suggested that the decision to implement opt-out versus opt-in testing is of little consequence to either the cost-effectiveness or the magnitude of the total HIV-related costs and benefits achieved for HIV testing programs. This is an important finding given that the choice of consent method has emerged in recent years as the most controversial of any of the components of a testing program. Some believe that requiring patients to opt-out of testing may compromise their autonomy[73]

while others claim that opt-out testing could normalize the testing process by treating it like other routine medical procedures.[62] Addressing this controversy will likely require sociological and philosophical inquiry, but to the extent that opt-out testing fails to make a substantial improvement in client testing throughput, it may be preferable to err on the side of caution and implement opt-in testing.

That said, this conclusion is predicated on data in a community in which test offer acceptance rates were very high. This conclusion is also based on the assumption that making testing provider-initiated will not decrease acceptance probabilities (see Subsection 8.2.2). Setting- and policy-specific measurements of acceptance probabilities will thus provide decision-makers with useful information in determining the ideal consent method to adopt.

8.2.4 AHI testing

In spite of a staggeringly high incidence rate, this thesis found AHI testing to be an expensive investment of HIV testing resources. Based on these results, it is not at all clear that AHI screening should become standard practice for adult African primary healthcare users in South Africa. However, it bears reemphasizing that this thesis did not consider benefits due to preventing further transmission of HIV infection by acutely infected patients. Future economic evaluations of AHI screening will need to account for these important benefits. Ideally, such analyses would capture not only the immediate or secondary transmission events prevented as a result of identifying singular AHI patients, but also the overall impact of such prevention on population transmission dynamics.

8.2.5 Modelling approaches

I conducted my analysis using the previously-published CEPAC simulation model. This model afforded me a highly sophisticated simulation of HIV disease progression, detection, and treatment (see Appendix A). By avoiding the need to 'reinvent the wheel,' I was able to focus attention on data collection and methodological issues (e.g., conducting a population-level analysis).

However, in choosing to conduct the economic evaluation in this thesis using the CEPAC simulation, I subjected my work to that model's limitations. As noted in Subsection 7.3.4, these included an inability to conduct PSA or account for transmission dynamics. In light of the clear importance of the treatment pathway to the cost-effectiveness of HIV screening, I am also concerned about the model's inability to simulate patients initially linked to care subsequently failing to adhere to treatment, whether due to issues of finances, motivation, or social circumstances.

While work is already underway to incorporate many of these features into CEPAC, with each addition comes added complexity and computing requirements. While computer power will inevitably improve, the pace of new developments in the field of HIV and CEPAC architects' innovation may well outstrip these improvements, resulting in a model with impossibly long runtimes and unwieldy code. Consequently, my research has led to me to believe that for models onto which new modules will be added to reflect new research, developments, and complexities, it may be wise to consider simpler model frameworks than microsimulation (e.g., Markov models, see Subsection 3.1.6). Such models are probably better suited for

facilitating both PSA and modelling secondary transmission.* At the same time, models should attempt to continue exploring the impact of new parameters defining the treatment pathway on the cost-effectiveness of HIV testing. In the spirit of collaborative research as conducted in this thesis, future investigators may wish to consider adding testing modules to previously-published Markov models used to examine treatment only.

8.2.6 HIV testing policy implementation in South Africa

In Subsection 4.3.3, I justified my definition of the eight expanded testing policies examined in this thesis as an attempt to generate actionable results indicating the comparative cost-effectiveness of policies which could be plausibly implemented in South Africa. My decision to conduct a population-level analysis was similarly based on the desire to provide decision-makers with data indicating the costs and effects of alternative testing policies for all members of their jurisdictions.

However, there are several important reasons why these results may in fact not be plausible for implementation in South Africa. One important reason lies in the results indicating the need to implement enhanced linkage-to-care programs whose effectiveness and costs were entirely assumed. Consequently, insofar as enhanced linkage-to-care is concerned, the results of this thesis should rather be considered an indication of the importance for conducting further research on alternative linkage-to-care methods (see Subsection 8.2.1). To be of use for future economic evaluations, such research would need to define linkage-to-care strategies; quantify the impact of

* An important caveat here is that although Markov models can provide simple static depictions of disease transmission, microsimulations are again needed for more sophisticated depictions of transmission which account for population transmission dynamics (see Subsection 3.1.6).

these strategies on rates of referral (Step 5), treatment (Step 6), and adherence (not examined in this thesis); and measure the costs of implementing these policies.

Although the estimated effects on throughput and costs for the other policy components examined in this thesis were based on more robust data, the policy options explored for these components are similarly of questionable feasibility. Again, the implementation of any expanded testing program in South Africa will raise questions of the country's capacity to absorb the additional caseload, an issue not addressed in this thesis (see Subsection 8.2.2). Moreover, the HIV testing literature has documented many barriers associated with HIV testing alone,[32] even without considering linkage-to-care. While it is outside the scope of this discussion to go into greater detail, these barriers can vary substantially across different settings, ranging from societal stigma discouraging testing among patients to lack of awareness among providers regarding the need to encourage patients to test. Each of these barriers may require its own tailored, setting-specific policy for circumvention.

8.3 Concluding comments

This thesis used data collected on rates and outcomes of testing in a small African community in South Africa together with models and secondary data to project the effectiveness and cost-effectiveness of alternative provider-initiated testing policies. By conducting a population-level analysis, it was possible to use these projections to estimate the costs and benefits of expanded testing for each member of the target population rather than solely for those individuals availing themselves of the testing program. The population-level analysis also permitted the measurement of current rates of testing and linkage-to-care. Finally, a modelling approach was adopted to

translate these measurements of client throughput into expected health gains for seropositive clients linked to treatment together with the associated costs of testing and treatment.

This thesis has determined that recent increases in testing and linkage-to-care rates have failed to keep pace with the epidemic and identify clients earlier in the course of infection. To the extent that each of these policies can be feasibly implemented in South Africa, this thesis has argued that maximizing testing resource allocation into linkage-to-care efforts will optimize the cost-effectiveness of testing programs. It has also argued that making testing provider-initiated will most effectively expand the coverage of treatment and care for the HIV-positive population in South Africa. This final chapter has highlighted the need for additional research and setting-specific appraisals prior to implementing either of these main recommendations. Nevertheless, I believe the results of this thesis have proven sufficiently robust under sensitivity analyses to serve as a useful starting point from which to craft future research and decision-making in response to the HIV epidemic in South Africa.

Appendix A:
Technical overview of the CEPAC model

This appendix provides a technical overview of the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) simulation model (see Subsection 4.2.2 for further discussion of the reasons I chose this model for use in my thesis). This discussion was placed in an appendix so as to differentiate clearly my own work, as presented in the body of this thesis, from that of the CEPAC collaborators.[*] I made no contribution to the original computer code comprising CEPAC nor did I assist in making any revisions or additions to this code. Rather, the original contribution of this thesis includes an application of this model to a new research question: estimating the cost-effectiveness of expanding human immunodeficiency virus (HIV) testing in South Africa.

CEPAC is a computer-based, Monte-Carlo, state-transition, simulation model designed to estimate the cost-effectiveness of various HIV-related interventions. "Monte Carlo" refers to the model's use of a random number generator together with user-defined probabilities and distributions to determine the pathways of disease infection, progression, detection, and treatment for individual patients one at a time. The aggregated costs incurred and benefits realized by these patients as a result of HIV-related interventions comprise the final or summarized output in the form of a cost-effectiveness ratio. "State-transition" refers to the model's characterization of the natural history of disease as a sequence of transitions between model-defined

[*] Walensky et al.[319] provides a listing of the names and affiliations of the current CEPAC collaborators.

health states.[82] In CEPAC, these transitions occur over one-month cycles. (See Subsection 3.1.6 for further discussion of these modelling terms.)

This thesis uses CEPAC version 30d (program match 201020378), which was completed on 25 May 2006. This version includes a component which permits modelling of the HIV testing process. For ease of reference, this Appendix will refer to this component as the 'screening model.' The facets of the model depicting treatment efficacy and natural disease progression will be referred to as the 'disease model.' A further discussion of the mechanics for each of these two models will be provided next. The reader is also directed to the technical appendix written by Paltiel et al. from whence this discussion of the CEPAC disease and screening models is largely drawn.[153]

Disease model

The CEPAC disease model generates hypothetical HIV-positive patients. It follows each of these patients until death with a running tally maintained of all HIV-related clinical events and associated costs. Upon a patient's death, summary statistics are recorded and a new patient generated. After simulating a number of patients defined by the user, the model's outputs include averages for cost, life years lived, and quality-adjusted life years (QALYs) lived per patient. These outputs are dependent upon CEPAC's seven distinct sets of parameters: (i) cohort characteristics, (ii) care costs, (iii) quality of life, (iv) HIV natural history, (v) treatment policies, (vi) antiretroviral treatment (ART) efficacy, and (vii) opportunistic infection (OI) prophylaxes efficacies. The model's many parameters mean that substantial data are required for each simulation but also that users have the flexibility to define a wide

range of scenarios, making it possible to evaluate HIV-related interventions for high- or low-prevalence populations and in high- or low-income settings.

Each hypothetical patient is assigned characteristics and an initial health state defined by the cohort characteristics parameters. The model comprises three general categories of health states for HIV-positive patients: (i) chronic-asymptomatic, (ii) chronic-symptomatic, and (iii) death. Within the two chronic categories are a series of health states stratified by seven ranges of viral load, or VL (0-20, 21-500, 501-3,000, 3,001-10,000, 10,001-30,000, 30,001-100,000, and >100,000 copies/mL), and six ranges of CD4 count (0-50, 51-100, 101-200, 201-300, 301-500, and >500 cells/mm^3).

The model runs in monthly cycles, during each of which patients exist in one of these health states. HIV-positive patients are usually in a chronic-asymptomatic state in which disease progression (CD4 decline) occurs. Chronic-symptomatic states represent complications of chronic infection such as OIs or acquired immune deficiency syndrome (AIDS) and become more likely as clients enter lower CD4 states. Death is the state to which all patients inevitably transition, although this may be triggered by a number of events including an acute OI, chronic HIV infection (e.g. wasting), or non-HIV-related causes (as defined by life table data entered in natural history parameters). These health states portray patients' resource use patterns at various stages of illness through the cost of care parameters and patient's health through the quality of life parameters.

Each patient's health is also modelled through each state's unique set of probabilities determining the likelihoods that patients will transition to other states during each

month-long cycle. In the absence of interventions, these probabilities are defined by the natural history parameters according to the following relationships: VL determines the rate of CD4 decline and CD4 count affects the probability of experiencing OIs or death. Past clinical events can also affect transition probabilities: a history of OIs increases the probability of death or OI occurrence.[†] Transition probabilities may be adjusted depending upon treatment provision (defined by the treatment policy parameters) and efficacy (defined by the parameters regarding the efficacies of ART and OI prophylaxes).

Screening model

A screening model has recently been added to CEPAC.[153] This model simulates the HIV testing process using inputs for an eighth set of parameters encompassing population-level epidemic descriptors, and descriptors related to testing including costs, frequency, sensitivity/specificity, and likelihood of subsequent linkage-to-care. Specifically, testing is simulated by assigning each newly-generated patient four HIV-related event times based upon time-to-event probability distributions: (i) time of HIV infection, t_i (ii) time of next HIV test performed within the context of a screening policy to be evaluated, t_p (iii) time of next HIV test performed within the context of any other background screening mechanism unrelated to the evaluated screening policy, t_b and (iv) time of non-AIDS related death, t_d.

Since patients may be uninfected at start ($t_i>0$) and either remain so until death ($t_i>t_d$), the screening model also defines a HIV-negative health state. Furthermore, since infection may occur during the simulation ($t_i<t_d$), an acute HIV infection (AHI) health

[†] This ability to account for each patient's clinical history is a unique feature made possible by avoiding the Markovian assumption (see Subsection 3.1.6).

state category is also defined by the screening model. As with the chronic health states, patient distributions into the HIV-negative and AHI health states are determined by user-defined distributions. All patients in the screening model are assumed to be undiagnosed, so these distributions in fact describe *undiagnosed* prevalence.

The screening model also includes parameters defining state transition probabilities specific to these two additional states. The transition probability between the HIV-negative and the AHI state (incidence) is defined by these parameters. Once patients enter an AHI state, a screening model parameter defines how many month-long cycles they will remain in that state before transferring to one of the chronic HIV-infected states. Upon entry into a chronic HIV-positive health state, patients are linked to the disease model.

While such patients linked to the disease model experience disease progression, they are ineligible for treatment within the disease model until their infection is detected, as indicated by the screening model. Detection may occur through one of three mechanisms. As mentioned throughout this thesis, patients may receive testing through the HIV testing policy whose cost-effectiveness is being evaluated or through unrelated program tests, referred to as "background screening" (see Section 2.2). Undiagnosed HIV-positive individuals also receive testing if they experience a clinical complication of chronic infection (e.g., a severe acute OI), so becoming symptomatic and compelled to access a healthcare facility.

Appendix B:
Summary of CEPAC inputs for parameters unrelated to testing or linkage-to-care

This thesis focuses on the data sources and implications of uncertainty in those sources for the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model's HIV testing and linkage-to-care parameters. However, as outlined in Appendix A, the majority of CEPAC parameters are unrelated to the human immunodeficiency virus (HIV) testing process. The inputs for these parameters have been drawn from the work of the CEPAC collaborators.

A brief discussion of the data sources used for all parameters unrelated to HIV testing is provided in this appendix. This discussion is organized according to the seven major categories of non-testing parameters defined within the disease model, as outlined in Appendix A. However, there are a handful of parameters in these seven categories which in fact model facets of the HIV testing process as conceived in this thesis (e.g., parameters for linkage-to-care). For the sake of consistency for readers familiar with CEPAC, mention is made throughout of parameters belonging to these seven categories which were believed to be relevant to the analysis in this thesis and so discussed in Chapter 7 instead of this appendix. The main discussion in this appendix is followed by a table summarizing CEPAC's non-testing parameters, the input values used for these parameters, and the data sources for these inputs (Table B.1). The reader is also referred to Appendix A for further details on the role CEPAC's non-testing parameters play in the overall model structure.

Cohort characteristics

Inputs for several of the cohort characteristics parameters were taken from the empirical data collection reported in Chapter 5. Specifically, these include the age and sex distribution of the target population and the rates of linkage-to-care for diagnosed HIV-infected individuals (see Sections 6.1 and 7.1). Regarding treatment adherence, the simplifying assumption is made that all cohort members exhibit perfect compliance to both OI prophylaxis and ART.

Natural history

Where possible, natural history data were taken from South African data sources, most notably the Cape Town AIDS Cohort (CTAC). CTAC is comprised predominantly of Africans referred for treatment and care from various primary healthcare facilities throughout Cape Town to the HIV clinics at Groote Schuur and New Somerset hospitals since 1984. CTAC results for the time period preceding ART availability inform the parameters for health state-specific monthly probabilities of experiencing OIs[26] and dying from chronic acquired immune deficiency syndrome (AIDS) and OIs.[141] Also, World Health Organization (WHO) life tables for South Africa were used for estimates of age-specific monthly mortality rates excluding deaths due to HIV and war.[320]

Inputs for other natural history parameters were taken from other settings given the lack of data specific to South Africa. Such alternative sources were preferentially drawn from sub-Saharan African studies: data describing the efficacy of ART in preventing chronic AIDS deaths and OI occurrence were taken from a Côte d'Ivoire-based study.[140] However, the lack of alternative sub-Saharan African data sources for CD4 decline necessitated use of the Multi-centre AIDS Cohort Study (MACS),

comprised of approximately 1,600 HIV-positive asymptomatic homosexual men in the United States of America (USA) initially recruited in 1984-1985.[142]

Costs of care

Cost data for HIV-related care were principally drawn from resource utilization reports previously used as parts of cost-effectiveness analyses (CEAs) of ART in South Africa.[56,57] Costs of routine HIV-related care, OI treatments, and death were all taken from these reports. Finally, costs of monitoring tests for HIV-positive patients (e.g., CD4 counts) were solicited from the director of the Desmond Tutu HIV Foundation (DTHF), the non-governmental organization (NGO) responsible for delivering HIV-related care to the study community examined in Chapter 5 (personal communication, Professor Robin Wood to Dr. Ken Freedberg). I ensured that all of these costs were converted to 2006 USA dollars using the methods presented in Subsection 7.1.2.

OI prophylaxes

Since cotrimoxazole is the only OI prophylaxis consistently recommended for use alongside ART in sub-Saharan Africa,[282] it was the only OI prophylaxis considered in this thesis. Data describing cotrimoxazole's efficacy were taken from studies based out of Côte d'Ivoire[321] and the United States.[322] All data describing cotrimoxazole's toxicity were drawn from Côte d'Ivoire-based studies.[321,323] The price of cotrimoxazole listed in the Hospitals Pharmaceutical Codelist for South Africa's Gauteng province was used for the cost of cotrimoxazole after conversion into 2006 USA dollars (see Chapter 7 for methods of conversion). Finally, it was assumed that for no clients would the efficacy of cotrimoxazole decrease over time (signalling

development of a drug-resistant OI) and that toxicities could occur as early as one month after prophylaxis initiation.

ART regimens

This thesis assumes availability of two lines of ART for citizens of South Africa. Choice of the regimens was based on both WHO guidelines and the recommendations of the DTHF director (personal communication, Professor Robin Wood to Dr. Rochelle Walensky). First-line treatment is defined as a non-nucleoside reverse transcriptase inhibitor (nevirapine) and two nucleoside/nucleotide reverse transcriptase inhibitors (lamivudine and zidovudine). Second-line treatment is defined as a protease inhibitor (lopinavir/ritonavir) and two nucleoside/nucleotide reverse transcriptase inhibitors (tenofovir disoproxil fumarate and emtrictabine). Efficacy and probability of failure for the first-line treatment was taken from a South African study[324] and review of ART trials throughout sub-Saharan Africa[325] while those for second-line treatment were based on a United Kingdom (UK) study.[326] For the purposes of using these data with CEPAC, the assumption was made that 80% of CD4 recovery attributable to ART occurs in the first two months of treatment with the remaining 20% occurs in the following four months.

All other ART data were taken from identical sources for both regimens. Costs of drugs accounting for recent price reductions were taken from a 2006 Medicins Sans Frontieres (MSF) report on ART prices; the lowest negotiated international prices were always used.[327] The probabilities of toxicity-related events due to ART were taken from a Côte d'Ivoire-based study[328] and the costs of treating such events were taken from the Gauteng Hospitals Pharmaceutical Codelist. When necessary, all of these costs were converted to 2006 USA dollars (see Chapter 7 for methodology). It

was assumed that patients would only suffer acute (no chronic) toxicity, that no patients would die of toxicity, and that toxicity could occur as early as three months after initiating ART. Finally, it was assumed that no patients would experience only partial suppression.

Treatment policies

Treatment policies within the model were based on guidance from the health departments of the city of Cape Town,[329] the Western Cape province,[330] South Africa,[331] and the WHO.[283] Specifically, ART was to be initiated for diagnosed HIV-positive patients when they received a CD4 count <200 cells/mm^3 or were afflicted with a severe fungal infection, toxoplasmosis, mycobacterium avium complex (MAC), pneumocystis pneumonia (PCP), or another OI classified by CEPAC as "severe." While patients were on first-line ART and any of these OIs occurred, CD4 dropped by >30%, or a major toxicity event was experienced, they were switched to second-line ART. Second-line ART was only stopped if CD4 dropped by >30% or they suffered a major toxicity event. Cotrimoxazole was initiated if CD4<200 or the patient was afflicted with a bacterial or fungal infection, tuberculosis (TB), toxoplasmosis, MAC, or PCP. Cotrimoxazole was stopped only if a major toxicity event was experienced.

The expert opinion of the DTHF director was used to inform all other simplifying assumptions related to treatment (personal communication, Professor Robin Wood to Dr. Rochelle Walensky). These included a scheduled clinic visit frequency of six months for all HIV-positive clients. During each of these visits, it was assumed that clients receive CD4 and VL monitoring tests and that these tests never experienced

errors. Finally, it was also assumed that all past OIs were acknowledged by medical personnel in deciding whether to start treatment for HIV-positive patients.

Miscellaneous

Two assumptions were made to inform miscellaneous parameters unaffiliated with the aforementioned seven major non-testing categories. First, it was assumed that no cost was incurred for undetected HIV infections beyond those resulting from OIs, as discussed above. Second, it was assumed that there was no change in CD4 which occurred as a result of the transition from acute to chronic infection.

Table B.1. Inputs for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Cohort Characteristics		
Probability of OI prophylaxis non-compliance	0	Assumption
Natural History		
Monthly chronic AIDS death probabilities, baseline - no ART (%)		CTAC: Badri et al.;[141] adjusted for input into CEPAC by B. Wang on 9 Jun 2006
No OI history		
CD4, very high	0.000946	
CD4, high	0.001604	
CD4, medium high	0.004107	
CD4, medium low	0.012697	
CD4, low	0.012697	
CD4, very low	0.033301	
Mild OI history		
CD4, very high	0.002950	
CD4, high	0.005492	
CD4, medium high	0.003838	
CD4, medium low	0.027630	
CD4, low	0.027630	
CD4, very low	0.079443	
Severe OI history		
CD4, very high	0.002950	
CD4, high	0.005492	
CD4, medium high	0.003838	
CD4, medium low	0.027630	
CD4, low	0.027630	
CD4, very low	0.079443	
Monthly chronic AIDS death probability multipliers, for clients on ART		Losina et al.;[140] adjusted for input into CEPAC by E. Losina on 22 Feb 2005
CD4, very high	0.040000	
CD4, high	0.040000	
CD4, medium high	0.040000	
CD4, medium low	0.090000	
CD4, low	0.090000	
CD4, very low	0.450000	
Monthly OI probabilities, by CD4 strata, baseline - no ART (%)		CTAC: Holmes et al.;[26] adjusted for input into CEPAC by B. Wang on 9 Jun 2006 and M. Fofana on 3 Jan 2007
Bacterial, minor		
CD4 VHI	0	
CD4 HI	0	
CD4 MHI	0	
CD4 MLO	0	
CD4 LO	0	
CD4 VLO	0	

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Monthly OI probabilities, by CD4 strata, baseline - no ART (%), cont'd:		
Bacterial, severe		CTAC: Holmes et al.;[26] adjusted for input into CEPAC by B. Wang on 9 Jun 2006 and M. Fofana on 3 Jan 2007
CD4, very high	0.000827	
CD4, high	0.000827	
CD4, medium high	0.001304	
CD4, medium low	0.002996	
CD4, low	0.002996	
CD4, very low	0.007050	
Fungal, minor		
CD4, very high	0.005945	
CD4, high	0.005945	
CD4, medium high	0.012791	
CD4, medium low	0.020464	
CD4, low	0.020464	
CD4, very low	0.035149	
Fungal, severe		
CD4, very high	0.000205	
CD4, high	0.000205	
CD4, medium high	0.001005	
CD4, medium low	0.004151	
CD4, low	0.004151	
CD4, very low	0.022172	
Tuberculosis		
CD4, very high	0.002082	
CD4, high	0.002082	
CD4, medium high	0.006746	
CD4, medium low	0.011376	
CD4, low	0.011376	
CD4, very low	0.019607	
Toxoplasmosis		
CD4, very high	0	
CD4, high	0	
CD4, medium high	0	
CD4, medium low	0.000224	
CD4, low	0.000224	
CD4, very low	0.000592	
Mycobacterium avian complex		
CD4, very high	0.000103	
CD4, high	0.000103	
CD4, medium high	0	
CD4, medium low	0.000334	
CD4, low	0.000334	
CD4, very low	0.002978	
Pneumocystis pneumonia		
CD4, very high	0.000102	
CD4, high	0.000102	
CD4, medium high	0	
CD4, medium low	0.000223	
CD4, low	0.000223	
CD4, very low	0.001195	

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Monthly OI probabilities, by CD4 strata, baseline - no ART (%), cont'd:		
Other, minor		CTAC: Holmes et al.;[26]
CD4, very high	0.025057	adjusted for input into CEPAC
CD4, high	0.025057	by B. Wang on 9 Jun 2006
CD4, medium high	0.031113	and M. Fofana on 3 Jan 2007
CD4, medium low	0.027004	
CD4, low	0.027004	
CD4, very low	0.030591	
Other, severe		
CD4, very high	0.002493	
CD4, high	0.002493	
CD4, medium high	0.002967	
CD4, medium low	0.006814	
CD4, low	0.006814	
CD4, very low	0.025737	
Monthly OI probability multipliers, for clients on ART		Losina et al.;[140] adjusted for input into CEPAC by E. Losina on 22 Feb 2005
Bacterial, minor	1.000000	
Bacterial, severe	0.680000	
Fungal, minor	1.000000	
Fungal, severe	0.680000	
Tuberculosis	1.000000	
Toxoplasmosis	0.680000	
Mycobacterium avian complex	0.680000	
Pneumocystis pneumonia	0.680000	
Other, minor	1.000000	
Other, severe	0.680000	
Monthly death from OI probabilities (%)		CTAC: Badri et al.;[141]
Bacterial, minor	0	adjusted for input into CEPAC
Bacterial, severe	0.028584	by B. Wang on 9 Jun 2006
Fungal, minor	0.013903	
Fungal, severe	0.042089	
Tuberculosis	0.017839	
Toxoplasmosis	0	
Mycobacterium avian complex	0.124535	
Pneumocystis pneumonia	0.133246	
Other, minor	0.003992	
Other, severe	0.080569	
Baseline monthly CD4 decline (mean, standard deviation)		Mellors et al.[142]
VL, very high	6.38, 5.06	
VL, high	6.38, 5.06	
VL, medium high	5.40, 4.33	
VL, medium	4.60, 3.76	
VL, medium low	3.73, 3.83	
VL, low	3.03, 2.72	
VL, very low	3.03, 2.72	

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Monthly non-AIDS death probabilities (%)		WHO;[320] adjusted by removing deaths attributable to AIDS or war (unpublished data), procured by S. Goldie
Males		
0	0.005192	
1-4	0.000360	
5-9	0.000127	
10-14	0.000089	
15-19	0.000162	
20-24	0.000241	
25-29	0.000264	
30-34	0.000315	
35-39	0.000411	
40-44	0.000568	
45-49	0.000810	
50-54	0.001175	
55-59	0.001752	
60-64	0.002537	
65-69	0.003732	
70-74	0.005670	
75-79	0.008550	
80-84	0.012900	
85-89	0.018837	
90-94	0.026616	
95-99	0.036388	
100+	0.048132	
Females		
0	0.004119	
1-4	0.000323	
5-9	0.000098	
10-14	0.000067	
15-19	0.000103	
20-24	0.000137	
25-29	0.000159	
30-34	0.000194	
35-39	0.000254	
40-44	0.000342	
45-49	0.000480	
50-54	0.000696	
55-59	0.001041	
60-64	0.001539	
65-69	0.002489	
70-74	0.004129	
75-79	0.006752	
80-84	0.010775	
85-89	0.016499	
90-94	0.024239	
95-99	0.034160	
100+	0.046182	

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Care Costs		
Acute OI event costs		Badri et al.,[57] Cleary et al.;[56] adjusted for input into CEPAC by Z. Lu on 28 Nov 2006 and M. Fofana on 17 May 2007; adjusted to 2006 USD by M. April on 1 Dec 2007
Bacterial, minor	0	
Bacterial, severe	987.55	
Fungal, minor	371.12	
Fungal, severe	740.48	
Tuberculosis	1046.90	
Toxoplasmosis	1661.91	
Mycobacterium avian complex	3462.16	
Pneumocystis pneumonia	11.14	
Other, minor	108.85	
Other, severe	558.12	
Monitoring test costs		Personal communication, R. Wood to K. Freedberg on 12 Jul 2005; adjusted to 2006 USD by M. April on 1 Dec 2007
CD4 tests	9.73	
HVL tests	48.63	
Death costs	469.52	Badri et al.,[57] adjusted for input into CEPAC by Z. Lu on 28 Nov 2006 and M. Fofana on 17 May 2007; adjusted to 2006 USD by M. April on 1 Dec 2007
Routine care costs		Badri et al.,[57] adjusted for input into CEPAC by Z. Lu on 28 Nov 2006 and M. Fofana on 17 May 2007; adjusted to 2006 USD by M. April on 1 Dec 2007
CD4, very high	18.13	
CD4, high	18.13	
CD4, medium high	18.13	
CD4, medium low	66.93	
CD4, low	66.93	
CD4, very low	124.09	
OI Prophylaxis		
Cotrimoxazole, probability of preventing OI (efficacy)		Yazdanpanah et al.,[321] Goldie et al.;[322] adjusted for input into CEPAC by M. Fofana on 18 Jan 2007
Bacterial, minor	0.4879060	
Bacterial, severe	0.4981480	
Fungal, minor	-0.4637300	
Fungal, severe	0	
Tuberculosis	0	
Toxoplasmosis	0.8327160	
Mycobacterium avian complex	0	
Pneumocystis pneumonia	0.973200	
Other, minor	0	
Other, severe	0.1787880	
Cotrimoxazole, monthly probability of resistance	0	Assumption

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Cotrimoxazole, one-time probabilities of toxicity-related events		Anglaret et al.;[323] Yazdanpanah et al.;[321] adjusted for input into CEPAC by M. Fofana on 18 Jan 2007
Minor event	0.1824000	
Major event	0.0672000	
Months to possible toxicity-related events following cotrimoxazole initiation	1	Assumption
TMP-SMX 3DS, costs		Gauteng Hospitals Numeric Pharmaceutical Codelist, 2004 (unpublished data), procured by N. Martinson; adjusted to 2006 USD by M. April on 1 Dec 2007
Monthly cost	1.16	
Minor toxicity event cost	11.14	
Major toxicity event cost	1607.00	
ART Regimens		
NNRTI + 2 NRTIs (1st line):		
3TC + NVP + AZT, monthly cost	21.42	MSF[327]
Monthly probabilities of toxicity-related events		Seyler et al.[328]
Minor event	0.0054000	
Major event	0.0054000	
Costs of toxicity-related events		Gauteng Hospitals Numeric Pharmaceutical Codelist, 2004 (unpublished data), procured by N. Martinson; adjusted to 2006 USD by M. April on 1 Dec 2007
Minor event	11.14	
Major event	1607.00	
Months to toxicity following toxicity-related event		Assumptions
Minor event	3	
Major event	6	
Monthly probability of death from major toxicity-related event	0	Assumption
Monthly probability of chronic toxicity	0	Assumption
Probability of viral suppression for months 1-6 of treatment	0.8920000	Akileswaran et al.,[325] Coetzee et al.;[324] adjusted for input into CEPAC by E. Losina on 30 Mar 2007
Probability of partial suppression	0	Assumption
Monthly probability of failure after 6 months of suppression	0.0104000	Akileswaran et al.,[325] Coetzee et al.;[324] adjusted for input into CEPAC by L. Mercincavage and E. Losina on 30 Mar 2007

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Monthly CD4 change on ART (mean, standard deviation)		Akileswaran et al.,[325] Coetzee et al.;[324] assumed 80% of CD4 benefit realized in 2 months, 20% over next 4 months, standard deviations assumed; adjusted for input into CEPAC by E. Losina on 17 May 2007
Months 1-2	73.60, 5.00	
Months 2-6	3.68, 1.50	
Post month 6	0.00, 0.00	
PI + NRTI (2nd line):		
LPV/r, monthly cost	41.67	MSF;[327] Delfraissy et al.[332]
Monthly probabilities of toxicity-related events		Seyler et al.[328]
Minor event	0.0054000	
Major event	0.0054000	
Costs of toxicity-related events		Gauteng Hospitals Numeric Pharmaceutical Codelist, 2004 (unpublished data), procured by N. Martinson; adjusted to 2006 USD by M. April on 1 Dec 2007
Minor event	11.14	
Major event	1607.00	
Months to toxicity following toxicity-related event		Assumptions
Minor event	3	
Major event	6	
Monthly probability of death from major toxicity-related event	0	Assumption
Monthly probability of chronic toxicity	0	Assumption
Probability of viral suppression for months 1-6 of treatment	0.7000000	Johnson et al.;[326] adjusted for input into CEPAC by E. Losina on 30 Mar 2007
Probability of partial suppression	0	Assumption
Monthly probability of failure after 6 months of suppression	0.0191000	Johnson et al.;[326] adjusted for input into CEPAC by L. Mercincavage and E. Losina on 30 Mar 2007
Monthly CD4 change on ART (mean, standard deviation)		Johnson et al.;[326] assumed 80% of CD4 benefit realized in 2 months, 20% over next 4 months, standard deviations assumed; adjusted for input into CEPAC by E. Losina on 17 May 2007
Months 1-2	60.40, 5.00	
Months 2-6	3.02, 1.50	
Post month 6	0.00, 0.00	

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Treatment Policies		
ART policies		Toms;[329] Provincial Administration Western Cape;[330] SADoH;[331] WHO[283]
1st line ART		
Initiation criteria		
CD4 count (cells/mm^3)	≤ 200	
OI	Fungal, severe Toxo. MAC PCP Other, severe	
Failure criteria		
CD4 count percent drop	30	
OIs	Fungal, severe Toxo. MAC PCP Other, severe	
Toxicity events	Major only	
2nd line ART		
Initiation criteria	1st line failure	
Failure criteria		
CD4 count percent drop	30	
OIs	None	
Toxicity events	Major only	
Cotrimoxazole policies		Toms;[329] WHO[282]
Initiation criteria		
CD4 count (cells/mm^3)	≤ 200	
OIs	Bacterial, min Bacterial, sev Fungal, min Fungal, sev TB Toxo. MAC PCP	
Failure criteria		
CD4 count (cells/mm^3)	> 200	
Frequency, monitoring tests (mths)		Personal communication, R. Wood to R. Walensky on 17 May 2007
CD4	6	
VL	6	
Probability, monitoring test errors		Assumptions
CD4	0	
VL	0	
Time between clinic visits (mths)	6	Personal communication, R. Wood to R. Walensky on 17 May 2007
Probability of detecting OI in patient histories	1	Assumption

Table B.1, cont'd. Input for CEPAC parameters unrelated to HIV testing.

Parameters	Values	Sources
Miscellaneous		
Monthly costs of undetected HIV infection	0	Assumption
Acute to chronic infection transition CD4 change	None	Assumption

OI: opportunistic infection
AIDS: acquired immune deficiency syndrome
ART: antiretroviral treatment
CTAC: Cape Town AIDS Cohort
VL: viral load
NNRTI: non-nucleoside reverse transcriptase inhibitor
NRTI: nucleoside reverse transcriptase inhibitor
3TC: lamivudine
NVP: nevirapine
AZT: zidovudine
PI: protease inhibitor
LPV/r: lopinavir/ritonavir

Appendix C:
AHIT model equations

As discussed in Subsection 7.1.1, AHIT is a model designed to circumvent the limitation resulting from CEPAC's definition of only a single set of testing parameters. The AHIT model solicits input on parameters describing two sets of tests: an initial rapid test protocol (in this thesis, two rapid tests performed in serial) and a subsequent AHI test protocol (in this thesis, a single test). Both sets of parameters are defined in precisely the same manner as CEPAC's test characteristics. AHIT then uses a series of mathematical relationships to effectively 'compress' these two sets of test inputs into a single set for use with CEPAC. This appendix reports those equations.

This appendix uses a system to define variables in which the first letter defines its nature: 'P' indicates the probability of occurence for a decision tree branch, 'N' the number of individuals passing through that branch, or 'C' the cost incurred for passing through that branch. The next letter indicates whether the variable belongs to an AHIT decision tree, indicated by 'A,' or CEPAC imitation tree, indicated by 'C' (see Subsection 7.1.1). This appendix considers only the HIV-negative client decision trees, but the equations are identical for the other three patient groups.

Figure C.1 recreates the AHIT decision tree for HIV-negative clients depicted by Figure 7.2. However, in this version, each branch is assigned a name such that it may be used for variable identification. Each of these variables is preceded by the letter 'A' since they all belong to an AHIT decision tree.

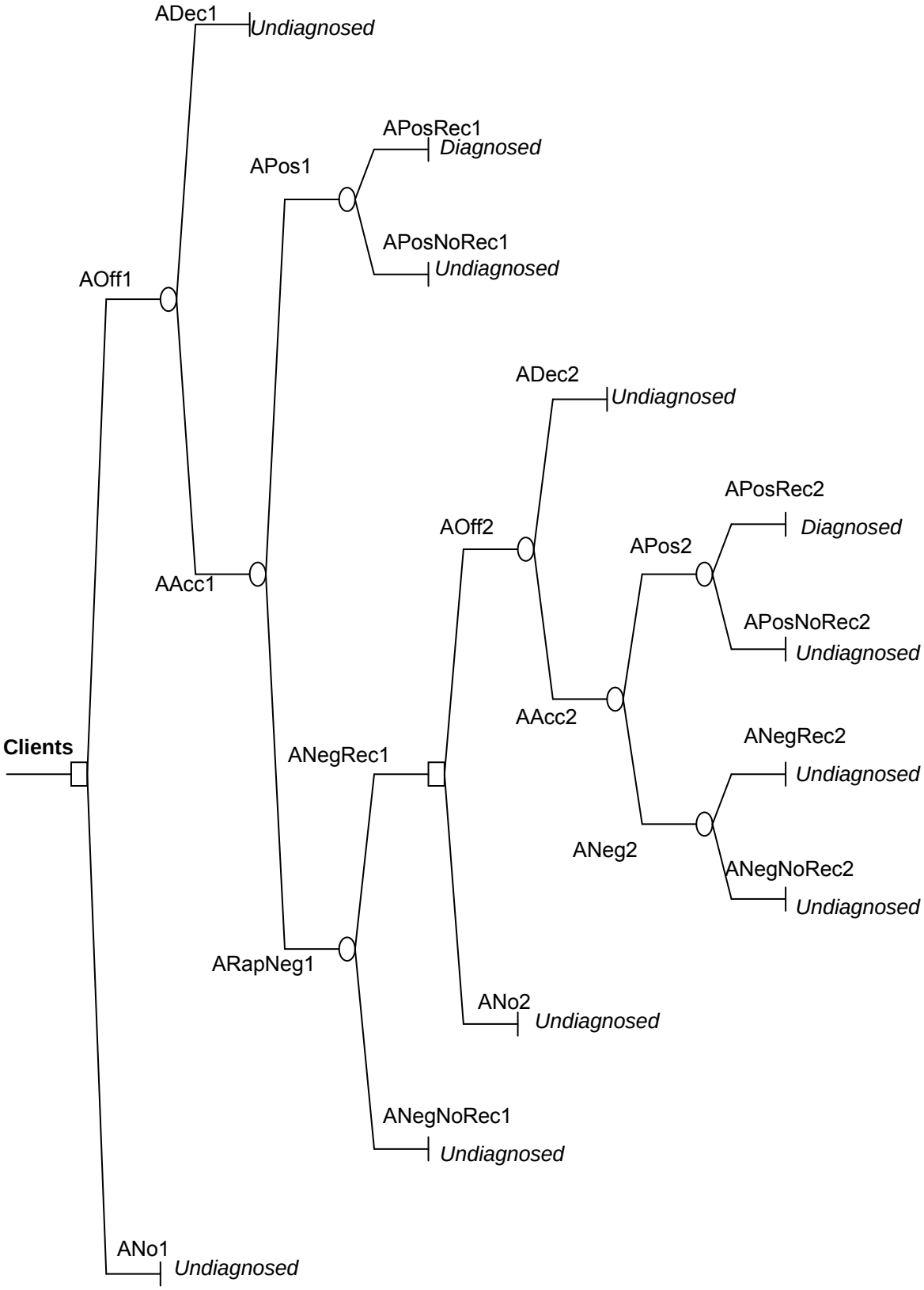

Figure C.1. Variable names associated with AHIT decision trees.

Next, Figure C.2 recreates the CEPAC imitation decision tree for HIV-negative clients depicted by Figure 7.3. Again, each branch is assigned a name such that it may be used for variable identification. As all of these variables apply to a CEPAC imitation tree, they are all preceded by the letter 'C;' estimates of the values of these variables comprise the output of AHIT.

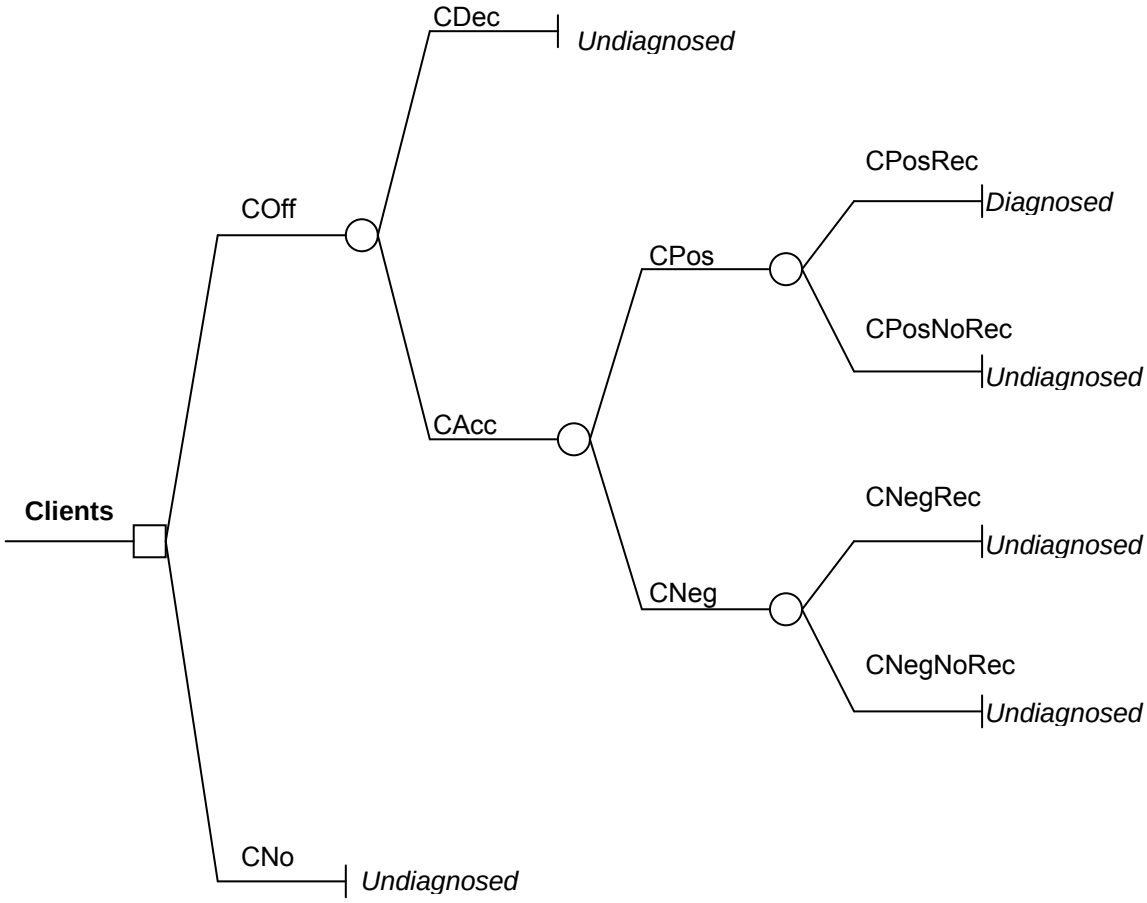

Figure C.2. Variable names associated with CEPAC imitation decision trees.

AHIT solicits input from users to define all cost and probabilities for each of the variables defined in Figure C.1. The objective of the model is then to generate values for all the parameters defined in Figure C.2. I will begin discussing equations for generating the probabilities. First, since AHIT output applies only to those patients in

CEPAC who have received test offers, I first assumed that all clients in AHIT were offered testing:

$$PCOff = 1 \quad \text{(C.1)}$$

$$PCNo = 0 \quad \text{(C.2)}$$

The remainder of the probabilities were defined as follows. Note that the sum of the probabilities extending from any decision node in Figure C.1 always equals one:

$$PCAcc = 1 - (PAAcc1 + PANo1) \quad \text{(C.3)}$$

$$PCDec = 1 - PCAcc \quad \text{(C.4)}$$

$$PCPos = \frac{(NAPos1 + NAPos2)}{(N - NADec1 - NANo1)} \quad \text{(C.5)}$$

$$PCNeg = 1 - PCPos \quad \text{(C.6)}$$

$$PCPosRec = \frac{(NAPosRec1 + NAPosRec2)}{(NAPos1 + NAPos2)} \quad \text{(C.7)}$$

$$PCPosNoRec = 1 - PCPosRec \quad \text{(C.8)}$$

CEPAC does not permit different probabilities of receiving test results based on those results. Consequently, the probabilities of test result receipt for negative test results was set equal to those calculated for positive test results in Equations C.7-C.8:

$$PCNegRec = PCPosRec \quad \text{(C.9)}$$

$$PCNegNoRec = PCPosNoRec \quad \text{(C.10)}$$

Next, Equations C.11 and C.12 for the costs associated with the CEPAC decisions trees are presented. The simplifying assumption was made that no costs were

incurred simply be offering tests. While some costs are undoubtedly incurred as a result of provider time, they are likely to be so small so as to be negligible:

$$CCOff = 0 \quad \text{(C.11)}$$

$$CCNo = 0 \quad \text{(C.12)}$$

The cost of test acceptance is reported by Equation C.13. Equation C.14 reflects the assumptions that no costs were incurred for clients who declined testing:

$$\begin{aligned} CCAcc = \; & (CAAcc2 * PAAcc2 * NAOff2 + \\ & CAAcc1 * PAAcc1 * NAOff1 + \\ & CAOff1 * PAOff1 * N + \\ & CAOff2 * PAOff2 * NANegRec1 + \\ & CADec1 * PADec1 * NAOff1 + \\ & CADec2 * PADec2 * NAOff2 + \\ & CANo1 * PANo1 * N + \\ & \underline{CANo2 * PANo2 * NANegRec1)} \\ & (N - NADec1 - NANo1) \end{aligned} \quad \text{(C.13)}$$

$$CCDec = 0 \quad \text{(C.14)}$$

Equations C.15 and C.16 report the costs of positive and negative test results. To simplify the calculations, these were assumed to include the costs of receiving these test results. Consequently, the costs of test result receipt reported by Equations C.17-C.20 were all set to 0.

$$\begin{aligned} CCPos = \; & (CAPos1 * PAPos1 * NAAcc1 + \\ & CAPos2 * PAPos2 * NAAcc2 + \\ & CAPosRec1 * PAPosRec1 * NAPos1 + \\ & \underline{CAPosRec2 * PAPosRec2 * NAPos2)} \\ & NAPos1 + NAPos2 \end{aligned} \quad \text{(C.15)}$$

$$CCNeg = \frac{(CANeg1 * PANeg1 * NAAcc1 + CANeg2 * PANeg2 * NAAcc2 + CANegRec1 * PANegRec1 * NANeg1 + CANegRec2 * PANegRec2 * NANeg2)}{NANeg2 + (1 - PANegRec1) * NANeg1} \quad (C.16)$$

$$CCPosRec = 0 \quad (C.17)$$

$$CCPosRecNo = 0 \quad (C.18)$$

$$CCNegRec = 0 \quad (C.19)$$

$$CCNegRecNo = 0 \quad (C.20)$$

Appendix D:
Literature review search terms

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present

1. HIV test$.mp
2. human immunodeficiency virus test$.mp
3. AIDS test$.mp
4. acquired immune deficiency syndrome test$.mp
5. HIV screen$.mp
6. human immunodeficiency virus screen$.mp
7. AIDS screen$.mp
8. acquired immune deficiency syndrome screen$.mp
9. HIV diagnos*s.mp
10. human immunodeficiency virus diagnos*s.mp
11. AIDS diagnos*s.mp
12. acquired immune deficiency syndrome diagnos*s.mp
13. HIV serodiagnos*s.mp
14. human immunodeficiency virus serodiagnos*s.mp
15. AIDS serodiagnos*s.mp
16. acquired immune deficiency syndrome serodiagnos*s.mp
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. economic$.mp
19. cost$.mp
20. exp economics/
21. exp economics, nursing/
22. exp economics, hospital/
23. exp economics, medical/
24. 18 or 19 or 20 or 21 or 22 or 23
25. 17 and 24
26. From 25, keep 1-1,041

EMBASE 1980 to 2008 Week 11

1. HIV test$.mp
2. human immunodeficiency virus test$.mp
3. AIDS test$.mp
4. acquired immune deficiency syndrome test$.mp
5. HIV screen$.mp
6. human immunodeficiency virus screen$.mp
7. AIDS screen$.mp
8. acquired immune deficiency syndrome screen$.mp
9. HIV diagnos*s.mp
10. human immunodeficiency virus diagnos*s.mp
11. AIDS diagnos*s.mp
12. acquired immune deficiency syndrome diagnos*s.mp
13. HIV serodiagnos*s.mp
14. human immunodeficiency virus serodiagnos*s.mp
15. AIDS serodiagnos*s.mp
16. acquired immune deficiency syndrome serodiagnos*s.mp
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. economic$.mp
19. cost$.mp
20. exp economics/
21. exp health economics/
22. exp health care cost/
23. 18 or 19 or 20 or 21 or 22
24. 17 and 23
25. From 24, keep 1-499

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