The value of weekly short message service interventions targeting medication adherence: A multi-national economic evaluation in HIV and tuberculosis infection

by

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Abstract

Introduction: The World Health Organization has ambitious goals to eliminate AIDS and TB globally. However, the plan is expensive and financial commitment to achieve this goal is uncertain. Mobile phone-based short message service (SMS) interventions have demonstrated the ability to improve HIV drug therapy adherence. My objective was to evaluate the cost-effectiveness of SMS-based adherence interventions in three settings, which have unique epidemics and health systems, yet struggle with similar adherence barriers. In this thesis, I also consider the value of conducting a cost-effectiveness evaluation before, during and after a randomized trial.

Method: This thesis has three parts. First, I evaluated the cost-effectiveness of SMS-based HIV drug adherence interventions in Kenya, where the interventions were first developed. Second, I evaluated the burden of non-adherence and cost sensitivity of SMS-based adherence interventions for latent tuberculosis infection (LTBI) drug therapy in British Columbia, where a trial of an SMS-based adherence intervention is underway. Finally, I evaluated 5,836 combinations of 15 HIV interventions, to understand the role of SMS interventions as part of a combination HIV intervention in India where a trial was being planned. Value was expressed in terms of incremental cost-effectiveness ratios (ICERs), which were a function of incremental costs and quality-adjusted life years (QALYs).

Results: In Kenya, the SMS interventions were highly cost-effective in the base case (ICER=$1,389/QALY), and remained cost-effective across most sensitivity analyses. In British

Columbia, hypothetical interventions that brought the population to full adherence to LTBI drug therapy could cost up to $450 per person per year and remain cost-effective. SMS interventions were least sensitive to cost and would likely be cost-effective if their efficacy were confirmed. Finally, in India, the SMS interventions were cost saving and were part of 4 of the 5 most efficient combination interventions out of 5,836 possible combinations.

Conclusion: The SMS interventions are cost-effective or cost saving when compared to the standard of care in multiple settings. Findings support the implementation of SMS interventions as part of HIV and TB care and suggest they could play an essential role in global containment of these diseases.

Preface

This thesis work was conducted collaboratively with research centers in Canada, the US, India and Kenya. I would like to acknowledge the contributions of my collaborators and mentors here.

For Chapter 2, I was responsible for conceptualizing the study in collaboration with Dr. Marra and Dr. Lynd, conducting data analysis and preparation of a final manuscript in collaboration with all co-authors (currently undergoing peer-review). Chapter 2 is based on work conducted jointly at the Collaboration for Outcomes Research and Evaluation (CORE) by Dr. Carlo Marra and Dr. Larry Lynd; at the African Medical and Research Foundation (AMREF) by Sarah Karanja; at the Ritvo lab by Dr. Paul Ritvo; and at the Vancouver Coastal Health Research Institute (VCHRI) by Mia van der Kop, Lidia Engle, Dr. Richard Lester and myself. I conducted statistical analysis, and wrote and edited the final manuscript. Research Ethics was approved by the UBC Behavioural Research Ethics Board under application number H10-00392.

For Chapter 3, I was responsible for conceptualizing the study in collaboration with Dr. Marra and Dr. Braithwaite, synthesizing input parameters (from trial data, literature reviews and cohort data analysis), specifying updates to the mathematical logic of an existing HIV simulation model, specifying appropriate simulation-based analyses, interpreting simulation outputs and preparation of a final manuscript in collaboration with all co-authors (currently undergoing peer-review). Chapter 3 is based on work conducted jointly at CORE by Dr. Carlo Marra; at the New York University (NYU) Center for Evaluation and Decision Science (CEDS) by Dr. Jason Kessler, Dr. Scott Braithwaite, Kimberly Nucifora and Leanne Zhou; at the Gillings School of Public Health by Dr. Harsha Thirumurthy; and at the VCHRI by Dr. Richard Lester and myself. I

wrote and edited most of the final manuscript (currently undergoing peer-review). The simulation modifications and high-powered cluster (HPC) computing were operationalized by Kimberly Nucifora and Leanne Zhou. Research Ethics was not required for the simulation-based study.

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For Chapter 4, I was responsible for conceptualization of the study in collaboration with Dr. Lester; development, debugging and parameterization of a simulation model in collaboration with Jonathon Campbell and conducting analyses; synthesis of results and preparation of a final manuscript in collaboration with all co-authors (currently undergoing peer-review). Chapter 4 is based on work conducted jointly at CORE by Jonathon Campbell, Fawziah Lalji and Mohsen Sadatsafavi, and at VCHRI by Kirsten Smilie, Dr. Richard Lester, Dr. James Johnston and myself. Research Ethics was not required for the simulation-based study. Part of this chapter has been published in a trial protocol. I wrote the section on the cost-effectiveness analysis in the final manuscript.

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van der Kop M. L., Memetovic J., Patel AR., Marra F., Sadatsafavi M., Hajek J. et al. (2014). The effect of weekly text-message communication on treatment completion among patients with latent tuberculosis infection: study protocol for a randomised controlled trial (WelTel LTBI). *BMJ open*, 4(4), e004362.

For Chapter 5, I was responsible for conceptualization of the study in collaboration with Dr. Braithwaite, parameterization of two HIV simulation models (based on literature review and administrative data analysis), literature reviews to identify relevant interventions for analysis, specifying simulation analyses, interpretation of results and preparation of the final manuscript in collaboration with all co-authors. Chapter 5 is based on work conducted at NYU CEDS by Dr. Kelly Ruggles, Dr. Scott Braithwaite, Kimberly Nucifora and Dr. Leanne Zhou; at Population council by Shrutika Sabarwal; and at VCHRI by Dr. Richard Lester and myself. Research Ethics was not required for the simulation-based study. This work was developed into two manuscripts (both currently undergoing peer-review) and I wrote and edited the manuscript related to this thesis and part of the manuscript not included in this thesis. The simulation modifications and HPC computing were operationalized by Kelly Ruggles, Kimberly Nucifora and Leanne Zhou.

One of the technology platform evaluated in this thesis (WelTel/SMS) has been developed by a non-profit organization and a private company. Dr. Richard Lester has financial as well as professional interests in both organizations. You are entitled to ask for more information about this potential for benefit from Dr. Lester. For inquiries, please contact rlester@mail.ubc.ca

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List of abbreviations

Abbreviation	Definition
AIDS	Acquired Immunodeficiency syndrome
AMPATH	Academic model providing access to healthcare
ANOVA	Analysis of variance
ART	Antiretroviral therapy
ASC	Adherence under standard care
AUC	Area under the curve
BC	British Columbia
CDC	Center for disease control
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
ENMB	Expected net monetary benefit
EVPI	Expected value of perfect information
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
INH	Isoniazid
INMB	Incremental net monetary benefit
LTBI	Latent tuberculosis infection
MCS	Mental component summary

NMB	Net monetary benefit
PCS	Physical component summary
PEF	Probability of being on the efficiency frontier
PLWH	People living with HIV
PLWHA	People living with HIV or AIDS
PrEP	Pre-exposure prophylaxis
QALY	Quality-adjusted life years
RCT	Randomized controlled trial
RIF	Rifampin
ROC	Receiver operator curve
SF12	Short-form 12 survey
SMS	Short message service
TasP	Treatment as prevention
TB	Tuberculosis
US	United States
VOI	Value of information
WHO	World Health Organization

Glossary

Term	Definition
Adherence	Taking a medication or following a treatment plan as directed.
Cascade of care	The sequence of treatment events from initial diagnosis with a disease to eventual stabilization or cure.
CD4 count	The number of human immune CD4 cells per unit of blood.
Decision analysis	A systematic framework of structuring and evaluating complex decisions with objective maximands or minimands.
Discount rate	The time value of money that incorporates preference for current spending over future spending; a measure of risk.
Latent tuberculosis	A tuberculosis infection that is inactive and minimally harmful to a host.
Markov model	A mathematical framework that describes recurrent probabilistic events to calculated long-term outcomes
Multilevel intervention	An intervention that can be delivered at multiple social levels (e.g. individual, group or community).
Reactivation	Active infection that arises from a latent infection rather than from contact transmission.
Retention in care	Consistent attendance for clinic appointments, lab tests and prescription pick-up
Viral load	The number of viral copies per unit of blood.
Viral suppression	A state of undetectable virus; the ultimate end-point for HIV treatment and care.

WHO stage	The severity of HIV infection defined by the symptoms.
Willingness to pay	The monetary value of one unit of a good or service.
Willingness to pay threshold	The monetary value of a year or adjusted year of life set by some national governments.

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I would like to acknowledge the support, mentorship and guidance of my supervisors, colleagues and mentors. Dr. Richard Lester has been a tremendous motivating force in achieving my goals and always supports big dreams when they are pursued with passion. He provided me with intellectual support and vision that allowed me to succeed in this program. He fostered an open, ambitious and collaborative research culture that I hope to carry forward in my future research endeavors. I would like to acknowledge my co-supervisor Dr. Larry Lynd for mentorship, guidance and supportive resources through CORE. Dr. Lynd has provided key research and career insights that helped me find my path. I would like to acknowledge the early supervision by Dr. Marra, who set my training on a strong foundation and connected me with resources and people that helped me build my research. I would like to thank Dr. Edward Mills for providing strategic insights that allowed me to overcome barriers in my work and gain a better understanding of domestic and global issues. I would like to acknowledge the mentorship of Dr. Scott Braithwaite, who has meaningfully influenced my work and thinking. Mia van der Kop has been a constant resource throughout my PhD. Dr. Jason Kessler and Dr. Mohsen Sadatsafavi both provided me with technical training and feedback on much of my work. Zafar Zafari, Kelly Ruggles, Jonathon Campbell, Joseph Babigumira and Kimberly Nucifora provided key insights and support throughout the process. I would like to personally thank each of my colleagues and collaborators in Canada, the USA, Kenya and India who have supported my research, but there are too many to list here. Finally, I would like to acknowledge financial support from NIHM grant #R01MH097558 and the US President's Emergency Plan for AIDS Relief grant number PHEKE.07.0045.

Dedication

This work is dedicated to my parents and family who are a constant source of inspiration and support.

1 Introduction

1.1 Research statement

In this thesis, I evaluate the cost-effectiveness of using Short Message Service (SMS, also known as "text-messaging") interventions to promote medication adherence. SMS messages can be up to 160 characters and are available for use on a vast majority of modern day mobile phones. SMS-based interventions have previously been shown to improve HIV medication adherence in randomized trials from Kenya (1, 2), are currently being tested in randomized trials for HIV and latent tuberculosis (LTBI) treatment adherence in British Columbia (BC)(3) and are being considered as part of a combination HIV treatment and prevention intervention in India. Medication non-adherence is a complex behaviour that leads to preventable mortality and morbidity.(4) Effective and cost-effective adherence interventions will be needed to manage the global HIV/TB co-epidemics, since medication adherence can impact both individual health and further transmission.

While SMS interventions show promise, evidence of their cost-effectiveness and efficiency relative to alternative healthcare investments is lacking.(5) In this thesis, I conduct cost-effectiveness evaluations (CEA) of SMS-based adherence interventions in distinct settings, with the aim of understanding their value across multiple health systems and disease areas. I hypothesized that SMS interventions are cost-effective, but their value depends on factors such as the target population and disease type. I therefore evaluate health and economic outcomes of these SMS interventions compared to the standard of care and/or appropriate alternatives in each setting. These evaluations start with the SMS-based adherence interventions alone and extend to combination strategies simultaneously targeting multiple risk factors.

The CEA was conducted among high-risk and low-risk populations and resource-rich and resource-poor settings, to contrast the cost-effectiveness of SMS-based adherence interventions while varying key characteristics that could affect their value. Through an evaluation in different settings, populations and diseases, I aimed to understand if SMS-interventions would be cost-effective when applied broadly. The initial SMS-based adherence intervention randomized trials took place in Kenya, where plans are underway for large-scale implementation. My first evaluation is generalized to HIV+ individuals initiating drug therapy in Kenya, to understand if the interventions are valuable if they were applied broadly. An SMS-based intervention is currently being studied in a trial in BC for its effectiveness at improving adherence to LTBI drug therapy among confirmed cases of LTBI. This setting provides a unique contrast for a CEA since it is resource-rich, and health impacts of non-adherence to LTBI therapy are different than for HIV. Finally, a trial is being planned for a multilevel intervention among high-risk HIV+ men (alcohol users) in Maharashtra, India. Many interventions outside of drug adherence were included in this analysis, since this population faced multiple risks.

The role of CEA was assessed before and during a randomized controlled trial; the value of using CEA at different stages of the research process is contrasted throughout this thesis. The typical role of CEA is to inform policy decisions about new technology adoption after trial completion. However, CEA could be useful during trials to estimate disease burden and examine current alternatives to an intervention under study to aid researchers in understanding if their intervention will be valuable if found effective. During the design phase of a trial, CEA could be used to estimate long-term health and economic outcomes of alternative interventions under consideration for a trial, to communicate the most valuable intervention to study. Practical and theoretical issues of using CEA as part of early stage translational research were explored in this thesis.

This thesis is structured according to the CEA conducted in each setting. Chapters 2 and 3 are components of a CEA inspired by the WelTel Kenya1 trial.(6) I evaluate the construct validity of the widely used Short-Form 12 survey (SF-12), then use the survey results to calculate health state utility values (HSUVs) of three health states commonly used in HIV simulation models. The HSUVs were then used as part of a model-based evaluation in Chapter 3, where I examine the long-term impact and value of SMS interventions in Kenya. In Chapter 4, I examine the potential value of SMS interventions if they were used to address non-adherence to LTBI therapy in BC, where a trial is currently under way. Finally in Chapter 5, I examine combination adherence and sexual risk reduction interventions for alcohol-misusing people living with HIV/AIDS (PLWHA) in India, where a trial is being planned. Non-adherence and sexual risk-taking may be influenced by depression and alcohol misuse, and in this final chapter, I evaluate combinations of 15 potential interventions to examine the value and likelihood of efficiency of alternative combinations.

1.2 Disease description and barriers to care

HIV/AIDS and tuberculosis (TB) are the two leading causes of death by infectious diseases, globally. In 2014, 1.5 million people died of TB and 1.2 million people died of HIV around the world; the two pandemics are linked, as 0.4 million who were co-infected with both HIV and TB died in 2014.(7) Clinical care for these two diseases is often delivered simultaneously due to the high degree of overlap in the patient populations. Anti-tuberculosis medications and antiretroviral therapy (ART) have become more widely available, reducing disease burden and mortality in many settings. However, financial constraints remain a barrier to accessing health services and lifesaving drug therapy.(8) Further, health outcomes remain sub-optimal because of barriers including poor drug adherence.

1.2.1 Human immunodeficiency virus

Human immunodeficiency viral (HIV) infection is a progressive disease that leads to acquired immunodeficiency syndrome (AIDS). The blood-borne pathogen is transmitted primarily through the exchange of bodily fluids during sexual activity or injection drug use. Recent scientific advances in drug therapy have transformed HIV/AIDS from a certain death sentence to a manageable chronic disease.(9) Aggressive treatment prevents further transmission so effectively that current clinical strategies include "treatment as prevention" (TaSP) and "pre-exposure prophylaxis" (PrEP) to protect high-risk uninfected people.(10) However, new transmissions continue to occur, leading to preventable deaths, health system costs and an ongoing global pandemic. Globally, many HIV-positive (HIV+) people are unaware of their status, compounding transmission issues.(11)

Immune system CD4 T-cells are crucial in mounting an immune response when infective antigens enter a human host. HIV is a unique virus that targets and replicates within CD4 cells. Over time, the HIV virus leads to destruction and depletion of CD4 cells, leading to AIDS.(9) Viral load is the number of copies of the virus present in the blood, and it has been shown to be a predictor of the rate of CD4 decline.(12) Once CD4 drops below 200 cells/ml, AIDS-defining illnesses such as opportunistic infections occur in PLWHA. AIDS results in significantly increased mortality, health system costs, hospitalization and adverse health outcomes.

The relationship between viral load and HIV transmission risk is well documented.(13) A widely cited study by Quinn et al. examined rates of transmission in heterosexual partners in which one partner was HIV-positive and the other HIV-negative. They found that transmission was rare from those partners with viral levels less than 1500 copies/ml.(13) Suppressed viral loads, via drug therapy, have also been shown to reduce transmission of HIV from mother to child during pregnancy and among sexual

partners infected with two different strains of HIV.(14-16) However, non-adherence prevents optimal health outcomes globally.(17)

1.2.2 Tuberculosis

Tuberculosis (TB) is a bacterial infection caused primarily by mycobacterium tuberculosis. The pathogen is transmitted by air and can cause an active infection or remain a latent infection.(18) Latent TB infection (LTBI) is generally contained by the host immune system, but can reactivate at any time. The World Health Organization (WHO) estimates that there are 2–3 billion people infected with LTBI worldwide, but only 5%–15% of those cases will reactivate within the host's lifetime.(7) Co-infection with HIV leads to greatly increased LTBI reactivation, and death. The risk of death from TB can range from 16% – 37% in PLWHA who are not on ART.(19) Aggressive drug treatment, adherence and prevention of TB reactivation are essential, particularly among high-risk populations.

1.2.3 Critical barriers in care

1.2.3.1 Medication adherence

A major issue in HIV and TB control is medication adherence once a patient begins therapy. HIV and LTBI treatments involve long courses of drug therapy and can cause serious side effects. In addition to missing daily doses for a number of reasons (e.g. forgetfulness or aversion due to side effects), patients can experience logistical barriers (e.g. irregular work schedule) or health system barriers (e.g. stock-outs) to achieving optimal adherence. The psychosocial factors leading to non-adherence are numerous and have been summarized in previous literature.(20) The result of non-adherence is inadequate infection suppression that ultimately leads to adverse health outcomes and further transmission.

The lifelong nature of HIV requires patients to consistently adhere to medications in order to prevent complications such as opportunistic infection, drug resistance or treatment failure. In HIV, adherence is measured as a proportion of pills taken as directed over time. Many regimens of ART require greater than 80%–90% adherence to achieve viral suppression. Treatment adherence to LTBI therapy is required to reduce the lifetime TB reactivation risk. Adherence to LTBI treatment is defined by the length of time an individual stays on drug therapy combined with the proportion of doses taken. For LTBI, the risk of TB reactivation is reduced by 93% with nine months of isoniazid therapy, but some protection is conferred with three or six months of isoniazid as well.(21) Consistent adherence dramatically reduces morbidity, mortality and the risk of further transmission for both diseases. Non-adherence rates for HIV and LTBI drug therapy vary widely, however some multicenter studies have observed less than 40% completion.(22-25) For this reason, affordable interventions that can improve adherence rates are a research priority.(26)

1.2.3.2 Retention in HIV care

Due to the lifelong nature of HIV, patient retention in long-term care is a critical issue. Patients can be lost at all points of the care cycle which spans from the initial diagnosis with HIV to the point of being on a stable regime of ART. In sub-Saharan Africa, an estimated 23% of HIV infected patients are lost to care or experience early mortality within the first year of diagnosis.(27) Furthermore, three year post-ART initiation, retention rates are reported to be 65% in Africa and 80% in Asia. Among the individuals lost to care, an estimated 43% are known to have died.(27) The mounting health system costs associated with interrupted HIV care threatens the solvency of efforts to control the disease. For this reason, cost-effective interventions aimed at reducing loss to care are a high priority in international HIV strategies.(26)

1.2.4 Brief disease epidemiology by setting

1.2.4.1 HIV in Kenya

Kenya is an East African nation that has been seriously impacted by HIV with an estimated 1.5 million (1.3 million – 1.8 million) PLWHA in 2015.(28) Further, there were approximately 36,000 (26,000 – 47,000) deaths due to AIDS.(28) Many patients remain without ART, leading to uncontrolled transmission that increases disease burden. In addition to poor adherence and retention, another issue facing HIV programs is late presentation to care, where individuals receive a diagnosis only once they are very ill and have a poor prognosis. The epidemic is generalized to the full population and can disproportionately affect women in many areas.(28) Interventions to improve engagement with HIV care are needed to address barriers to optimal care.

1.2.4.2 LTBI and TB in British Columbia, Canada

British Columbia is a Canadian province with a low incidence of TB and LTBI. The goals of prevention programs in the province are to reduce TB incidence, prevalence, morbidity and mortality through interrupting transmission of infectious cases and providing screening and preventative treatment for latent infections.(29) There were 257 cases of active TB in BC in 2013, with a majority of cases coming from foreign born and Indigenous populations.(29) The ultimate goal is to achieve a TB incidence of less than 100 cases per million people by 2030 in all populations.(30) To achieve this goal, reservoirs of LTBI must be reduced through preventative therapy. However, adherence to the long-course of LTBI treatment has been observed to be less than 40% in some large studies.(22-25) SMS-based adherence interventions are currently being tested in a randomized controlled trial to improve completion of isoniazid or rifampicin based preventative therapy.(3)

1.2.4.3 HIV in Maharashtra, India

India has the third largest HIV epidemic in the world with an estimated 2.1 million (1.7 million – 2.6 million) PLWHA in 2015.(31) There were approximately 68,000 (47,000 – 99,000) deaths due to AIDS in 2015.(31) In Maharashtra state, an estimated 171,740 of the 315,852 PLWHA were on ART in 2014.(32) The epidemic is concentrated among high risk groups, including sex workers, injection drug uses, men who have sex with men and migrant workers. Alcohol misuse is prevalent in many of these risk groups and is a barrier to HIV management efforts. Unhealthy alcohol use is defined as five or more drinks on the same occasion once within 30 days.(33) A team of Indian and US institutions is collaborating to address risk factors including drug adherence and alcohol use in a cohort of PLWHA in Maharashtra, India.

1.2.5 Disease simulation studies

Disease simulations are useful tools for estimating disease burden, evaluating programmatic impact or predicting future impact of new interventions. HIV models have been extensively developed and can be broadly classified into two categories: HIV progression simulations and HIV epidemic simulations.(34-36) TB models have also been used for policy and intervention evaluations.(37, 38) Disease simulation models can take several forms, depending on the complexity of the disease and study question.(39, 40)

Microsimulations and transmission models can account for complex disease prognosis, patient-level heterogeneity and secondary transmission.(41-43) Simulations estimate health outcomes (e.g., quality-adjusted life years (QALY); number of transmissions) and economic outcomes (e.g., total healthcare spending; intervention costs). Short-run simulations can represent a few years, while long-run simulations can represent patient lifetimes or the course of an epidemic over many years. Model inputs

can come from census reports, pilot data, expert opinion or previously conducted studies. Although the strength of input evidence can vary, uncertainty can be reflected through a probabilistic analysis (PA) where the simulation is repeated across plausible probability distributions of all inputs.(41) Simulation complexity and time horizon depend on the clinical context, research questions and types of intervention under consideration.

1.2.6 Mobile phone SMS adherence interventions

Cell phone usage has surged globally, and healthcare applications of the technology are growing.(44) Several systematic reviews highlight promising evidence of SMS-based interventions to improve ART adherence, but distinctions of intervention design and delivery may affect efficacy.(1, 2, 5, 45-47) Scale-up of mHealth interventions is fragmented, with questions arising about the appropriateness, validity and applicability of the wide array of interventions.(48) However, enthusiasm for mHealth remains high because of the potential for reaching so many people, particularly marginalized populations.

SMS-based adherence interventions have been previously studied, however their cost-effectiveness remains unknown.(5, 47) Estimates of cost-effectiveness can convey the opportunity costs of investing in SMS-based adherence interventions compared to other programs, such as expanded testing or medication programs. With a global push to finance expansion of ART to more people, funding agencies may undervalue the opportunity cost relative to improving adherence of PLWHA receiving ART. Thus, a formal evaluation of SMS-based adherence interventions can help policymakers understand the funding decisions they face in terms of cost-effectiveness and opportunity costs.

1.3 Cost-effectiveness evaluations in HIV and TB

Global healthcare development financing, including HIV and TB programs in resource-poor settings, has grown remarkably over the past 30 years. However, after a number of recent financial crises, global austerity has stunted current and future global health funding. Year-over-year growth in funding for global health topped 10% annually between 2001-2010, but in recent years, growth has been significantly lower.(49) In addition, the share of financing for healthcare programs is shifting away from donor governments and towards local governments.(49) A contraction in funds would likely prevent the WHO vision of an AIDS- and TB-free world. However hope remains, as even with lackluster economic growth, global health assistance has not radically contracted in recent years.(49) The future remains uncertain, and cost-effective or cost-saving interventions are desperately needed to extend the health impact of limited funds.

Economic evaluations of HIV and TB interventions are a critical step to the long-term solvency of treatment and prevention programs globally. In addition to informing policy decisions, understanding the value of new interventions is fundamental for public awareness and uptake by the health system. Cost-effectiveness evaluations are commonly used to assess new health technologies or programs. Evaluations estimate the impact of new interventions on the prognosis of disease, with explicit consideration of financial efficiency or programmatic budget constraints. Evaluations can be part of a prospective study, where the data are generated through a trial or observational study, or they can be simulation-based, where data about the natural history of the disease and intervention impact come from a variety of sources. Disease burden can be estimated in the form of early mortality, non-fatal morbidity (e.g., disability or pain) and, in the case of infectious diseases, cases of further transmission. The purpose of drug therapy, preventative programs or other interventions is to mitigate the burden of disease for patients and society; their value is a function of their efficiency at achieving this goal.

Economic efficiency is generally defined in this thesis as a ratio of incremental costs to incremental health gained.(50, 51)

As part of this research, I conducted CEAs in two disease areas and in three health systems with varying costs. As such, the CEAs required characterization of both health care costs and HSUV in each setting. Where data was unavailable, reasonable assumptions were made and tested through sensitivity analyses. The broad goal of CEAs is to inform policymakers about whether or not to use a new technology at the local (i.e., hospital) or national level. However in one study, I evaluated the usefulness of CEA prior to initiating a trial and assessed the impact of stakeholder constraints on the optimal intervention design. Cost-effectiveness analysis has been suggested as way to prioritize research, although applications are rare.(52) Carlson and colleagues recently demonstrated the usefulness of CEA in prioritizing multiple cancer genomic tests under consideration for further study.(53) They showed that explanation and presentation of CEA results to decision-makers had an impact on their ranking of research priorities. Globally, limited pilot studies or theoretical works have used CEA to inform research prioritization.(54-58) However, CEA has not previously been used to inform intervention selection and design during the formative phase of an RCT.

1.3.1 Quality-adjusted life years: A measure of health

Cost-effectiveness evaluations aim to identify ways to maximize health in the most efficient way. Thus, a measurement of health is required to conduct formal evaluations of new interventions, medications or programs. The quality-adjusted life year (QALY) is a single measure of disease burden that includes loss of life and welfare due to disease. Calculating QALYs relies on HSUV that are elicited through a variety of instruments or studies of individuals with disease or members of society.(39, 51) The HSUV are multiplied by the amount of time an individual spends in the

corresponding health state and summed over a specified period of time to derive the QALY. The difference between average population QALY and average QALY from a population with disease represents the burden of that disease measured in QALYs lost.(39) Within the QALY framework, the utility score for perfect health is one and for death is zero.(39)

The HSUV are generally country-specific, but HIV/AIDS CEAs have used similar health states across settings.(34) A systematic review of HIV utilities suggests values of: 0.70 for AIDS; 0.82 for symptomatic HIV; and 0.94 for asymptomatic HIV.(59) The HSUV for typically used HIV health states have not been evaluated in some settings, including Kenya. The TB-related HSUV have been evaluated in BC and are 0.82 for LTBI on treatment and 0.62 for an active case of TB. The QALY metric is preferred for evaluations by most national agencies that make country-specific healthcare funding decisions.(51, 60-63)

1.3.2 Cost-effectiveness threshold and willingness to pay

For the sake of equity and efficiency in the allocation of scarce healthcare resources, national governments or other healthcare payers must make explicit decisions about what new technologies to adopt or reject. Cost-effectiveness evaluations and other forms of decision analysis explicitly characterize the efficiency of a new health technology to produce health (i.e. to produce QALYs) to aid funding decisions. The incremental costs (i.e., added costs due to the intervention or cost savings due to the intervention) and incremental health gains (i.e., change in QALY or other measure of health) give rise to an incremental cost-effectiveness ratio (ICER). Other economic considerations can also be factored into a CEA, including productivity gains or health systems savings, but the overall goal is to maximize health given societal financial constraints. The trade-offs and scarcity of resources give rise to a theoretical willingness to pay for health in the form of a threshold at which a technology is

considered cost-effective. The threshold in Canada has been suggested to be $50,000/QALY, but could range from $20,000-$100,000/QALY when ethical and political considerations are take into account.(64)

The threshold in many countries, including Kenya and India, is unknown. The WHO recommends the per capita gross domestic product (GDP) of a country as the *very* cost-effectivene threshold, and three times the GDP as the cost-effectiveness threshold.(65) The WHO has also published thresholds for its 14 global defined regions.(65) However, many ethical issues arise when basing the threshold on countries' GDPs, due to the variation in national wealth. An alternative approach is to benchmark new technologies to currently employed technologies and compare their relative efficiency at producing health (i.e., cost per QALY). Incremental cost-effectiveness ratios can be compared directly from independent studies if each study reports generalizable estimates (and similar methods), or a single analysis can be conducted considering several alternatives and the relative efficiency of each option at producing health.

1.3.3 Model-based cost-effectiveness analysis

For the sake of brevity, I will briefly describe some of the methods of CEA that are relevant to this thesis. The primary focus of this thesis is on cost-utility evaluations measuring health in QALYs, with some discussion of other secondary measures of effectiveness. Randomized controlled trials (RCTs) are a strong source of evidence for CEAs, as they minimize the potential for biased inferences in several ways.(66) CEAs as part of a trial investigate the impact of the intervention on both clinical and economic endpoints. Costs of care (e.g., testing, drugs, procedures) and intervention-related costs (e.g., labour, equipment training) can be collected in both arms along with patient-level spending related to clinic attendance, missed work and incidental expenses. A variety of statistical procedures are

available to test if costs are significantly different between the treatment and control arms.(66) Effectiveness can be reported as a surrogate measure (e.g., adherence or virological suppression) or directly as QALYs, if HSUV were collected as part of the trial.

Often, trials are insufficiently powered to detect significant differences in QALYs or follow-up is too short for meaningful economic differences to occur.(66) This is the currently the case in SMS intervention trials that have generally reported efficacy for one-year adherence outcomes, but had an statistically insignificant impacts on mortality or healthcare spending in one year.(6, 67) Model-based evaluations rely on data from multiple sources to estimate longer-term outcomes.(51) The advantages of model-based evaluations are increased generalizability and comparability of results to other model-based evaluations, but these come at a loss of internal validity.

The previously described disease models can be adapted into economic models through the addition of economic inputs, additional calculations and outputs. Inputs to a CEA model can be broadly classified into costs, HSUV, probabilities and rates of outcomes and downstream health events. The efficacy of interventions could act by modifying the probabilities or rates of adverse health or economic events. In some instances, data may not be available for some parameters in a model and assumptions must be made. Chapters 3-5 use model-based designs to assess the value of SMS-based adherence interventions over longer time horizons in three distinct settings (Kenya, Canada and India).

1.3.3.1 CEA study population

The first step in a CEA is identifying and characterizing the target population that can benefit from an intervention. Previous studies have conducted cost-effectiveness evaluations of new interventions targeting the entire patient population(36) or targeting high-risk groups.(68) The CEAs in Kenya and

Canada are conducted in the general patient population, while the CEA in India is conducted in a high-risk alcohol-using group.

1.3.3.2 Evaluating SMS-based adherence interventions

Often, trials report an intermediate outcome to which it is difficult to assign an economic value. Further, intermediate outcomes in one disease area (e.g., asthma exacerbations) are not immediately comparable to intermediate outcomes in another (e.g., blood glucose control). Throughout this thesis, mathematical models are used to link intermediate endpoints with the final endpoints of interest: transmission, costs and QALYs. Previous SMS-based trials and meta-analyses have reported a proportion of patients that were adherent to their medications after a period of observation.(1, 2)The binary indicator of adherence was transformed into QALYs through a mathematical framework that describes disease prognosis under various adherence levels. The SMS-based interventions serve to improve the proportion of adherent individuals, thus improving their long-term health.

1.3.3.3 Previous HIV and TB model-based evaluations

The simplest form of mathematical model involves a decision tree where two or more probabilistic outcomes stem from an initial choice or event. A Markov model is a more complex form of decision tree that repeats calculations according to a specified time cycle and event probabilities. Markov models have been used in the past to describe the value of HIV screening strategies and to evaluate the cost-effectiveness of LTBI drug treatment.(37, 69)

If patient-level characteristics become important to disease prognosis or intervention efficacy, the Markov model becomes computationally and visually unwieldy. An individual microsimulation or other more complex model design is preferred for more complex questions. Microsimulation has been

used to describe important HIV/AIDS guideline changes or interventions in the past and is the more common form of HIV simulation study.(70-72)

Finally, transmission models can capture population dynamics of disease transmission that are useful for estimating the number of transmissions prevented by interventions. The outcomes are at the population level and these models can also be used to estimate health system spending and QALYs. Previous transmission model evaluations have answered important HIV and TB questions including the prospects for global TB elimination and the cost-effectiveness of earlier ART initiation.(36, 38)

1.3.3.4 Interpretation of results of model-based evaluations

The output of a mathematical model includes expected health and economic outcomes. Further, a probabilistic analysis (PA) can be used to estimate non-parametric uncertainty intervals of simulated results.(73) Simulated outcomes and their associated uncertainty bounds can be interpreted in multiple ways. Competing options can be ranked in terms of their efficiency at achieving clinical endpoints at costs by calculating ICERs.(51) Alternatively, simulation cost and QALY outcomes can be combined into a single net monetary benefit (NMB) statistic.(74) Based on expected NMB (ENMB) from PA, results can be used to plot a cost-effectiveness acceptability curve (CEAC) that displays the probability that an option constitutes the most cost-effective option at a given "willingness to pay" (λ) threshold.(39, 51)

There are two schools of thought regarding healthcare spending policy. One involves using a defined λ threshold to guide funding decisions. Canada and the UK are examples of countries that use thresholds as part of health technology assessments, though other considerations can influence final decisions.(63, 64) Other countries, including the US and Germany, use alternatives to a defined λ threshold,(75) and

instead base funding decisions on an efficiency frontier.(76) Under this framework, healthcare budgets are spent on efficient options until they are fully spent, but on occasion, technologies with very high ICERs might be funded. There are no established rules for CEA in India or Kenya. A sensitivity analysis of the λ threshold is included in all of the model-based studies in this thesis based on plausible values.

1.4 Knowledge gaps

It is unknown if the widely used Short-Form 12 (SF-12) survey as it was originally designed can evaluate health outcomes in Kenya. The SF-12 is a crucial tool in health technology assessments because it can measure both quality of life and preference-based health states to derive QALYs. The survey has not been validated among PLWHA in Kenya. It is important to demonstrate construct validity of the survey before using it to measure HSUV or including survey results in a formal economic evaluation. A validated survey could be used to estimate HSUV of common HIV health states, which currently remain unknown in Kenya.

The value of SMS interventions is unknown in any setting. A recent systematic review of adherence interventions has called for a cost-effectiveness evaluation(5). The SMS interventions were initially shown to improve adherence in Kenya, and the cost-effectiveness remains unknown compared to the standard of care. SMS-based adherence interventions were subsequently hypothesized to improve adherence to LTBI prophylactic drug therapy in BC.(3) However, the burden of non-adherence is currently unknown in BC, as is the potential value of SMS interventions relative to alternatives. Finally, a trial is being planned for a combination HIV intervention in India and SMS-based interventions could be combined with other interventions. It is unknown if SMS-based interventions would be part of the most cost-effective combinations.

Furthermore, it is unknown if decision analysis and simulations can be useful to inform combination intervention selection and design. Typical health economic models and methods have been used to conduct post-hoc analysis to inform adoption of technologies. It is unknown if conducting decision analysis prior to initiation of a trial could make the process more efficient by identifying in advance the optimal interventions with the highest expected value.

1.5 Thesis overview

In my first two studies (outlined in Chapters 2 and 3), I validated the widely used SF-12 survey in Kenya to measure HSUV, then investigated the cost-effectiveness of weekly SMS for HIV drug adherence in Kenya. Using trial data, I evaluated the construct validity of a Kiswahili translated SF-12 survey by testing its ability to discriminate baseline quality of life and HSUVs of study participants with varying severities of HIV. I calculated HSUVs for disease states defined by CD4 count and by symptom severity.

I proceeded to conduct a model-based evaluation of weekly SMS using a well-established and validated east-African HIV decision-analytic model. I specified the inputs and analysis based on data from two SMS intervention trials and other literature. I conducted a scenario analysis by varying the baseline population adherence to show how cost-effectiveness changed as population adherence increased. I found that weekly SMS was cost-effective by WHO standards in Kenya. I also compared SMS interventions under optimal *test and treat guidelines* that are currently being implemented for global HIV management.(10) I found that in all scenarios, SMS is highly cost-effective and would remain valuable under test and treat guidelines.

In my second study (outlined in Chapter 4), I investigated the value of weekly SMS intervention compared to usual care for adherence to LTBI drug therapy in BC. I created a BC-specific microsimulation model using inputs from published literature, and estimated the burden of non-adherence and the value of hypothetical adherence interventions to solve this issue. In secondary analysis, I examined the cost-effectiveness of several potential adherence interventions including SMS interventions. Cost data were unpublished or unavailable for some interventions, so I based my analysis on efficacy and uncertainty reported in systematic reviews of these interventions. I presented the likelihood that each would be cost-effective compared to standard care as a function of price. I found that weekly SMS had the highest likelihood of being cost-effective compared to standard care, and was least sensitive to price changes. Peer-support had the highest likelihood of being cost-effective in multi-comparator analysis assuming its price was comparable to the other interventions.

In my final study (outlined in Chapter 5), I used simulation to examine the value of weekly SMS as part of a package of HIV interventions in India. I parameterized two well-established HIV models for India: one multi-state progression model and one dynamic compartmental transmission model. I conducted an analysis using combinations of 15 single-focus interventions, and identified valuable intervention combinations for a future trial. I investigated the impact of imposing budget constraints or risk constraints to show how the results would change based on decision-maker preferences or implicit constraints. In this final chapter, I discuss the application of simulation to improve pre-trial decision-making by identifying valuable research targets a priori, while explicitly considering important decision-maker constraints.

British Columbia is a resource-rich setting with low incidence, while Kenya and India are resource-poor settings with high incidence. Kenya has a generalized HIV epidemic, while India has an epidemic

concentrated in high-risk groups. Due to the widespread use of cell phones, this evaluation was conducted in distinct diseases and settings to understand if value would be preserved if the intervention were applied broadly. Additionally, each CEA was conducted at different stages of the research process; an evaluation was conducted before, during and after a randomized controlled trial. The value of doing a decision analysis at each stage was contrasted to understand the role of economic evaluation in making research more efficient and relevant to policymaking and implementation.

2 The validity of the SF-12 and SF6D instruments in people living with HIV/AIDS in Kenya

2.1 Background

Health-related quality of life (HRQoL) and health state utility value (HSUV) measurements are vital components of healthcare program and technology evaluations. HRQoL is a multi-dimensional measure of an individual or group's perceived health status, while HSUV ranks societal preferences for various states of health.(77, 78) HRQoL is used to measure functional changes in health as a clinical outcome of health interventions, while HSUV is used to describe the relative economic value of health interventions as a function of their ability to move patients to more preferred states of health. While the two measures are related, they are theoretically distinct in their derivation, application and interpretation. Accurate measurement of HSUV and HRQoL require validated instruments; the limited number of such instruments has been an impediment to healthcare research in East Africa.

Instruments to measure HRQoL can be disease-specific or generic, depending on the goal of a study and the desire for specificity or generalizability of findings.(79) A generic HRQoL measure that is widely used in clinical trials is the 36-item Medical Outcomes Survey (SF-36). It was developed by the RAND corporation as part of the Medical Outcomes Study.(80) A more concise version, the 12-item Medical Outcomes Survey (SF-12), derived from the MOS-36, has been developed.(81) The SF-12 measures eight dimensions of health: physical functioning (two items), social functioning (one item), role limitations due to physical problems (two items), role

limitations due to emotional problems (two items), mental health (two items), vitality (four items), bodily pain (two items) and general health perception (five items). Furthermore, two component summary scores can be generated from the eight health domains: the physical component summary (PCS) and the mental health component summary (MCS).

An understanding of societal preferences for various health states are needed for cost-effectiveness evaluation of new health technologies, programs and interventions. HRQoL provides a descriptive measure of patient health, but not a measure of relative value. The SF-12 PCS and MCS scores cannot be used to calculate quality-adjusted life years (QALY). Because of the widespread use of the SF-12 and SF-36, Braziers and Roberts generated a conversion algorithm to describe societal preferences for health states defined by these instruments.(77) They elicited societal preferences of the general UK population for a number of health states, generated by the SF-12 and SF-36 using a standard gamble.(77) The algorithm generates the SF6D score, a value between 0.30 and 1; the SF6D scores are typically used in cost-effectiveness evaluations to estimate QALYs.(39, 77)

The SF-12 is one of the only instruments that can evaluate both HRQoL and HSUV.(81, 82) The SF-12 is commonly used to collect HRQoL and can be converted into the SF6D score to characterize HSUV. The SF-12 is commonly used for health technology evaluations in resource-rich settings, but rarely used in East Africa. The SF-12 can describe a large range of health states, and can be a particularly useful tool to evaluate the health of PLWHA at all stages of the disease. To date, the discriminative abilities of the PCS, MCS and SF6D have not been investigated by HIV severity in East Africa. The objective of this study was to examine the performance of SF-

12-derived HRQoL and SF6D-derived HSUV scores, calculated based on a Kiswahili-translated and adapted SF-12 survey in Kenya. In this study, we evaluated whether HRQoL and HSUV scores from a sample of PLWHA could discriminate between well-defined severity groups. Since HIV/AIDS is the leading cause of death in most East African nations, this validation is important for future use of the SF-12 to assess both health and economic outcomes.(83)

2.2 Methods

2.2.1 Study design and setting

This cross-sectional study, which took place between May 2007 and October 2009, used data from a randomized controlled trial (RCT) in Nairobi, Kenya (N=538) (ClinicalTrials.gov number, NCT00830622).(6) Baseline data were collected prior to initiating ART or receiving the intervention. Data from participants in both trial arms were pooled to conduct these analyses. This multi-site trial involved three HIV clinics, which were located in demographically and ethnographically diverse settings.(6)

2.2.2 Participants

Inclusion criteria were ART naive, aged 18 years or above, access to a mobile phone, and the ability to text-message or have somebody who could text-message on their behalf. Patients who met the inclusion criteria and consented to participate were randomized to either receive a cell phone-based adherence intervention or standard care only. The study protocol was approved by the University of Manitoba and Kenyatta National Hospital ethics review boards.(6)

2.2.3 Data and measures

A translated and adapted version of the SF-12 survey was administered to participants at baseline, along with a survey that collected data on gender, age, income and rural/urban residence. CD4 count was collected (FACScan, Becton Dickinson, Sunnyvale, CA, USA) as part of routine clinical care, and viral load (Amplicor, Roche Diagnostics, Mannheim, Germany) was assessed as part of the trial protocol.(6) Research clinicians administering the baseline survey assessed the World Health Organization (WHO) clinical stage of HIV infection.(6)

2.2.4 Theoretical foundation

A longer form of the SF-12, the SF-36, has been translated and adapted for use in 40 countries as part of the International Quality of Life Assessment (IQOLA) project.(84) Kiswahili, the primary language in many East African nations, was not among the original IQOLA project translations. However, two subsequent studies translated and evaluated a Kiswahili-translated SF-36 survey.(85, 86) Wagner et al. evaluated content, quality and scaling of the translated survey in a general Kenyan population, demonstrating that the SF-36 survey performed comparably to its UK counterpart.(85) Wyss et al. extended this work by assessing the validity of the SF-36, using a method of known group validation.(86) They demonstrated that the SF-36 could discriminate health status between groups with known differences in health based on theory or evidence. The discriminative ability of a HRQoL survey is an important validation step to ensure the survey can adequately capture outcomes of interest.(87) The SF-36 is cumbersome to administer in research settings, so the briefer SF-12 was created.(81) The SF-12 has been shown to retain much of the descriptive ability and validity of the SF-36. While previous research supports the use of a

Kiswahili SF-36, a focused evaluation of the SF-12 among PLWHA has not been conducted in East Africa.

2.2.5 Translation and adaptation process

An international team of healthcare professionals and researchers translated the English SF-12 into Kiswahili, based on IQOLA recommendations. The survey was reviewed by a multidisciplinary focus group of English- and Kiswahili-speaking healthcare providers and researchers, for relevance, ease of understanding and cultural appropriateness. Where necessary, items and response options were slightly modified and culturally adapted to make the questionnaire relevant and appropriate for use in a Kenyan context. Literature reviews and expert opinion were used to inform changes to the survey. For example, "climbing stairs" in the original SF-12 was changed to "climbing a hill," based on a previous study using the SF-36 in Tanzania.(85, 86) After translating the survey into Kiswahili, it was translated back into English and assessed by a focus group of English-speaking healthcare researchers to ensure consistency. The survey was pre-tested on a sample of 20 Kenyan patients and healthcare staff to evaluate cultural appropriateness and understanding.

2.2.6 Validation

The construct validity of the survey was investigated using known group validation.(86) This method involves demonstrating that the PCS, MCS or SF6D survey scores are able to discriminate scores between groups known *a priori* to have differences in their health status. Three established criteria were used to classify HIV severity: CD4 cell count, viral load and WHO clinical stage of HIV infection.

HRQoL and HSUV were hypothesized to be lower in more advanced HIV disease stages, independently of how severity was defined. Further, since HIV is predominantly a physical disease, it was hypothesized that physical scores would show greater differences than mental health scores. The specific hypotheses were: A. MCS, PCS and SF6D scores would be lower in patients with CD4<200; B. MCS, PCS and SF6D scores would be lower in patients with viral load >55,000 copies/ml; and C. MCS, PCS and SF6D scores would be lower in patients in WHO stages two, three and four compared to individuals in WHO stage 1. Since WHO stage 1 patients are asymptomatic, it was suspected that there would be a bigger difference in HRQoL and HSUV between these patients and more symptomatic patients.(59)

2.2.7 Severity threshold definitions

The United States (US) Centers for Disease Control (CDC) severity stages, based on CD4 cell count, were used as the first definition of disease severity.(88) Stage 1 includes patients with a CD4 count ≥500 cells/mm^3; stage 2 includes patients with a CD4 count between 200 and 499 cells/mm^3; and stage 3 includes patients with a CD4 count <200 cells/mm^3. The vast majority of patients initiating ART have CD4 near or below 350 cells/mm^3, in accordance with the ART treatment guidelines in Kenya at the time. Further, presentation to care with advanced HIV has been defined as having a CD4 count below 200 cells/mm^3.(89) Thus, to ensure an adequate sample in both groups, individuals were dichotomized above and below a CD4 count of 200 cells/mm^3, reflecting a comparison of patients with advanced HIV infection to those without advanced HIV infection.

The second definition of severity was based on a previous US study that used viral load threshold to classify patients.(87) Viral load is associated with disease progression: an increased viral load indicates advanced disease and predicts progression to AIDS or death.(12) Individuals were classified above or below 55,000 copies/ml to assess differences in the scores and draw descriptive comparisons to the previous US sample.(87)

The third definition of severity was the WHO HIV clinical staging system, which is based on physical symptoms. The WHO clinical stages are particularly useful in limited-resource settings, as CD4 cell counts are not always available. Symptoms have been grouped into four stages. Stage 1 patients are asymptomatic; stage 2 patients have mild symptoms such as rash or upper respiratory tract infections; stage 3 patients have moderate to severe symptoms such as unexplained chronic diarrhea for greater than one month; and stage 4 patients have severe to life-threatening symptoms such as extreme weight loss or opportunistic infections.

Based on the three definitions of severity, the sample was categorized into two groups based on their CD4 count or viral load threshold, and four groups according to WHO clinical stages. I assessed the PCS, MCS and SF6D, compared scores between each group and evaluated the discriminative ability of the scores.

2.2.8 Statistical analysis

2.2.8.1 Validation analysis

After conducting a descriptive analysis of the baseline characteristics of the study population, the PCS and MCS scores were derived using US weights, and SF6D scores were derived based on

UK weights.(77, 81, 90) The mean PCS, MCS and SF6D scores were calculated in each of the severity categories. The SF-12 was designed to give a population mean MCS and PCS of 50, with a standard deviation of 10 in a disease-free US population.(81) The minimum clinically significant difference (MCID) for both PCS and MCS scores has been suggested to be in the range of 3–5 points; however, MCID for HRQoL scores are not well-established.(91) A difference of 3 points was used to interpret the clinical significance of differences, but caution is suggested in interpreting the MCID since a 1-point change could be meaningful if it came at no additional cost.(91) The MCID for the SF6D has been suggested to be 0.033 (95% CI 0.029 to 0.037).(92) For CD4 and viral load threshold analyses, t-tests were used to test for differences between the two groups. For the WHO clinical stage analysis, we used Analysis of Variance (ANOVA) with Tukey's range test to test for differences in scores between the four groups. Participants with missing CD4 counts, viral load or WHO stage were excluded from the respective analysis.

Receiver operator characteristic (ROC) curves were used as a second test of the discriminative ability of the instruments.(87, 93) Traditionally, an ROC plots the sensitivity by 1-specificity of a diagnostic test to determine the ability of the test to discriminate between a diseased and non-diseased population. ROC curves have previously been used to determine the construct validity of an instrument by evaluating if the instrument can correctly discriminate between two groups known to have differing HRQoL.(87) Calculating the AUC required data for each individual on their severity classification based on clinical data (e.g. CD4) and classification according to the survey score (e.g. SF6D). To derive the classification according to the survey score, a decision rule was specified such that if an individual's score was above a value *x*, they would be classified

in one severity category, and if below x, they would be in the other category. The correct severity classification was specified by the clinical data. For each value of *x,* the number of correct and incorrect classifications was recorded. This information was used to evaluate the sensitivity and specificity of the survey score for each value of *x*. The sensitivity was plotted against 1-specificity to create the ROC curve.

The area under the ROC curve (AUC) measures the discriminative ability of a particular score for a given severity category comparison (e.g. CD4≥200 vs. CD4<200). The AUC is a measure of signal to noise of an instrument.(93) An AUC of 1 indicates perfect discriminatory ability; an AUC of between 0.8 to 1 shows good to excellent ability to discriminate; an AUC of between 0.7 to 0.8 shows fair discriminative ability; an AUC of between 0.60 and 0.70 shows weak ability to discriminate; an AUC below 0.60 indicates a failure to discriminate between groups; and an AUC of 0.50 suggests the instrument is no more useful to predict the group to which an individual belongs than flipping a coin.(93) The AUC of the three scores was evaluated according to five severity classification comparisons resulting in a total of 15 evaluations.

2.3 Results

The sample had 538 participants, with greater representation by females (n= 350/538; 65%) and urban residents (n= 436/538, 81%). Table 2-1 shows the characteristics of the sample separated by severity category. CD4 count data were complete; however, 9 (1.7%) participants had missing SF-12 responses; 43 (8.0%) were missing viral load data; and 72 (13.3%) were missing WHO clinical stage and these participants were excluded from the respective analysis. Table 2-2 summarizes the mean scores by severity group, and Table 2-3 lists the AUC results of each

score. We observed statistically and clinically significant differences in PCS scores in several comparisons. The MCS had a poor signal in all comparisons, indicating that it did not discriminate well across groups. The SF6D scores also show monotonic trends in the hypothesized direction in all analyses, and there were statistically significant differences in several comparisons (Table 2-2). Figure 2-1 to 2-3 show box-plots of the SF6D for each severity group comparison, and Figure 2-4 and 2-5 show the ROC curves generated through these analyses.

2.3.1 Results by CD4 count threshold

Mean PCS and SF6D scores were significantly lower in patients with CD4<200 cells/mm^3 than in patients above that threshold. A box plot of the SF6D by CD4 severity category is shown in Figure 2-1. The PCS was 4.2 units lower, suggesting a clinically significant result based on the MCID. We also compared mean values of PCS and MCS scores to a US sample, and scores from our sample were comparable to the previously reported estimates (Table 2-4).(87) The mean MCS score was also lower in patients with CD4<200 cells/mm^3, but the difference was not statistically or clinically significant. The AUC for all three scores were in the weak to poor range, indicating that they had limited ability to distinguish these groups (0.57-0.61).

2.3.2 Results by viral load threshold

The SF6D score was statistically significantly lower in patients with a viral load >55,000 copies/ml, and the difference met the specified MCID requirement. A box plot of the SF6D by viral load category is shown in Figure 2-2. The PCS and MCS scores were also lower, but neither statistically nor clinically significant. The results were comparable to a previously

reported sample (Table 2-4). The AUC was poor and nearly 0.5 for MCS, indicating that the survey could not discriminate between these populations.

2.3.3 Results by WHO stage

Both the PCS and SF6D had a statistically significant monotonic downward trend as severity increased. The box plot of the SF6D by WHO stage in Figure 3 shows this trend and also shows a reduction in variance about the mean as severity increased to WHO stage 4. The difference in PCS scores between stage 1 and stages 2, 3 and 4 was 2.1, 5.1 and 8.6 points respectively, indicating a clinically significant difference in physical health as HIV progresses from stage 1–4. The AUC of the PCS and SF6D were 0.71 and 0.68 respectively, indicating that the scores had fair discriminatory ability between WHO stages 1 and 4 (Figure 2-4). There were no statistically significant differences in mean MCS scores by WHO stages, although there appeared to be a monotonic trend downwards as disease severity increased.

2.4 Discussion

This study shows that PCS and SF6D scores derived from a Kenyan modified and translated SF-12 survey can discriminate HIV disease severity using both WHO clinical staging and CD4 cell count thresholds severity definitions. These findings suggest construct validity of the modified SF-12 and may have important implications for the use of the instrument in Kenya and other East African nations. Findings suggest that the SF-12 may be used as a tool to measure physical health as part of program and intervention evaluations. Furthermore, the SF-12 survey can be scored to derive an SF6D preference-based measure that can be used to calculate QALYs. The SF-6D scores declined with increased severity of disease and could theoretically rank health

states in a valid order in practice. These instruments could be particularly important to support the increasing demand for measurement and evaluation of HIV/AIDS programs. Additionally, our results have described the mean and distribution of a variety of HIV health states, and the results could be used in mathematical models to calculate QALYs, estimate disease burden and/or conduct economic evaluations in Kenya.

The WHO stages were perhaps the most accurate indication of HRQoL since the system relies on the presence or absence of a variety of symptoms based on HIV severity. Data were collected from highly trained research nurses as part of an internationally funded randomized trial, adding a greater level of scrutiny to data collection and accuracy of classification. We observed the largest differences in PCS and SF6D between WHO stage 1 and more progressive stages. Another strong indication of patient health in HIV is CD4 cell counts. We observed moderate differences in health based on CD4 threshold, but physical health was once again clinically and statistically lower in the more advanced stage. We showed the weakest signal of discriminatory ability using the viral load threshold. Since viral load can be high in patients who are otherwise healthy, this finding may have more to do with the severity threshold definition, rather than the survey's ability. The MCS was not discriminative in any comparison, suggesting that an alternate instrument would be needed to capture this domain of health in PLWHA.

These results were consistent with previous studies of HRQoL and HSUV in PLWHA. Delate et al. reported mean SF-12 summary scores in a sample of US PLWHA.(87) The mean PCS and MCS scores we observed in a Kenyan population have similar means and standard deviations to the US sample. In a systematic review of HIV/AIDS-focused HSUV studies, Tengs et al. pooled

utility values for three HIV health states: asymptomatic HIV, symptomatic HIV and AIDS; they reported HSUVs of 0.94, 0.82 and 0.70 respectively.(59) The mean HSUVs we observed were generally lower (0.61 – 0.73) than those reported in the systematic review (Table 2). However, the review summarized evidence of HSUV of a broad sample of PLWHA, while the cohort in this study was assessed at a particularly vulnerable time: ART initiation. Within severity groups by CD4 definitions, the average HSUV may have improved over time due to adaptation to disease and drug treatment.(94)

There were several limitations to this study. First, normative data from the United States was used to calculate the PCS and MCS and scoring data from the UK was used to calculate the SF6D scores. External scoring was used due to a lack of a local scoring algorithm for the SF-12 or SF6D in Kenya or a similar setting. Previous studies in Africa have used scoring data from other settings as a surrogate to overcome this limitation, however future studies are needed to evaluate these important measures in Kenya and other African settings.(95, 96) Second, there were missing WHO stage and viral load data for several participants. There was an adequate sample size to show statistically significant differences between groups; however, the direction of the potential bias due to missing data is unknown. Since the missing data may have been due to administrative errors, there would likely be no systematic pattern in missing patients. Third, measurement errors in the tests used to estimate CD4 counts and viral load could cause individuals who were near the threshold values to be misclassified, causing non-differential misclassification bias. Misclassification of individuals would bias the analysis towards the null, since mean values would converge between severity groups. Since there was a statistically significant difference that met the MCID, the impact of this bias may be limited. Finally, the

survey had been modified from its original questions, so theoretical constructs may have been affected. The survey appears to perform as designed in main scores derived from the survey, but more nuanced measures of health status were not assessed in this study.

The SF-12 is widely used in clinical trials in the US and Europe as an objective measure of HRQoL associated with new drug therapies and health interventions. The SF-12 could accompany clinical trials being conducted in Kenya and in other areas in East Africa to help quantify HRQoL and HSUV that have previously gone unmeasured. Further research is needed to show the ability of the SF-12 survey to detect changes in quality of life over time as patients' health status changes. Further research is also needed to determine Kenya-specific scoring for both the SF-12 and SF6D instruments, and to test the survey in a broad range of diseases.

2.5 Conclusion

This study confirms the construct validity of a translated and adapted SF-12 survey. Through a description of HSUV of commonly used HIV health states for economic models, the study provides potentially useful measures for economic evaluation. Interestingly, the mean HSUV are lower than values observed in HIV cohorts from other settings.(59) These HSUV will be used in the simulation-based evaluation in the next chapter. This study is an early step towards the increased use of the SF-12, SF6D and other HRQoL instruments in East Africa.

2.6 Figures

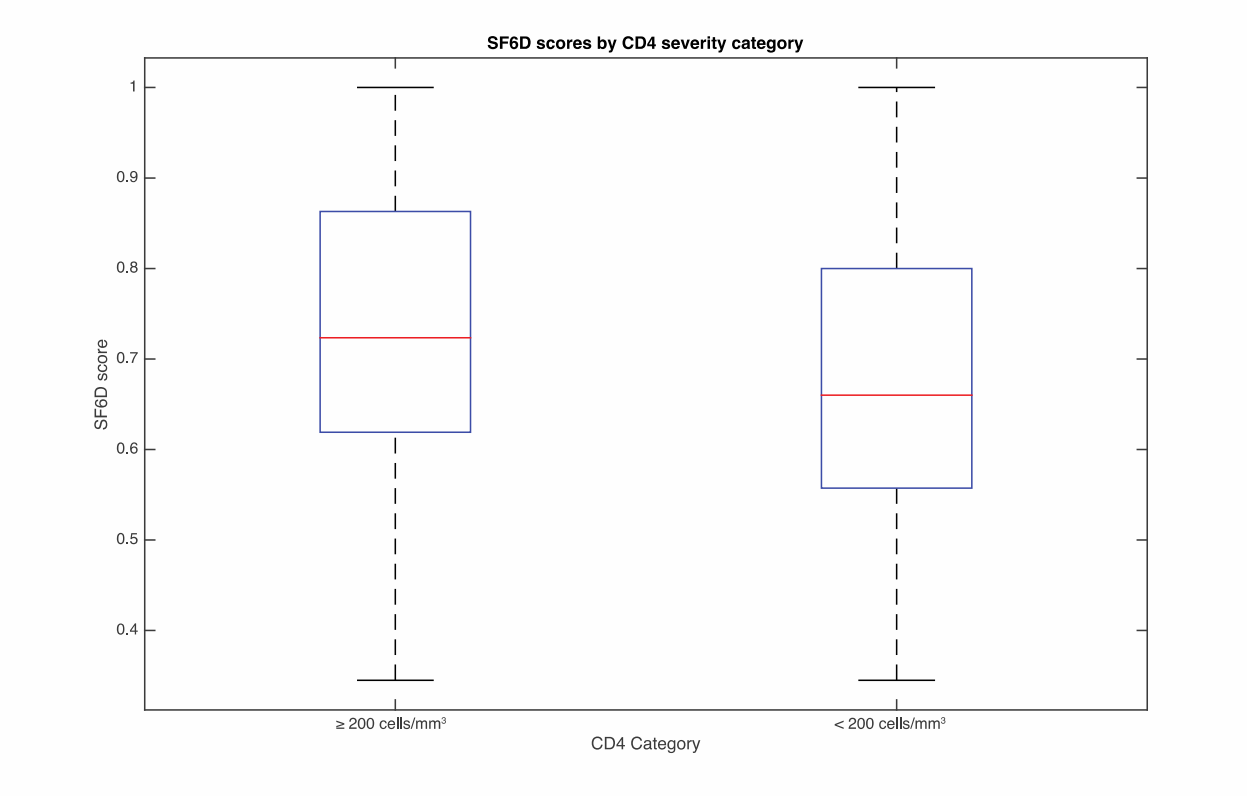

Figure 2-1. A box plot showing the distribution of SF6D scores by CD4 category. The SF6D is bound by 0.30 and 1 and has been reported to have floor effects.(39, 97, 98) For this reason, the upper and lower limits appear to be similar. However, the difference in mean is visible in these data.

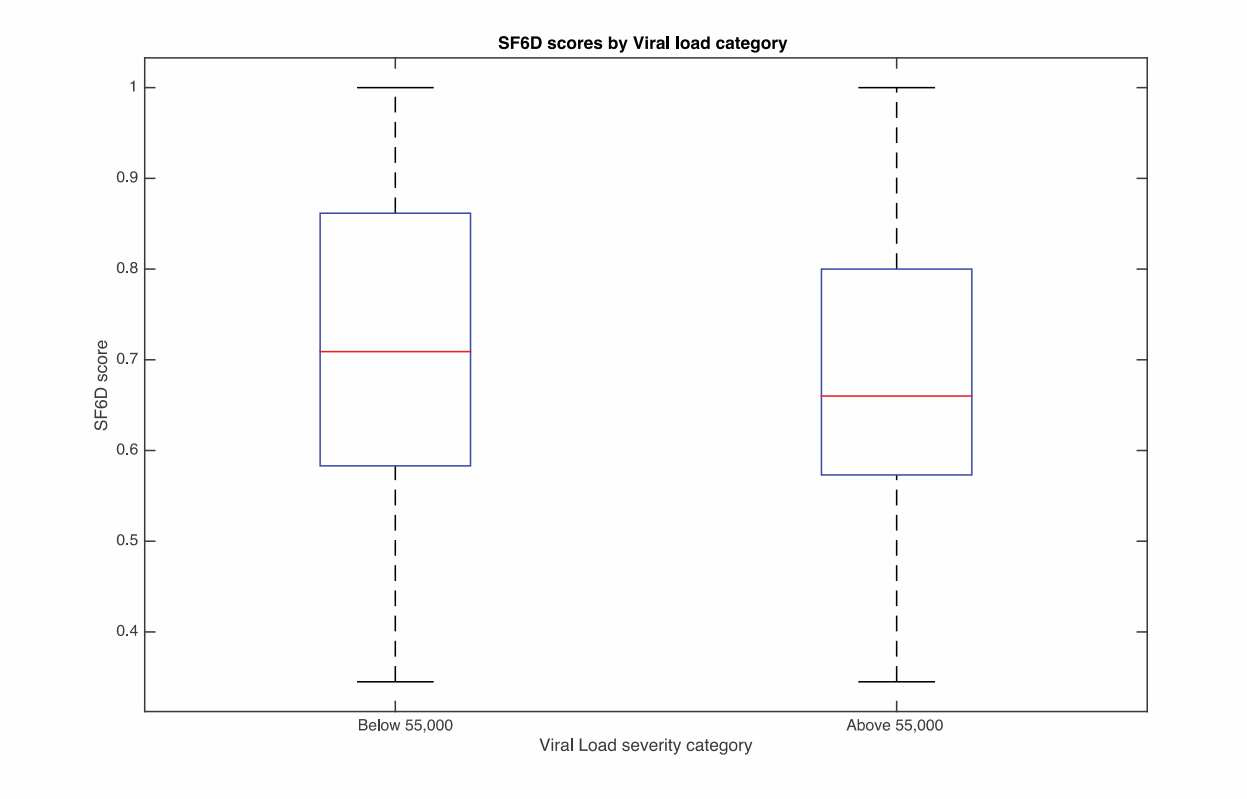

Figure 2-2. A box plot showing the distribution of SF6D scores by viral load severity category. Once again, the upper and lower limits appear to be similar, however, the difference in mean and variance are visible in these data.

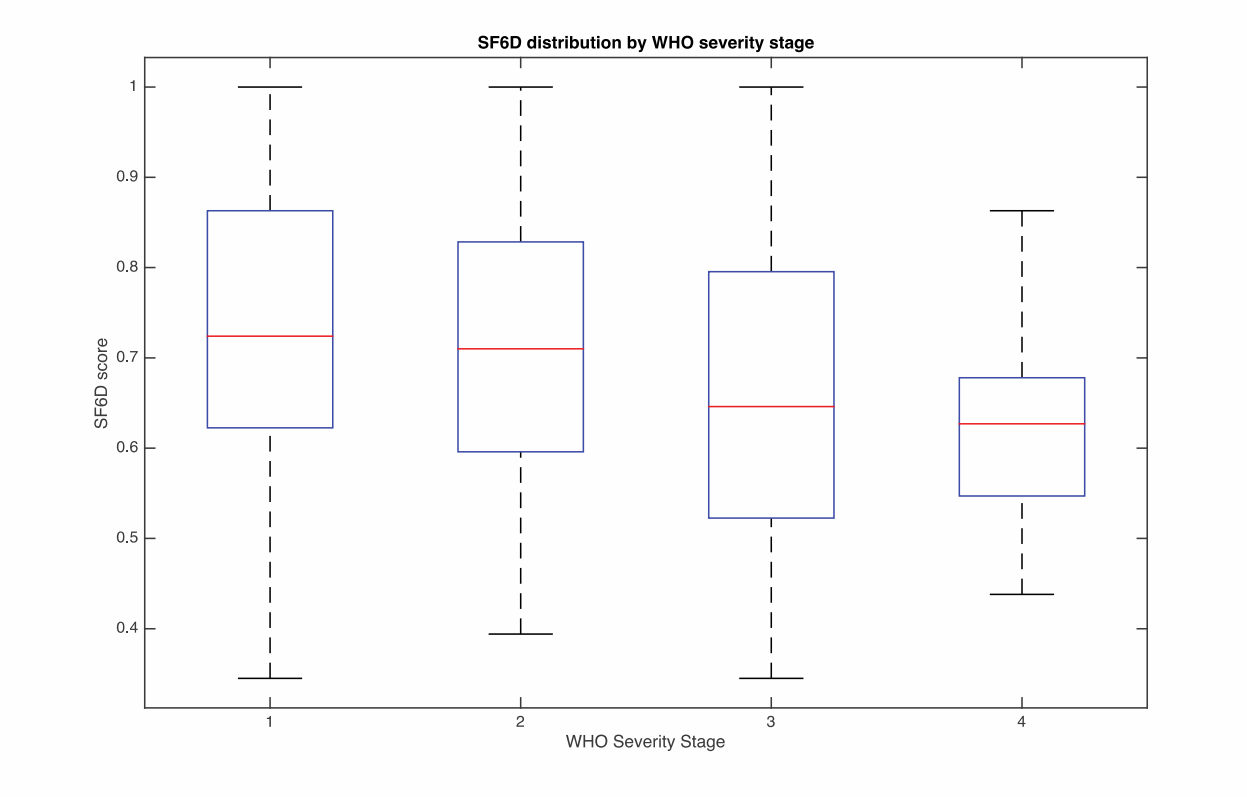

Figure 2-3. A box plot showing the distribution of SF6D scores by WHO stage. The floor effects were slightly less impactful with this more granular classification of disease severity. A decreasing monotonic trend in mean SF6D scores is seen as the severity stage increases. The variance of SF6D scores is also reduced in WHO stage 4, which incidentally had the smallest sample within these categories.

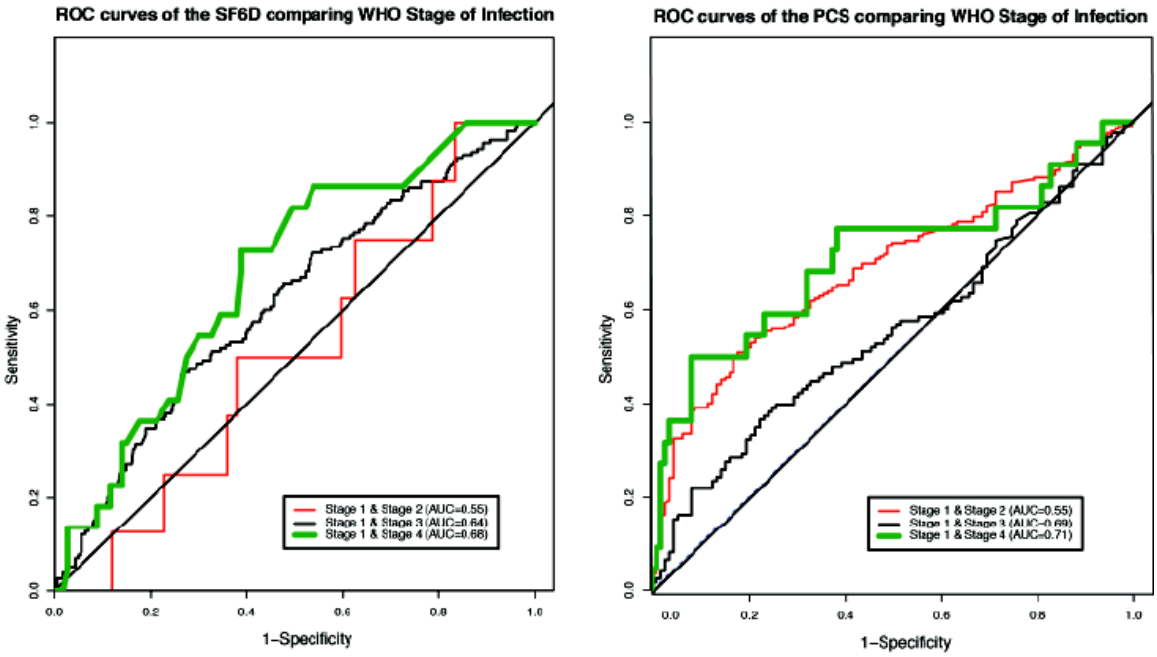

Figure 2-4. The PCS and SF6D ROC curves when comparing WHO stage 1 to more advanced stages. The area under the ROC curve (AUC) is a measure of signal to noise of an instrument. The signal appears to improve as the severity gap between the comparison groups increases. This indicates discriminatory ability of both survey scores and gives face validity to them since the survey is correctly measuring what it was designed to measure.

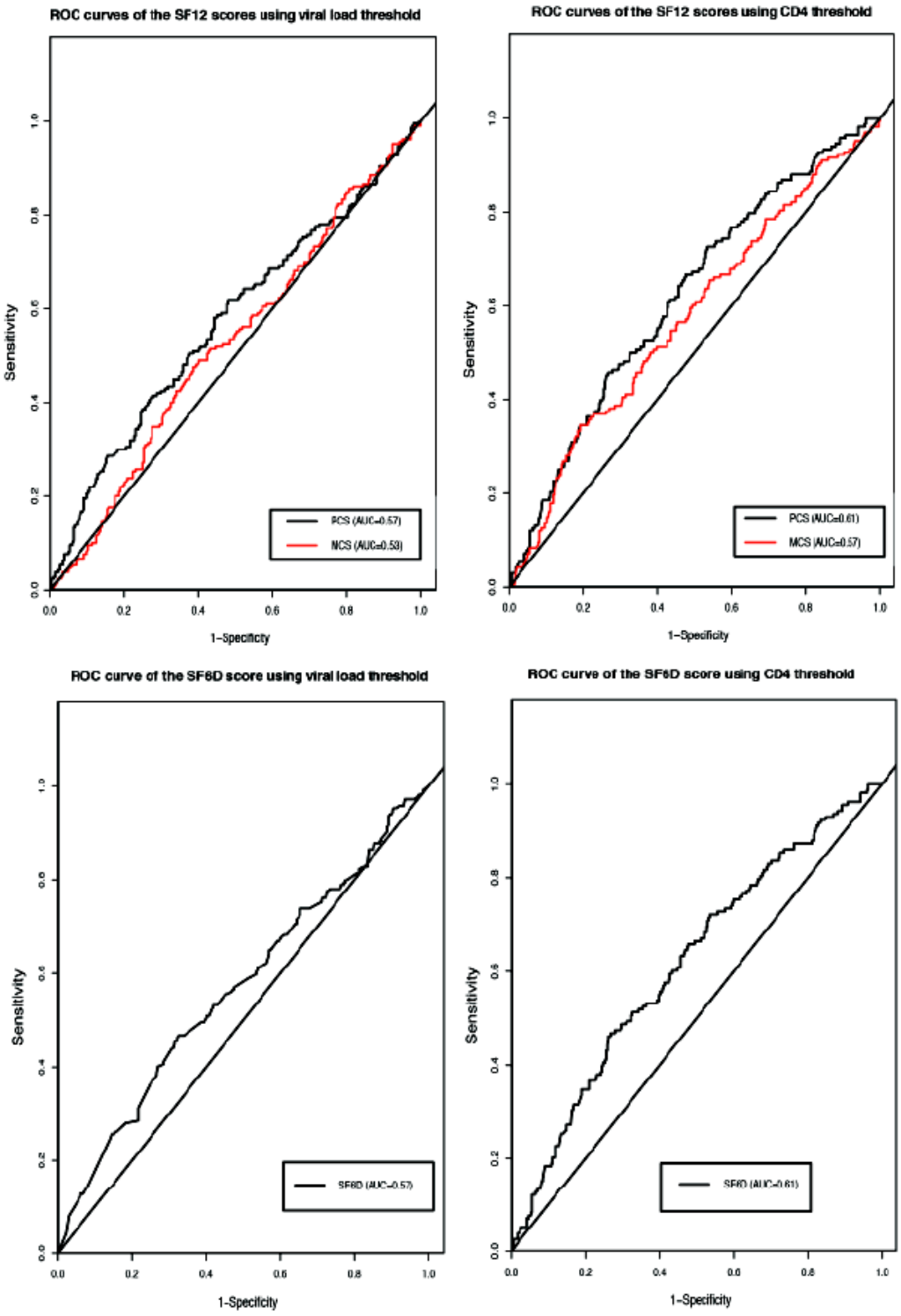

Figure 2-5. The ROC curves of all SF-12 derived scores using CD4 and viral load thresholds. The signal was weaker in this comparison, partly because of the more general definitions of severity. The SF6D and PCS once again had a stronger signal than the MCS.

2.7 Tables

Table 2-1: Characteristics of sample separated by severity category

	CD4<200 N=364 N(%)	CD4 ≥200 N= 169 N(%)	VL >55,000 N=281 N(%)	VL ≤55,000 N=214 N(%)	Stage 1 N=114 N(%)	Stage 2 N=126 N(%)	Stage 3 N=204 N(%)	Stage 4 N=22 N(%)
Male Gender	136 (37)	51 (30)	114 (41)	62 (29)	30 (26)	48 (38)	72 (35)	7 (32)
Age								
20-29	62 (17)	37 (22)	46 (16)	43 (20)	30 (26)	19 (15)	39 (19)	4(18)
30-39	184 (51)	88 (52)	148 (53)	104 (49)	63 (55)	59 (47)	95 (47)	10 (45)
40-49	89 (24)	32 (19)	68 (24)	48 (22)	16 (14)	24 (19)	51 (25)	8 (36)
50+	30 (8)	12 (7)	19 (7)	19 (9)	5 (4)	3 (2)	19 (9)	0 (0)
Income (Schillings)								
≤2,000	93 (29)	43 (29)	58 (23)	65 (35)	26 (27)	29 (25)	57 (32)	6 (30)
2,001 - 10,000	140 (43)	71 (48)	114 (45)	80 (43)	41 (43)	59 (51)	84 (48)	4 (20)
10,001 - 40,000	75 (23)	30 (20)	64 (25)	36 (19)	25 (26)	24 (20)	27 (15)	10 (50)
>40,000	14 (4)	5 (3)	15 (6)	4 (2)	3 (3)	3 (2)	8 (5)	0 (0)
Urban Res.	295 (81)	139 (82)	238 (85)	170 (79)	107 (94)	116 (92)	137 (67)	18 (82)

***VL = viral load**

Table 2-2: Comparison of mean HRQoL and HSUV scores by severity subgroup

Sub Group	PCS (SD) ~	MCS (SD) ~	SF6D (SD) ~
CD4<200 N= 361	41.1 (11.0) *	43.4 (10.7)	0.67(0.15) *
CD4 ≥ 200 N= 168	45.3 (10.3) *	45.7 (11.0)	0.72(0.15) *
Viral Load > 55000 N=278	41.4 (10.7)	43.8 (10.9)	0.67 (0.15) *
Viral Load ≤ 55000 N= 213	43.8 (11.2)	44.5 (10.8)	0.71 (0.16) *
WHO Stage 1 N=114	46.7 (8.6)**	45.7 (11.1)	0.73 (0.15) **
WHO Stage 2 N=126	44.6 (10.2)	44.6 (10.3)	0.71 (0.15)
WHO Stage 3 N=204	39.5 (11.3) **	42.6 (11.0)	0.66 (0.16) **
WHO Stage 4 N=22	38.1 (12.0) **	42.5 (10.2)	0.61 (0.13) **

~ Standard Deviation

* Statistically significant difference between severity group p<0.01

** Statistically significant difference between severity group p<0.001 based on ANOVA with post-hoc Tukey's procedure

Table 2-3: Comparisons Area under the ROC curve (AUC) by severity subgroup

Comparison Groups	PCS AUC	MCS AUC	SF6D AUC
CD4<200 vs CD4 ≥200	0.61	0.57	0.61
Viral Load ≤55000 vs >55000	0.57	0.53	0.57
WHO stage 1 vs stage 2	0.55	0.54	0.55
WHO stage 1 vs stage 3	0.69	0.59	0.64
WHO stage 1 vs stage 4	0.71	0.59	0.68

Table 2-4: Comparison of mean HRQoL scores to a US sample of PLWHA

	PCS Kenya Mean (SD*)	MCS Kenya Mean (SD)	PCS USA(87) Mean (SD)	MCS USA(87) Mean (SD)
CD4 ≥ 200 cells/mm^3	45.3 (10.3)	45.7 (11.0)	45.3(11.3)	42.6 (9.6)
CD4 < 200 cells/mm^3	41.1 (11.0)	43.4(10.7)	40.1 (11.4)	43.3(9.8)
Viral load ≤ 55,000 copies/ml	43.8 (11.2)	44.5 (10.8)	44.5 (11.6)	42.9 (9.5)
Viral load > 55,000 copies/ml	41.4 (10.7)	43.8 (11.2)	40.2 (11.5)	41.6 (10.2)

3 The cost-effectiveness of mobile phone interventions to improve adherence to HIV therapy in Kenya

3.1 Background

Mobile phones are a viable technology to improve healthcare delivery because of their widespread global availability.(99) The global technology boom has fueled an emergence of mobile health applications delivered through text-messages, also known as Short Message Service (SMS). Some SMS interventions have strong randomized controlled trial (RCT) evidence to improve medication adherence, yet have not been implemented at scale, which represents a lost opportunity for global health.(48) One promising application of SMS interventions is to enhance HIV treatment programs. In 2012, 35.3 million people were living with HIV worldwide, including 1.6 million people in Kenya.(36) Life-saving antiretroviral therapy (ART) has become increasingly available, and has meaningfully impacted health outcomes and HIV transmission.

The World Health Organization (WHO) recently announced that 17 million people worldwide were on ART at the end of 2015, and the organization is pushing for more widespread test and treat strategies.(100) Two major challenges still facing global HIV treatment efforts are poor adherence to daily doses of ART, and poor retention in care. Adherence above 90%–95% is needed for many regimens of ART to have optimal treatment outcomes; however, adherence has been shown to be lower in many

populations.(5, 27) Retention rates are also poor; in African ART programs, average patient retention three years after treatment initiation is estimated to be 65%.(27) The major consequence of both poor adherence and poor retention is reduced viral suppression, which can accelerate progression to AIDS as well as increase HIV transmission. It is unclear whether limited budgets could more efficiently save lives by expanding ART further or by focusing on interventions to improve existing recipient engagement in treatment and care.

A body of literature suggests that some SMS interventions can address non-adherence to medication, including ART. Independently conducted systematic reviews of randomized controlled trials of SMS interventions delivered weekly concluded that reminders and SMS-based patient engagement improved adherence to ART (RR 1.28).(1, 2, 45) Systematic reviews of all interventions that target ART non-adherence suggested that SMS interventions have one of the strongest levels of supportive evidence.(1, 5) Further, SMS intervention might also improve retention in care (RR 1.69).(6) The breadth of evidence supporting the use of SMS interventions led to the WHO recommending SMS to promote adherence in the organization's 2013 Consolidated Guidelines on the use of ART.(101)

Despite compelling evidence, effective SMS adherence interventions have not been implemented to scale. Previous studies have used computer simulation models to determine the cost-effectiveness of ART expansion.(36, 70, 71) However, there have been no cost-effectiveness evaluations describing the incremental value of SMS

adherence interventions, so it is unclear how investment in them would compare to expansion of ART or to other potential HIV interventions.(5, 47) Thus, the objective of this study was to examine the cost-effectiveness of a weekly SMS-based adherence intervention compared to usual care in people living with HIV/AIDS (PLWHA) initiating ART in Kenya.

3.2 Methods

3.2.1 Definitions

Adherence is defined as the extent to which individuals adhere to daily doses of ART, and a threshold of 90% was used to differentiate highly adherent from sub-optimally adherent individuals. *Adherence under standard care* (ASC) is defined as the proportion of individuals who are highly adherent under the standard of care in Kenya, which includes one or two adherence counseling sessions at ART initiation.(6) Also under standard care, peer-support and participation in support groups were suggested, but not mandated.(6) *Retention-in-care* is defined as consistent prescription pick-up of ART, and reporting for regular care and CD4 testing. *Dropout* refers to an individual who has *disengaged from care* and is no longer receiving regular care or medication refills.

3.2.2 Model overview

The target population of this analysis was Kenyan PLWHA initiating ART who own mobile phones. An individual-level HIV microsimulation model was used to estimate the long-term health and economic impacts of weekly SMS adherence interventions

compared to standard care. A previously published stochastic, second-order Monte Carlo simulation model of HIV progression was revised for this analysis.(43, 102) Cohorts of one million individuals were simulated from the time of ART initiation to death from either HIV/AIDS or background causes. The adherence intervention cost and effectiveness as well as adherence behavior were based on clinical data observed in two randomized trials. Additional parameters came from literature reviews and from a previously conducted study of the Academic Model for the Prevention and Treatment of HIV (AMPATH) cohort, a multiyear cohort in East Africa.(68, 103, 104) The simulated cohort characteristics (e.g., age) matched the data observed in the two trials and AMPATH cohort in order to generalize the findings of this study across Kenya.

3.2.3 Model structure

The model simulated HIV progression using relationships between multiple inputs including CD4 count, viral load and adherence to ART (Figure 3-1). The model used a daily time cycle and monitored events including daily adherence to one of two regimens of ART, changes in viral load, changes in CD4 count, development of drug resistance and development of events that could impact healthcare spending.

Each individual entered the simulation with a CD4 count drawn from a distribution matching clinical data observed in a large East African cohort.(105) The daily viral load and patient characteristics (e.g. gender, age) affected the daily changes in CD4 cell count based on the natural history of HIV disease.(12) A high viral load caused the CD4 cell count to drop rapidly over time, while a suppressed viral load allowed for CD4 recovery

over time. Individuals were at risk of HIV-related events (e.g. hospitalization) and mortality throughout their lifetime, but the risk of these events greatly increased at lower CD4 counts. The CD4 cell count also defined health states used to calculate quality-adjusted life years (QALYs) according to three categories: CD4 < 100 cells/mm^3, CD4 between 101 cells/mm^3 and 199 cells/mm^3 and CD4 > 200 cells/mm^3. The accrual of drugs and blood testing costs remained consistent (as a function of an individual's adherence to therapy and retention in care), while costs of hospitalization and care accrued faster at lower CD4 counts, attributable to the increased incidence of AIDS-related events. Due to the importance of CD4 count in determining costs and health outputs, the simulation was previously calibrated to changes in CD4 counts over time observed in Kenya.(102) The calibration was confirmed for this analysis.

An individual's CD4 count, viral load and age affected their probability of death from HIV/AIDS, which increased over time. Individuals were also at risk of death from background causes, and their age and gender affected this probability over time. The background mortality rate came from East African life tables.(106) HIV/AIDS-related deaths were tracked separately from background causes in the simulation.

Disengagement from care assumed individuals were off drug therapy and did not attend regular appointments. Once *disengaged,* CD4 declined based on individual characteristics and the natural history of disease.(12) The CD4 count continued to decline until a simulated individual either returned to care or died. The probability of returning to care or death was a function of an individual's CD4 count, and the probability of both events

increased as CD4 count declined. Individuals were at risk of dropout and return to care based on rates observed in a large East Africa cohort.(105) Additional details about the disengagement component of the simulation can be found elsewhere.(107) The potential for SMS interventions to reduce this risk was explored in secondary analysis by reducing the rate of dropout.

Individuals exited the simulation upon death and their total health care costs and QALYs were calculated. The model outputs included individual level outcomes, but not secondary transmission. Outcomes were discounted at 3%, and average discounted costs and QALYs for the cohort were used to calculate the incremental cost-effectiveness ratios. The model has been previously validated through its ability to predict clinical outcomes matching North American and East African cohort data.(70, 102) Additional technical detail about the model development and calibration can be found in previous publications.(43, 70, 102)

3.2.4 How adherence and adherence interventions were modeled

3.2.4.1 SMS intervention evidence

A literature review of SMS interventions was conducted, revealing multiple systematic reviews that summarized the adherence effects of weekly SMS.(1, 2, 45) The review by Hovarth et al.(2) incidentally only included RCTs from Kenya and presented the most conservative SMS intervention effect size. The conservative effect size was selected in the base case analysis to present a conservative estimate of cost-effectiveness. The effect size was varied across the published 95% confidence interval in sensitivity analysis. Two

SMS randomized controlled trials were included in Hovarth et al.'s weekly intervention analysis: one studied one-way supportive SMS reminders while the other studied two-way SMS-based individual engagement. Details of the intervention costs and effects are discussed in greater detail below.

3.2.4.2 How adherence affected HIV outcomes

Simulated individuals maintained an average lifetime adherence between 0%–100%, and their prognosis and health system utilization were impacted by their adherence. Simulated individuals experienced fluctuating CD4 counts and viral load (as a function of their adherence) and were also at risk of developing drug resistance. Daily adherence was based on an individuals' propensity to adhere as defined by the input. Their adherence affected their rate of drug resistance development, CD4 count rebound or decline, and rate of viral suppression or rebound. Individuals entered the simulation with a baseline viral load (copies of HIV per ml) drawn from a log-normal distribution matching clinical observations from a large east African cohort (Table 3-1).(105)

A first-line regimen and a second-line regimen of ART (listed in Table 3-1) were included in this simulation, based on drug availability in Kenya. Each regimen differentially affected the viral load over time. The time to achieve the maximum reduction was a function of the ART regimen, level of adherence and presence of resistance. The maximum reductions (assuming perfect adherence and no drug resistance) for each regimen are listed in Table 3-1 and were based on observations from a previous study.(35)

Individuals who were perfectly adherent with no resistance experienced a daily viral load reduction according to an exponential function that approached the maximum reduction. If an individual was non-adherent or developed resistance, the maximum reduction value was lowered proportionally for that day, causing the exponential function to change. If drug therapy was stopped or a dose was missed, their viral load would return to the baseline viral load according to the same exponential function in reverse. The function describing the relationship between drug adherence and viral load suppression was informed by a previous study.(108) Additional details of the adherence logic have been published elsewhere.(109-111)

3.2.4.3 How adherence intervention effects were simulated

At the start of each run, individual adherence was specified, and the individual maintained that level of adherence as an average over their lifetime, with some variability in their daily adherence. The simulated cohort consisted of highly adherent individuals whose input was specified between 90%–100% of daily ART doses and sub-optimally adherent individuals whose input was specified to be >90% of daily doses. The adherence interventions acted by increasing the number of highly adherent values drawn at baseline (Figure 3-3).

The distribution of individual adherence within the highly adherent and sub-optimally adherent categories was based on the patient-level adherence observed in one randomized trial (Figure 3-2).(67) A distribution of adherence was created based on the Pop-Eleches

et al. trial data, because they used MEMS caps to measure individual adherence. MEMS caps have been suggested to be a more conservative measurement of adherence compared to self-report used by the Lester et al. trial (Figure 3-2).(6) A simplifying assumption was made that the distribution of adherence within each category remained consistent, since an improvement in the adherence distribution attributable to the intervention was not apparent in the data. In other words, if an individual was classified as sub-optimally adherent, the probability of their adherence input being drawn as 63% was the same for the intervention and standard care simulations.

3.2.4.4 Adherence under standard care

A key assumption in this analysis was the proportion of highly adherent individuals with no intervention in place. The trials included in this analysis reported different endpoint proportions of highly adherent individuals in the control group. Endpoint control group adherence was used as a proxy for the simulated *proportion of high adherence under standard care* (ASC). The Lester et al. trial found 50% were highly adherent, and the Pop-Eleches et al. trial found that 40% of individuals were highly adherent in the control group. For the base case analysis, the Lester et al. control group was conservatively chosen to reflect ASC (Figure 3-2).

To derive the proportion of individual that were highly adherent with the SMS intervention, the ASC input was multiplied by the intervention effectiveness input. For example, if the ASC was 40% and the intervention relative risk of adherence was 1.1, the proportion of highly adherent individuals with the SMS intervention would be 44%. To

increase the generalizability of our analysis, a sensitivity analysis was conducted over a wide range of plausible ASC, to show how the value of the SMS intervention would change with alternative assumptions about population ASC.

3.2.4.5 SMS intervention effectiveness

The two RCTs from Kenya tested similar but distinct weekly SMS interventions. The trial conducted by Lester et al.(6) tested SMS-based patient engagement where individuals and providers could keep in contact via weekly two-way SMS messages. Individuals received an SMS once a week that read *"Mambo"* (meaning "How are you?"), to which they could respond *"Sawa"* ("Fine") or *"Shida"* ("Problem"). If an individual responded *Shida* or did not respond within 48 hours, a nurse would follow up with a phone call. The two-way engagement intervention not only increased one-year ART adherence (RR=1.24 p=0.006), but also increased viral load suppression (RR=1.14 p=0.04).(6) Additionally, Lester et al results showed trend to improve retention in care (RR=1.69 p=0.094).(6) A subsequent qualitative study suggests that the intensive engagement allowed nurses to manage their patients better through active awareness of their health status and engagement with the clinic.(112) The estimate of SMS effectiveness is based upon the Lester et al. trial, which was not fully powered to measure retention. A plausible base case and uncertainty interval for estimates of retention benefits (RR=1.69; Range= 1 – 3.23) was explored, based on the reported result from the Lester et al. trial.(6)

The trial conducted by Pop-Eleches et al.(67) tested weekly and daily supportive SMS by sending messages of support to patients along with a reminder to take medications.

Messages were sent once a week, but individuals did not have an option to respond. This trial found that weekly supportive SMS increased 48-week ART adherence (RR=1.34 p=0.01), and found that daily messages did not improve adherence compared to usual care.(67) Since the two trials from Kenya showed similar efficacy and were statistically indistinguishable, the pooled efficacy estimate from Hovarth et al. (RR=1.28) was used in the base case analysis.(2)

3.2.4.6 SMS intervention costs

The intervention costs during the trials consisted of initial staff training, SMS airtime, overhead and technology maintenance, and in the case of two-way SMS, labour to respond to individuals experiencing problems. Based on trial data, overhead, technology and SMS costs in both interventions were comparable and so were assumed to be the same. However, technology improvements have been made that affect the cost and scalability of these interventions. The efficiency gains using a digital platform have allowed clinics to manage more patients with less staff, thus reducing clinic-level costs, but have led to increased technology, training and maintenance costs at the programmatic level. Technological advances could improve the reliability and efficiency of the system, but require more support and have a higher chance of technical errors. Thus, the annual cost of the SMS intervention at full scale remains uncertain.

Labour costs to provide two-way SMS were higher due to nurse responses; however, qualitative trial data suggest that nurses save time in other areas of their work, such as patient follow-up, as a result of the intervention. A minority of individuals (less than

10%) required triage for problems; however, follow-up efficiencies may have been realized across all individuals receiving the engagement SMS. Thus, the labour costs were assumed to be the same in our base case analysis due to this possible offset. While trial data suggest the current average cost of the intervention might be lower, we assumed a $15 annual cost in our base case to consider unknown scale-up risks to the cost and provide a conservative estimate of cost-effectiveness. A wide range of intervention costs were explored in one-way sensitivity analyses to address any differences in cost between the interventions or overestimates in our base case. A multivariate sensitivity analysis also shows the relationship between intervention costs and three other key model inputs. A lifetime annual cost was assumed in most analyses, but a one-time cost was tested in sensitivity analysis.

3.2.5 Additional simulation settings

Costs were evaluated from a health system perspective. Drug costs for each regimen of ART were provided through personal communication with research staff in Nairobi, and were based on quotes from the Kenya Pharma, an agency mandated to supply ART for CDC/PEPFAR funded projects.(113) ART regimens used by simulated individuals reflected current Kenyan treatment guidelines, which are based on WHO treatment guidelines.(101) Additional treatment costs including hospitalization and outpatient HIV care costs were derived from AMPATH databases. Kenyan HSUVs based on CD4 count categories (<100 cells/mm^3, 101-200 cells/mm^3 and >201 cells/mm^3) were measured from the Lester et al. trial data.

3.2.6 Analysis

3.2.6.1 Base case analysis

The model outputs included five-year mortality, life expectancy, quality-adjusted life expectancy and lifetime costs. Mortality and morbidity outcomes were combined into QALYs, because of the extensive body of published literature quantifying global individual preferences for health states in HIV and because HSUV were available through trial data.(59) The strategies compared were SMS intervention to standard care, and results were summarized using incremental cost-effectiveness ratios (ICERs). The base case analysis focused on adherence outcomes. Lifetime health benefit of the SMS interventions were assumed in the base case analysis. Lifetime annual costs of the interventions were assumed, reflecting the idea that these interventions would be providing lifelong support and engagement for PLWHA. Cost and QALY outcomes were discounted at 3% based on WHO guidelines, and a lifetime horizon was used. The WHO suggests that an intervention in select African countries, including Kenya, is cost-effective at less than $US 6,461/QALY, and very cost-effective at less than $US 2,154/QALY.(65) These thresholds were used to interpret the final results. Sensitivity analyses were conducted by varying key model parameters that were relevant to the final results. Parameter uncertainty was derived from the best available evidence or plausible uncertainty ranges were used if no data were available (Table 3-1).

3.2.6.2 Secondary analysis

Based on the potential retention benefits observed in the Lester et al. trial, a secondary analysis included both adherence and retention outcomes. A mean, strong and weak

efficacy was tested for both adherence and retention effects to examine the change in ICER under various scenarios. These analyses were repeated across the same range of ASC assumptions as the base case and sensitivity analyses.

3.2.6.3 Sensitivity analyses

A total of seven sensitivity analyses were included. The first sensitivity analysis was a one-way sensitivity analysis of key model parameters, testing the impact of individual parameters on the final ICER. The second analysis compared the base case analysis to a hypothetical scenario of expanded testing and treatment. The WHO and other global HIV agencies aim to expand ART to a far greater number of individuals to move towards an AIDS-free generation. This analysis considered the value of SMS interventions within the test and treat strategy and compared current guideline-based care to a future scenario where individuals in Kenya would initiate ART at much higher CD4 counts.

The final sensitivity analyses tested a wide range of ASC assumptions, a shorter period of SMS intervention effect durability and alternative HSUVs based on US data for HIV health states. Several ASC assumptions were tested from 30% to 90% to understand the value of SMS in different populations of PLWHA. A series of analyses were conducted where the effect of the intervention was nullified over 1, 5 and 10 years. The analysis was repeated assuming a one-time and lifetime intervention cost to examine a comprehensive range of scenarios. In the next sensitivity analysis, the HSUV previously measured in a US population were used in a sensitivity analysis as well as unadjusted life years to understand the impact of HSUV on the final results. Finally, a multivariate sensitivity

analysis was conducted to evaluate the interaction of four key simulation inputs: intervention costs, effectiveness, ASC and average CD4 count at ART initiation.

3.3 Results

3.3.1 Base case and secondary analyses results

In the base case analysis, the SMS interventions were found to improve survival and were very cost-effective by WHO standards (Table 3-2a). Based on the ASC observed in the Lester et al. trial, the average survival time was found to increase from 22.53 years to 22.95 years, and found the ICER was found to be $1,389/QALY. Based on the ASC observed in the Pop-Eleches et al. trial, average individual survival time was found to increase from 22.11 years to 22.64 years, and found the ICER was found to be $1,232/QALY.

In a secondary analysis, an additional retention in care benefit was considered. When a retention benefit was included, survival improved above the primary analysis (24.35 years vs. 22.95 years) and the cost-effectiveness ratio decreased relative to the primary analysis ($1,166/QALY and $1,125/QALY, respectively). Lifetime outcomes based on ASC from both trials are presented in Table 3-2b.

3.3.2 One-way sensitivity analysis results

The robustness of our results was tested through one-way sensitivity analysis of critical model inputs. Table 3-3 lists the parameters with the most influence on the final ICER.

The annual program cost had the highest impact on the ICER, and at the upper value of cost of $45 per patient per year, the ICER was $2,867, suggesting that SMS intervention is still cost-effective by WHO standards (Table 3-3). Average individual survival had higher variation, but the ICER was not significantly impacted by changes in most parameters. In most one-way sensitivity analyses, the intervention remained below the WHO cost-effective threshold for region Afro-E.

3.3.3 Additional sensitivity and scenario analyses

The value of the SMS was tested under various assumptions of ASC (Table 3-4). The intervention was cost-effective across most scenarios, even when ASC was 90%. The ICER was also calculated using unadjusted life years, and results were similar to the ICER calculated using QALYs. An attenuated efficacy of the SMS intervention was tested over 1, 5 and 10 years. This sensitivity analysis was conducted assuming a one-time program cost (Table 3-5) and a lifetime intervention cost (Table 3-6). In both scenarios, SMS intervention remained cost-effective, but survival benefits were attenuated. Outcomes were also assessed using SF6D utility scores from Kenya and SMS-based adherence interventions remained cost-effective. The results are presented in Table 3-7.

The relationship between intervention costs and effectiveness and their combined impact on the ICER can be seen Figure 3-4. Threshold values are suggested for the SMS intervention costs at different levels of the other three variables. Under an assumption of a strong intervention effect, SMS interventions could cost up to $50 and remain cost-

effective in many scenarios. Conversely, with a weak intervention effect, the intervention was no longer cost-effective at prices higher than $15 is most scenarios. At an intervention cost of $5, the SMS interventions were cost-effective or very cost-effective in all scenarios tested.

3.4 Discussion

This study shows that two types of weekly SMS interventions – one-way reminders and two-way engagement – are cost-effective by WHO standards. A wide-range of scenarios and assumptions about model inputs were explored to strengthen our findings. The ICER was $1,389/ QALY in the base case, and when SMS intervention effectiveness was varied over a plausible range, the ICER ranged from $1,080 to $5,139/QALY. In addition to being highly cost-effective by WHO standards, SMS interventions could provide much-needed support for individuals to remain engaged by the health system, and improve patient follow-up in the case of two-way messages. Due to the widespread availability of cell phones, these interventions could be scaled up using current infrastructure. These findings have important implication for ART delivery programs, which seek ways to contain HIV epidemics at low costs.

In addition to the WHO thresholds for cost-effectiveness, a second benchmark of cost-effectiveness is a comparison to past budget-constrained decisions. A previously studied budget-constrained decision was to increase the ART initiation threshold from CD4 $\leq$200cells/mm^3 to CD4 $\leq$350 cells/mm^3. Two studies describe the cost-effectiveness of this decision using decision analytic modeling. Braithewaite et al. estimated the ICER of

this decision was $2,600/QALY.(102) A second, independent study by Walensky et al. estimated an ICER of $1,200/life year saved.(71) This study did not include quality of life adjustments, so the ICER may be underestimated relative to an estimate with inclusion of a quality of life adjustment. The ICER for the SMS interventions was found to be $1,389/QALY with no retention benefits and $1,166/QALY with retention benefits. Our results suggest that investment in SMS programs for individuals receiving ART could have comparable, or potentially better, efficiency than the previously implemented decision of expanded ART.

The value of SMS interventions was explored in the context of test and treat strategies that recommend immediate initiation of ART once an individual has tested positive for HIV. The move from current guidelines to test and treat guidelines had an ICER ranging from $497 to $528, suggesting that the strategy would be highly cost-effective relative to today, assuming there were no added implementation costs. However in most test and treat scenarios, the SMS intervention remained cost-effective by WHO standards (Table 3-4). This result suggests that the value of SMS interventions would be maintained within expanded treatment recommendations and could aid the success of expanded treatment initiatives.

Data beyond the one-year trial period are lacking in terms of the effects of the interventions. In our most extreme scenario of attenuated intervention effect, the intervention effects were lost one year after the intervention, and individuals that were newly-high adherers reverted back to having a lifetime adherence level <90%. The SMS-

based adherence interventions remained cost-effective, suggesting that the value would be preserved even if the effectiveness wore off over time. It was clear that lifelong application of the intervention was less cost-effective than a one-year application, however, the potential for added patient satisfaction and engagement might justify some of the cost.

Aside from cost-effectiveness, the rationale for using funds to support SMS interventions is likely to be stronger if the interventions have positive health and economic externalities *or* if the interventions help improve outcomes for poor beneficiaries and therefore increase equity in health outcomes.(114) SMS interventions could meet both of these additional criteria. One major positive externality of improved adherence is the prevention of further transmission. Treatment as prevention has gained significant favour in recent HIV management strategies.(115) Low-cost ways to improve adherence are recognized as critical to prevent the spread of HIV in Kenya and beyond. Additionally, SMS interventions are advantageous in terms of ability to reach rural and extremely poor individuals. Much of the infrastructure to provide the interventions exists due to the widespread cell phone expansion that has occurred in Kenya and other countries. Cell phones are commonly available, and the programmatic costs are relatively low due to automation of most tasks. The engagement SMS programs may have an additional reach, in that individuals would not required to own their own phones but could access the service through a friend, family member or treatment partner.

This study has several important limitations. First, individual level adherence data came from the Pop-Eleches et al. trial in Western Kenya, but may not be representative of broader populations. To address this limitation, findings were tested under varying ASC to understand the impact on the final ICER. As more refined individual level adherence data become available, this limitation can be further addressed in subsequent iterations of the model. Second, secondary transmission was not evaluated in the outcomes. Treatment as prevention, or the now accepted concept that suppressed viral load prevents further transmission, was not formally considered and would have led to greater health system savings. The cost-effectiveness of these interventions would be improved if those benefits were modeled and could even be cost saving in the long run. However, at the individual patient level, we are able to confirm SMS intervention is cost-effective. Finally, uncertainty distributions for key inputs were unknown, so a probabilistic analysis was not possible. Instead, a wide range of scenarios was included to evaluate the cost-effectiveness of these interventions under different assumptions. Analyses included higher or lower ASC and implementation of the SMS-based adherence interventions alongside a test and treat strategy.

3.5 Conclusion

The main policy implication of the findings is that the strategic use of SMS can improve ART outcomes in Kenya and beyond. In addition to being a cost-effective use of scarce funds, these programs have the opportunity to reach poor and rural individuals and increase communication between individuals and providers in a tangible way. Further research is needed to identify the most efficient ways to implement SMS programs, and

to investigate the relationship between retention and adherence. Introduction of these programs in extended settings would allow for further investigation of differential benefits in sub-groups.

3.6 Figures

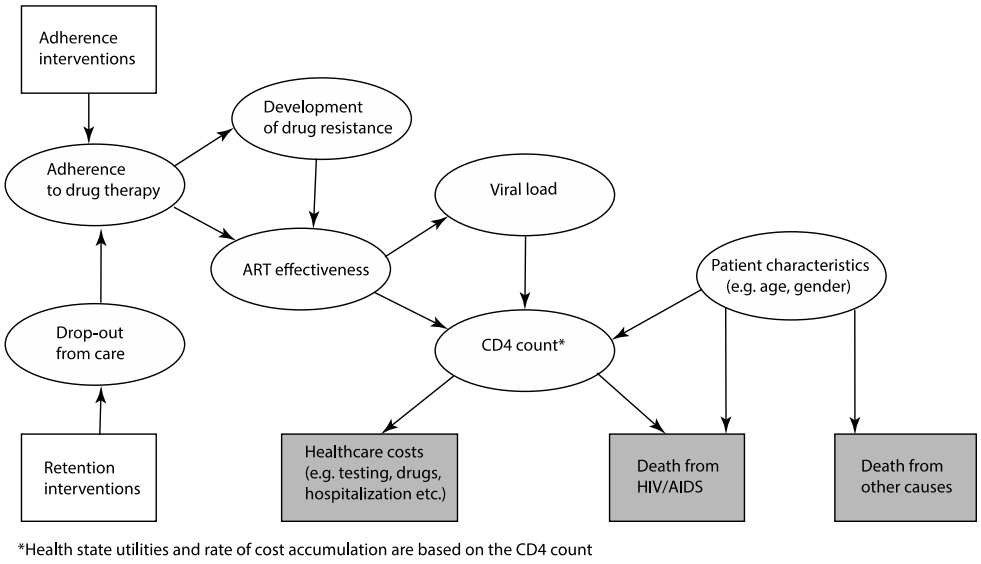

Figure 3-1. An influence diagram depicting the relationship between drug adherence, ART effectiveness and simulation outputs (shaded boxes). Individuals began the simulation with a specified adherence input according to the observed adherence in Figure 3-2. The adherence interventions served to increase the proportion of adherence inputs drawn between 90%–100%. Individuals could drop out of care and their adherence would drop to 0%. In secondary analysis, the interventions were simulated to reduce the probability of dropout in secondary analyses.

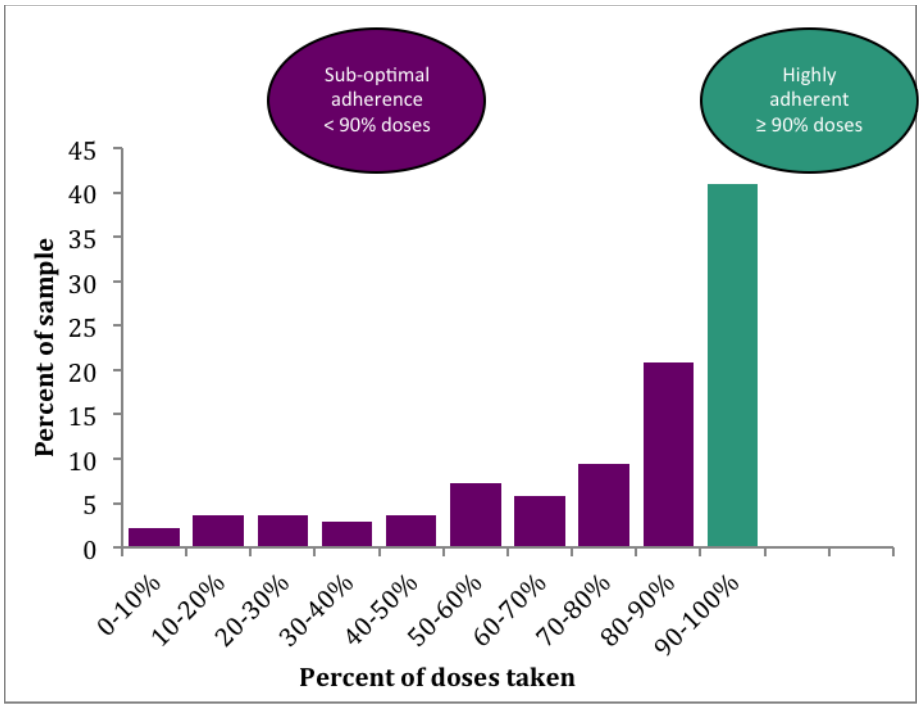

Figure 3-2. Data showing individual adherence at end-point from the Pop-Eleches et al. trial. A distribution was created based on this data to model individual adherence. Patients were categorized as highly adherent or sub-optimally adherent. The effect of SMS intervention was to increase the proportion of individuals that were highly adherent. The distribution of individual adherence did not appear to change between the intervention and control arm in this trial, so the distribution within each category was assumed to be unaffected by the SMS interventions in the simulations.

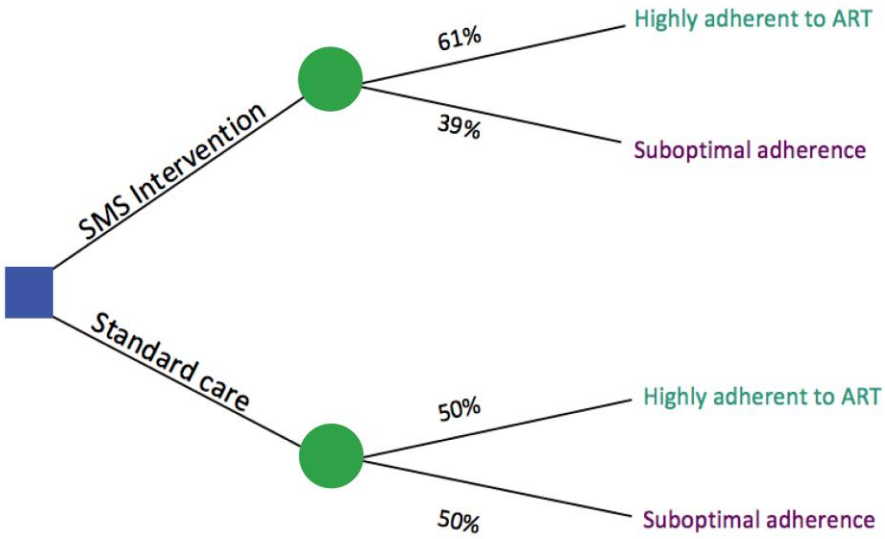

Figure 3-3. A one-year decision tree of trial outcomes for the base case analysis. We modeled individual-level adherence based on individual level trial data and classified individuals as either highly adherent or sub-optimally adherent. Individual outcomes were then estimated using the microsimulation depicted in Figure 3-1 to determine lifetime HIV-related cost and health outcomes.

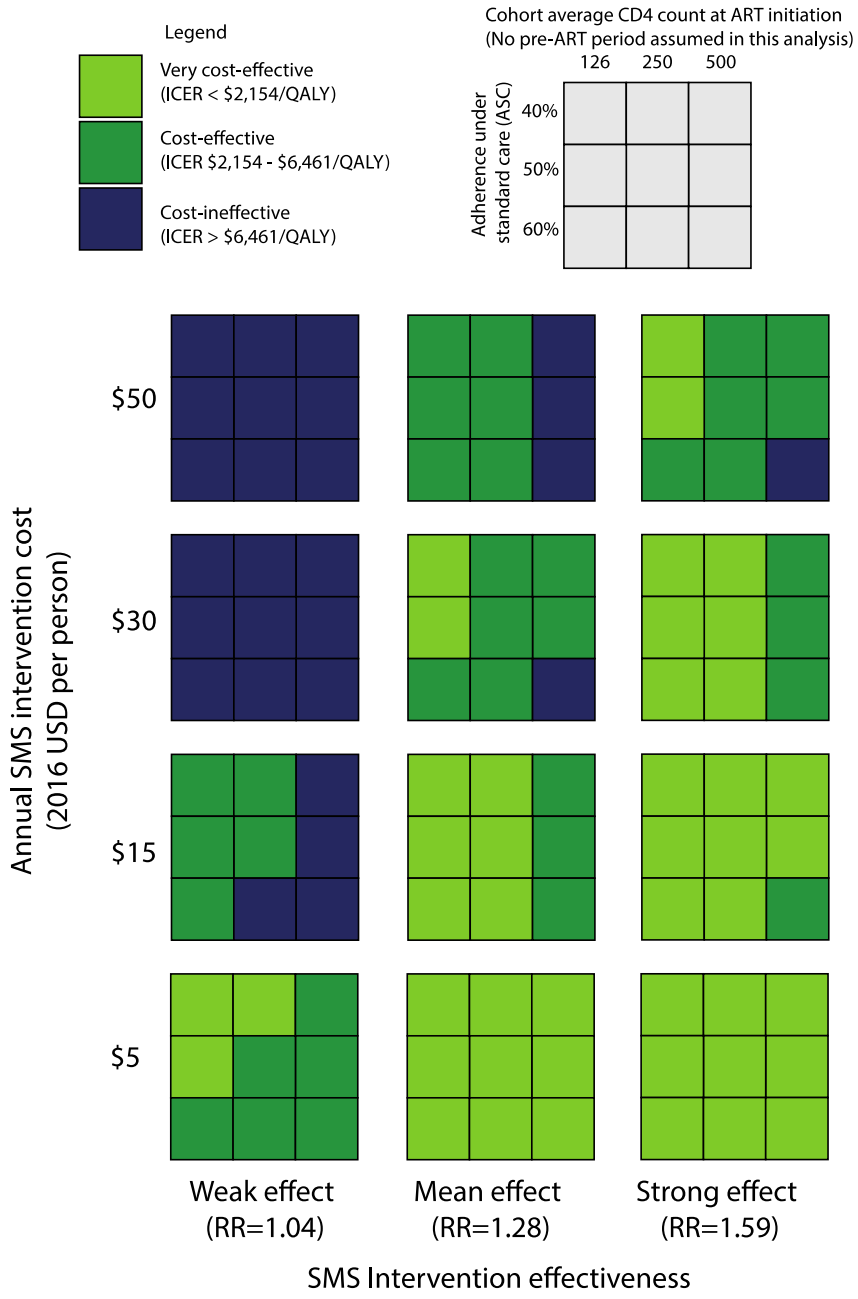

Figure 3-4. A multivariate sensitivity analysis showing how the ICER would change under different inputs and assumptions. The average CD4 count at ART initiation was varied and individuals were assumed to start ART with no waiting period. Thresholds at which the intervention was no longer cost-effective can be seen when a variable is increased one level and the box turns blue.

3.7 Tables

Table 3-1: Simulation input parameters

Model parameter in simulation	Base case	Plausible range	Source
Population Characteristics			
Age (mean)	39 (SD 9)	N/A	AMPATH
Average baseline CD4 count (cells/mm^3)	126	250 & 300	AMPATH
Average baseline viral load (Log 10 units)	4.5 (SD 1)	N/A	AMPATH
% Male	38%	N/A	AMPATH
Proportion highly adherent with standard care (ASC)	50%	30% to 90%	Lester et al.(6)
Costs (2016 USD)			
Initial cART regimen	$131	Varied from 0.5X to 1.5X	Personal communication
Second cART regimen	$286	Varied from 0.5X to 1.5X	Personal communication
Average cost of inpatient care per episode	$429	Varied from 0.5X to 1.5X	AMPATH
Annual outpatient care cost excl. ART	$319	Varied from 0.5X to 1.5X	AMPATH
Cost of viral load test	$25	Varied from 0.5X to 1.5X	Personal communication
Cost of CD4 test	$5.5	Varied from 0.5X to 1.5X	Personal communication
Utility			
Decrease in utility with ART	0.053	Not varied	N/A
HSUV with CD4 < 100 cells/mm^3	0.65	0.81	Trial data and Freedberg et al.(72)

Model parameter in simulation	Base case	Plausible range	Source
HSUV with CD4 101 cells/mm^3 to 199 cells/mm^3	0.69	0.87	Trial data and Freedberg et al.(72)
HSUV with CD4 > 200 cells/mm^3	0.72	0.94	Trial data and Freedberg et al.(72)
ART efficacy parameters			
Viral load decrement with cART of 2 NRTI + Efavirenz at 100% adherence (Log 10 units)	3.09	Not varied	Braithwaite et al.(35)
Viral load decrement with ART consisting of boosted PI at100% adherence (Log 10 units)	2.68	Not varied	Braithwaite et al.(35)
Retention in care parameters			
Probability of disengagement from clinic (per month)*	0.4 - 2.4%	Not varied	Kessler et al.(68)
Relative risk of treatment failure when disengaged	3.32	Not varied	Kessler et al.(68)
Intervention costs and effects			
Relative risk of adherence to ART	1.28	1.04 to 1.59	Hovarth et al.(2)
Relative risk of remaining engaged	1.69	0 to 3.23	Lester et al.(6)
Annual cost of intervention per patient **	$15	$5 to $45	Project budgets

** Risk of disengagement increased as time passed from ART initiation over this range*

***Cost comprised of initial staff training, SMS, overhead, technology maintenance and labor*

Table 3-2a: Incremental cost-effectiveness of SMS intervention: Base case with adherence effects

Simulation description†	Discounted costs	Discounted QALY	ICER compared to standard care (USD/QALY)	Mean survival time
Population adherence under standard care of 40%				
Standard care	$7,049	9.46	Reference	22.11
SMS mean effect	$7,292	9.66	$1,232	22.64
Range*	($7,186 to $7,379)	(9.49 to 9.79)	($1,000 to $3,822)	(22.21 to 22.99)
Population adherence under standard care of 50%				
Standard care	$7,147	9.61	Reference	22.53
SMS mean effect	$7,368	9.77	$1,389	22.95
Range*	($7,281 to $7,443)	(9.64 to 9.89)	($1,080 to $5,139)	(22.60 to 23.26)

† Intervention cost = $15USD per patient per year

* Range is based on variation of the SMS intervention effectiveness alone

Table 3-2b: Incremental cost-effectiveness of SMS intervention: Secondary analyses with adherence and retention effects

Simulation description†	Discounted costs	Discounted QALY	ICER compared to standard care (USD/QALY)	Mean survival time (Years)
Population adherence under standard care of 40%				
Standard care	$7,049	9.46	Reference	22.11
SMS mean effect with retention benefits	$7,715	10.05	$1,125	24.01
Range*	($7,602 to $7,813)	(9.89 to 10.19)	($1,045 to $1,292)	(23.56 to 24.40)
Population adherence under standard care of 50%				
Standard care	$7,147	9.61	Reference	22.53
SMS mean effect with retention benefits	$7,802	10.17	$1,166	24.35
Range*	($7,703 to $7,877)	(10.03 to 10.29)	($1,084 to $1,322)	(23.97 to 24.66)

† Intervention cost = $15USD per patient per year

* Range is based on variation of the SMS intervention effectiveness alone

Table 3-3: Select one-way sensitivity analyses of the model inputs

Parameter varied†	Discounted costs (2016 USD)	Mean discounted QALY	ICER compared to respective standard care	Mean survival time (Years)
Base case analysis				
Standard care	$7,147	9.61	Reference	22.53
SMS intervention	$7,368	9.77	$1,389	22.95
Average CD4 count at ART initiation = 200				
Standard care	$7,404	10.12	Reference	23.91
SMS intervention	$7,607	10.26	$1,535	24.27
Average CD4 count at ART initiation = 300				
Standard care	$7,555	10.63	Reference	25.21
SMS intervention	$7,733	10.73	$1,701	25.51
Cost of first line ART high				
Standard care	$7,708	9.61	Reference	22.53
SMS intervention	$7,937	9.77	$1,440	22.95
Cost of first line ART low				
Standard care	$6,586	9.61	Reference	22.53
SMS intervention	$6,799	9.77	$1,337	22.95
Cost of second line ART high				
Standard care	$7,831	9.61	Reference	22.53
SMS intervention	$8,063	9.77	$1,462	22.95
Cost of second line ART low				
Standard care	$6,463	9.61	Reference	22.53
SMS intervention	$6,673	9.77	$1,316	22.95

Parameter varied†	Discounted costs (2016 USD)	Mean discounted QALY	ICER compared to respective standard care	Mean survival time (years)
Standard care	$9,282	9.61	Reference	22.53
SMS intervention	$9,535	9.77	$1,595	22.95
Cost of annual outpatient care low				
Standard care	$5,013	9.61	Reference	22.53
SMS intervention	$5,201	9.77	$1,182	22.95
Cost of inpatient care per episode high				
Standard care	$7,199	9.61	Reference	22.53
SMS intervention	$7,416	9.77	$1,369	22.95
Cost of inpatient care per episode low				
Standard care	$7,095	9.61	Reference	22.53
SMS intervention	$7,319	9.77	$1,409	22.95
Cost of intervention = $5				
Standard care	$7,147	9.61	Reference	22.53
SMS intervention	$7,290	9.77	$896	22.95
Cost of intervention = $25				
Standard care	$7,147	9.61	Reference	22.53
SMS intervention	$7,446	9.77	$1,881	22.95
Cost of intervention = $35				
Standard care	$7,147	9.61	Reference	22.53
SMS intervention	$7,525	9.77	$2,374	22.95
Cost of intervention = $45				
Standard care	$7,147	9.61	Reference	22.53
SMS intervention	$7,603	9.77	$2,867	22.95

† Based on mean intervention adherence efficacy alone and ASC=50%; Intervention cost = $15USD per patient per year

Table 3-4: Incremental cost-effectiveness of SMS intervention under assumptions of current guidelines and future test and treat guidelines

Simulation description†	Treatment guideline *	Mean Discounted costs	Discounted QALY	ICER with guideline based care	ICER with current care**
Population adherence under standard care of 40%					
Standard care	Current	$7,064	9.47	Reference	Reference
SMS mean effect and no retention effect	Current	$7,307	9.66	$1,245	$1,245
SMS weak effect and no retention effect	Current	$7,201	9.50	$4,028	$4,028
SMS strong effect and no retention effect	Current	$7,393	9.80	$1,006	$1,006
Standard care	TT	$7,064	11.37	Reference	$528
SMS mean effect and no retention effect	TT	$8,226	11.44	$2,378	$591
SMS weak effect and no retention effect	TT	$8,204	11.38	$9,826	$596
SMS strong effect and no retention effect	TT	$8,234	11.47	$1,611	$584
Population adherence under standard care of 50%					
Standard care	Current	$7,159	9.62	Reference	Reference
SMS mean effect and no retention effect	Current	$7,383	9.78	$1,402	$1,402
SMS weak effect and no retention effect	Current	$7,296	9.65	$4,695	$4,695
SMS strong effect and no retention effect	Current	$7,457	9.89	$1,090	$1,090
Standard care	TT	$8,089	11.42	Reference	$516
SMS mean effect and no retention effect	TT	$8,231	11.47	$3,078	$580
SMS weak effect and no retention effect	TT	$8,223	11.43	$12,140	$587
SMS strong effect and no retention effect	TT	$8,244	11.50	$1,935	$577

Simulation description†	Treatment guideline *	Mean Discounted costs	Discounted QALY	ICER with guideline based care	ICER with current care**
Population adherence under standard care of 60%					
Standard care	Current	$7,255	9.76	Reference	Reference
SMS mean effect and no retention effect	Current	$7,460	9.90	$1,540	$1,150
SMS weak effect and no retention effect	Current	$7,387	9.79	$5,745	$4,556
SMS strong effect and no retention effect	Current	$7,518	9.99	$1,175	$880
Standard care	TT	$8,099	11.46	Reference	$497
SMS mean effect and no retention effect	TT	$8,244	11.50	$3,703	$569
SMS weak effect and no retention effect	TT	$8,231	11.47	$16,499	$572
SMS strong effect and no retention effect	TT	$8,256	11.53	$2,210	$566

* TT=Test and treat and assumes there is no ART initiation threshold and average population CD4 counts are 500 cell/mm^3 at ART initiation. Current guidelines assume an ART initiation threshold of 500 cell/mm^3 and average population CD4 count of 126 cell/mm^3 at ART initiation.

** Test and treat 'standard care' shows the cost-effectiveness of expanded treatment without improvements in adherence.

† Based on mean intervention adherence efficacy alone; Intervention cost = $15USD per patient per year.

Table 3-5: Incremental cost-effectiveness of SMS intervention: Sensitivity analysis with an ascending adherence under standard care

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	ICER compared to respective standard care	Mean survival time (Years)
Population adherence under standard care of 30%				
Standard care	$6,955	9.31	Reference	21.72
SMS mean effect and no retention effect	$7,217	9.54	$1,149	22.34
SMS weak effect and no retention effect	$7,097	9.36	$3,242	21.84
SMS strong effect and no retention effect	$7,318	9.70	$947	22.75
SMS mean effect with mean retention effect	$7,635	9.93	$1,095	23.69
SMS weak effect including mean retention effect	$7,504	9.74	$1,277	23.17
SMS strong effect including mean retention effect	$7,746	10.09	$1,014	24.13
SMS mean effect with strong retention effect	$8,225	10.23	$1,387	24.74
SMS weak effect including strong retention effect	$8,073	10.02	$1,573	24.17
SMS strong effect including strong retention effect	$8,348	10.39	$1,288	25.20
Population adherence under standard care of 40%				
Standard care	$7,049	9.46	Reference	22.11
SMS mean effect and no retention effect	$7,292	9.66	$1,232	22.64
SMS weak effect and no retention effect	$7,186	9.49	$3,822	22.21
SMS strong effect and no retention effect	$7,379	9.79	$1,000	22.99

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	ICER compared to respective standard care	Mean survival time (Years)
SMS mean effect with mean retention effect	$7,715	10.05	$1,125	24.01
SMS weak effect including mean retention effect	$7,602	9.89	$1,292	23.56
SMS strong effect including mean retention effect	$7,813	10.19	$1,045	24.40
SMS mean effect with strong retention effect	$8,317	10.35	$1,417	25.09
SMS weak effect including strong retention effect	$8,187	10.18	$1,584	24.60
SMS strong effect including strong retention effect	$8,421	10.49	$1,325	25.48
Population adherence under standard care of 50%				
Standard care	$7,147	9.61		22.53
SMS mean effect and no retention effect	$7,368	9.77	$1,389	22.95
SMS weak effect and no retention effect	$7,281	9.64	$5,139	22.60
SMS strong effect and no retention effect	$7,443	9.89	$1,080	23.26
SMS mean effect with mean retention effect	$7,802	10.17	$1,166	24.35
SMS weak effect including mean retention effect	$7,703	10.03	$1,322	23.97
SMS strong effect including mean retention effect	$7,877	10.29	$1,084	24.66
SMS mean effect with strong retention effect	$8,408	10.48	$1,461	25.43
SMS weak effect including strong retention effect	$8,303	10.33	$1,603	25.03
SMS strong effect including strong retention effect	$8,492	10.59	$1,375	25.75

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	ICER compared to respective standard care	Mean survival time (Years)
Population adherence under standard care of 60%				
Standard care	$7,243	9.76		22.92
SMS mean effect and no retention effect	$7,446	9.89	$1,525	23.27
SMS weak effect and no retention effect	$7,373	9.78	$5,932	22.97
SMS strong effect and no retention effect	$7,504	9.98	$1,177	23.51
SMS mean effect with mean retention effect	$7,880	10.29	$1,195	24.67
SMS weak effect including mean retention effect	$7,808	10.18	$1,333	24.38
SMS strong effect including mean retention effect	$7,943	10.38	$1,119	24.93
SMS mean effect with strong retention effect	$8,496	10.60	$1,494	25.77
SMS weak effect including strong retention effect	$8,415	10.49	$1,610	25.46
SMS strong effect including strong retention effect	$8,567	10.69	$1,415	26.03
Population adherence under standard care of 70%				
Standard care	$7,340	9.91		23.32
SMS mean effect and no retention effect	$7,521	10.01	$1,887	23.58
SMS weak effect and no retention effect	$7,468	9.93	$8,040	23.36
SMS strong effect and no retention effect	$7,570	10.08	$1,363	23.77
SMS mean effect with mean retention effect	$7,963	10.41	$1,240	25.01
SMS weak effect including mean retention effect	$7,906	10.33	$1,345	24.78

Simulation description†	Mean discounted cost (2016 USD)	Mean discounted QALY	ICER compared to respective standard care	Mean survival time (Years)
SMS strong effect including mean retention effect	$8,011	10.48	$1,174	25.20
SMS mean effect with strong retention effect	$8,590	10.72	$1,535	26.12
SMS weak effect including strong retention effect	$8,526	10.64	$1,630	25.88
SMS strong effect including strong retention effect	$8,645	10.80	$1,468	26.33
Population adherence under standard care of 80%				
Standard care	$7,437	10.06		23.72
SMS mean effect and no retention effect	$7,601	10.13	$2,556	23.90
SMS weak effect and no retention effect	$7,567	10.07	$10,759	23.76
SMS strong effect and no retention effect	$7,631	10.17	$1,806	24.01
SMS mean effect with mean retention effect	$8,043	10.53	$1,292	25.33
SMS weak effect including mean retention effect	$8,008	10.48	$1,373	25.19
SMS strong effect including mean retention effect	$8,078	10.58	$1,239	25.46
SMS mean effect with strong retention effect	$8,681	10.85	$1,582	26.46
SMS weak effect including strong retention effect	$8,642	10.79	$1,645	26.31
SMS strong effect including strong retention effect	$8,716	10.89	$1,535	26.60

Simulation description†	Mean discounted cost (2016 USD)	Mean discounted QALY	ICER compared to respective standard care	Mean survival time (Years)
Population adherence under standard care of 90%				
Standard care	$7,531	10.20		24.10
SMS mean effect and no retention effect	$7,672	10.23	$4,556	24.18
SMS weak effect and no retention effect	$7,656	10.21	$24,970	24.11
SMS strong effect and no retention effect	$7,688	10.26	$2,905	24.24
SMS mean effect with mean retention effect	$8,133	10.66	$1,330	25.68
SMS weak effect including mean retention effect	$8,114	10.63	$1,370	25.60
SMS strong effect including mean retention effect	$8,148	10.68	$1,302	25.74
SMS mean effect with strong retention effect	$8,775	10.97	$1,618	26.82
SMS weak effect including strong retention effect	$8,752	10.94	$1,650	26.73
SMS strong effect including strong retention effect	$8,794	11.01	$1,565	26.89

† Based on Intervention cost = $15USD per patient per year

Table 3-6: Incremental cost-effectiveness ratios of SMS intervention: Sensitivity analysis assuming utility weights observed in a US population and incremental cost-effectiveness using unadjusted life-years

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	Mean discounted life year	ICER compared to standard care ($/QALY)	ICER compared to standard care ($/Life Year)	Mean survival time (Years)
Population adherence under standard care of 30%						
Standard care	$6,955	12.33	13.96	Reference	Reference	21.72
SMS mean effect and no retention effect	$7,217	12.63	14.29	$856	$787	22.34
SMS weak effect and no retention effect	$7,097	12.39	14.02	$2,378	$2,229	21.84
SMS strong effect and no retention effect	$7,318	12.84	14.52	$707	$650	22.75
SMS mean effect with mean retention effect	$7,635	13.16	14.90	$813	$721	23.69
SMS weak effect including mean retention effect	$7,504	12.91	14.63	$943	$826	23.17
SMS strong effect including mean retention effect	$7,746	13.38	15.14	$753	$672	24.13
SMS mean effect with strong retention effect	$8,225	13.56	15.36	$1,027	$905	24.74
SMS weak effect including strong retention effect	$8,073	13.29	15.06	$1,163	$1,015	24.17
SMS strong effect including strong retention effect	$8,348	13.79	15.61	$954	$845	25.20
Population adherence under standard care of 40%						
Standard care	$7,049	12.52	14.17	Reference	Reference	22.11
SMS mean effect and no retention effect	$7,292	12.79	14.46	$920	$846	22.64
SMS weak effect and no retention effect	$7,186	12.57	14.23	$2,866	$2,646	22.21

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	Mean discounted life year	ICER compared to standard care ($/QALY)	ICER compared to standard care ($/Life Year)	Mean survival time (Years)
SMS strong effect and no retention effect	$7,379	12.96	14.65	$746	$686	22.99
SMS mean effect with mean retention effect	$7,715	13.32	15.08	$834	$738	24.01
SMS weak effect including mean retention effect	$7,602	13.10	14.84	$955	$835	23.56
SMS strong effect including mean retention effect	$7,813	13.51	15.28	$776	$691	24.40
SMS mean effect with strong retention effect	$8,317	13.73	15.55	$1,050	$923	25.09
SMS weak effect including strong retention effect	$8,187	13.50	15.29	$1,170	$1,020	24.60
SMS strong effect including strong retention effect	$8,421	13.92	15.75	$983	$868	25.48
Population adherence under standard care of 50%						
Standard care	$7,147	12.73	14.40	Reference	Reference	22.53
SMS mean effect and no retention effect	$7,368	12.94	14.63	$1,037	$952	22.95
SMS weak effect and no retention effect	$7,281	12.76	14.44	$3,712	$3,426	22.60
SMS strong effect and no retention effect	$7,443	13.10	14.80	$807	$740	23.26
SMS mean effect with mean retention effect	$7,802	13.49	15.26	$864	$762	24.35
SMS weak effect including mean retention effect	$7,703	13.30	15.05	$978	$852	23.97
SMS strong effect including mean retention effect	$7,877	13.64	15.42	$803	$712	24.66
SMS mean effect with strong retention effect	$8,408	13.89	15.73	$1,081	$948	25.43
SMS weak effect including strong retention effect	$8,303	13.70	15.52	$1,184	$1,031	25.03
SMS strong effect including strong retention effect	$8,492	14.05	15.90	$1,018	$897	25.75

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	Mean discounted life year	ICER compared to standard care ($/QALY)	ICER compared to standard care ($/Life Year)	Mean survival time (Years)
Population adherence under standard care of 60%						
Standard care	$7,243	12.92	14.61	Reference	Reference	22.92
SMS mean effect and no retention effect	$7,446	13.10	14.80	$1,139	$1,045	23.27
SMS weak effect and no retention effect	$7,373	12.95	14.64	$4,500	$4,210	22.97
SMS strong effect and no retention effect	$7,504	13.22	14.93	$877	$807	23.51
SMS mean effect with mean retention effect	$7,880	13.64	15.43	$884	$779	24.67
SMS weak effect including mean retention effect	$7,808	13.50	15.27	$987	$859	24.38
SMS strong effect including mean retention effect	$7,943	13.77	15.56	$829	$734	24.93
SMS mean effect with strong retention effect	$8,496	14.06	15.91	$1,105	$968	25.77
SMS weak effect including strong retention effect	$8,415	13.91	15.74	$1,191	$1,037	25.46
SMS strong effect including strong retention effect	$8,567	14.19	16.05	$1,047	$921	26.03
Population adherence under standard care of 70%						
Standard care	$7,340	13.13	14.83	Reference	Reference	23.32
SMS mean effect and no retention effect	$7,521	13.26	14.97	$1,393	$1,285	23.58
SMS weak effect and no retention effect	$7,468	13.15	14.85	$5,847	$5,593	23.36
SMS strong effect and no retention effect	$7,570	13.35	15.08	$1,015	$932	23.77
SMS mean effect with mean retention effect	$7,963	13.81	15.61	$917	$805	25.01
SMS weak effect including mean retention effect	$7,906	13.70	15.49	$995	$866	24.78

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	Mean discounted life year	ICER compared to standard care ($/QALY)	ICER compared to standard care ($/Life Year)	Mean survival time (Years)
SMS strong effect including mean retention effect	$8,011	13.90	15.71	$868	$766	25.20
SMS mean effect with strong retention effect	$8,590	14.23	16.09	$1,134	$991	26.12
SMS weak effect including strong retention effect	$8,526	14.11	15.97	$1,203	$1,046	25.88
SMS strong effect including strong retention effect	$8,645	14.33	16.20	$1,086	$953	26.33
Population adherence under standard care of 80%						
Standard care	$7,437	13.33	15.05	Reference	Reference	23.72
SMS mean effect and no retention effect	$7,601	13.42	15.15	$1,902	$1,740	23.90
SMS weak effect and no retention effect	$7,567	13.35	15.07	$7,595	$6,795	23.76
SMS strong effect and no retention effect	$7,631	13.47	15.21	$1,333	$1,223	24.01
SMS mean effect with mean retention effect	$8,043	13.96	15.78	$954	$835	25.33
SMS weak effect including mean retention effect	$8,008	13.89	15.70	$1,011	$880	25.19
SMS strong effect including mean retention effect	$8,078	14.03	15.85	$915	$804	25.46
SMS mean effect with strong retention effect	$8,681	14.39	16.27	$1,168	$1,018	26.46
SMS weak effect including strong retention effect	$8,642	14.32	16.20	$1,213	$1,054	26.31
SMS strong effect including strong retention effect	$8,716	14.46	16.34	$1,133	$991	26.60
Population adherence under standard care of 90%						
Standard care	$7,531	13.52	15.26	Reference	Reference	24.10

Simulation description†	Mean discounted costs (2016 USD)	Mean discounted QALY	Mean discounted life year	ICER compared to standard care ($/QALY)	ICER compared to standard care ($/Life Year)	Mean survival time (Years)
SMS mean effect and no retention effect	$7,672	13.56	15.31	$4,556	$3,363	24.18
SMS weak effect and no retention effect	$7,656	13.53	15.27	$24,970	$17,836	24.11
SMS strong effect and no retention effect	$7,688	13.59	15.34	$2,905	$2,178	24.24
SMS mean effect with mean retention effect	$8,133	14.13	15.96	$1,313	$983	25.68
SMS weak effect including mean retention effect	$8,114	14.10	15.92	$1,351	$1,011	25.60
SMS strong effect including mean retention effect	$8,148	14.16	16.00	$1,283	$961	25.74
SMS mean effect with strong retention effect	$8,775	14.56	16.46	$1,595	$1,194	26.82
SMS weak effect including strong retention effect	$8,752	14.52	16.41	$1,628	$1,219	26.73
SMS strong effect including strong retention effect	$8,794	14.60	16.50	$1,569	$1,174	26.89

Table 3-7: Cost-effectiveness of SMS interventions with attenuated effect over time and one-time program costs

Simulation description†	Mean Discounted costs (2016 USD)	Discounted QALY	ICER compared to respective standard care	Mean survival time (years)
Standard care	$7,144	9.61	Reference	22.51
Intervention efficacy nullified over 1 year				
SMS mean effect and no retention effect	$7,212	9.70	$742	22.72
SMS weak effect and no retention effect	$7,163	9.62	$1,282	22.53
SMS strong effect and no retention effect	$7,254	9.77	$676	22.88
Intervention efficacy nullified over 5 years				
SMS mean effect and no retention effect	$7,742	10.10	$1,223	22.74
SMS weak effect and no retention effect	$7,691	10.02	$1,333	22.55
SMS strong effect and no retention effect	$7,772	10.15	$1,152	22.92
Intervention efficacy nullified over 10 years				
SMS mean effect and no retention effect	$8,167	10.39	$1,301	22.80
SMS weak effect and no retention effect	$8,116	10.32	$1,371	22.54
SMS strong effect and no retention effect	$8,203	10.45	$1,254	22.99

†Assumes ASC = 50% and intervention costs $15 per person in the first year only

Table 3-8: Cost-effectiveness of SMS intervention with attenuated effect over time and life-time program costs

Simulation description†	Mean Discounted costs (2016 USD)	Discounted QALY	ICER compared to respective standard care	Mean survival time (Years)
Standard care	$7,144	9.61	Reference	22.51
Intervention efficacy nullified over 1 year				
SMS mean effect and no retention effect	$7,317	9.70	$1,857	22.72
SMS weak effect and no retention effect	$7,266	9.62	$7,775	22.53
SMS strong effect and no retention effect	$7,359	9.77	$1,316	22.88
Intervention efficacy nullified over 5 years				
SMS mean effect and no retention effect	$7,742	10.10	$1,223	22.74
SMS weak effect and no retention effect	$7,691	10.02	$1,333	22.55
SMS strong effect and no retention effect	$7,772	10.15	$1,152	22.92
Intervention efficacy nullified over 10 years				
SMS mean effect and no retention effect	$8,340	10.39	$1,520	22.80
SMS weak effect and no retention effect	$8,287	10.32	$1,613	22.55
SMS strong effect and no retention effect	$8,377	10.45	$1,459	22.99

†Assumes ASC = 50% and lifetime intervention costs $15 per person per year

4 The potential value of improving medication adherence for latent tuberculosis infection in British Columbia

4.1 Background

The World Health Organization (WHO) has set a goal of global tuberculosis (TB) elimination by 2050.(30) Drug treatment of latent TB infection (LTBI) has been identified as a priority action for TB elimination in low incidence regions; however, LTBI screening and treatment can only impact TB incidence with high proportions of uptake and completion.(116) Unfortunately, in most LTBI prevention and treatment programs, adherence to LTBI therapy is low, with some multicenter studies observing less than 40% completion.(22-25) To address this issue, the United States Centers for Disease Control (CDC) has set an objective of having 81% of TB contacts complete prophylactic therapy by 2020.(117) To reach this ambitious target, cost-effective adherence interventions will be required.

The long duration and adverse drug reactions of LTBI therapy are among the some of the complex barriers to adherence. Non-adherence leads to a higher lifetime risk of active TB, leading to higher health system costs and transmission. The burden of non-adherence and the potential value of new adherence interventions are not well understood in British Columbia (BC), a low TB incidence region with an annual TB incidence of 5.0 per 100,000 people. The health and economic benefits of improved LTBI drug adherence

could be high, as improved adherence could have a significant impact on TB epidemiology.

Several adherence interventions are being considered to improve LTBI therapy adherence.(3, 118) Planning of future trials or implementation strategies can be enhanced with an understanding of their potential cost-effectiveness. Thus the aims of this study were to estimate the burden of non-adherence and to estimate the maximum allowable cost of hypothetical new interventions. The health impact and cost-sensitivity of four existing adherence interventions were also evaluated.

4.2 Methods

4.2.1 Model overview

An individual-level (micro-simulation) model was developed to represent LTBI cases that were initiating drug therapy. Cohorts of 100,000 individuals were simulated to estimate the impact of adherence improvement to LTBI therapy on health and economic outputs. Figure 4-1 is an influence diagram that depicts the logic of the model. Adherence interventions affected the level of drug adherence within adherence categories of two regiments of LTBI drug therapy, while holding all other variables constant. Treatment adherence affected the LTBI drug therapy effectiveness, which in turn affected the lifetime risk of TB-reactivation.

TB reactivation risk was defined as the probability that individuals could develop TB at each cycle of the simulation. This probability was modified by LTBI treatment and level

of treatment adherence. The simulation had an annual cycle length, and individuals could enter the absorbing death state at any cycle through background or TB-related death. Each individual was simulated for 25 years to estimate the number of TB cases, TB deaths, healthcare costs and quality-adjusted life years (QALYs). Average outcomes of the entire cohort were recorded at the end of each run of 100,000 individuals. Input parameters were varied across specified uncertainty distributions during probabilistic analyses (Table 4-1). Model parameters and their probability distributions, representing uncertainty about their true values, came from published literature or other secondary sources (Table 4-1). If constructing probability distributions from the available data was not feasible, plausible distributions were specified based on expert opinion. Average outcomes of the probabilistic analyses over 10,000 runs were reported in the final results. The model was developed using TreeAge Pro 2016 software (Williamstown, Massachusetts, US).

4.2.2 Adherence and effect of adherence interventions

In Canada, standard first-line LTBI therapy is nine months of daily isoniazid (INH), so this was used as the first treatment regimen in the simulation. (119) Individuals were categorized into four groups of adherence to INH: completed ≥80% of doses (fully adherent); completed ≥6 months of therapy, but < 80% of doses; completed 3 to 6 months of therapy; completed <3 months of therapy. Based on standard clinical care in Canada, if an individual developed intolerance to INH therapy, they were simulated to switch to a 4-month regimen of daily Rifampin (RIF).(119) Individuals were categorized as *completed* or *did not complete therapy* for RIF, given the lower duration of treatment compared with

INH therapy. Under *standard care*, the proportion of adherent individuals within each category was modeled based on clinical observations in large multi-centered studies.(22-24, 118)

4.2.3 How adherence intervention effects were simulated

Irrespective of the regimen used, adherence interventions effects were simulated to improve the proportion of simulated patients that were fully adherent. This was operationalized by multiplying the intervention effectiveness input (relative risk) by the baseline adherence value, thus increasing the proportion of the cohort in the high adherence category. For example in a given run of the simulation, if the intervention effectiveness input of 1.10 was drawn and the proportion adherent to INH input of 60% was drawn, the proportion of individual adherent to INH for that run would be 66% with the SMS intervention and it would be compared to simulation outputs assuming 60% highly adherent to INH under standard care. The remaining 34% of non-adherent individuals to INH would be proportionally distributed into three non-adherent subgroups for INH (<80%, 3-6mo, <3mo). The logic was similar for RIF, but with only two categories; the interventions increased the proportion in the *completed* category and the remainder was categorized as *not completed*.

The distribution of individual within the three categories of non-adherence for INH matched observations from a previous study, and a simplifying assumption was made that this distribution was fixed throughout the analysis.(24) In other words, if 40% of a simulated cohort were in the non-adherent group for INH, they would be distributed

within these three categories (<80%, 3-6mo, <3mo) with the same proportions (0.33, 0.37 and 0.30 respectively) as a simulated cohort with 30% non-adherence to INH.

4.2.4 Decision tree

Individuals entered the simulation in a decision tree that represents the outcomes of the first year of LTBI drug therapy (Figure 4-2). During this time, individuals were at risk of adverse drug events resulting in death, adverse drug events resulting in therapeutic change, or treatment completion with a varying degree of adherence to one of two regimens of LTBI therapy. If an individual survived to the end of the decision tree, they would have either completed the first regiment of drug therapy in one of four mutually exclusive categories of adherence or completed the second regimen in one of two mutually exclusive categories of adherence. The cost of drug therapy over this period was a function of the regimen used and adherence level for each individual (Table 4-1 lists the costs of each regimen).

4.2.5 Risk reduction of TB reactivation

Based on the category of adherence to drug therapy and the drug regimen completed, simulated individuals entered a Markov model in the "LTBI" state with a differential annual reactivation risk for TB (Figure 4-2). The reactivation risk reduction taken from published sources was multiplied by the annual risk of TB reactivation for untreated individuals (0.003).(120) Annual TB reactivation risk reduction with INH therapy was simulated based on observations from the WHO IUAT study.(20) Annual TB reactivation risk reduction with RIF was simulated based on best estimates of efficacy from a

published report.(117) Partial protective effects were given for less than full adherence to INH treatment, based on the partial protective effects observed in the WHO IUAT study. There is a lack of evidence that partial RIF completion offers a protective effect, so no partial protective effect were assumed for less than full adherence. The reductions in lifetime TB risk by drug regimen and adherence category are listed in Table 4-1.

4.2.6 State-transition model

Simulated individuals entered the state transition model in the LTBI state with a differential risk of TB reactivation. From the LTBI state, individuals could develop TB or die of background causes. Individuals with no protective effect of drug therapy (due to non-adherence) were assigned the full risk of TB reactivation (annual probability = 0.003), while the remaining individuals had a reduced risk based on their adherence and drug regimen.(119, 120) The annual transition probability from the LTBI state to the active TB state was assumed to be constant over time, matching clinical observations from a previous study.(120) The risk of background death was based on the BC life table and correspondingly, the transition probability from LTBI to death increased with age.(121) The number of TB cases developed in the simulated cohort was tracked and reported.

If an individual developed TB, they incurred diagnosis and treatment costs including testing, drug therapy, contact tracing and inpatient costs. From this state, individuals could move to a “previous TB” state or “ death” state. The risk of death with active TB matched clinical observations reported in the Canadian Tuberculosis Standards.(119) The

effectiveness of TB drug therapy governed the transition probability to the "previous TB" state, and the input also came from the Canadian Tuberculosis Standards.(119) One level of secondary transmission was modeled deterministically by applying the average number of secondary transmissions to each case of active TB, a method that has been applied in previous simulation studies.(122, 123) The average cost of the secondary case of TB was added to the overall cost of the episode of TB care. The number of TB deaths in the simulated cohort was tracked and reported.

The "previous TB" state reflected an individual who had been treated for active TB and survived. According to some studies, individuals are at heightened risk of relapse during the first two years after receiving active TB treatment.(124, 125) As such, the simulation assumed a risk of TB reactivation for the first two years after receiving TB drug therapy. Beyond two years, a simplifying assumption was made that individuals had no risk of relapse for TB. Individuals in the "previous TB" state could transition to death from background causes, based on age-specific background mortality probabilities.

4.2.7 Additional simulation settings

The model was fully probabilistic aside from the deterministic intervention cost inputs, which were varied deterministically to assess the maximum allowable cost and cost sensitivity of the interventions. A health system perspective was used to estimate costs. TB diagnosis and care costs were based on a Canadian national report.(126) Costs of LTBI drug therapy and monitoring were provided by the British Columbia Centre for Disease Control (BCCDC), a centralized provincial public health agency responsible for

the majority of diagnoses and treatments of active and latent TB infections in the province. Costs measured in previous years were adjusted to 2016 Canadian dollars using the OECD consumer price indices data.(127) Health state utility values (HSUVs) for TB and LTBI states were obtained from a recent study that used the SF-36 survey to estimate these values.(128) The costs and QALYs were discounted at a rate of 3%. A WTP threshold of CAD $50,000/QALY was used to interpret all results in the base case.(64)

4.2.8 Existing adherence interventions

A literature review was conducted to identify potential adherence interventions that could improve LTBI drug therapy adherence. Two systematic reviews were identified that summarized the effectiveness of various HIV or TB adherence interventions.(19, 20) The WHO LTBI management guidelines for low-incidence countries also reported potential interventions.(21) These reviews summarized evidence largely from randomized controlled trials from multiple settings and were the most relevant sources for intervention efficacy. Other interventions were considered, but excluded because they were significantly more expensive (e.g. directly observed therapy).

Four existing adherence intervention types were considered in this evaluation. The first intervention came from a review that summarized evidence of material incentives to promote adherence to long-course LTBI or TB drug therapy.(20) The incentives could include monetary rewards or other types of economic rewards (e.g. food) for adherence. The pooled estimate for adherence incentives compared to standard care was used in the current analysis (RR= 1.04 95% CI 0.97 – 1.13). During the probabilistic simulations, the

effectiveness estimates of all interventions were drawn from lognormal distributions matching the pooled point estimates and uncertainty intervals. The next two adherence interventions came from a review that summarized evidence for weekly text-message (SMS) adherence support and enhanced adherence counseling.(19) The weekly SMS interventions were described in a previous chapter; briefly, they include one-way reminder messages to individuals or two-way engagement messages that have an option for patient response. For the purpose of this study, the pooled effect size of SMS interventions was used (RR=1.23 95% CI 1.05 – 1.16). Enhanced adherence counseling involved more intensive patient education, monitoring and counseling related to the importance of drug therapy adherence. Basic adherence counseling is typically provided at prescription pick-up in most settings; however, this review summarized evidence of trials studying an enhancement or supplement to standard adherence counseling.(1) The specific enhancements varied between the included studies, but included up to three additional counseling sessions focused on the importance of adherence.(19) Adherence counseling could also be enhanced through regular patient education sessions, monitoring of adherence using diaries and motivational interviewing.(129-131) Once again, the pooled effect size was used to specify the input distribution used in the simulation (RR=1.09 95% CI 1.01-1.15).

The WHO guidelines highlighted three studies of peer-support interventions.(4, 21-23) In this type of intervention, an individual who has previously completed LTBI treatment would support an individual who is initiating treatment. Peers supporters could also be a friend or family member of the individual initiating drug therapy. In either case, the peer-

supporter receives some training on how to support the patient and provide ongoing adherence support throughout their drug therapy. The effect sizes reported in these three studies were pooled to derive the effectiveness estimate used in this analysis (RR=1.10).

Cost data were unavailable for some interventions, so empirical probability distributions could not be specified. An alternative approach was used to estimate the value of these interventions by assigning deterministic costs to each intervention and assessing the cost-effectiveness acceptability at different levels of costs. The results describe the relationship between intervention cost and the likelihood of being cost-effective (the sensitivity of each intervention to cost). The interventions were evaluated individually compared to standard care to estimate the relationship between intervention cost and cost-effectiveness acceptability (i.e. probability of being cost-effective over standard care).

4.2.9 Analytical approach

In the primary analysis, the health and economic outcomes of a *full adherence* scenario were compared to the *current adherence* scenario to evaluate the impact on TB cases, TB deaths and costs. Potential adherence interventions could alleviate the burden and are critical for TB elimination strategies. A *hypothetical intervention* was simulated and compared to the *current adherence* scenario. The relationship between a hypothetical intervention's efficacy and maximum allowable cost such that it remained cost-effective was estimated.

In a secondary analysis, four interventions were compared to standard care. The interventions were evaluated individually compared to standard care to separately estimate a relationship between intervention cost and cost-effectiveness acceptability. Subsequently, the interventions were evaluated together with standard care under an assumption of equal intervention costs. The cost-effectiveness acceptability was plotted as a function of the intervention cost to estimate this relationship in a combined analysis.

4.2.10 Sensitivity analysis

Aside from the probabilistic analysis, key assumptions were varied in the model. The time horizon and WTP threshold were varied to examine their impact on the final results. The primary analysis was re-evaluated using 5- and 10-year horizons, and the primary and secondary analyses were re-evaluated using WTP thresholds of $20,000 and $100,000.

4.3 Results

4.3.1 Primary results: The impact of full adherence on TB outcomes and hypothetical intervention maximum allowable cost

Among a low to moderate risk LTBI population, TB cases could be reduced from 90.3 cases per 100,000 person-years with current adherence to 35.9 cases per 100,000 person-years with perfect adherence. TB-related deaths could be reduced from 7.9 deaths per 100,000 person-years to 3.1 deaths per 100,000 person-years (Table 4-2). This represents a 60% reduction in new TB cases and deaths. When non-adherence was eliminated,

health increased by 12,000 QALY in a simulated population of a million LTBI individuals.

Achieving full adherence would likely require intensive intervention(s) and be associated with significant costs. A hypothetical intervention that increased relative adherence by 10% could cost up to $220 per patient and still be cost-effective at a WTP of $50,000. An intervention that increased relative adherence by 40% would bring the population to nearly full adherence and could have a maximum allowable cost of $975 per patient to remain cost-effective (Figure 4-3).

4.3.2 Secondary results: Evaluation of potential interventions and their sensitivity to cost

Table 4-3 provides the base case outputs for the four existing interventions. In a simulated population of a million individuals, the four existing adherence interventions added between 900 and 2,400 QALYs, reduced new TB cases by 9.5%–12.1% and reduced TB deaths by 5.0%–12.5% over a 25-year horizon. Weekly SMS-based adherence interventions appeared to have the greatest health impacts and were least sensitive to price (Figure 4-4). Adherence incentives had a steep drop in likelihood of being cost-effective as their cost increased (Figure 4-4). When all interventions were compared together, peer-support appeared to have the highest likelihood of being the most cost-effective option, irrespective of costs (Figure 4-5). Weekly SMS interventions were in a similar range to peer-support interventions in terms of cost-effectiveness acceptability. If there were slight price differences between these two options, the

cheaper one would likely be the optimal intervention. Adherence incentives were unlikely to be the most cost-effective option.

4.3.3 Sensitivity analysis results

In sensitivity analysis, 5- and 10-year time horizons had little impact on the relative reduction of TB incidence and deaths (~60%), but the number of cases was reduced (Table 4-4). At a 5-year time horizon, full adherence would have an ICER of $110,066/QALY because of increased drug spending that is not offset by future savings in TB care costs. Shorter model time horizons reduced the impact of the interventions proportionally. The likelihood of cost-effectiveness of all interventions dropped sharply as price rose at a WTP threshold of $20,000. At a WTP threshold of $100,000, the likelihood of being cost-effective was high for all interventions except adherence incentives and findings were insensitive to intervention costs. (Figure 4-7). In the combined analysis, standard care was heavily favoured at a WTP threshold of $20,000 (Figure 4-8).

4.4 Discussion

4.4.1 The burden of non-adherence and value of a hypothetical intervention

This study is the first to evaluate the burden of non-adherence to LTBI drug therapy in BC and to estimate the potential value of interventions. The financial and health benefits of eliminating non-adherence were apparent in our analysis. We found that full LTBI drug treatment adherence could prevent about 60% of future TB cases and deaths among

individuals with low to moderate risk LTBI. This reduction could potentially impact TB incidence at a population level, but would require intensive interventions to achieve. Findings suggest that the maximum allowable cost for an intervention(s) that brings all individuals to full adherence to remain cost-effective is $450 per patient. While this average intervention cost may be acceptable at an individual level, it would be difficult to implement at a population level due to its impact on healthcare spending. Lower cost interventions could address non-adherence in the low-risk population, reserving high cost interventions for higher risk individuals.

4.4.2 The potential value of adherence interventions and their sensitivity to cost

Important differences were found in the likelihood of cost-effectiveness and sensitivity to cost of existing adherence interventions. Peer-support and weekly SMS were least sensitive to price changes, and are most likely to cost-effectively improve patient health outcomes. The weekly SMS intervention has a high likelihood of being cost-effective relative to standard care; however, there was some uncertainty of the value of weekly SMS support provided by the health clinic compared to peer-support provided by patient caregivers, family or friends. There could be potential for these two interventions to be synergistic, but data was unavailable to model that relationship. Enhanced adherence counseling could also be a valuable intervention, but comes at a risk of inefficiency relative to weekly SMS or peer-support. Adherence incentives were highly sensitive to cost and the probability of being cost-effective quickly drops as price increases. In a comparison with all other interventions, adherence incentives had a very low chance of being cost-effective relative to alternatives, assuming they are in the same range of cost.

Previous analyses have assessed the cost-effectiveness of different regimens of LTBI therapy, but none evaluated the value of interventions that directly target drug adherence.(132-137) Some studies compared the cost-effectiveness of INH to RIF, and suggest that shorter course RIF could be a more efficient first-line therapy. Current evidence of RIF non-inferiority to INH is lacking, so it remains second-line therapy.(132) If RIF becomes first-line therapy, or combination INH and rifapentine therapy is approved for use in Canada, the value of these adherence interventions could change, and adherence interventions should be re-evaluated under these new guidelines.

4.4.3 Limitations

This study has several limitations. First, there was a lack of cost data for the interventions tested in this analysis. The value of the interventions was presented as a function of their cost to convey their cost-sensitivity. Next, intervention effectiveness data came from settings with a varying degree of generalizability to this study population. This limited the analysis to a comparison of health benefits as well as a hypothetical analysis of the relative value of adherence interventions. As more detailed data are collected through current and future studies, this analysis can be extended to include the observed data. Finally, an additional limitation was that dynamic transmission was excluded, but determinist transmission was included. Consideration of higher order dynamic transmission could increase the benefits of TB cases prevented, so the estimates presented here may be underestimated. Finally, the budget impacts of scaling these interventions in BC were not considered. The interventions could be scaled up to the full

population or a subset depending on their value and feasibility, and availability of program staff. Without adequate data, the budget impact of these programs remains unknown.

Further research is needed to understand the synergies between these interventions. Most of them would be valuable to implement individually; however, none can address the burden of non-adherence fully. A combination of interventions will be needed, but the efficiency and benefits of a combination intervention requires additional study of the feasibility. Additionally, it is unclear how much investment should be made in improving adherence relative to identifying LTBI cases or promoting treatment acceptance among existing LTBI patients. Currently, about 50% of patients that would benefit from prophylactic therapy are lost before they initiate drugs.(138) Increasing the number of patients on therapy would also be a valuable strategy.

4.5 Conclusion

These findings describe the value of currently available and hypothetical adherence interventions and suggest their maximum allowable cost to remain cost-effective in BC. Clinicians and researchers of new adherence interventions could use these results to understand the maximum allowable costs of their intervention based on hypothesized efficacy, or to understand if their intervention is feasible based on the efficacy needed to support known or hypothesized intervention costs. Based on the intervention set we evaluated, the weekly SMS intervention had the highest likelihood of being cost-effective, followed by peer-support and then enhanced adherence counseling. The major

costs would be staff training, labour/peer-time, overhead and in some cases, technology development costs. Adherence incentives appear to be the most uncertain strategy, and should be kept as a last choice given the availability of more efficient alternatives.

4.6 Figures

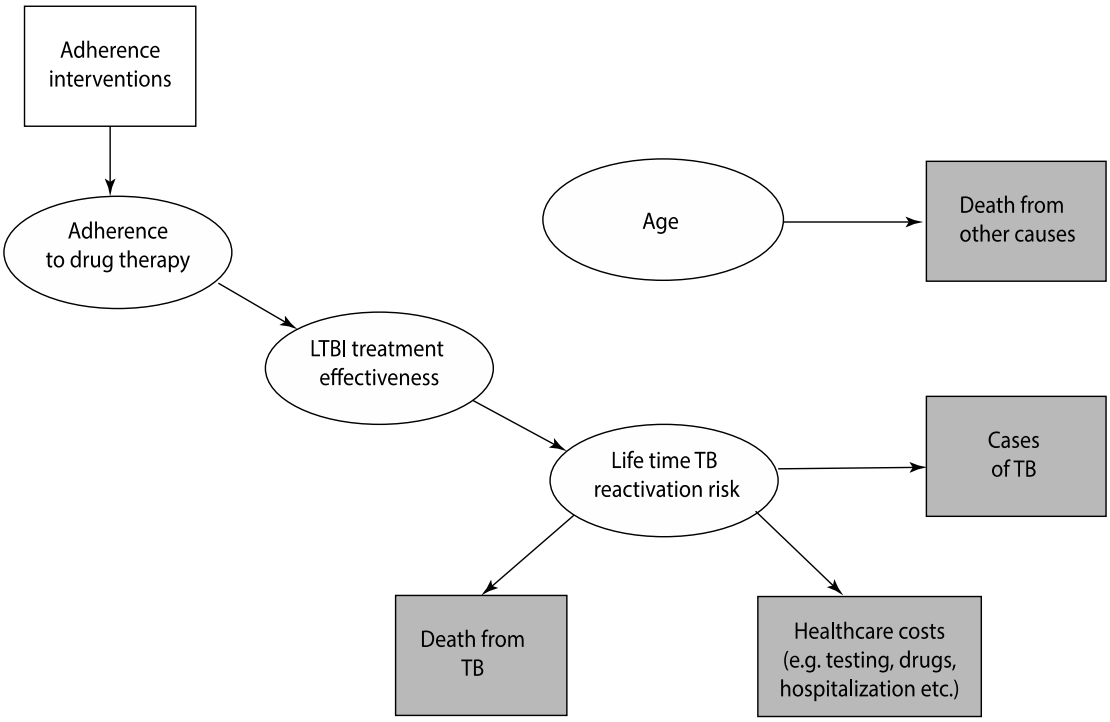

Figure 4-1. An influence diagram depicting the relationship between adherence interventions, treatment effectiveness and lifetime TB-related outputs. The lifetime reactivation risk of TB was affected by treatment adherence to LTBI drug therapy. The degree of adherence for the cohort affected the incidence of TB, costs of TB care and incidence of TB-related deaths. Cohorts of 100,000 individuals were simulated to estimate LTBI treatment outcomes under standard care and with adherence interventions.

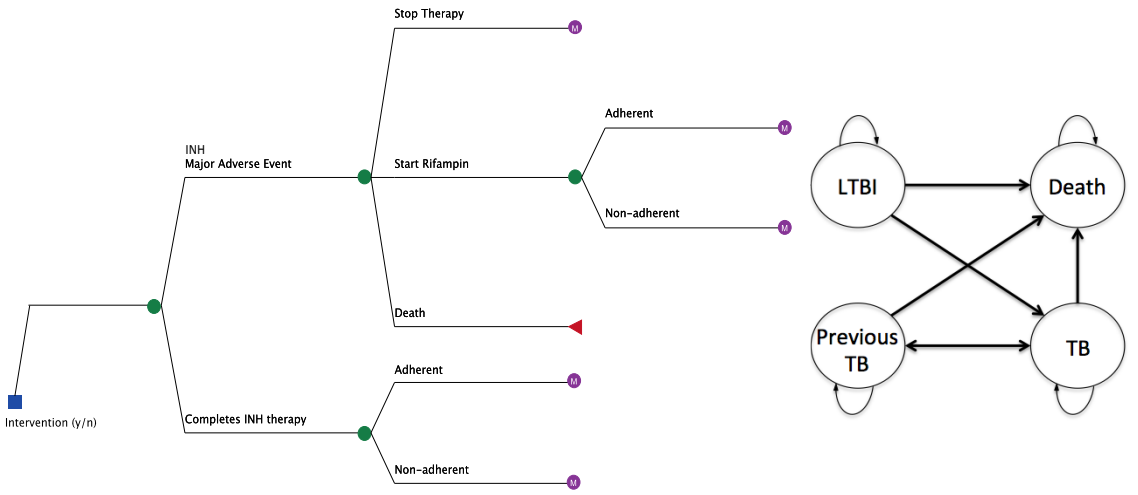

Figure 4-2. A two-stage decision analytic model depicting LTBI treatment outcomes. The decision tree on the left reflects INH as first choice therapy followed by RIF in cases of treatment failure or intolerance. The second stage was a Markov model simulating the remaining time horizon, where patients could transition between four states. Death was the absorbing state, and individuals could enter this state via TB death or background death.

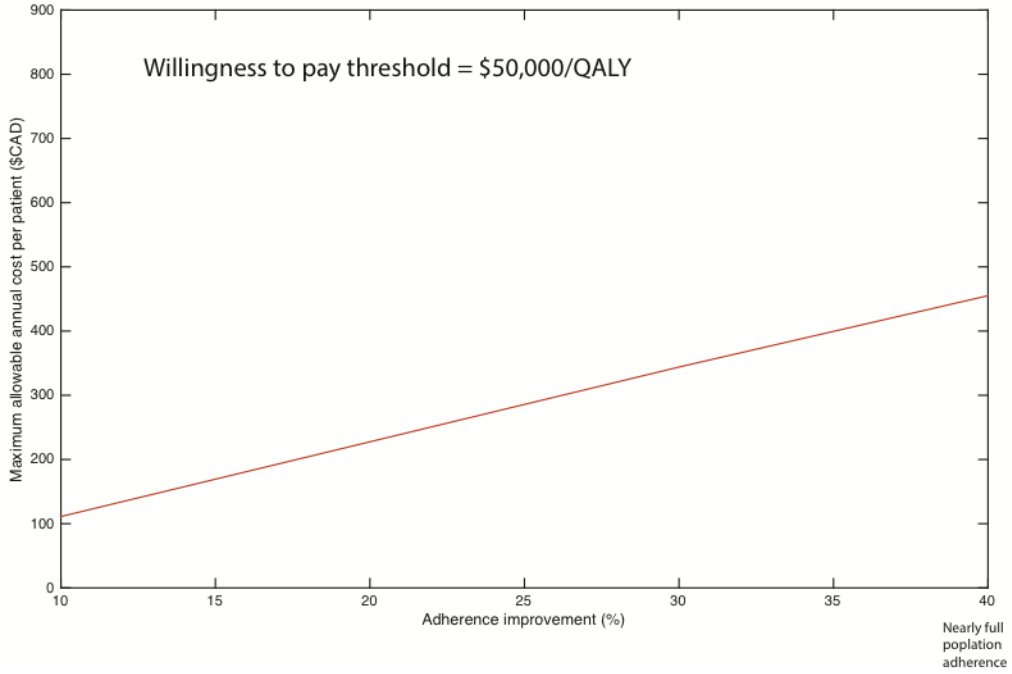

Figure 4-3. The relationship between an intervention's effectiveness at improving adherence and maximum allowable cost at a WTP threshold of $50,000/QALY. Our primary analysis focused on the maximum allowable spending based on the efficacy of an intervention(s) that could improve adherence.

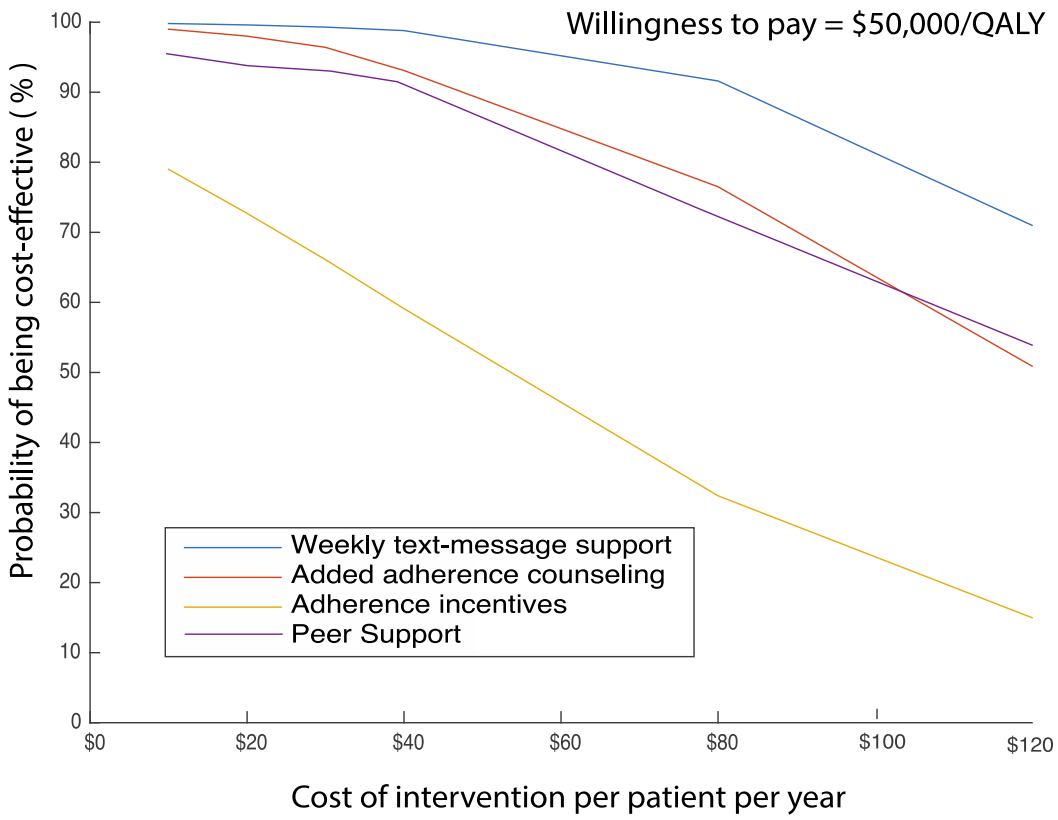

Figure 4-4. The likelihood that each intervention would be cost-effective (when interventions were individually compared to standard care) plotted as a function of intervention price. Weekly SMS was the least sensitive to price and would offer the highest probability of being cost-effective at most prices.

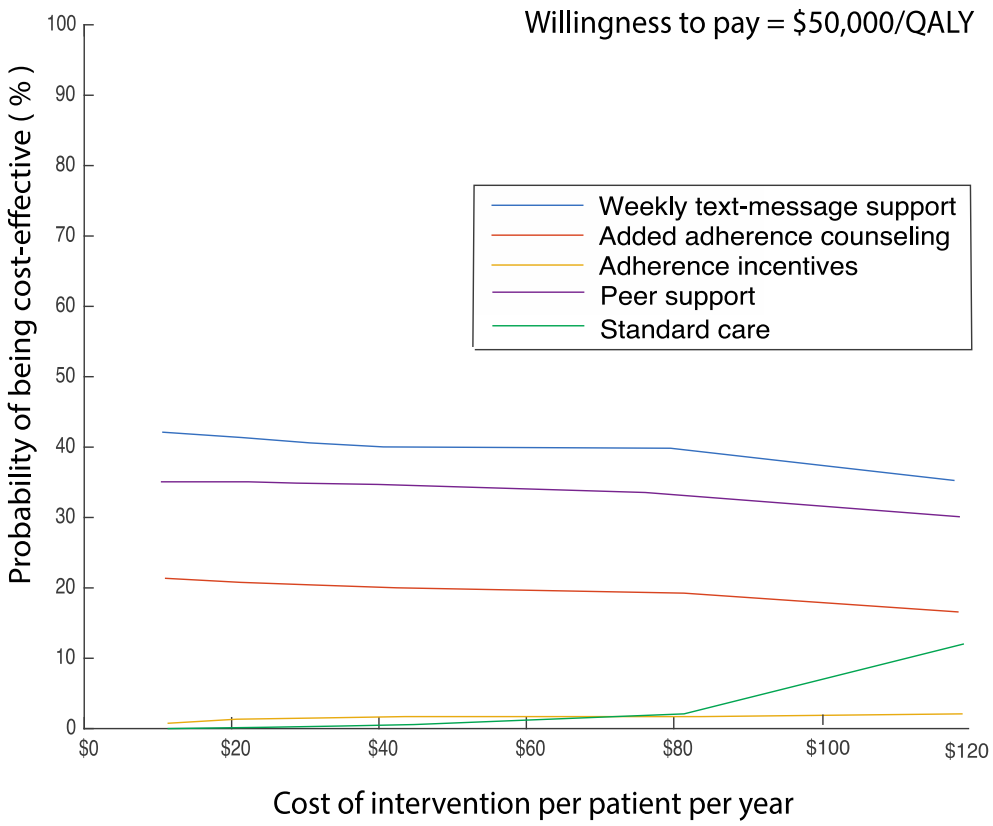

Figure 4-5. The cost-effectiveness acceptability curve (CEAC) when all options were compared together. In this graph, all interventions are compared to each other and to standard care. The price of each intervention is assumed to be equal. Interestingly, the peer-support intervention surpassed the enhanced adherence intervention for likelihood of value, but the opposite was true in the comparison against standard care (Figure 3). Adherence interventions had no chance of being the most cost-effective option among these alternatives.

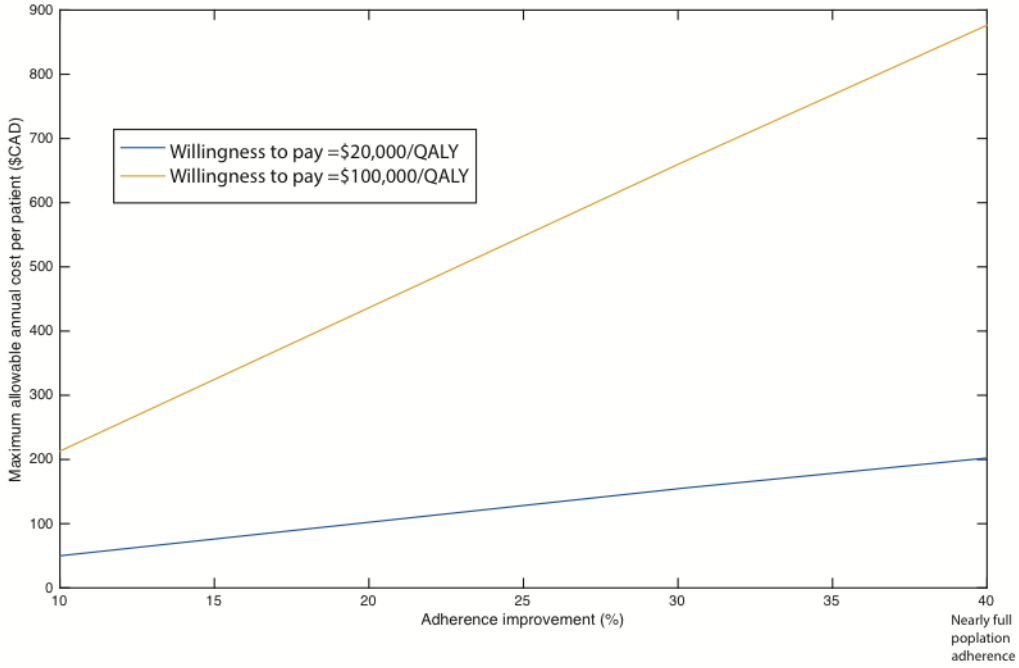

Figure 4-6. The relationship between maximum allowable cost and efficacy was dependent on the willingness to pay per QALY threshold and led to wide variation in the estimates. While the threshold does not theoretically vary at the regulatory level, it is not a well-established value. The maximum value of the interventions could be subject to debate based on the WTP threshold.

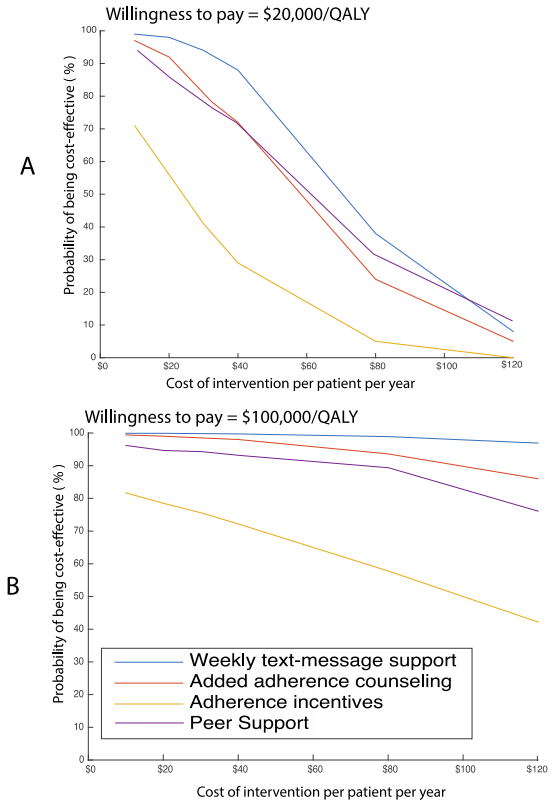

Figure 4-7. **The impact of the WTP threshold on the CEAC when interventions were individually compared to standard care.** Fig A shows the lowest willingness to pay per QALY (WTP) and the likelihood of value quickly drops as the intervention costs rise. In Fig B, willingness to pay was high and all interventions were less sensitive to cost changes and more comparable in likelihood of value with the exception of adherence incentives. SMS interventions remained the least sensitive to uncertainty in intervention cost.

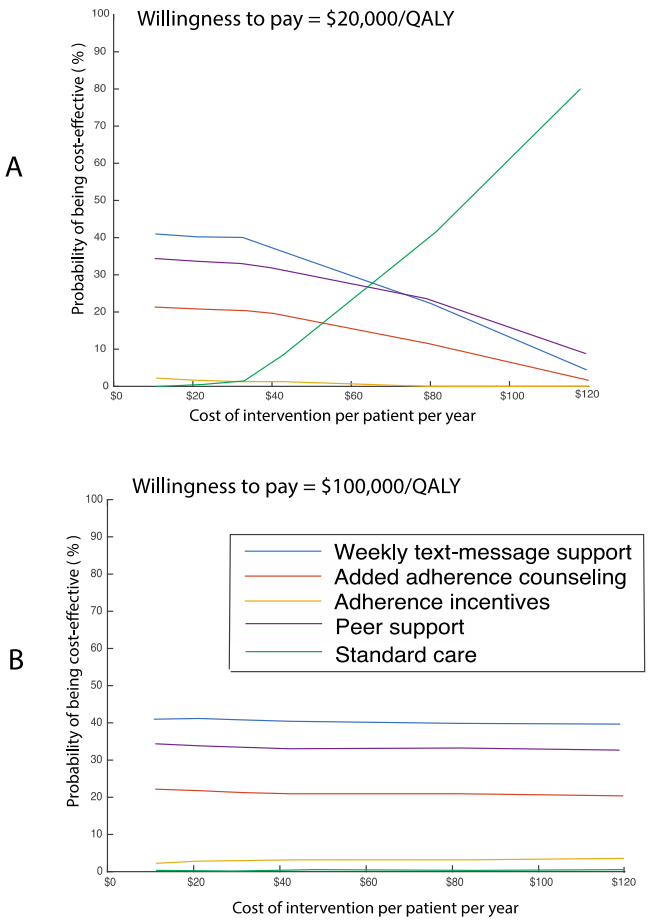

Figure 4-8. **The impact of the WTP threshold on the CEAC during a comparison of all options together.** In Fig A, standard care quickly passes all interventions as price rises above $70 per patient per year. At higher WTP, SMS intervention once again has the highest likelihood of value, closely followed by peer-support interventions. There is uncertainty in which would be the most valuable option between these two and value may come down to the lower cost option.

4.7 Tables:

Table 4-1: LTBI adherence model inputs

Parameter or Input	Base case	Range	Distribution (parameters)	Reference
Cohort population data				
Age	40	Not varied		Assumption
Prob(Background death)*	0.0037	Varied with age	N/A	(121)
Tuberculosis-related probabilities				
Prob(Annual TB activation | No LTBI treatment)	0.003	distribution	Beta (16.6, 5599.4)	(120)
Prob(Cure | TB drug treatment)	0.87	distribution	Beta (1399, 200)	(139)
Prob(Secondary transmissions per active TB case)	0.55	0.75x – 1.25x	Uniform	(140)
Prob(TB reactivation within 2 yrs | TB treatment comp)	0.036	distribution	Beta (1636, 43799)	(124, 125)
Prob(death with active TB)	0.075	distribution	Beta (129, 1401)	(119)
LTBI treatment clinical outcomes				
INH treatment outcomes				
Probability of full completion of INH therapy	0.61	distribution	Beta (1430, 901)	(137, 141-145)
Sub categories in the low adherence group:	Complement of previous parameter distributed into three sub categories			
Probability of completing 6 to 9 months of INH	0.33	Not varied	N/A	(141)
Probability of completing 3 to 6 months of INH	0.37	Not varied	N/A	(141)
Probability of completing 0 to 3 months of INH	0.30	Not varied	N/A	(141)
Prob(stopping INH in first month | Adverse event)	0.52	Not Varied	N/A	(22)
Prob(major INH adverse event requiring stoppage)	0.06	distribution	Beta (134, 2095)	(137, 143-145)
Prob(death | major INH adverse event)	0.00012	distribution	Beta (3, 245828)	(146)
Reduction in 5 year active TB incidence with:				
Full INH completion	93%	distribution	Beta (1, 4542)	(21)
Greater than 6 months of INH completion, but <80%	69%	distribution	Beta (5, 5432)	(21)
3 to 6 months INH completion	31%	distribution	Beta (12, 6027)	(21)
< 3 months INH completion	0%	Not varied	N/A	(21)

* Probability of background death increased with age according to data from the British Columbia life table.

Parameter or Input	Base case	Range	Distribution	Reference
RIF treatment outcomes				
Prob(RIF initiation | INH failure)	0.5	0.25 - 0.75	Uniform	Assumption
Probability of full completion of RIF therapy	0.75	distribution	Beta (1704, 553)	(137, 142-145)
Risk of RIF adverse event requiring stoppage	0.029	distribution	Beta (56, 2043)	(137, 143-145)
Reduction in 5 year active TB incidence with:				
Full RIF completion	77.5%	65 - 90%	Uniform	(147)
Partial RIF completion	0%	Not varied	N/A	Assumption
Costs data (2015 Canadian dollars)				
LTBI treatment and care with INH (Full completion cost; reduced for partial completion)	$935	0.75x – 1.25x	Uniform	BCCDC
LTBI treatment and care with RIF (Full completion cost; reduced for partial completion)	$545	0.75x – 1.25x	Uniform	BCCDC
Cost of TB diagnosis	$390	0.75x – 1.25x	Uniform	(126)
Annual outpatient TB treatment and care	$1,590	0.75x – 1.25x	Uniform	(126)
Annual inpatient TB treatment and care	$11,640	0.75x – 1.25x	Uniform	(126)
Cost of major adverse event	$710	0.75x – 1.25x	Uniform	(37)
Utilities				
Healthy or asymptomatic LTBI	1	N/A		Assumption
LTBI on treatment	0.82	0.9x – 1.1x	Uniform	(128)
Active TB	0.62	0.9x – 1.1x	Uniform	(128)
Intervention impact on adherence rates	RR**			
Adherence incentives	1.04	0.97 – 1.13	Log-normal**	(103)
Enhanced adherence counseling	1.09	1.01 – 1.15	Log-normal**	(1)
Peer support intervention	1.10	1.00 – 1.29	Log-normal**	(118, 148)
Weekly SMS adherence support	1.11	1.05 – 1.16	Log-normal**	(1)

**Uncertainty distribution ranges listed here are based on 95% confidence interval reported in original studies; the mean of the log-normal distribution matches the Relative Risk (RR) listed in this table and the standard deviation of the log-normal distribution was derived using the formula: Ln(upper CI)- Ln(lower CI) / 3.92

Table 4-2: Outcomes associated with current and full adherence scenarios over 25 years			
	Current adherence	**100% Adherence**	**Difference in outcomes**
25-year treatment outcomes			
Average discounted costs	$1,133	$1,091	-$42
Average discounted QALY	17.3319	17.3439	0.0120
Average ICER	Reference	Cost-saving	--
TB cases*	90.3	35.9	54.4
TB deaths*	7.9	3.1	4.8

* Per 100,000 person years

Table 4-3: The potential health impacts of existing adherence interventions over 25 years					
	Standard Care	**Weekly SMS adherence support**	**Adherence incentives**	**Enhanced adherence counseling**	**Peer-support**
Average Discounted QALY	17.3320	17.3344	17.3329	17.3340	17.3342
TB Cases*	90.7	79.8	86.6	81.5	80.7
TB Deaths*	8.0	7.0	7.6	7.2	7.1

* Per 100,000 person years

Table 4-4: Outcomes associated with current and full adherence scenarios over 5 and 10 years			
	Standard care	**100% Adherence**	**Difference in outcomes**
5-year treatment outcomes			
Average discounted costs	$858	$980	$122
Average discounted QALY	4.5212	4.5223	0.0011
Average ICER	Reference	$110,066	--
TB cases*	75.1	29.3	45.8
TB deaths*	6.6	2.6	4.0
10-year treatment outcomes			
Average discounted costs	$942	$1,014	$72
Average discounted QALY	8.5518	8.5550	0.0032
Average ICER	Reference	$22,850	--
TB cases*	86.4	35.2	51.2
TB deaths*	7.6	3.1	4.5

* Per 100,000 person years

Table 4-5: The potential health impact of existing adherence interventions over 5 and 10 years					
	Standard Care	**Weekly SMS adherence support**	**Adherence incentives**	**Enhanced adherence counseling**	**Peer-support**
5 year treatment outcomes					
Average Discounted QALY	4.5254	4.5256	4.5255	4.5257	4.5256
TB Cases*	75.6	66.5	72.2	68.0	67.3
TB Deaths*	6.7	5.9	6.4	6.0	5.9
10 year treatment outcomes					
Average Discounted QALY	8.5503	8.5509	8.5505	8.5508	8.5509
TB Cases*	86.7	76.3	82.8	78.0	77.2
TB Deaths*	6.7	7.6	7.3	6.9	6.8

* Per 100,000 person years

5 Using SMS-based adherence interventions as part of a multilevel HIV intervention in Maharashtra, India

5.1 Background

Randomized controlled trials (RCTs) have long been regarded as the gold standard for generating new medical evidence.(149) However, resource constraints limit the number of RCTs that can be conducted. Decision analytic modeling can estimate potential outcomes and risks of new interventions under consideration for an RCT using the best available information.(41, 51) Research funders could prioritize alternative intervention designs using decision analysis by finding the design that maximizes expected value. However, in addition to traditional measures of efficiency, programmatic constraints should be explicitly incorporated into early stage decision analyses.

The World Health Organization (WHO) has announced the goal of an AIDS-free generation by 2030, and an intensive focus on programmatic efficiency is needed to extend the limited financial resources available to achieve this goal.(10) Many member states face salient budget constraints along with uncertainty regarding future programmatic budgets. Further, research funds are limited, but new interventions and technologies will definitely be needed to achieve the WHO goal. Behavioral interventions are crucial to manage risk factors related to HIV progression and further transmission. Combination approaches are increasingly needed to manage the global pandemic, but

have not been robustly evaluated for combined efficacy. Studying the vast array of permutations is not financially or operationally possible.

Programmatic funders could have a variety of implicit constraints when making decisions about both research and implementation. Some may only make adoption recommendations based on evidence supported by RCTs. Single-focused behavioral interventions may have been evaluated individually but not collectively, raising programmatic questions about their feasibility, effectiveness, scalability and value. Additionally, short-term budget constraints may be imposed due to the desire to maximize benefits today because of the possibility of less funding in the future. In this case, strategies that are most efficient may not abide by a budget constraint, and the number of strategies evaluated for efficiency will be lower. Finally, risk may be an important funder constraint. Decision-makers not only may want to maximize average health benefits, but may prefer a high likelihood that a substantial health benefit accrues, even if the magnitude of that substantial benefit is smaller than the average.(150) Communicating risk information as part of a decision analysis can improve decision transparency to address this constraint.

There are an estimated 2.1 million people living with HIV/AIDS (PLWHA) in India.(151) A team of Indian and US institutions is developing a multilevel behavioral HIV intervention with constituent interventions at the individual, group and community level in the Indian state of Maharashtra. By combining several behavioral intervention approaches, the goal of the multilevel intervention is to reduce risks among alcohol-using

men on antiretroviral therapy (ART). The objective of this study was to evaluate the configurations under consideration using decision analysis. Given the programmatic funder constraints described above, three scenarios were evaluated: (1) No constraint ["maximize expected value"], (2) the combination must maximize expected value within short-term budget constraints ["maximize expected value within a budget constraint"] and (3) the combination must maximize expected value within a risk threshold ["maximize expected value within an uncertainty constraint"]. Under these scenarios, I sought to identify the optimal constituents of a multilevel intervention to support intervention design discussions for the trial team.

5.2 Methods

5.2.1 Overview

For the purpose of this work, *constituent intervention* refers to an individual intervention addressing an HIV risk factor, such as motivational interviewing to address alcohol-use or cognitive behavioral therapy to address depression. *Multilevel intervention* refers to one or more constituent interventions in combination, and different permutations of these constituent interventions would result in different *configurations* of the multilevel intervention. This evaluation examined different ways the constituents could be configured to achieve optimal outcomes based on the three scenarios (maximize expected value, maximize expected value within a budget constraint and maximize expected value within an uncertainty constraint).

5.2.2 Simulating multilevel interventions

5.2.2.1 Identification of constituent interventions

A literature review was conducted to identify appropriate constituent interventions to compose the multilevel intervention. Two primary goals of the multilevel intervention are to reduce antiretroviral (ART) non-adherence and to reduce the risk of HIV transmission. Single-focused interventions address one of four risk factors including: alcohol-use, depression, non-adherence to ART or risky sexual behavior (i.e., condom non-use and development of non-HIV STIs). Individual and group interventions addressed patient-level risks, while community-level interventions focused on risks in the broader population. The total time of the individual and group components could be modified such that multiple risk factors could be addressed. For example, the individual component could focus on alcohol-use, depression and non-adherence, but it would increase the time (and variable cost of labour) to address all three. Additionally, an intervention could be delivered briefly (e.g., alcohol-related motivational interview for 60 min) or at length (e.g. alcohol-related motivational interview for 240 min). The efficacies of long or brief interventions were estimated by pooling outcomes from individual trials that studied long or brief versions of the same intervention.

Table 5-1 lists the identified constituent interventions along with their cost and efficacy data, and the published sources they were derived from. Constituent interventions were restricted to those with a randomized trial(s) to limit unobservable confounding. If time data were published, the total time required for the behavioral interventions and hourly counselor wage in India were used to calculate the variable cost of labour. Labour costs

were increased to account for program administration costs based on a WHO report of average HIV program costs.(152)

5.2.2.2 Forming combinations of constituent interventions

Based on the combinations of 15 constituent interventions, 5,836 possible alternative configurations were iterated for the multilevel intervention, ranging from single interventions to all interventions combined together. Since the long and brief versions of the same counseling strategy would not be implemented together, the logical combinations could include up to nine constituents, because six pairs of interventions were mutually exclusive. The calculation below summarizes how the combinations were derived from the 15 constituent interventions based on the number of constituents.

Calculation of the number of combinations (brief and long versions of the same intervention would not logically be combined together):

$$Combinations\ of\ 9\ constituents = 2^6$$

$$Combinations\ of\ 8\ constituents = 2^6\binom{3}{2} + 2^5\binom{6}{5}$$

$$Combinations\ of\ 7\ constituents = 2^6\binom{3}{1} + 2^5\binom{6}{5}\binom{3}{2} + 2^4\binom{6}{4}$$

$$Combinations\ of\ 6\ constituents = 2^6 + 2^5\binom{6}{5}\binom{3}{1} + 2^4\binom{6}{4}\binom{3}{2} + 2^3\binom{6}{3}$$

$$Combinations\ of\ 5\ constituents = 2^5\binom{6}{5} + 2^4\binom{6}{4}\binom{3}{1} + 2^3\binom{6}{3}\binom{3}{2} + 2^2\binom{6}{2}$$

$$Combinations\ of\ 4\ constituents = 2^4\binom{6}{4} + 2^3\binom{6}{3}\binom{3}{1} + 2^2\binom{6}{2}\binom{3}{2} + 2^1\binom{6}{1}$$

$$Combinations\ of\ 3\ constituents = 2^3\binom{6}{3} + 2^2\binom{6}{3}\binom{3}{1} + 2^1\binom{6}{1}\binom{3}{2} + 1$$

$$Combinations\ of\ 2\ constituents = 2^2\binom{6}{2} + 2^1\binom{6}{1}\binom{3}{1} + 2^3$$

$$Single\ constituents = 2^1\binom{6}{1} + \binom{3}{1}$$

5.2.2.3 Simulating intervention combinations

Monte Carlo simulation was used to draw parameters from pre-specified uncertainty distributions during probabilistic analyses. Uncertainty distributions for intervention effectiveness inputs were derived from the 95% confidence intervals reported in published reviews, and during simulation, the inputs were independently drawn from lognormal distributions. Intervention costs were independently drawn from uniform distributions over plausible ranges, because data was insufficient to create uncertainty distributions. The interventions were assumed to be independent when drawing from the distributions of their respective costs and effectiveness. Programmatic staff, researchers and clinicians from India provided insights when assumptions were needed.

Two interventions addressing different risks were assumed to have additive effects. For example, if an adherence intervention and a sex-risk intervention were combined, the combination would result in a reduction in both non-adherence and sexual risk taking. The level of reduction corresponded with the input of effectiveness for each intervention, which was varied probabilistically. However, if two interventions acted on the same risk, no synergy was assumed and the higher effect size was used. For example, if the individual sexual risk intervention was combined with the group sexual risk intervention, the higher effect size was used in the simulation as the total effect size of the

combination. However, the costs of both were included, since both were being delivered. This became important during probabilistic analysis, because the group intervention had the higher effect size in some runs, while the individual intervention had the higher effect size in others. As a result, the expected QALYs of the combination could be higher than the expected QALYs of each individual component in isolation. Without this mechanism, there would be no combinations with both an individual and group intervention for the same risk factor – an assumption that was not agreeable to the Indian stakeholders. The expected values for outcomes associated with each combination (e.g., costs, QALYs, transmissions etc.) were calculated by taking the average of the outcome distributions.

5.2.3 Decision analytic model

A decision analytic model was developed for the Indian state of Maharashtra with component modules: a disease progression module and a transmission module. Further model details including development, parameterization and calibration of the modules can be found elsewhere.(68, 102) The progression module was calibrated and validated to patient-level survival, time to viral failure and CD4 response data based on administrative data from Maharashtra or literature.(153) The transmission module estimated population outcomes including the number of HIV transmissions, costs of treatment and care and quality adjusted life years (QALYs) within a simulated population of Maharashtra over 20 years. The transmission model was calibrated to Indian HIV incidence, prevalence, death and number of people on treatment based on published data from UNAIDS.(154)

5.2.4 Additional simulation settings and inputs

Model inputs and their uncertainty distribution are listed in Tables 5-1 to 5-4. There were four categories of inputs in this analysis: intervention costs and effectiveness inputs, HIV progression inputs, HIV transmission inputs and HIV risk behavior inputs. Two main sources were used to estimate inputs or to derive calibration data: state-level administrative data from Maharashtra collected from HIV clinics between 2007-2014 (n=23,701) and literature reviews. The administrative data provided patient-level characteristics for the progression model including CD4 count trajectory over time, survival and the distribution of patient characteristics that altered HIV progression. Other risk factors relationships including sexual risk-taking and adherence to ART were derived from the published literature (Table 5-4). A health system payer perspective was used to estimate costs and a 3% discount was used based on WHO recommendation.(65) Results were interpreted using two cost-effectiveness thresholds approximating the range published by the WHO for the south-east Asia region ($5,000 and $15,000USD/QALY).(155)

5.2.5 Iteratively narrowing down the possibilities

The lengthy computational time required for a PA using this complex model with thousands of configurations of multilevel interventions (n=5,836) presented a technical barrier for this analysis. Thus, the configurations were assessed in three rounds. In the first round, a deterministic analysis was conducted to find the most efficient single-focused constituent interventions. Based on results, the most efficient constituent interventions were combined in a second round of probabilistic analysis. In the second

round, a two-way probabilistic analysis (varying only intervention costs and effects) was conducted in a smaller set of combinations. Combinations that had at least a 1% chance of being on the efficiency frontier or at least a 1% chance of being the most cost-effective configuration based on the cost-effectiveness acceptability curves (CEAC) at two values of λ ($5,000/QALY and $15,000USD/QALY) were included in the final analysis.

5.2.6 Identifying optimal choices

After the second round of filtering, remaining combinations were assessed in a full PA by simultaneously varying all parameters. Using PA results, CEACs were constructed and the probability of being on the efficiency frontier (PEF) was calculated. The PEF is calculated by deriving the efficiency frontier for each iteration of a PA and calculating the probability that a configuration would be on the efficiency frontier.(156) Results were interpreted using the three decision-maker scenarios that are described in greater detail below.

5.2.7 Funder scenario 1: Maximize expected value

This scenario reflects the fact that some funders would be unconstrained in their decision, and would make a choice based on efficiency and expected value alone. Prevailing decision theory suggests that maximizing expected value at the relevant λ is the primary objective when evaluating new interventions.(157, 158) With this in mind, the most valuable configuration to study would be the one that maximized ENMB at a plausible value of λ. The λ threshold is unknown in India and cannot easily be estimated by looking at past budget-constrained decisions. A plausible value of λ was evaluated based on

WHO guidance that recommends approximately three times the GDP of a country as a threshold; India's per capita GDP was $1,582 USD in 2014.(65, 159) Additionally, the WHO website suggests a threshold range of $1,990 to $14,876 (2005 international $) across Asia. Thus, thresholds of $5,000/QALY and $15,000/QALY (2016 USD) were used to reflect two plausible values for the λ threshold, and the influence of threshold on the optimal choice was assessed.

5.2.8 Funder scenario 2: Maximize expected value within a budget constraint

Budget constraints could prevent some options from being adopted regardless of how cost-effective or efficient they are. While it might be argued that this constraint can be operationalized within conventional decision analytic practice by employing a suitably high discount rate, the time horizons considered by policymakers often end abruptly, leading to discontinuities in time preference evaluation that are incompatible with the continuous assumptions implicit in discount rates. Decision-makers are often aware of risks to their future budgets, but unaware of when and by how much their funding could be cut. Thus, they may impose constraints on how much an intervention could cost. The optimal option were evaluated when annual program costs were hypothetically constrained at $200,000 and $400,000 to observe the impact on final results. The optimal options were plotted under each constraint using the efficiency frontier technique outlined in Hunink et al.(51)

5.2.9 Funder scenario 3: Maximize expected value within an uncertainty constraint

Risk-averse decision-makers could choose to forego some expected value for a lower-risk option over a higher-risk option.(150) Thus in the final scenario, the influence of a risk-averse decision-maker on the optimal choice was assessed. To communicate risk and uncertainty, a PEF was used along with the traditional CEAC to overcome a previously reported limitation of the CEAC.(157, 160) While the CEAC plots the probability of an option being the most cost-effective option at multiple WTP thresholds, it cannot distinguish between alternatives with different variance in their outcomes (i.e., different joint distributions of incremental costs and effectiveness).(160) Two alternatives can have the same CEAC if they have the same proportion of their incremental joint distributions above and below the WTP threshold even if they each have vastly different outcome uncertainty. The PEF uses the incremental joint distribution directly in its calculation, so we used it as a complementary method to the CEAC to communicate risk. To reflect a risk-averse decision-maker the optimal choice was evaluated with an arbitrary constraint that options be more likely than not to be on the efficient frontier, meaning they must have a PEF > 50%.

5.3 Results

5.3.1 Results of deterministic filtering process

5,876 combinations were formed and deterministic analysis was conducted to find 20-year HIV and intervention costs and QALYs. Intervention configurations were identified that were cost saving, cost-effective and not cost-effective relative to standard care, and

plotted on an efficiency frontier. Compared to standard care, approximately 23% of the combinations were cost saving and 27% were cost-effective at λ=$15,000/QALY. The ICER of combinations that were not cost saving ranged from $30/QALY to $250,000/QALY. Considering all options together, the most efficient combinations contained at least one of these seven interventions: individual long alcohol counseling, individual long sexual risk counseling, group brief sexual-risk counseling, group long sexual-risk counseling, community-level sexual risk intervention, individual brief adherence counseling and weekly text-message adherence support. These seven were ultimately chosen for the final rounds of PA.

5.3.2 Results of probabilistic analysis

The deterministic analysis yielded configurations with a stark contrast in affordability and outcomes. Although some combinations with the community-level sexual risk intervention had a favourable PEF, they were dominated by standard care over the relevant threshold range λ. Five configurations were on the efficiency frontier based on expected value, had reasonable PEF (27%-54%) and were cost-saving compared to standard care (Table 5-5). Of these five, the configuration with the highest PEF differed from the most affordable configuration by about $50,000 per year and differed from the configuration that prevented the most HIV transmissions by 175 new cases.

5.3.3 Funder scenario 1: Maximize expected value

Funders may consider one of the five configurations on the efficiency frontier as the best candidate. They would choose to study the alternative that maximized ENMB, but the

option changed based on the λ threshold. The configurations that maximized ENMB included: *long individual alcohol counseling, individual weekly text-message support, long sex-risk group counseling and long individual counseling for sex-risk* at λ=$15,000/QALY; and *in-depth individual alcohol counseling, individual weekly text-message support and long sex-risk group counseling* λ=$5,000/QALY.

5.3.4 Funder scenario 2: Maximize expected value within a budget constraint

Assuming an annual budget constraint of $200,000, two configurations maximized health benefits and met the constraint (Figure 5-4A). Assuming an annual budget constraint of $400,000, four options maximized health benefits and met the constraint (Figure 5-4B). In the unconstrained efficiency frontier, one of the configurations was eliminated through extended dominance by a more expensive but more efficient option (Figure 5-4C).

5.3.5 Funder scenario 3: Maximize expected value within an uncertainty constraint

In the last scenario, the risk-tolerance of decision-makers was considered. If funders were risk-averse, they would consider the risk of inefficiency more explicitly in their decisions. The top choice assuming a risk constraint of PEF >50% was a combination of *in-depth individual alcohol counseling, individual weekly text-message support and brief sex-risk group counseling* (53%). Decision-makers could impose any level of risk and choose alternatives based on expected value in conjunction with risk (Figure 5-5). The risk of inefficiency rose along with programmatic costs and intensity of intervention combinations.

5.4 Discussion

In this study, decision analysis was used to estimate the value of alternative designs of a multilevel behavioral HIV intervention. The options were narrowed from 5,836 to less than a dozen by systematically evaluating long-term health and economic outcomes. The final efficiency frontier (Figure 5-3) shows five alternatives that could be valuable to study, assuming no other constraints. However, in addition to the WTP threshold, the optimal combination could depend on implicit decision-maker constraints including annual programmatic budget and risk. Intuitively, the less expensive options were the optimal choice when the WTP threshold was low (~$1,000/QALY) and combinations with higher expected health benefits were the optimal choice when WTP was high ($15,000/QALY). However, imposing a budget constraint led to optimal options that were off the unconstrained efficiency frontier. The implication is that the optimal research target might not be the most efficient option, but might have a higher chance of health system adoption because of affordability when scaled up. While national or global agencies may specify a WTP threshold, a shadow threshold may exist based on operational restrictions faced by implementation agencies in many settings. Making the trade-offs explicit through decision analysis can provide meaningful input to the intervention design prior to initiating a trial.

A notable insight of these analyses is that expected value could only be improved by allowing substantial uncertainty of efficiency relative to alternatives, a situation unlikely to be acceptable to risk-averse stakeholders. In particular, as the delivery time or number

of sexual risk reduction constituents increased, the uncertainty of efficiency also increased. This finding was consistent across our analyses, suggested that a risk-averse research-stakeholder would favour a multilevel intervention with a single brief sexual-risk counseling constituent rather than an intervention with multiple or long sexual-risk counseling constituents. Because the risk tolerance of an organization is difficult to identify, the probability of efficiency can be displayed along with expected value to give research stakeholders a more transparent understanding of the decisions they are making.

This study had several limitations. In a simulation, reality is simplified into a mathematical model to reflect likely future outcomes. The input data and model structure can have unknown biases or imperfections. Extensive calibration was conducted with the simulation to epidemic and surveillance data, and probabilistic analysis was conducted to limit the bias introduced by uncertainties. Additionally, there could have been synergies or diminishing returns when two interventions were combined, but without data, these could not be included. The fact that these relationships could not be included may have biased the results toward undervaluing or overvaluing some combinations. As these data become available through future studies, the simulations can be updated. Finally, literature review data about intervention effectiveness had a varying degree of generalizability to the target population and expert opinion was needed to make reasonable assumptions for some parameters. The uncertainty distributions were based on the best available information, but bias in the inputs could affect the final results in an unknown direction.

Findings suggest five configurations that could efficiently and affordably maximize ENMB at the plausible WTP threshold in India. Delaying implementation of potentially efficacious interventions would result in loss of health in the short-term, even if their efficacy remains unknown. However, since disinvestment in interventions is rarely possible, accurate information is also needed before making heavy investments in new interventions. Funders of healthcare must often decide between taking a risk by implementing promising yet under-tested interventions or demanding further research to ensure appropriate health system development.

5.5 Conclusion

Under three alternative scenarios, optimal configurations of the multilevel intervention were identified. Findings suggest that simulations can aid decisions by communicating the risk, projected benefits and implications of a delayed decision. By organizing options into high and low value, decision-making can be streamlined and incorporate a variety of implicit decision constraints. A similar analysis can be done with interventions targeting risks at different points along the HIV cascade of care (ie. testing interventions vs retention interventions vs expanded treatment access vs expanded viral load testing). This type of systematic evaluation prior to trial initiation could improve the efficiency of the research process and provides a tool for transparent discussion of the pros and cons of different options. Further research is needed to explore this method for other disease areas and intervention types

5.6 Figures

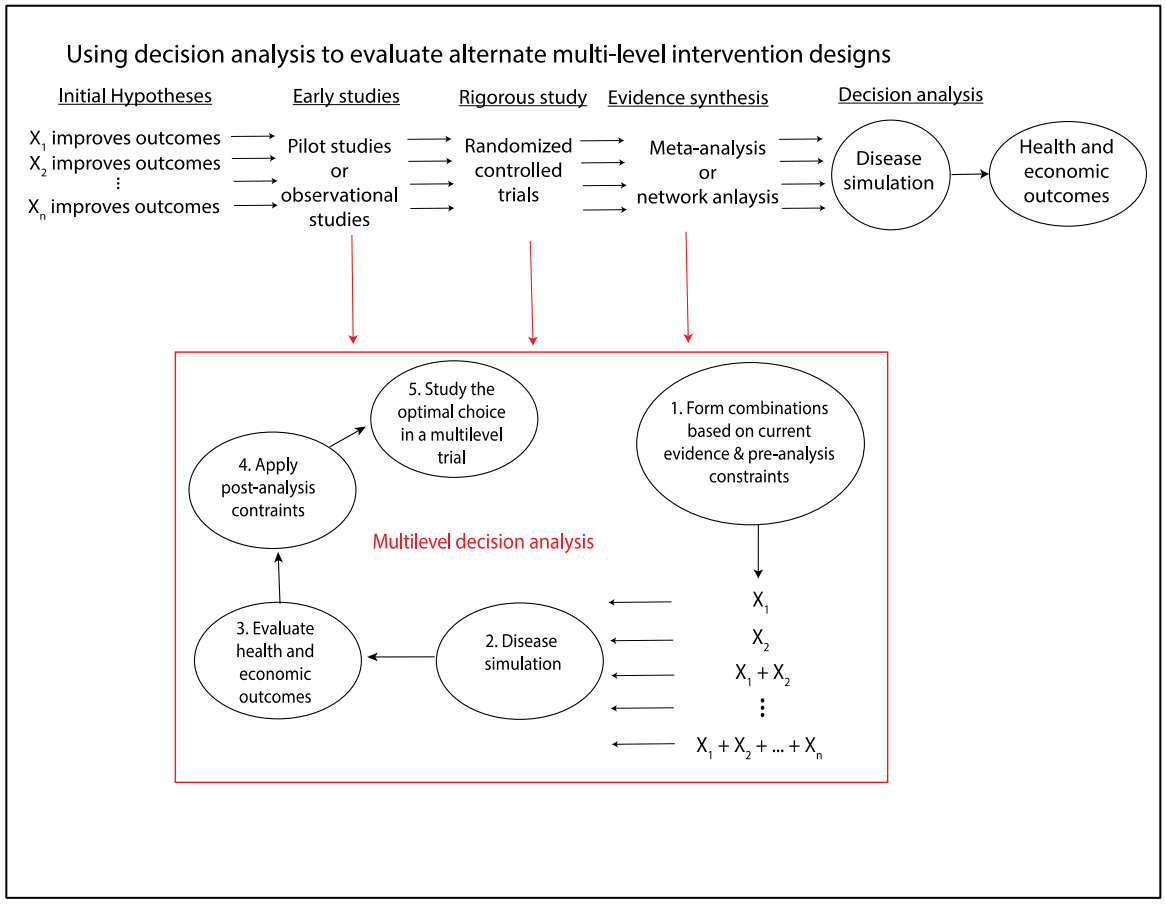

Figure 5-1. A multilevel decision analysis can be conducted prior to launching a new study. Individual interventions are typically evaluated individually and have variation in their level of evidence. Combinations of individual interventions have an unknown effect, but information about constituents can inform a decision analysis. Since it is impossible to study every combination, identifying the most efficient choices *a priori* could make the research process more efficient. Funder constraints should be explicitly considered during this process to ensure the choices under study are feasible for eventual implementation.

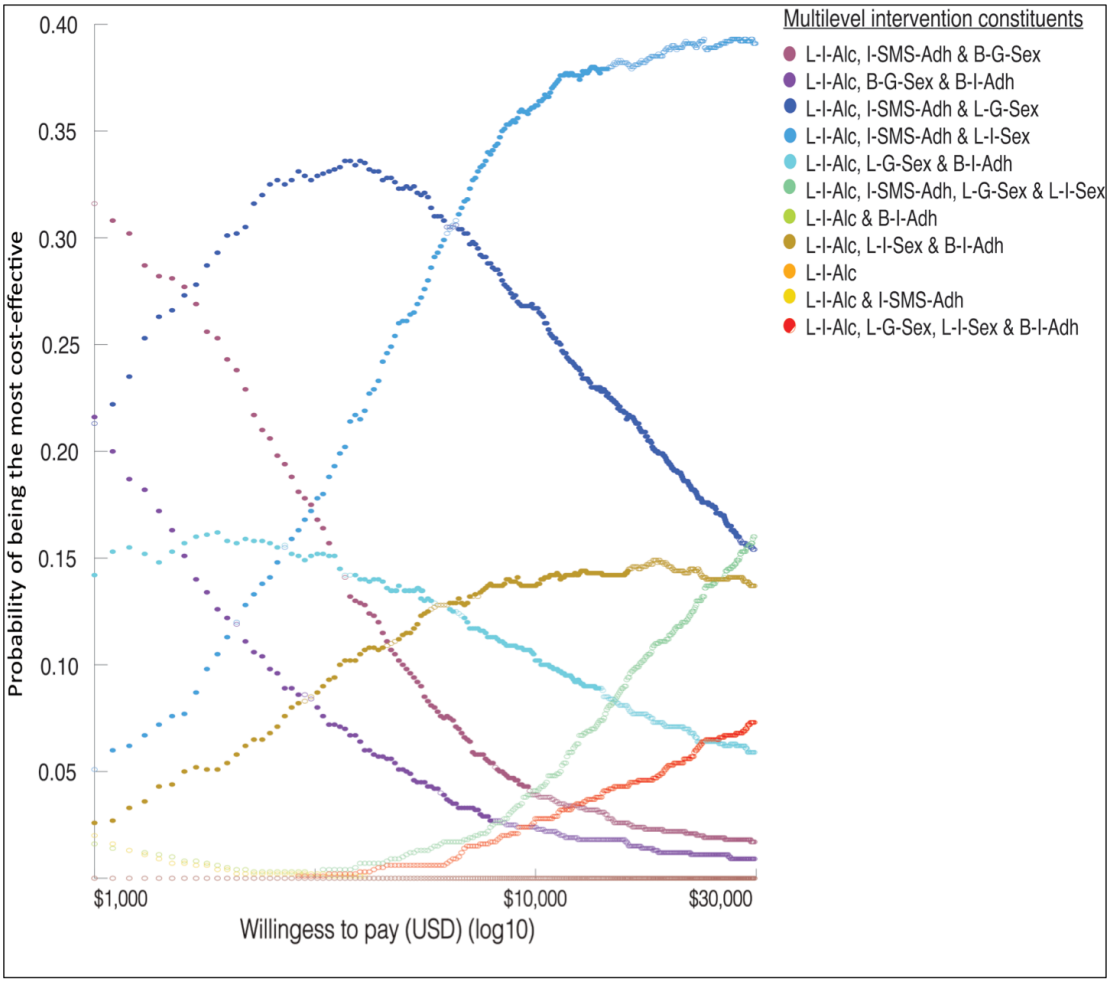

Figure 5-2. The cost-effectiveness acceptability curve (CEAC) shows the probability of being the most cost-effective option at different willingness-to-pay thresholds. The optimal choice changed as the threshold increased. Each option has a relatively low probability, suggesting that there is a high chance that other options could have a higher value in many of the iterations of PA. According to the CEAC, a configuration of 1,2 & 5 has the highest chance of being cost-effective, but requires a higher WTP to be considered valuable. Decision makers may want to understand risks, since they want to maximize the chances of being efficient with future healthcare budgets.

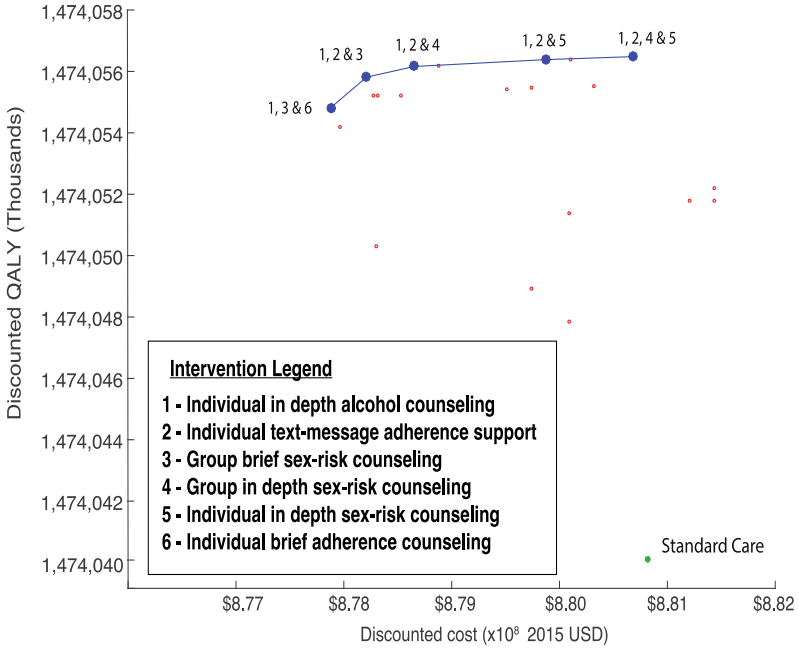

Figure 5-3. The efficiency frontier. These five configurations were the most efficient, but each had different programmatic costs and probability of being most efficient. Decision analysis eliminated 5,815 of the 5,836 options, leaving 21 choices to consider

Figure 5-4. Optimal options considering programmatic budget constraints.

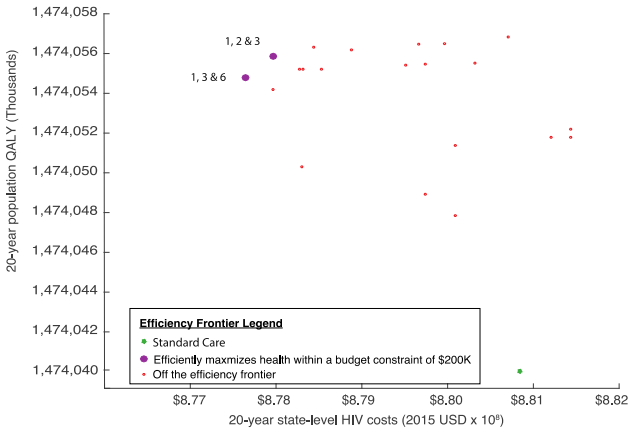

Figure 5-4A. The optimal options with a one-year program cost below $200K. If a funder perceived uncertainty in future healthcare budgets, they may impose a restriction on what to study based on annual program costs.

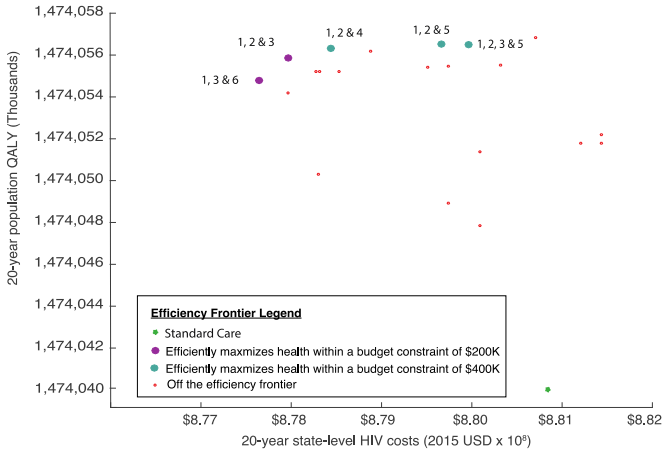

Figure 5-4B. The optimal options with a one-year program cost below $400K.

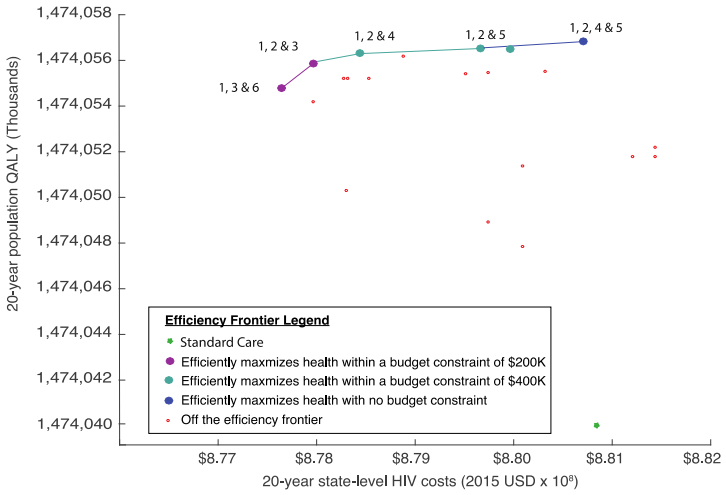

Figure 5-4C. Under no affordability constraint, all five options are once again considered.

Figure 5-5. Optimal options considering a risk-averse decision maker.

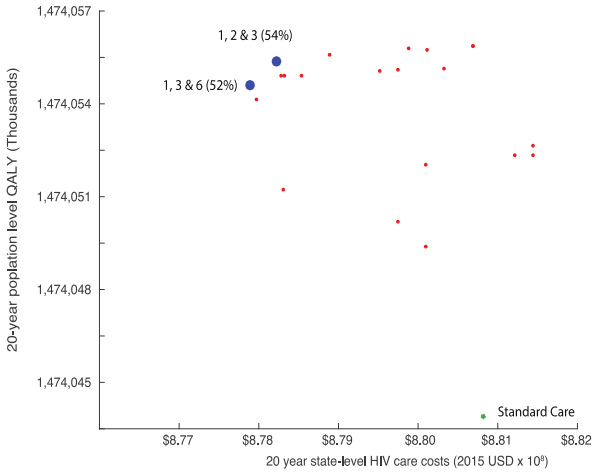

Figure 5-5A. The optimal options with a constraint of having at least a 50% chance of being on the efficiency frontier would leave two of the five options.

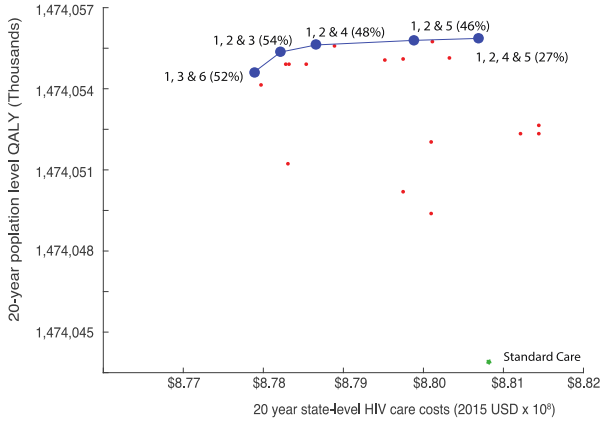

Figure 5-5B. Some decision makers make an implicit trade-off between risk and expected value.

5.7 Tables

Table 5-1: Intervention cost and efficacy inputs

Intervention	Risk mediator	Relative risk*	Range**	Cost	Range	Source
Brief individual alcohol counseling	Alcohol use	0.68	0.50 – 0.93	$1.64	0.5x – 1.5x	(161)
In-depth individual alcohol counseling	Alcohol use	0.36	0.15 – 0.82	$6.56	0.5x – 1.5x	(161)
Brief group alcohol counseling	Alcohol use	0.62	0.42 – 0.91	$1.64	0.5x – 1.5x	(161)
In-depth group alcohol counseling	Alcohol use	0.47	0.25 – 0.86	$5.90	0.5x – 1.5x	(161)
Brief individual sex-risk counseling	Condom use	1.15	1.03 – 1.26	$1.64	0.5x – 1.5x	(162)
	STI prevalence	0.84	0.73 – 0.96			
In-depth individual sex-risk counseling	Condom use	1.52	1.10 – 2.00	$14.76	0.5x – 1.5x	(162)
	STI prevalence	0.64	0.44 – 0.89			
Brief group sex-risk counseling	Condom use	1.23	1.05 – 1.41	$1.64	0.5x – 1.5x	(162)
	STI prevalence	0.81	0.68 – 0.95			
In-depth group sex-risk counseling	Condom use	1.38	1.08 – 1.70	$5.90	0.5x – 1.5x	(162)
	STI prevalence	0.71	0.54 – 0.92			

Intervention	Risk mediator	Relative risk*	Range**	Cost	Range	Source
Community sex-risk reduction	Condom use	1.2	1.03 – 1.40	$6.67	0.5x – 1.5x	(163)
	STI prevalence	0.78	0.59 – 1.04			
Brief individual depression counseling	Depression	0.84	0.43 – 1.33	$13.12	0.5x – 1.5x	(164)
In-depth individual depression counseling	Depression	0.62	0.28 – 1.10	$36.08	0.5x – 1.5x	(164)
Brief group depression counseling	Depression	0.81	0.65 – 0.97	$3.61	0.5x – 1.5x	(164)
In-depth group depression counseling	Depression	0.71	0.58 – 0.84	$7.22	0.5x – 1.5x	(164)
Brief adherence counseling	ART adherence	1.09	1.01 – 1.15	$2.46	0.5x – 1.5x	(1)
Weekly SMS support	ART adherence	1.11	1.05 – 1.16	$6.56	0.5x – 1.5x	(1)

**Uncertainty distribution ranges listed here are based on 95% confidence interval reported in original studies **All effectiveness parameters were drawn from log-normal distributions during the simulation. The mean of each respective log-normal distribution matches the relative risk listed in this table and the standard deviation of the log-normal distribution was derived using the formula: Ln(upper CI)- Ln(lower CI) / 3.92*

Table 5-2: Progression Model Inputs

Parameter or Input	Base case	Sensitivity Analysis Limits	Reference
Population data			
Average initial patient age (SD)	41 (9)	…	Admin data analysis
Average initial CD4 count (SD)	214 (174)	…	Admin data analysis
Proportion men	0.60	…	Admin data analysis
Costs of care & treatment (2014 USD)			
Cost of a viral load test	$49.54	…	(165)
Cost of a CD4 test	$6.32	…	(165)
Annual cost of outpatient care	$132.18	$90 - $297	(36, 165, 166)
Annual hospital cost:			
if CD4 <200	$347.25	…	(167)
if CD4 >200 and <350	$40.85	…	(167)
if CD4 >350	$5.72	…	(166, 167)
Monthly drug costs			
Regimen 1	$11.86	…	(165)
Regimen 2	$49.27	…	(165)
Compliance/tolerance			
Overall adherence to ART	74%	…	(168)
Prob. of non-adherence if previously non-adherent	90%	…	(42)
Utilities			
Decrement in utility due to ART	-0.053	…	(169)
Utility if CD4 < 100	0.81	±0.05	(170)
Utility if CD4 < 200	0.87	±0.05	(170)
Utility if CD4 ≥ 200	0.94	±0.05	(170)
Other			
Probability of death from HIV if AIDS vs. non-AIDS	2.33	2.01-2.69	(171)
AIDS			
Mutation rate	0.18 per year	…	(109)
Mutation rate based on viral load	**3.3**	…	(42)

Table 5-3: Transmission Model Inputs: Epidemic inputs

Parameter or Input	Value	Sensitivity Analysis Range	Distribution	Reference
Population characteristics				
Population of Maharashtra	91,496,195	…	…	(40)
Age at which a person becomes sexually active	19	17-21	Uniform	(172)
Prevalence of unhealthy alcohol use (Men)	18.5%	9.3 – 27.8%	Uniform	Pilot data
Prevalence of unhealthy alcohol use (Women)	1.6%	0.96 - 2.24%	Normal	(173)
Proportion of population that injects drugs	0.005%	0.005 - 0.008%	Uniform	(174, 175)
Probability of not being tested for HIV in 1997 (start of calibration period)	0	…	…	(88)
Proportion of detected people with HIV in 1997 (start of calibration period)	0	…	…	(176)
Sexual risk groups/partnerships characteristics				
Straight males in population				
Proportion abstinent	31%	21 - 41%	Uniform	(172, 177)
Proportion in stable, monogamous relationships	51%	…	…	(172, 178)
Proportion in non-monogamous relationships	16%	16 - 26%	Uniform	(175, 177, 178)
Proportion in migrant workers/high risk sex	2%	2 – 3.3%	Uniform	(88, 175, 179)
Straight females in population				
Proportion abstinent	26%	10 - 42%	Uniform	(172, 177)
Proportion in stable, monogamous relationships	71%	…	…	(172, 180)
Proportion in non-monogamous relationships	2.4%	2.4 – 3.9%	Uniform	(172, 175, 177, 180)
Proportion in commercial sex workers/high risk sex	0.3%	0.3 – 0.49%	Uniform	(175, 181)
Gay males in population	0.09%	0.09% - 0.15%	Uniform	(174, 175)
Proportion abstinent	0	…	…	Assumption
Proportion in stable, monogamous relationships	22.9%	19.2 – 26.5%	Normal	(182)

Parameter or Input	Value	Sensitivity Analysis Range	Distribution	Reference
Proportion in non-monogamous relationships	67.2%	…	…	Assumption
Proportion in high risk sexual activity group	9.7%	9.7 – 15.8%	Normal	(175, 182)
Average duration (years) of relationships				
Stable, monogamous relationships	30	15 - 45	Uniform	Assumption
Non-monogamous relationships	1	0.5 - 1.5	Uniform	Assumption
High risk sexual activity	0.5	0.25 - 0.75	Uniform	Assumption
Median number of concurrent relationships				
Stable, monogamous relationships	1	…	…	(183)
Non-monogamous relationships	3	1.5 - 4.5	Uniform	(183)
High risk sexual activity	10	5 - 15	Uniform	(183)
Clinical Data				
Mean set point CD4 count (standard deviation)	644 (260)	161 – 1449 (65 – 585)	Normal	(184)
Mean set point log viral load (SD)	4.5 (0.99)	2.2 - 6.7	Normal	(184)
Transmission Rates				
Per act probability of infecting a sexual partner				
Males (infecting a female partner)	0.0008	0.0004 - 0.001	Normal	(185)
Females (infecting a male partner)	0.0004	0.0002 - 0.0006	Normal	(185)
MSM	0.002	0.0008 - 0.003	Normal	
IDU specific characteristics				
Number of shared injections per partnership	102	54 - 150	Uniform	(182)
Proportion of IDUs who are abstinent	13%	…	…	(172)
Proportion of IDU males in monogamous relationships	19%	…	…	(182)
Proportion of IDU males in non-monogamous relationships	34%	…	…	Assumption
Proportion of IDU males in high risk sexual activity group	34%	…	…	(182)
Number of needle-sharing partners per year	5	2.5 - 7.5	Uniform	(186)

Table 5-4: Risk behavior inputs in general population and sub-groups

Parameter or Input	Base case	Sensitivity Analysis Range	Distribution Type	Reference
General population risk	**Proportion**			
Annual probability of condom non-use	0.73	0.73 – 0.82	Normal	**(172, 175)**
Annual probability of not being tested for HIV	0.98	0.96 – 0.99	Uniform	**(40, 176)**
Annual probability of ART non-adherence	0.26	0.26 – 0.36	Normal	**(168, 175)**
Annual probability of loss to follow-up	0.26	0.23 – 0.29	Normal	**(187)**
Point prevalence of not being circumcised	0.8	0.68 – 0.92	Uniform	**(40, 188)**
Point prevalence of untreated STI	0.06	0.06 – 0.10	Normal	**(172, 175)**
Female vs. male	**RR**			
RR of condom non-use	1.08	1.06 – 1.11	Log-Normal	**(172)**
Gay vs. straight	**RR**			
RR of condom non-use	0.63	0.6 – 0.66	Log-Normal	**(182)**
RR of not being tested for HIV	0.31	0.28 – 0.35	Log-Normal	**(182)**
Bisexual vs. straight	**RR**			
RR of not being tested for HIV	0.31	0.28 – 0.35	Log-Normal	**Assumption**
Non-monogamous vs. monogamous	**RR**			
RR of condom non-use	1.14	1.13 – 1.16	Log-Normal	**(182)**
RR of not being tested for HIV	0.81	0.79 – 0.82	Log-Normal	**(182)**
High risk sexual activity vs. monogamous	**RR**			
RR of condom non-use	0.16	0.15 – 0.18	Log-Normal	**(182)**
RR of not being tested for HIV	0.23	0.22 – 0.25	Log-Normal	**(182)**
RR of untreated STI	8.85	7.4 – 10.3	Log-Normal	**(172)**
Alcohol use vs. no Alcohol use	**RR**			
RR of condom non-use	1.29	1 – 1.58	Uniform	**(189)**
RR of ART non-adherence	2.33	1.17 – 3.5	Uniform	**(190-193)**
RR of untreated STI	1.72	1.4 – 2.05	Uniform	**(194-197)**
IDU vs. non-IDU	**RR**			
RR of condom non-use	0.62	0.55 – 0.7	Log-Normal	**(182)**
RR of not being tested for HIV	0.6	0.54 – 0.67	Log-Normal	**(182)**

Parameter or Input	Base case	Sensitivity Analysis Range	Distribution Type	Reference
RR of ART non-adherence	2	1 – 3	Normal	**Assumption**
RR of untreated STI	1.43	1.22 – 1.63	Log-Normal	**(182)**
RR of LTFU prior to linkage	2	1 – 3	Normal	**Assumption**
HIV+ vs. HIV-	**RR**			
RR of condom non-use	0.47	0.4 – 0.54	Log-Normal	**(198)**
RR of not being circumcised	2.22	1.16 – 6.67	Log-Normal	**(199)**

*RR = Relative risk

Table 5-5: Health and economic outcomes of top configurations arranged with ascending one-year program costs

Multilevel intervention composition*	Expected population level costs	Expected population level QALY	ICER vs. standard care	One-year program costs	HIV cases averted	Probability of being on the efficiency frontier (%)
Standard Care	$880,834,786	1,474,040,186	…	$0	…	2.30%
I-B-Adh	$877,886,846	1,474,054,825	$33	$31,226	954	1.3%
G-B-Sex & I-B-Adh	$877,966,550	1,474,054,191	Dominant	$52,044	1263	5.3%
I-SMS-Adh	$880,107,740	1,474,049,745	Dominant	$83,177	1260	2.7%
I-L-Alc	$878,217,292	1,474,055,812	Dominant	$83,177	1818	19.2%
I-L-Alc & I-B-Adh	$878,278,058	1,474,055,212	Dominant	$114,445	2346	25.5%
I-L-Alc, G-B-Sex & I-B-Adh	$878,301,562	1,474,050,326	Dominant	$135,267	2515	52.1%
I-SMS-Adh & G-L-Sex	$878,314,256	1,474,055,193	Dominant	$158,235	1711	1.7%
I-L-Alc & I-SMS-Adh	$878,537,963	1,474,055,234	Dominant	$166,512	2512	16.1%
I-L-Alc, I-SMS-Adh & G-B-Sex	$878,657,987	1,474,056,160	Dominant	$187,335	2671	53.9%
I-L-Alc, G-L-Sex, & I-B-Adh	$878,883,648	1,474,056,199	Dominant	$189,403	2613	29.4%
I-L-Alc, G-B-Sex, G-L-Sex & I-B-Adh	$879,521,379	1,474,055,430	Dominant	$210,225	2624	3.2%
I-L-Alc, I-SMS-Adh & G-L-Sex	$879,741,646	1,474,048,942	Dominant	$241,476	2763	48.0%

Multilevel intervention composition*	Expected population level costs	Expected population level QALY	ICER vs. standard care	One-year program costs	HIV cases averted	Probability of being on the efficiency frontier (%)
I-L-Alc, I-SMS-Adh, G-B-Sex & G-L-Sex	$879,751,639	1,474,055,458	Dominant	$262,299	2773	5.3%
I-SMS-Adh, G-B-Sex & I-L-Sex	$879,875,274	1,474,056,385	$52	$270,664	1814	0.7%
I-L-Alc, I-L-Sex, I-B-Adh	$880,095,290	1,474,047,829	Dominant	$291,485	1826	0.2%
I-SMS-Adh, I-L-Sex & I-B-Adh	$880,096,379	1,474,051,378	$50	$301,840	2674	20.1%
I-SMS-Adh & G-L-Sex	$880,106,922	1,474,056,412	Dominant	$301,895	1883	0.1%
I-L-Alc, I-SMS-Adh & I-L-Sex	$880,328,187	1,474,055,534	Dominant	$322,662	2681	1.8%
I-L-Alc, I-SMS-Adh, G-B-Sex & I-L-Sex	$880,687,980	1,474,056,483	Dominant	$353,922	2820	46.1%
I-L-Alc, G-L-Sex, I-L-Sex & I-B-Adh	$881,218,121	1,474,051,765	Dominant	$374,745	2827	4.4%
I-L-Alc, I-SMS-Adh, G-L-Sex & I-L-Sex	$881,436,201	1,474,052,203	Dominant	$376,798	2701	11.1%

* L=Long; B=Brief; I=Individual; G=Group; Alc=Alcohol; Adh=Adherence; SMS=Weekly text-messages;

Bolded configurations contain the weekly SMS interventions

6 Discussion and conclusions

6.1 Summary of study findings

The relative cost-effectiveness of SMS-based adherence interventions – within the wide investment space facing HIV and TB program funders – was not previously known in Kenya, British Columbia or Maharashtra. Further, it was not known if these interventions should be implemented generally or targeted to high-risk groups. In this thesis, the current or potential cost-effectiveness of SMS interventions was described in these three settings, which included resource-rich and resource-poor settings. I found that SMS is cost-effective to improve HIV drug adherence based on patient-level outcomes in Kenya and cost saving in India based on patient-level outcomes and transmission outcomes. SMS intervention would be cost-effective for LTBI drug therapy adherence in BC, if it has similar effectiveness in this new therapeutic area.

In a chapter 2, I found that the SF-12 is a valid tool for measuring HRQoL and HSUV, suggesting that this tool can be employed in future studies involving Kenyan PLWHA. In chapter 3, the incremental cost-effectiveness ratios of SMS-based adherence interventions were well below the WHO WTP threshold, suggesting they would be efficient if applied among average Kenyan PLWHA. The cost-effectiveness would increase further if they were targeted to high risk-groups. I evaluated a wide range of scenarios including different adherence rates under standard care and different treatment guideline assumptions. The SMS-based adherence interventions remained cost-effective in most scenarios. If the two-way SMS intervention can improve retention, my findings suggest

that this design would be more cost-effective (ICER=$1,037/QALY without retention benefits vs ICER=$864/QALY with retention benefits), offsetting some of the costs of a two-way system compared to a one-way system.

In BC, SMS-based adherence interventions would be one of the top choices among existing adherence interventions and were least sensitive to intervention cost, suggesting that there is a lower risk in investment where scale-up costs are uncertain. The preventable mortality and morbidity of non-adherence to LTBI drug therapy was quantified and a hypothetical intervention could cost up to $450 per person to bring the population of confirmed LTBI cases initiating drug therapy up to full adherence.

SMS-based adherence interventions were cost saving in Maharashtra, India, where they were evaluated in a particularly high-risk group: alcohol-users. Further, SMS interventions were part of four out of five of the most efficient combinations in a comparison of 5,836 different permutations of a comprehensive multilevel intervention. Findings suggest that SMS-based adherence interventions could have a role in a comprehensive HIV management strategy for this population. This work also demonstrates the value of conducting a cost-effectiveness evaluation prior to initiating a new study. New studies serve to update the body of knowledge surrounding medical interventions and systematic evaluation of options prior to initiating a costly study can be helpful to guide research investment decisions. I showed how commonly encountered decision-maker constraints changed the optimal option and findings suggest these constraints should be considered in advance of heavy investment in trials or other studies.

6.2 Unique contributions, implications and impact

This thesis research has several implications and contributions. First, I contributed to an understanding of the value of SMS interventions in Kenya, where health systems are searching for cost-effective ways to improve HIV drug adherence. In addition to being cost-effective in Kenya now, SMS interventions would retain their value in the WHO's expanded *test and treat* scenario. The ICER remained well below the WTP threshold in the base case analysis and findings suggest that SMS could address non-adherence issues that would otherwise dampen the benefits of expanded treatment. Since SMS interventions would remain useful in the future, current scale-up efforts and infrastructure development would be justified in the long run.

Second, I found that health state utility values (HSUVs) are feasible to collect in resource-limited settings and estimated the HSUV of three common HIV health states. The implication is that QALYs can be used in economic evaluations, disease burden measurement and other studies. The QALY is a measure of societal welfare loss due to disease and has a strong theoretical foundation because of its explicit inclusion of patient and societal preferences.(39, 61) While the WHO recommened disability adjusted life years are convenient to use, they assign the same burden weights to diseases across nations, ignoring the heterogeneity that arises from local societal preferences. Patient-centered care is the current paradigm of health policy in resource-rich countries. Healthcare policies are made with explicit acknowledgment of and consultation with patients that are living with the diseases. While a fully patient-centric model is not

feasible in resource-limited settings, small steps can be taken to incorporate the patient's perspective into research and policy. More widespread collection of HSUVs within the countries is one such step, and the validation of the SF-12 in this thesis is a step towards better data collection. By moving towards wider collection of patient-centered outcomes, multinational decision-makers can tailor policymaking to the best interest of member states rather than taking a standardized approach to health policymaking.

Third, I contributed to an understanding of the burden of non-adherence to LTBI drug therapy in BC and estimated the potential value of hypothetical and existing adherence interventions. The evaluation in BC illustrated how improvements in adherence to prophylactic TB therapy could reduce future TB cases, deaths and costs. Similar simulation studies can be conducted to assess the value of SMS interventions in any disease area. In cases where the impacts of adherence on health outcomes are high, the SMS interventions might be considered for implementation without additional trials. Value of information (VOI) is a formal economic method that could evaluate the maximum societal economic gains that can be derived from further study. With a wealth of existing evidence, a formal VOI evaluation should be conducted prior to initiating additional SMS intervention trials, since funds might be better spent on implementation.

Fourth, I contributed to an understanding of the value of using CEA in the earlier stages of clinical and translational research. The work in India suggests that decision analysis can be employed earlier in the scientific and policy-making process by evaluating potential outcomes prior to initiating costly trials. Multilevel and combination approaches

will be increasingly needed to manage HIV and TB, but would also be useful in other disease areas. A multilevel decision analysis can isolate the most valuable alternatives to make decision-making more streamlined. Constraints can be imposed to allow decision-makers to filter through thousands of alternatives to identify top choices for study. Formal discussions, qualitative studies and pilot data would still be needed, but the decision analysis can supplement the process by narrowing down options. If trade-offs are made explicit for stakeholders, eventual implementation might be more successful, since constraints are considered prior to initiating a new study.

6.3 Strengths and limitations

The major strength of this study is that it was conducted in a range of settings, yet the findings were consistent. The SMS interventions remained cost-effective despite varying healthcare costs and other unique attributes of these settings and diseases. This might reduce the need for further analysis if the interventions were being considered in alternate settings or disease areas. A second strength is that a wide range of sensitivity and scenario analyses was also included to test the impacts of modeling assumptions. Finally, feedback from end-user researchers, policymakers and clinicians were incorporated into each component of this analysis. With input from end-users of the information throughout the analysis, the findings can be more useful and applicable for policy and decision-making.

A limitation of this study is that the SMS intervention costs were not well characterized. As the intervention is scaled up and as the software improves, intervention cost could

increase if technology support and maintenance rise and decrease if efficiency gains are made through economies of scale. The cost remains broadly characterized based on data from study settings and assumptions, but is ultimately uncertain without real-world data from broader implementation. In sensitivity analyses, I tested a large range of costs for the intervention to provide a comprehensive range of ICERs, and most analyses suggest the intervention remained cost-effective at the upper limits of cost plausibility. The intervention costs also had a limited impact on final results in one-way sensitivity analyses. A second limitation is the assumption of generalizability of these analyses to broader populations in each setting. Patient-level heterogeneity was captured in each of the models, however data to describe inputs came from specific cohorts, studies or databases. The direction and extent of bias created by assumptions of generalizability is unknown. In two studies, I conducted a probabilistic analysis to mitigate this bias, but uncertainty distributions were also taken from external sources in some cases. As with every model-based evaluation, data reliability and accuracy can affect the final results.

6.4 Future directions

Further research is needed to understand the integration of SMS interventions within the broader health system. For example, the appropriate provider of two-way SMS interventions remains uncertain, with many unique setting-specific factors to consider. In a resource-rich setting, pharmacists would be one choice. Adherence is most readily observable by pharmacists and by the data generated at the pharmacy level. To engage vulnerable populations, the appropriate provider might be social workers or nurses in specialized clinics. Using physicians as part of a two-way SMS system would raise the

labour costs and might not improve the average efficacy of the intervention, but in some instances, individuals might benefit from more intensive help. In resource-limited settings, pharmacy systems are underdeveloped, so pharmacist would not be the optimal choice. Comprehensive care is typically delivered at generalized health clinics. Several provider-types at the clinic level could potentially manage the interventions, though patient preferences would likely play a role. Nurses, community workers and even remotely housed staff could be the appropriate provider of the intervention. Further research would be needed to understand if the intervention would remain effective, if the follow-up was being provided by a centralized staff, rather than the clinic staff that delivers regular care to the patients.

Additional real world evidence in needed to confirm the effectiveness of SMS at scale. The population impacts simulated in this thesis assume an impact that is scalable and sustainable. A diminishing effect was tested in one evaluation and reduced the cost-effectiveness of the interventions. In practice, diminishing effects may be apparent by disengagement with the platform over time. Observational studies should be conducted alongside scale-up efforts to investigate the durability of effect and understand the patient level factors that influence intervention effectiveness. Furthermore, health system efficiencies that might be gained through seamless provider-patient communication can be evaluated at scale.

Finally, additional capabilities of SMS based interventions need exploration through additional research. Engagement can improve many aspects of care including patient

support and clinician awareness of patient problems. In addition to patient-level improvements, the data generated through population-level SMS responses can be used for surveillance of disease patterns, identification of health system inadequacies and faster response to emergency situations. For example, containment of an outbreak could be enhanced through a health system based SMS communication platform that can guide a population on appropriate measures and provide information for individuals to protect themselves. As a second example, the patient-generated data could highlight barriers to care. If medication stock outs were reported to be a common reason for non-adherence in a particular health clinic, it could highlight a broader supply chain issue within that clinic or surrounding region. With improved data collection, synthesis and reporting, policy makers and researchers have the capability to proactively address health system emergencies and inadequacies. The potential for SMS based technology to improve care in this regard needs further study and development.

6.5 Implementation

By 2030, the WHO's goal is to achieve a global AIDS-free generation by identifying 95% of all HIV cases, getting 95% of PLWH on ART and getting 95% of people on ART to achieve viral suppression.(200) Further, the WHO aims to end TB by 2050 through universal access to TB care, reductions in latent TB reservoirs and aggressive research in new treatments.(201) Global HIV and TB programs are currently far from these goals, and total annual spending on global health programs has topped $31.3 billion USD.(49) In light of growing financial uncertainty, achieving the WHO's ambitious goals will require extreme scrutiny when it comes to spending every last dollar and maximizing

return on investments at every turn. Structured decision analysis can be useful to guide healthcare decisions from research to implementation. Whether funds are being invested in research or in effective therapies and programs, decision-makers must employ a balanced scientific and economic lens when making their decisions. Eradicating global epidemics and lifting the immense burden of these diseases depend upon it.

The treatment cascade of care for all diseases begins with identification of cases and ends with individuals achieving favourable health outcomes, usually after some form of drug or other therapy. Treatment adherence improves health outcomes and prevents further transmission in the case of infectious diseases. Communication and coordination between healthcare providers, patients and funders is essential across the entire cascade. Cell phones have streamlined communication, data collection and coordination between key stakeholders in many ways. This research suggest that SMS-based adherence interventions are cost-effective in multiple settings and can be implemented with low infrastructure development or training. Future research and programmatic funds should be wisely allocated to appropriate SMS-based interventions to ensure they are targeted to the appropriate populations.

6.6 Conclusions

In this thesis, the value of conducting cost-effectiveness studies at different stages of the research process was assessed. Decision analysis and cost-effectiveness evaluation were shown to be valuable before, during and after a randomized trial. Prior to initiation of a new study, a decision analysis can systematically characterize important decision-maker constraints and estimate the potential impact of new interventions. Using this process,

research could be conducted more efficiently, since cost-effectiveness and health system constraints are considered prior to initiation of a study. The resulting interventions have a higher chance of being accepted by the health system. During a trial, a cost-effectiveness evaluation can estimate the burden of disease and potential value an intervention relative to feasible alternatives. This can expedite the uptake of the intervention, since its value has been considered in tandem with evidence generation. This process relies on at least some existing evidence, so it may be limited to scenarios where an intervention is being applied in a new setting or disease area. Finally, a cost-effectiveness evaluation using trial data and simulation can make an argument for adoption and uptake after a trial has been conducted. Evidence-informed care and policy depend on these analyses for uptake of efficient technologies and ensuring the health system makes wise investments.

In this thesis, the cost-effectiveness of SMS-based adherence interventions was evaluated in resource-rich and resource-poor settings. Findings suggest that SMS-based adherence interventions should be implemented broadly in Kenya, where they can efficiently improve health outcomes of current HIV programs. In a future scenario, where all individuals would initiate drug therapy immediately after diagnosis, the interventions would remain cost-effective. The interventions should be considered as part of LTBI drug therapy in BC, if they are found to be effective in an ongoing trial. Non-adherence to LTBI drug therapy is a barrier to achieving TB elimination goals in BC, and SMS-based adherence interventions could be an efficient solution among other things. Finally in Maharashtra, SMS-based adherence interventions would be part of the most efficient multilevel interventions to manage HIV-risks among alcohol-users living with HIV. A

multilevel approach can be tailored to the risks faced by specific patient populations, but since non-adherence is widespread among many sub-groups, SMS-based adherence interventions may have broad applicability.

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