Mathematical Modeling and Cost-Effectiveness of Antiretroviral-Based HIV-1 Prevention Strategies

Brooke E. Nichols

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Mathematical Modeling and Cost-Effectiveness of Antiretroviral-Based HIV-1 Prevention Strategies

Wiskundige modellering en kosteneffectiviteit van HIV-1 preventiestrategieën op basis van antiretrovirale geneesmiddelen

Thesis

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by
Brooke Elizabeth Nichols
born in New York City, United States of America

ERASMUS UNIVERSITEIT ROTTERDAM

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Voor Robbert en Matthijs

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ABBREVIATIONS

3TC: lamivudine
ACER: average cost-effectiveness ratio
AIDS: acquired immune deficiency syndrome
ART: antiretroviral therapy
ARV: antiretroviral (drug)
D4T: stavudine
ddI: didanosine
DRM: drug resistance mutation
EFV: efavirenz
FDA: United States Food and Drug Administration
FTC: emtricitabine
GDP: gross domestic product
HIV: human immunodeficiency virus
ICER: incremental cost-effectiveness ratio
IND: indinavir
IQR: interquartile range
JCRC: Joint Clinical Research Centre
MSM: men who have sex with men
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
NVP: nevirapine
PASER: PharmAccess African Studies to Evaluate Resistance
PEPFAR: President's Emergency Plan for AIDS Relief
PI: protease inhibitor
PrEP: pre-exposure prophylaxis
QALY: quality adjusted life year
SLT: stochastic league table
STI: sexually transmitted infection
TAM: thymidine analogue mutation
T&T: test and treat
TDR: transmitted drug resistance
TDRM: transmitted drug resistance mutation
VCT: voluntary counselling and testing
VL: viral load
WHO: World Health Organization
ZDV: zidovudine

Background

Chapter 1

General Introduction

HIV Epidemiology

The human immunodeficiency virus, or HIV, is the virus that causes acquired immune deficiency syndrome (AIDS). There are currently 35 million people living with HIV, and each year there are more than two million new HIV infections worldwide.[1] While HIV was spreading quickly across MSM communities in resource rich settings in the 1980s, HIV was also getting a strong foothold among heterosexuals across Africa,[2] and later in Asia.[3] The epidemic is now most strongly concentrated in sub-Saharan Africa, with 70% of the worlds' HIV cases.[1]

There has been a rise in the number of new HIV infections in several countries and in specific risk groups such as among men who have sex with men (MSM) in Europe.[1] In the Netherlands, the number of newly infected MSM rose 57% between 2001 and 2013.[4] This increase is primarily attributed to increases in sexual risk behavior.[5]

Meanwhile, while there are still over a million new infections per year in sub-Saharan Africa, the number of new infections in sub-Saharan Africa has been decreasing.[1] This decrease has been attributed primarily to 1) a decline in sexual risk behavior[6] and 2) large-scale rollout of antiretroviral treatment. When patients are successfully on antiretroviral treatment, they cannot generally transmit their infection.[1, 7]

HIV Natural History & Treatment

There are several stages of HIV infection: the acute stage, chronic stage and the AIDS stage. The acute stage of infection lasts between 10 and 16 weeks, and is characterized by high infectiousness.[8, 9] This is due to high HIV RNA replication that takes place during that period. HIV RNA in plasma is the key determinant of infectiousness.[8, 10] The chronic stage of infection is much longer, approximately 8 years, and far less infectious than the acute stage due to low levels of HIV RNA in plasma.[9, 11] The AIDS stage lasts approximately 1-2 years.[9, 12] A patient in the AIDS stage is 3-5 times more infectious than in the chronic stage.[9, 12] At any point during infection, antiretroviral treatment can be initiated and stop further disease progression. Depending on when antiretroviral treatment is initiated, HIV-infected individuals can expect a near-full life expectancy.[13]

Currently, patients initiate treatment based on their CD4 cell count. Before 2010, the WHO recommended to initiate treatment in the AIDS stage of disease, or at a CD4<200 cells/µl.[6] From 2010-2013, the World Health Organization recommended treatment at a CD4 cell count of <350 cells/µl, and since 2013 treatment initiation at CD4 <500 cells/µl has been recommended.[14]

HIV Treatment and Drug Resistance

HIV is characterized by its high genetic variability, and as such can easily select for resistance-associated mutations.[15] When the genetic barrier is high enough, or when the number of viral mutations needed to escape selective drug pressure is large enough, then a patient can be suppressed on antiretroviral treatment and the risk of acquired drug resistance is strongly reduced. In general, three different antiretroviral drugs from two different classes of drugs must be used in order to have a sufficiently high genetic barrier and effectively suppress HIV so that HIV RNA is undetectable in plasma.[15]

If a patient is not fully adherent to treatment however, especially early on in treatment, the virus can select for drug resistance associated mutations. This is called an acquired mutation. Patients with an acquired HIV mutation can also further transmit their virus, which is called transmission of resistance. Drug resistance can also be transmitted from one antiretroviral naïve patient to the next untreated individual. Epidemiological studies have reported that the primary source of transmitted resistance comes from antiretroviral naïve patients.[16, 17] Transmission of resistance that affects first-line treatment can jeopardize initial antiretroviral therapy and should therefore be avoided.[18]

There are several ART program-level strategies that can help mitigate the emergence and transmission of drug resistance.[19-21] The WHO has recently recommended monitoring patients by measuring plasma HIV RNA level, or viral load testing, which can reduce transmission of drug resistance if implemented at regular intervals (every 6 or 12 monthly). Viral load testing can reduce the emergence of HIV drug resistance by early identification of patients with virological failure, prompting intensified adherence counselling and switch to second-line ART as necessary, thereby minimizing emergence of HIV drug resistance.[19, 21] Second, prompt switching to a protease-inhibitor based second-line regimen of individuals experiencing virological failure has been associated with a reduced risk for drug resistance.[20, 22] Finally, pre-therapy genotypic resistance testing to select a fully active regimens guide may mitigate acquired drug resistance.[23, 24] These three strategies carry additional costs however and are not routinely available in sub-Saharan Africa.

HIV Prevention using antiretroviral drugs

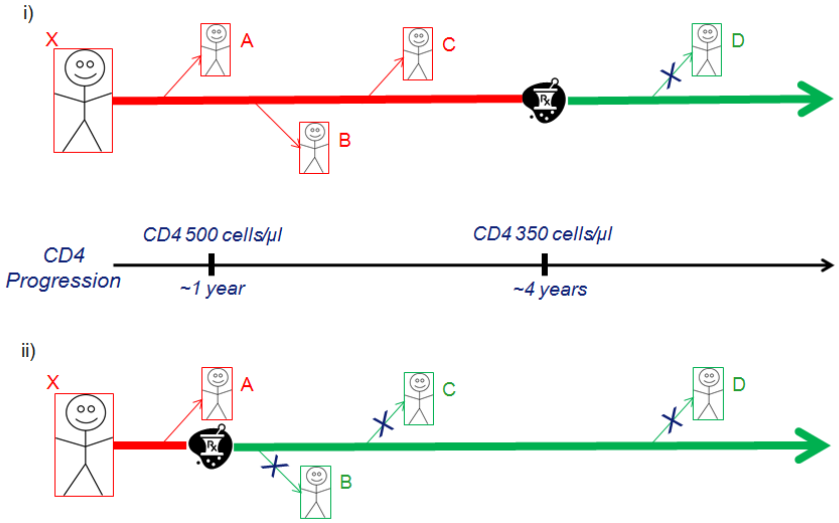
Several prevention strategies using antiretroviral drugs have been shown to be effective in reducing new HIV infections:

Treatment as prevention

The CD4 threshold at which treatment is initiated has an impact on HIV prevention. As soon as a patient is successfully suppressed on antiretroviral therapy, they are no longer infectious. The preventative impact of earlier treatment initiation has been shown in a

randomized clinical trial. Patients who start treatment early (defined as initiating when the CD4 cell count is between 350 and 550 cells/µl) have a 96% reduced risk of transmitting HIV to their sexual partners as compared to patients who defer treatment until a CD4 cell count of <250 cells/µl [7]. Figure 1 depicts how treatment as prevention in Patient X works. If treatment is initiated at a CD4 cell count of 350 cells/µl (i), approximately four years after initial infection, our hypothetical Patient X will infect Contacts A, B, & C. Patient X then begins treatment when their CD4 cell count drops to 350 cells/µl, and the infection to contact D is prevented. If Patient X had initiated treatment at a CD4 count of 500 cells/µl (ii), then the infections to Contacts B and C could also have been prevented.

Figure 1. *Treatment as prevention schematic*



This preventative effect of treatment is one of the reasons that the World Health Organization now recommends earlier treatment initiation at a CD4 count of <500 cells/µl.[14] It is unknown, however, what the population level effectiveness of treatment as prevention will be.

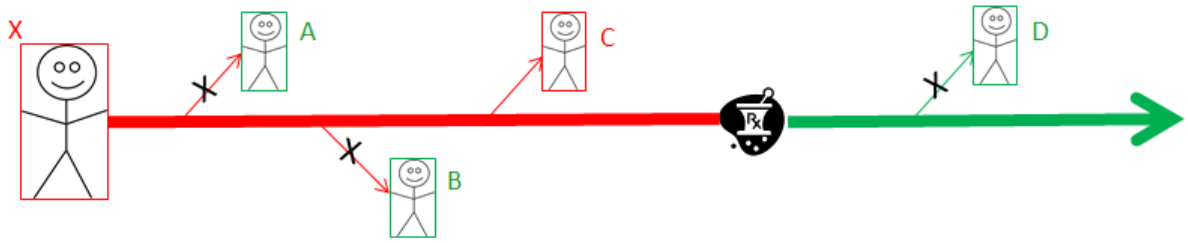
A major challenge to treatment as prevention, even in resource-rich settings, is the ability to get people into care early in infection. In sub-Saharan Africa, as many as 60% of individuals are diagnosed late with a CD4 cell count <350 cells/µl.[25] Even in Europe, as many as 44% of MSM are diagnosed late. One way to get patients into care earlier is through partner notification.[26] If partners are notified, they can be diagnosed sooner and initiate treatment.

A fear of earlier treatment initiation in sub-Saharan Africa is the potential for increased levels of drug resistance.[18] This is especially the case as viral load and drug resistance testing are not routinely performed. This poses a problem to sub-Saharan Africa in particular as there are limited options for antiretroviral treatment. Thus, if there is a wide circulation of resistance to first-line therapy, treatment options will be severely limited. Ways to expand treatment but limited resistance are therefore of utmost importance.

Pre-exposure prophylaxis

Antiretroviral drugs can also be given to uninfected individuals to prevent infection. This is known as pre-exposure prophylaxis (PrEP). It has been shown that the more adherent a person is to PrEP, the more effective it is in preventing HIV infection.[27] Daily oral PrEP with tenofovir and emtricitabine has been shown to prevent 44–75% of new HIV infections.[28-30] Two studies[31, 32] have found no protective effect of PrEP on prevention of new infections, due to limited adherence. Figure 2 represents how PrEP works when effective. Contacts A and B start pre-exposure prophylaxis to prevent HIV. Contact C does not use pre-exposure prophylaxis. When infectious Patient X has sexual contact with Contacts A and B, the infection in Contacts A and B are therefore prevented.

Figure 2. *Pre-exposure prophylaxis schematic*



There is concern that PrEP could also lead to an increase in drug resistance. This is of particular concern in sub-Saharan Africa as there are few treatment options available, and the drugs used for PrEP, tenofovir and emtricitabine, are also the drugs recommended for first-line treatment.[33] Thus, when implementing treatment as prevention or PrEP on a wide scale, the potential for an increase in resistance should be taken into account.

Microbicides

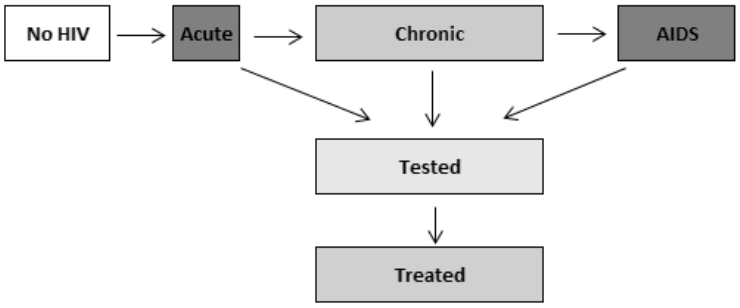
Microbicides containing antiretroviral drugs have also been shown to be effective in preventing new HIV infections in one study.[34] In this study, a topical gel containing tenofovir applied intra-vaginally, compared to placebo, reduced HIV acquisition by 39%.[34] The mechanism for prevention is similar to that in Figure 2. Another study[31] did not find a protective effect of antiretroviral-containing microbicides, likely due to lack of adherence.[35] Microbicides are not discussed further in this thesis.

Mathematical modeling and cost-effectiveness

Current studies on treatment as prevention and PrEP show the efficacy of both methods under well-controlled conditions. Determining the real-life population-level effectiveness of both prevention methods will require long-term prospective epidemiological studies. These studies would have to be unfeasibly large, expensive and time-consuming. Mathematical modeling is a tool that can be used to predict the impact of treatment as prevention and

PrEP in the long-run. The basic structure of the deterministic models used in this thesis is shown in Figure 3.

Figure 3. *Basic design of deterministic model of HIV infection*



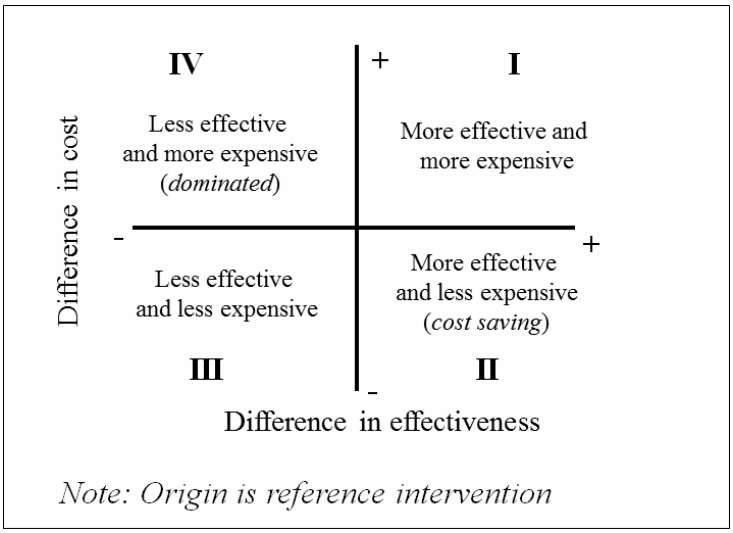
All models divide disease progression into three basic stages, described earlier, based on duration and infectiousness. In the models of this thesis, individuals can test positive for HIV at any point in infection depending on the test rate of the modeled population. Once people test positive, they can initiate treatment, depending on the observed treatment threshold. Once a patient initiates treatment, their infectiousness is assumed to be reduced by 90-100%.[7] This basic model has then been adapted to suit the different research questions throughout this thesis.

In addition to the preventative impact of antiretroviral-based prevention strategies, more information is needed to determine what interventions provide the best value for money. It is therefore imperative that cost-effectiveness analyses be conducted to not only determine the best intervention in terms of infections prevented, but what the most cost-effective interventions are. For a cost-effectiveness analysis, two types of information are needed: 1) how much the intervention (Intervention B) costs or saves compared to the reference intervention (Intervention A), and 2) how many quality adjusted life years (QALYs) you gain or lose by implementing an intervention (Intervention B) compared to a reference intervention (Intervention A). A QALY of 1 is considered to be a year of life lived in perfect health. The cost effectiveness ratio is calculated as follows:

$$\frac{\text{Cost of Intervention B} - \text{Cost of Intervention A}}{\text{Effectiveness of Intervention B} - \text{Effectiveness of Intervention A}}$$

Figure 4 shows how to interpret results on cost-effectiveness. Most cost-effectiveness results fall in quadrant 1, where Intervention B is more effective but also costs more. Within this quadrant, the World Health Organization defines an intervention as cost-effective if it costs less than three times the gross domestic product per capita of a country per QALY gained. In general, if an intervention falls in quadrant 2, it should always be done, as it is cost saving, and if an intervention falls in quadrant 4, it should never be done, as it costs more and is less effective (also called 'dominated').

Figure 4. *The cost-effectiveness plane(adapted from Drummond 2005[36])*



One limitation to cost-effectiveness analyses is the lack of budgetary analysis. Even if an intervention is cost-effective, there may be no budget to implement the intervention. The use of stochastic league tables is one way to incorporate budget limitations into a cost-effectiveness analysis.[37-39] Stochastic league tables provide a probability that a given intervention is the best way to maximize health in a population given a fixed budget. It is then possible to see what the best interventions could be, in terms of health gained, given a range of budgets.

Research aims

The overarching aim of this thesis is to identify optimal antiretroviral-based strategies to prevent new HIV infections in terms of infections averted and costs incurred. To address the overarching aim, we also evaluated the following sub-aims:

i. Evaluate the impact of treatment as prevention, pre-exposure prophylaxis, and partner notification on the epidemic in terms of infections averted and life-years saved using mathematical models.
ii. Determine the impact of earlier antiretroviral treatment and pre-exposure prophylaxis on transmitted HIV drug resistance.
iii. Identify the cost-effectiveness of different antiretroviral-based prevention techniques and cost-effectiveness of methods that can reduce drug resistance.

Outline of thesis

This thesis includes an in-depth review (Chapter 2) of the previous work on mathematical modeling of treatment as prevention or 'test and treat', as well as a review of the studies on transmitted drug resistance that were available at the start of this PhD research.

Part 1 of this thesis focuses on the use of treatment as prevention for HIV prevention. **Chapter 3** addresses the impact of treatment as prevention in regards to infections averted and predicted rates of transmitted drug resistance in Eastern Africa. In **Chapter 4**, the use of various patient monitoring techniques are modeled to identify which are the most cost-effective techniques that reduce the prevalence of transmitted drug resistance in Eastern Africa. In resource-rich settings, treatment as prevention can also reduce the number of new infections. **Chapter 5** looks at how a partner notification system can reduce the HIV-1 epidemic among men who have sex with men (MSM) in the Netherlands by getting patients into care earlier.

Part 2 of this thesis focuses on the use of pre-exposure prophylaxis for HIV prevention. **Chapter 6** investigates the epidemic impact and cost-effectiveness of pre-exposure prophylaxis in Zambia. **Chapter 7** then assesses the impact of the use of pre-exposure prophylaxis on drug resistance across three different mathematical models focused in sub-Saharan Africa.

Part 3 combines both pre-exposure prophylaxis and treatment as prevention in one model to investigate not only which prevention techniques are more cost-effective, but also to identify what prevention techniques are affordable (**Chapter 8**).

The results of this thesis are then discussed and summarized in **Chapter 9**.

Chapter 2

Test and treat strategies for prevention of HIV infection: impact of antiretroviral drug resistance

Brooke E. Nichols, Charles A.B. Boucher, David A.M.C. van de Vijver

Journal of Internal Medicine 2011; 270(6):532-49

ABSTRACT

'Test and treat' is a strategy in which widespread screening for human immunodeficiency virus (HIV) is followed by immediate antiretroviral therapy for those testing positive, thereby potentially reducing infectiousness in larger cohorts of infected patients. However, there is a concern that test and treat could lead to increased the levels of transmissible drug-resistant HIV, especially if viral load and/or drug resistance is not routinely monitored. Reviews of the existing literature show that up to now, even in the absence of laboratory tests, drug resistance has not created major problems in sub-Saharan Africa. Here, we discuss the current evidence for the effectiveness of a preventive test and treat approach and the challenges and implications for daily clinical practice and public health.

INTRODUCTION

Despite extensive prevention efforts, in 2009 there were still 2.6 million new HIV infections worldwide. Most of these new infections occurred in Sub-Saharan Africa.[6] A strong increase in the HIV epidemic has been observed in Central Asia and Eastern Europe, where the reported number of people living with HIV almost tripled from 530,000 in 2000 to an estimated 1.4 million in 2009.[6] Worldwide, for every two patients who start antiretroviral therapy, five become newly infected. Thus, there is a growing need for more effective methods to curb the epidemic.[40]

A novel potential prevention strategy is referred to as 'test and treat' (T&T) in which universal testing for HIV is combined with immediate antiretroviral therapy for those individuals found infected.[41] Universal testing may be able to prevent new infections as individuals who become aware of their HIV status could reduce their risk behaviour.[42] In addition, immediate antiretroviral therapy of infected individuals can prevent new infections as antiretroviral drugs suppress viral replication and thereby the HIV RNA load, which is a key factor determining transmissibility of HIV.[10] This reduction in infectiousness because of treatment has also been confirmed in recent studies.[7, 43-47]

Montaner *et al.* were among the first to propose the T&T approach.[41] Granich *et al.* then further explored the benefits of this approach in a mathematical modelling study.[48] Based on their model, they predicted that annual voluntary HIV screening followed by immediate start of antiretroviral drugs for those individuals who test positive, regardless of their CD4 count, could reduce the HIV pandemic to one incident case of HIV per 1,000 people per year by 2016. However, they made several assumptions, which may not be easily implemented in daily practice and therefore received some criticism.[49-56]

A specific concern using T&T may be the development of drug resistant transmissible viruses. The efficacy of treatment of HIV infection can be limited by the development of (cross-) drug resistant viruses. Expanded access to drugs in a T&T program will increase the number of individuals tak**ing** antiretroviral drugs and as such may lead to an increased absolute number of patients in whom drug resistance emerges. As a consequence, more people will need second-line treatment. A further problem may then be that drug resistant viruses will be transmitted to others.[24, 57, 58] Transmitted drug resistance has clinical ramifications as it is associated with virological failure in patients who receive at least one antiretroviral drug to which the virus has lost susceptibility.[59] In addition, drug resistance can have important implications for public health as it leads to a rebound in viral load,[60] which increases transmissibility of the virus.

The objective of this review is to investigate the epidemiological evidence for the potential benefits of T&T. We will discuss the challenges and implications of this approach for public health and daily clinical practice. We will then consider the potential impact of antiretroviral drug resistance on the effectiveness of T&T, focusing on resistance in sub-Saharan Africa

where most new infections occur and where most benefit from a T&T approach might be expected.

Effectiveness of 'test and treat'

Mathematical modelling has been used extensively to predict if T&T could be an effective strategy for prevention of new infections with HIV.[41, 48, 61-66] Mathematical models involve the deconstruction of transmission of HIV into its key elements to reconstruct a dynamic model of the way these elements interact. Using available evidence on each of these components, the model can then generate predictions.[67, 68]

In this section, we will review the mathematical models that studied the potential impact of T&T (summarized in Table 1). The models can be divided into three groups based on the era in which they were developed. The first models were developed during the period in which the exact effect of antiretrovirals on transmissibility was largely unknown. These models were used to investigate the impact of changes in risk behaviour. In the second era, modelling gained a lot of momentum, was used to study the effect of T&T on the epidemic in general and generated controversy. In the third era, the models were adapted for more realistic assumptions and incorporated additional prevention methods.

The early models on the impact of risk behaviour

Testing for HIV can have important benefits as it could lead to a reduction in new infections in the population. This potential reduction can be ascribed to changes in risk behaviour. Individuals who test positive for HIV can reduce their number of sexual partners[42, 69, 70] or use condoms consistently. But there is concern that due to the strong benefits of antiretroviral therapy on morbidity and mortality,[71] the fear of becoming infected with HIV will be reduced. This may in turn lead to increases in sexual risk behaviour.

The first models were published in the early 2000s and examined the impact of changes in risk behaviour on the epidemic. The initial two models were calibrated to the epidemic of North American men who have sex with men (MSM). These models were developed to look at the long-term effectiveness and possible benefits derived from antiretroviral therapy.[61, 62]

The first early model, by Blower et al., investigated the effectiveness of antiretroviral therapy in preventing new infections and the impact of a change in risk behaviours.[61] The differences in infectiousness of patients in the various stages of HIV infection was not incorporated.[9] The model showed that antiretroviral therapy can be effective in preventing new infections. However, it also revealed that this benefit will be nullified if risk behaviour increases.

Another early model indicated that: (i) a decrease in sexual risk behaviour could mean an end to the HIV epidemic; (ii) that the epidemic would be stable if there was no change in risk behaviour; but (iii) it would escalate if risk behaviour increased.[62] Within the given

parameters, this model showed that eradication of HIV is possible, although it could take 100 years or more to achieve.

In conclusion, without taking the exact effects on transmissibility into account, the early models demonstrated that increased risk behaviour can offset the benefits of T&T.

Table 1. *Summary of main assumptions and main conclusions of studies that were reviewed on modelling the impact of 'test and treat'*

Study	Location	Assumptions related to testing	Assumptions related to treatment	Conclusions
Extent of reduction in transmission due to a reduced viral load unknown				
[61]	San Francisco	No assumptions	Antiretroviral treatment started in 50-90% of patients	Antiretroviral therapy can be effective in preventing HIV, but increases in risk behaviour can counteract this benefit.
[62]	San Francisco	No assumptions	Antiretroviral treatment started in 50-90%; 50-99% reduction in infectiousness	Increased HIV-risk behaviour can nullify benefits of treatment.
Extent of reduction in transmission due to a reduced viral load known				
[41]	Hyper endemic settings	All HIV-infected individuals identified	All HIV-infected people given antiretroviral therapy in first year of rollout	HIV prevalence could be reduced from >7 cases per 1000 people to <0.1 cases per 1000 in 45 years.
[63]	British Columbia	No assumptions	Therapy started at a CD4 count of ≤200 cells/µL	Increasing antiretroviral coverage from 50 to 100% reduces the number of new infections from 400 to 225 per year
[48]	South Africa	Universal testing	Immediate start of treatment after positive HIV test	HIV incidence reduced to less than 1 case per 1000 people within a decade, prevalence of HIV reduced to <1% within 50 years.
Extent of reduction in transmission due to a reduced viral load known and realistic assumptions used				
[66]	South Africa	90% of the population tested in the first two years	Immediate treatment with improved linkage to care and reduced loss-to-follow-up	Reduction of 73.2% of new infections

[65]	Washington D.C.	Annual screening	Start of treatment after positive HIV test	27.3% reduction in time spent with detectable viral load

Effect of antiretroviral therapy on infectiousness

Before discussing the models in the second era, it is important to review the evidence for a reduction in infectiousness because of antiretroviral therapy. Several studies have quantified the effect of antiretroviral drugs on reduction in HIV infectiousness. The results showed that antiretroviral therapy strongly reduces transmissibility in serodiscordant couples, ranging from no transmission to a 92% reduction in transmission (Table 2).[7, 43-47] The largest study included 3381 serodiscordant couples from seven countries in sub-Saharan Africa. A strong point of this study was that it used phylogenetics to determine whether HIV was transmitted inside or outside the serodiscordant relationship. From a total of 142 HIV transmissions observed in the study, more than 25% occurred through a partner other than the one followed in the study. Of the phylogenetically linked transmissions, only one transmission occurred in the partnerships in which the infected partner was on antiretroviral therapy, leading to a 92% reduction in transmission.[43] This strong reduction was also confirmed in the recent HPTN 052 study, in which investigators examined the effect of early start of treatment in serodiscordant couples versus delayed start of treatment in 1763 couples from nine countries. Of the 28 phylogenetically linked transmissions that occurred during follow-up, 27 occurred in the delayed treatment group and one in the early treatment group, resulting in a 96% reduction in the early therapy group compared with the delayed treatment group.[7]

Table 2. *Summary of articles investigating reduction of infectivity on antiretroviral therapy*

Study	Location	Design	N	Mean Follow-up time	Reduction in infectivity[1]
[432]	Sub-Saharan Africa	Prospective cohort	3381	2 years	92%
[7 2]	World	Prospective cohort	1763	1.7 years	96%
[44]	Uganda	Prospective cohort	926	0.5 years	98%
[45]	World	Meta-analysis	5021		100%[3]
[47]	Spain	Cross-sectional	625	3.1 years	100%
[46]	Uganda	Prospective cohort	250	1.54 years	100%

[1]Compared to untreated infectiousness
[2]Used phylogenetics to genetically link transmission
[3]When patient on ART has viral load <400 copies/mL

Models of universal T&T including effect of antiretroviral therapy on the infectiousness

Studies published after the early 2000s benefited from the knowledge that viral load is the key driver of transmission in HIV,[10] and that antiretroviral therapy can strongly reduce the viral load.[72] Treatment can therefore have the advantage of reducing the infectiousness of HIV-positive patients on antiretroviral therapy.

The model that brought much attention and subsequent controversy to T&T was published in 2009 by Granich *et al.*[48] This model was based on the South African epidemic and predicted that HIV incidence could be reduced to less than one case per 1000 people per year by 2016, and that the prevalence would be reduced to <1% within 50 years. These results were based on the impact of testing all people in the community (aged 15+) for HIV every year, and starting people on treatment immediately following a positive test result.[48] Similar results of a modelling study indicating that T&T can lead to global elimination of the HIV pandemic within 50 years were reported by Montaner *et al.*[41]

Post controversy models including combination prevention

Subsequent models focused on T&T in combination with other prevention strategies. One study was conducted in South Africa and compared the effectiveness of T&T alone or in combination with approaches that reduce the number of individuals lost to follow-up and that increase linkage to care. The model demonstrated that the combination of T&T-associated reduction in loss to follow-up and increased linkage to care could have nearly a 75% reduction in new infections over 10 years, and T&T alone could reduce new infections by 33%, compared to no intervention.[66]

Another study, conducted in Washington DC, used modelling to compare the impact of a regular T&T approach with an optimized T&T plan. The optimized strategy in this model involved improving adherence and assumed a higher suppressive efficacy than reported in the literature. The model predicted that the population-time spent with transmissible HIV RNA in the next 5 years with the optimized strategy had a 27.3% decrease, and a 14.7% decrease with the regular T&T strategy, both compared to no intervention.[65] An optimized prevention strategy would therefore avoid more infections than a regular T&T approach.

Epidemiologic evidence

All predictions of T&T have been based on modelling. Clear epidemiological evidence has only been described in ecological studies. Ecological studies compare group- or population-level exposure to a group-level outcome. Consequently, individual risk cannot be inferred from these types of studies.

An ecological study examined the impact of coverage of antiretroviral therapy, population-level viral load and the HIV incidence between 1996 and 2009 in British Columbia.[73] A strong correlation was found between the number of patients on antiretroviral therapy and the reduction in the number of new infections ($P < 0.0001$). Similarly, a significant association between the reduction in community viral load (i.e. the mean value of the most recent viral load in a community) and the decrease in number of newly diagnosed and reported HIV infections was also shown from 2004 to 2009 in San Francisco.[74] Because of the ecological nature of these studies, causality cannot be assumed; increasing antiretroviral therapy coverage in these studies could simply be coincidental with an overall decrease in incidence in the population.

T&T in daily practice

Mathematical models are inherently limited by the assumptions that are used to construct them.[75] Assumptions that are too optimistic may result in an unrealistically strong reduction in the HIV epidemic. Later, we will outline the challenges that may limit T&T as a prevention strategy and discuss the implications of T&T for clinical practice and public health.

Universal testing

Universal testing may not be feasible in daily practice. First, testing everybody for HIV would be difficult,[49] although not impossible.[76] It would also be challenging to repeat testing on a yearly basis, as proposed in the universal T&T strategy.[77]

Another challenge of universal HIV testing is the window period of antibody-based HIV tests. In this brief window, acute HIV infections (first 10–16 weeks of infection) are highly infectious, and these infections may be missed.[8] This may, however, be addressed by novel fourth-generation testing strategies that measure p24 antigen and antibodies. The window period in these fourth-generation tests is reduced to about 2 weeks. There is a concern that in low-prevalence settings (e.g. most resource-rich settings), the positive predictive value of the tests is too low for the identification of acutely infected individuals. This in turn can lead to the risk of false-positive results in universal testing. To address this, public health programmes in Seattle and San Francisco use a targeted testing approach that restricts testing to high-risk individuals**.**[78]

Additional interventions

The model by Granich et al.,[48] which predicted an elimination of the HIV pandemic, assumed that other preventive interventions would help to reduce transmission. These interventions include male circumcision,[79-83] treatment of curable sexually transmitted infections,[84, 85] and behaviour-change programs (in some settings).[86-88] The authors assumed that these other

interventions together would reduce transmission by 40% and would be rolled out in parallel with the T&T programmes.[48]

Male circumcision

Three randomized controlled trials have shown that male circumcision can reduce heterosexual transmission from women to men. A meta-analysis that combined the results of these trials found that circumcision reduced transmission by between 38% and 66% over 24 months.[83] For male circumcision to have an impact on a universal scale, however, it must be accepted in all communities. Several studies have examined the acceptability of adult male circumcision in Africa and have shown that 40–62% of uncircumcised men are willing to undergo circumcision.[89-91] The risk of transmission is not decreased for a woman if her HIV-infected partner is circumcised.[80]

In many resource-rich settings, sexual transmission between MSM accounts for a majority of new infections.[92, 93] One randomized controlled trial is currently ongoing in China to determine whether circumcision reduces new infections amongst MSM. A recent meta-analysis examined several observational studies that determined whether male circumcision can reduce new infections amongst MSM. The authors of the meta-analysis concluded that the studies were very heterogeneous and that there is currently not enough evidence to recommend male circumcision for HIV prevention amongst MSM.[94]

Treatment of curable sexually transmissible diseases

There are conflicting results regarding the impact of curable sexually transmissible diseases on HIV transmission. It does, however, appear that the treatment of these curable diseases results in a reduction in new HIV infections of between 3% and 38%.[84, 85, 95] In a more recent study, the effectiveness of treatment of curable sexually transmitted infections appeared to be 13.1% (95% confidence interval: 8.9–17.8%).[96]

Behaviour change

The early models on T&T found that behaviour change in the sense of a reduction in new partners could reduce the number of new infections. This result has been confirmed by behavioural change programmes amongst heterosexuals in Uganda, which have been shown to have up to a 70% reduction in new HIV infections.[87] These programmes have to be very culturally specific and are not necessarily effective in all settings.[79] Of note, a recent study from Israel reported an increase in risk behaviour amongst MSM.[97] According to the early mathematical models, such an increase can nullify the benefits of T&T. Therefore, prevention programmes in high-risk populations are still needed.

Immediate treatment irrespective of CD4 T-cell count

A mathematical model predicted that the success of a T&T approach depends on immediate treatment regardless of CD4 T-cell count.[48] The model investigated the potential impact on

the incidence of HIV by placing patients on treatment at a CD4 count of ≤200 and ≤350 cells mm^3 with varying degrees of coverage. It was predicted that with 50% coverage of HIV-positive patients and 78.5% adherence, which had been observed in this population, the number of new infections would increase over time. However, with coverage increased to between 75% and 100%, a reduction in new annual infections of between 40% and 67%, respectively, would occur.

Earlier start of treatment at higher CD4 counts is not only beneficial for public health but also offers clinical benefits.[98] Several observational cohort studies reported reduced mortality in those who start treatment at a CD4 count >500 cells mm^3 as compared to those who start treatment at between 350 and 500 cells mm^3.[99-102] (The reduction in mortality did not reach statistical significance in all studies[101, 102]). One large observational study including 20 971 individuals from Europe and the USA found that initiation of treatment at a CD4 count of 500 cells mm^3 reduced acquired immunodeficiency syndrome (AIDS)-free survival by 38% versus initiation at a threshold of 350 cells mm^3, and by 90% versus a threshold of 200 cells mm^3.[102] Lower CD4 counts were found to be independent risk factors for AIDS-related and non-AIDS-related malignancies.[103] Some guidelines therefore recommend starting treatment in asymptomatic patients with a CD4 count >500 cells mm^3.[98] It should, however, be noted that the evidence for the treatment start at such high CD4 levels comes from observational studies, which can be limited by the potential for bias because of unmeasured confounding.[104] A randomized clinical trial (the START study) is currently underway with patients randomly allocated to start treatment at a CD4 count >500 cells mm^{3}or to defer treatment until a CD4 count between 350 and 500 cells mm^3.[104]

A favourable impact of early treatment on the HIV epidemic will also depend on the CD4 count at the time that patients are diagnosed. Of importance, many patients are only diagnosed at CD4 counts that are far <500 cells mm^3. A UK study reported that one of three patients first presented with a CD4 count of <200 cells mm^3.[105] Studies including multiple centres in Europe[57] and North-America[106] reported that more than 50% of patients were identified in treatment centres with a CD4 count of <350 cells mm^3.[57, 106] Increased testing of populations with a high risk of HIV to identify patients at an earlier stage of infection is therefore recommended.

Although immediate treatment offers benefits to patients, providing antiretrovirals at high CD4 T-cell counts can be challenging in resource-poor settings because of financial constraints. For instance, some hospitals in Uganda place new patients on waiting lists as they do not have the resources to provide them with antiretroviral drugs.[107] The current World Health Organization (WHO) guidelines recommend starting treatment in resource-limited settings at a CD4 count of 350 cells mm^3.[108]

Retention of patients in HIV care

A systematic review looking at programmes in sub-Saharan Africa that provided antiretroviral therapy found that not all patients retained in care, especially at the 24-month time-point.[109] The authors reviewed 32 publications that reported on 33 cohorts, which totalled 74 192 patients in 13 countries. The weighted mean retention rates for 6, 12 and 24 months were 79.1%, 75.0% and 61.6%, respectively. This is important because patients who stop treatment will have a rebound in viraemia, which results in increased infectivity.

An even bigger challenge may be keeping within the care system asymptomatic HIV-infected patients who are not eligible yet for treatment. These patients, who are on average younger and have a higher CD4 count, may continue to spread the virus.[110]

Drug resistance

A novel prevention strategy such as T&T is most urgently needed in sub-Saharan Africa. This strong need for the prevention of new infections in this part of the world is illustrated by the disproportionally high number of individuals living with HIV/AIDS. UNAIDS has estimated that amongst 33 million individuals infected with HIV in the world in 2009, more than 22 million are living in sub-Saharan Africa. Similarly, almost 70% of all new HIV infections worldwide occurred in this region.[6]

Substantial levels of drug resistance can potentially occur in a T&T programme in sub-Saharan Africa because of the limited virological monitoring that is available. Expensive viral load assays are frequently unavailable in this area.[19] Therapy failure resulting in viraemia is therefore often identified on the basis of clinical events.[111, 112] This delayed the identification of viraemia allows the virus to replicate in the presence of antiretroviral drugs, which almost invariably leads to the emergence of HIV drug resistance.[113] This can have important clinical ramifications in sub-Saharan Africa as second-line treatment required to treat drug-resistant HIV is expensive and often unavailable.[114, 115]

Drug resistant HIV can be transmitted to others.[24, 58] Studies from Europe found that about 10% of patients become infected with a drug resistant variant.[57, 59, 116] Patients that become infected with a drug resistant virus are more likely to experience virological failure.[59] In addition, they may in turn transmit their drug resistant virus to others.[117, 118] Transmitted drug resistance may be a particular problem in sub-Saharan Africa as a genotypic-resistance test, which determines drug-resistance-associated mutations, is expensive and not readily available.

Later, we will discuss the epidemiology of the emergence and transmission of drug-resistant HIV across the world. We will start by giving a brief overview of the epidemiology in resource-rich settings. We will then review the recent literature on the emergence and

transmission of drug resistance in sub-Saharan Africa and discuss the impact of resistance on the effectiveness of the T&T programme in this region.

Epidemiology of drug resistant HIV in resource-rich settings

Valuable insight into the epidemiology of drug-resistant HIV can be obtained from resource-rich settings. In Europe, about 10% of patients are diagnosed with a drug-resistant virus.[57, 116, 119] It is noteworthy that the prevalence of transmission of drug-resistant HIV has stabilized in recent years.[57] Limited information is available about the risk of emergence of drug resistance during treatment with antiretroviral agents. A study from the UK reported that the cumulative risk of drug resistance was 28% after 8 years.[120] It should be noted that this proportion may decrease in the coming years as treatment has improved during the past decade. This is also highlighted by a report that the proportion of patients with undetectable viral loads increased from 65% in 2000 to 87% in 2008 in British Columbia.[72]

The results of studies from resource-rich settings cannot be extrapolated to developing countries. First, treatment in resource-rich settings has been available for a longer period of time. In the past, before combination antiretroviral therapy was introduced, treatment was suboptimal and was associated with rapid emergence of drug resistance. There is evidence that resistance to zidovudine, which was given as monotherapy in the early 1990s, is still circulating.[119] Second, sophisticated laboratory tests are not available on a large scale in resource-limited settings.

Emergence of drug resistance in sub-Saharan Africa

Table 3 summarizes the results of studies of the risk of drug resistance amongst patients who used antiretroviral drugs in Africa.[111, 112, 121-128] The studies were conducted between the end of 2002 and 2008. Most studies were cross-sectional and collected samples for resistance testing at one moment in time and recorded how long patients had been taking treatment up to that time-point. The vast majority of patients had advanced disease with a CD4 count of <200 cells mm^3 when they started treatment. Individuals had been taking antiretrovirals for a period ranging from 6 months[127, 128] to more than 3 years.[122, 125]

The choice of antiretroviral drug therapy was fairly consistent in the studies. Patients in all studies used a thymidine analogue (zidovudine or stavudine), lamivudine and a non-nucleoside reverse transcriptase inhibitor (NNRTI).[111, 112, 121-128] It should be noted that stavudine is no longer recommended because of high rates of side effects including lactic acidosis and lipodystrophy.[111, 121-123] One study from Botswana included patients who used zidovudine, didanosine and an NNRTI.[125] In three studies, a minority of patients received protease inhibitors[121, 122, 128] that are usually used for second-line treatment.

Table 3. *Summary of results from studies that reported on the emergence of resistance in patients starting combination antiretroviral therapy in Africa*

	Location	**Time**	**Design**	**Duration treatment**	**N**	**Antiretrovirals[1]**	**Measurement of viral load**	**Resistance[2]**
[111]	South-Africa	2002-'08	retrospective cohort	Median 17 (6-31) months	3727	ZDV / 3TC / NNRTI	Every 6 months	Any resistance mutation (estimate): 11.3%[3] TAMs: 9% (0.7%) M184V: 56% (4.2%) NNRTI: 93% (7.0%)
[112]	Entebbe, Uganda	2004	longitudinal	48 weeks	300	ZDV / 3TC / NVP[4]	Not available to guide treatment	Any resistance mutation (week 48): 10.8% TAMs: 28% (3%) M184V: 72% (7.8%) NNRTI: 72% (7.8%)
[121]	Malawi	2004	Cross-sectional	Median 9.5 (7.4-15.2) months	398	ZDV or D4T /3TC / NNRTI (n=396), ZDV/3TC/IND(n=2)	Not available to guide treatment	Any resistance mutation: 12.3% TAMs: 12% (1.5%) taken from [19] M184V: 76% (9.3%) NNRTI: 94% (11.6%) K65R: 10% (1.2%)
[122]	Soweto, South-Africa	2008	cross-sectional	>12 months; 63.9% for more >36 months	998	NNRTI-based (1st line, 89%), PI-based (2nd line, 11%)	Available to guide treatment	Any resistance mutation (estimate): 10.8%[3] TAMs: 17% (1.4%) M184V: 66% (5.6%) NNRTI: 94% (8.0%)
[123]	Abidjan, Côte d'Ivoire	2006-'07	cross-sectional	12 months	942	D4T or ZDV / 3TC / NNRTI	After 6 and 12 months	Any resistance mutation: 11.2% TAMs: 8% (0.5%) M184V: 69% (7.7%) NNRTI: 87% (9.8%)
[124]	Maputo, Mozambique	2006	cross-sectional	At least 12 months	149	D4T or ZDV / 3TC / NNRTI	Not available to guide treatment	Any resistance mutation: 5.3% TAMs: 63% (3.3%) M184V: 88% (4.6%)

	Location	Time	Design	Duration treatment	N	Antiretrovirals[1]	Measurement of viral load	Resistance[2]
								NNRTI: 100% (5.3%)
[125]	Gaborone, Botswana	2002-'04	Longitudinal	Median 104 (IQR 78-136) weeks	650	ZDV/ddI/NNRTI, or D4T or ZDV / 3TC/ NNRTI	Every 2 months	ZDV/ddI after one year: 5.3%, after two years: 13.5% Non-ZDV/ddI after one year: 1.0%, after two years: 3.2%
[126]	Manyara, Tanzania	2007-'08	Cross-sectional	Median 22 (IQR 14-30) months	212	ZDV or D4T / 3TC / NNRTI	Only in patients with suspicion of virological failure	Any resistance mutation: 8.5% TAMs: 33% (2.8%) M184I/V: 78% (6.6%) NNRTI: 100% (8.5%) K65R: 6% (0.5%)
[127]	Yaoundé, Cameroon	2002-'03	longitudinal	24 weeks	60	D4T / 3TC / NVP	Every visit	Any resistance mutation: 3.3% TAMs: 0% M184I/V: 50% (1.7%) NNRTI: 100% (3.3%)
[128]	N'Djamena, Chad	2006	longitudinal	6 months	88	D4T/3TC and NVP (81%) or indinavir (19%)	Not available to guide treatment	Any resistance mutation: 25% TAMs: 18% (4.5%) M184I/V: 82% (20.5%) NNRTI: 77% (19.3%)

[1] Abbreviation of drugs in alphabetic order: 3TC = lamivudine, D4T = stavudine, ddI = didanosine, IND = indinavir, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, NVP = nevirapine, PI = Protease Inhibitor, ZDV = zidovudine

[2] Resistance to particular (classes of) antiretroviral drugs.[19, 129]. TAMs = Thymidine Analogue (zidovudine, stavudine) Mutations, M184V confers resistance to lamivudine and emtricitabine, K65R confers resistance to tenofovir.

[3] Based on calculation of data provided in paper

[4] The study included an arm ZDV/3TC/ABC which is not presented here

Risk of emergence of resistance in resource-poor settings

The results of the studies demonstrated that resistance was generally limited with a prevalence ranging between 1% and 12%.[111, 112, 121-127] One study from Chad did, however, report a substantial prevalence of 25% amongst patients. It is not known why the prevalence was so high especially as follow-up was only 24 weeks.[128] Another study also reported a higher prevalence of resistance of 13.5%.[125] However, patients in this study used didanosine, which is no longer recommended in first-line regimens.[98, 130]

Gupta *et al.* have previously reported that frequent monitoring of the viral load limits the emergence of drug resistance.[19] The studies summarized in Table 4 confirm this finding with the lowest prevalence (<5%) reported in studies in which the viral load was determined at every visit.[125, 127] Studies in which virological monitoring was less frequent, or not performed, showed a prevalence ranging between 5.3% and 25%.[111, 112, 121-123, 126]

Emergence of resistance to particular (classes of) antiretroviral drugs

It is also important to know to which (classes of) antiretroviral drug resistance emerged. Resistance against NNRTIs was most frequently reported (72–100% of plasma samples with at least one resistance-associated mutation). Similarly, the lamivudine-resistance-associated M184I/V mutations were also observed in the virus of most patients in whom resistance developed (range 50–80%). Thymidine analogue mutations that confer resistance to stavudine and zidovudine were detected in up to 33% of samples with any resistance. In the majority of cases, the tenofovir-associated K65R mutation was not detected, which is most probably due to the fact that tenofovir was not used.

The substantial difference in the occurrence of resistance to different drugs can be explained by dissimilarities in the genetic barrier to drug resistance. The genetic barrier is defined as the number of mutations required to overcome drug selective pressure.[131, 132] The NNRTIs and lamivudine have a genetic barrier of one.[133] Because of this low genetic barrier, HIV can quickly select for resistance when patients continue using these drugs during virological failure. Drug resistance is therefore most commonly found against NNRTIs and lamivudine. Conversely, the thymidine analogues, stavudine and zidovudine, have a higher genetic barrier, especially when combined with lamivudine or emtricitabine, as relevant resistance to these drugs involves the accumulation of several mutations.[134]

Emergence of drug resistance in T&T

Recent studies have shown that drug resistance emerged in only a limited proportion of patients who started treatment.[112, 121, 122, 124, 125, 127, 128, 135-137] An important strategy that was associated with a reduced risk of resistance was intensive monitoring of viral load.[138] A T&T programme may therefore benefit from inexpensive point-of-care viral load testing to identify early virological failure which can limit the emergence of resistance.[138]

Table 4. *Recent studies reporting on the prevalence of transmission of drug resistant HIV in Africa*

							Resistance (%)[1]					
	Location	**Time**	**N**	**Description of included patients**	**CD4 - median**	**viral load - median**	**Any**	**TAMs**	**M184V**	**K65R**	**NNRTI**	**PI**
[139]	Bobo Dioulasso, Burkina Faso	n/a	51	Pregnant women	637	3.8	0	0	0	0	0	0
[139]	Abidjan, Côte d'Ivoire	n/a	48	Pregnant women	681	ND	0	0	0	0	0	0
[139]	Dakar, Senegal	n/a	48	VCT attendees[2]	652	4.1	0	0	0	0	0	0
[140]	Rakai, Uganda	1998-2003	104	Newly infected	516	4.9	5.8	2.9	0	0	0	2.9
[141]	N'Djamena, Chad	2006-'07	34	First pregnancy and <25 years	n/a	n/a	0	0	0	0	0	0
[141]	Yaoundé, Cameroon		44		n/a	n/a	6.8	2.2	0	0	4.5	0
[141]	Douala, Cameroon		34		n/a	n/a	5.9	2.9	2.9	0	2.9	0
[142]	Maputo, Mozambique	2002-'04	68[3]	Drug naïve	355	4.4 (mean)	5.9	5.9	4.4	0	1.5	0
[143]	Ouagadougou, Burkina Faso	2004-'06	104	Drug naïve with a viral load>1,000	175	5.5	12.5	10.6	0	0	2.9	0
[144]	Lusaka, Zambia	2007-'08	557	Drug naïve	130	4.9	5.2	0.7	0.4	0.8	3.4	1.1
[145]	Dar es Salaam, Tanzania	2004-'05	44	Youth 13-25 yrs	228	n/a	9.1	2.3	4.5	2.3	9.1	0
[146]	Gaborone, Botswana	2007	33	First pregnancy and <25 years	n/a	n/a	0	0	0	0	0	0
[146]	Francistown, Botswana	2007	39		n/a	n/a	0	0	0	0	0	0
[147]	Nairobi/Mtwapa/Kilifi, Kenya	2006-'09	64	MSM, SW and their clients[4]	n/a	n/a	3.1	1.6	0	0	1.6	0
[147]	Entebbe, Uganda	2006-'09	26	HIV discordant couples, VCT[2] attendees	n/a	n/a	19.2	3.8	0	0	7.7	3.8

[147]	Masaka, Uganda	2006-'09	66	HIV discordant couples	n/a	n/a	1.5	0	0	0	0	1.5
[147]	Kigali, Rwanda	2006-'09	78		n/a	n/a	7.7	1.3	0	0	5.1	1.3
[147]	Lusaka/Copperbelt, Zambia	2006-'09	169		n/a	n/a	2.4	1.2	0.6	0	1.2	0

[1] Resistance to particular (classes of) antiretroviral drugs. Any = presence of at least one drug resistance associated mutations, TAMs = Thymidine Analogue (zidovudine, stavudine) Mutations, M184V confers resistance to lamivudine and emtricitabine, K65R confers resistance to tenofovir, NNRTI is presence of at least one mutation that confers resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI), PI is resistance to protease inhibitors.

[2] VCT = Voluntary Counselling and Testing

[3] study included 104 patients from whom 68 RT genotype could be obtained

[4] MSM= Men-having-Sex-with-Men, SW=Sex Workers

Another potential strategy may be the use of a first-line regimen consisting of tenofovir, emtricitabine and an NNRTI. The WHO currently recommends two different regimens as first-line therapy. The first consists of zidovudine, lamivudine and an NNRTI, and the second consists of tenofovir, emtricitabine and an NNRTI.[108] The latter regimen is not used frequently in Africa.[148] Randomized clinical trials in resource-rich settings have shown that a regimen of tenofovir, emtricitabine and the NNRTI efavirenz is associated with a 33% lower rate of emergence of resistance compared to a regimen of zidovudine, lamivudine and efavirenz.[149] This lower rate of resistance should, however, be confirmed in clinical practice in Africa. A further argument for the use of a tenofovir-containing regimen as first-line treatment may be that patients failing a tenofovir-containing regimen may develop a K65R resistance mutation. Viruses with a K65R mutation are sensitive to zidovudine, which could then be used as part of a second-line regimen when needed.

Transmission of drug resistance

A large number of studies have investigated the prevalence of transmission of resistance in Africa. It is beyond the scope of this review to discuss all these studies (but several reviews have been published on this topic[24, 58, 150-152]). We will only consider studies that were published between the beginning of 2009 and March 2011[139-147] (Table 4).

Prevalence of transmission of drug resistance

Most recently published studies on transmission of drug resistance in sub-Saharan Africa showed a prevalence of <8%.[139-147] This is an important finding as this level of resistance is lower than the prevalence of 10–15% found in many resource-rich settings.[57, 151, 153]

The prevalence of transmission of drug resistance could increase for several reasons in the coming years. First, the availability of antiretroviral drugs has increased considerably only in recent years making emergence and transmission of drug resistance more likely. Second, it is difficult to identify patients who have recently been infected with HIV.[146] As a consequence, it is likely that studies to date have included individuals who were infected at a time when antiretrovirals were only available to a limited extent. Over time, studies will include more patients who became infected when antiretrovirals were more readily available, which may result in a higher prevalence of transmission of resistance than has been reported.

Transmission of resistance to particular (classes of) antiretroviral drugs

In most studies, transmission of resistance was highest for NNRTIs.[24, 58, 139, 141-143, 145, 147, 152] There are two possible explanations for this. First, resistance to this class of antiretroviral drugs was also most frequently found in viral isolates obtained from treated patients (Table 3). There are two possible explanations for this. First, resistance to this class of antiretroviral drugs was also most frequently found in viral isolates obtained from treated patients.[154, 155]

Around the year 2000, it was shown that single-dose nevirapine given to the mother at labour onset and to the newborn baby within 72 h after birth reduces the HIV transmission rate.[156] This simple regimen was sufficient to stimulate the establishment of extensive programmes to prevent vertical HIV transmission in low-resource settings worldwide.[157] Resistance to nevirapine can, however, emerge quickly due to its relatively long half-life and low genetic barrier to resistance.[157] Recent use of single-dose nevirapine is associated with a higher probability of virological failure amongst women who start treatment with an NNRTI-containing regimen.[154, 155] As access to antiretroviral drugs has increased during the last years, more durable responses can now be achieved with triple combination therapy at a wider scale.[157] Resistance emerging as a consequence of such prophylactic use of nevirapine can also be transmitted to others. As access to antiretroviral drugs has increased during recent years, more durable responses can now be achieved with triple combination therapy on a wider scale.[157]

Thymidine analogue associated mutations were also reported in most studies shown in Table 4. These mutations were also commonly found in European studies on the transmission of resistance.[57, 116, 119]

The M184V mutation was found in only small proportions of antiretroviral naïve patients (Table 4). At first glance, this is surprising as the M184V mutation was one of the most common mutations in treated patients in whom resistance emerged (Table 3). Studies from resource-rich settings do, however, confirm that transmission of the M184V mutation is limited[57, 117, 158-160] despite high levels of this mutation in samples from treatment-exposed individuals.[161-163] The low prevalence of this mutation in antiretroviral-naïve patients can be explained by rapid reversion to wild type after transmission. Reversion can occur because the M184V mutation results in a virus that replicates less efficiently than a drug-susceptible wild-type virus.[164] Thus, the drug-resistant virus could be outgrown by faster-replicating revertant viruses. Another explanation for the low levels of transmission of the M184V is that this mutation strongly reduces the viral load.[165, 166] As viral load is key to the transmission of the virus,[167] M184V-containing viruses are less likely to be transmitted.

Transmission of the K65R mutation was rare and only reported in two studies.[144, 145] It is not surprising that transmission of K65R was not found in most studies as this mutation was also uncommon in studies on acquired resistance (see Table 3). Moreover, K65R-containing HIV strains are, similar to viruses including M184V, associated with a lower viral load[168] which makes transmission of this mutation less likely.

Resistance to protease inhibitors was reported in a few studies, albeit at a limited level of at most 3.8%. Protease inhibitors are not widely used in Africa as they are expensive[115] and are reserved for second-line treatment.[114, 122] Some protease inhibitor resistance-associated mutations occur naturally at a low level in HIV subtypes A, C, D and G,[169] which are common in Africa.[58, 170] These polymorphic mutations may explain the low level of transmitted protease inhibitor resistance found in some studies.

It should be noted that virtually all epidemiological studies in resource-poor and in resource-rich settings used population sequencing to identify drug-resistance-associated mutations. Population sequencing does not allow quantification of minority species that are present in <25% of the viral populations infecting a patient. There have been several reports of the presence of resistance-associated mutations as minority species in viral samples from antiretroviral-naïve patients.[171-175] Of note, the presence of minority species is associated with a reduced virological response.[173, 175]

Impact of transmitted resistance on T&T

Transmission of drug resistance can strongly reduce the benefits of a T&T programme. However, in a successful T&T programme increased numbers of patients will start treatment, which may lead to larger number of patients in whom drug-resistant viruses emerge. These viruses can be transmitted to others. Treatment options are limited in Africa and it is therefore likely that if transmission of resistance occurs, future antiretroviral therapy in a newly infected individual may be affected. Treatment of a transmitted drug-resistant variant is associated with an increased risk of virological failure.[59] Patients infected with a drug-resistant variant may therefore continue to spread their virus to others, leading to forward transmission.

Studies in resource-rich countries have identified transmission networks of drug-resistant HIV.[16, 176] These networks consist of antiretroviral-naïve patients who become infected with drug-resistant variants and who in turn may infect others. Transmission of drug resistance could therefore lead to self-sustaining epidemics.

Treatment guidelines in resource-rich settings recommend genotypic testing in antiretroviral-naïve patients to detect the presence of transmitted drug resistance and to adapt first-line treatment accordingly.[98, 177] However, genotypic-resistance tests are expensive and not always available in Africa. There is therefore an urgent need for inexpensive genotyping methods. In addition, a wider range of antiretroviral drugs could benefit the care of HIV-infected patients in Africa so that alternative options are available for patients who become infected with a drug-resistant virus.

DISCUSSION

We have reviewed the epidemiological evidence for the potential benefits of T&T**.** This evidence comes predominantly from mathematical models that predicted that a strategy of T&T can prevent new infections. Some models even forecast that T&T could reduce the prevalence to <1% within 50 years.[41, 48] However, the models predicting such a strong reduction of the HIV pandemic used optimistic assumptions that may not be achieved in daily practice. Further epidemiological evidence comes from ecological studies that found an

association between increasing numbers of patients on antiretroviral therapy and a reduction in new infections with HIV.[73, 74]

The strategies that have been studied in mathematical models have been based on testing and treating as many people as possible. This may not result in the most efficient use of available resources. We suggest a strategy in which selected populations known to have a higher risk for infection are targeted for T&T. Most couples living with HIV/AIDS in Sub-Saharan Africa are serodiscordant.[178] One targeted approach could be earlier treatment at higher CD4 counts of infected partners in these serodiscordant couples. In addition, contact tracing could also be implemented by identifying and offering testing to the sexual partners of people who test positive for HIV.[179]

In this review, we have also discussed the potential impact of drug resistance on the effectiveness of a T&T programme. We limited this discussion to sub-Saharan Africa, where most new HIV infections worldwide occur. In addition, virological monitoring of patients is frequently not available in sub-Saharan Africa. It is therefore not possible to identify virological failure and development of drug resistance in a timely manner. Nonetheless, current levels of acquired and transmitted drug resistance are limited in sub-Saharan Africa, but this may change after implementation of T&T. In a T&T programme, the proportion of patients who are affected by drug resistance could remain the same. However, as more patients receive treatment, more patients could also be affected by drug resistance.

Several prevention strategies using antiretrovirals have shown to be effective in reducing new infections with HIV. These strategies include antiretrovirals for prevention of mother-to-child-transmission,[154, 155] topical tenofovir as an intra-vaginally applied microbicide,[34] and tenofovir combined with emtricitabine as pre-exposure prophylaxis.[28] These antiretroviral drugs may also be used in a T&T programme. There are potential risks associated with using the same drugs for both prevention and for treatment. This has been shown in study from Zambia that reported that recent use of nevirapine for prevention of mother-to-child-transmission was associated with a higher probability of virological failure [58]. There is some limited evidence that the benefits of pre-exposure prophylaxis may outweigh the risks associated with increasing levels of resistance,[33, 180, 181] but this has to be confirmed in clinical practice.

In conclusion, T&T is a promising prevention strategy. However, its benefits have only been shown in mathematical models and ecological studies. The promise of T&T should therefore be confirmed in large-scale prospective and epidemiological studies. Emergence and transmission of drug resistance is currently not a major problem. But more patients will receive treatment in a T&T programme. In addition, antiretroviral drugs used for treatment may also be used for prevention as pre-exposure prophylaxis and as a microbicide. We therefore recommend surveillance of drug resistance in areas in which T&T is introduced to confirm that drug-resistance levels remain limited.

Part I

Treatment as Prevention

Chapter 3

Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: A modeling study

Brooke E. Nichols, Kim C.E. Sigaloff, Cissy Kityo, Kishor Mandaliya,
Raph L. Hamers, Silvia Bertagnolio, Michael R. Jordan,
Charles A.B. Boucher, Tobias F. Rinke de Wit,
David A.M.C. van de Vijver

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ABSTRACT

Background Earlier antiretroviral therapy initiation can reduce the incidence of HIV-1. This benefit can be offset by increased transmitted drug resistance (TDR). We compared the preventative benefits of reducing incident infections with the potential TDR increase in East Africa.

Methods A mathematical model was constructed to represent Kampala, Uganda, and Mombasa, Kenya. We predicted the effect of initiating treatment at different immunological thresholds (<350, <500 CD4 cells/μL) on infections averted and mutation-specific TDR prevalence over 10 years compared to initiating treatment at CD4<200 cells/μL.

Results When initiating treatment at CD4<350 cells/μL we predict 18 (Interquartile-range 11-31) and 46 (IQR 30-83) infections averted for each additional case of TDR in Kampala and Mombasa, respectively, and 22 (IQR 17-35) and 32 (IQR 21-57) infections averted when initiating at <500. TDR is predicted to increase most strongly when initiating treatment at CD4<500 cells/μL, from 8.3% (IQR 7·7%-9·0%) and 12.3% (IQR 11·7%-13·1%) in 2012 to 19·0 % (IQR 16·5%-21·8%) and 19·2% (IQR 17·1%-21·5%) in 10 years in Kampala and Mombasa respectively. The TDR epidemic at all immunological thresholds was comprised mainly of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs). When 80-100% of individuals with virological failure are timely switched to second-line, TDR is predicted to decline irrespective of treatment initiation threshold.

Conclusion Averted HIV infections due to the expansion of antiretroviral treatment eligibility offset the risk of transmitted drug-resistance, as defined by more infections averted than TDR gained. The effectiveness of first-line NNRTI-based therapy can be preserved by improving switching practices to second-line therapy.

INTRODUCTION

Since 2010, the World Health Organization (WHO) recommends earlier initiation of combination antiretroviral therapy (ART) for HIV-infected persons in resource-limited countries. A shift in the immunological criteria for treatment initiation from <200 to <350 CD4 cells/μL, has resulted in a substantial increase in the number of people eligible to initiate ART.[182] In addition to the individual clinical benefits,[7] earlier initiation of ART may reduce HIV incidence rates and the concept of treatment as prevention has attracted attention as a means to reduce the global HIV epidemic.[7]

As access to ART expands in resource-limited countries, concerns surrounding increasing numbers of patient failing treatment and the subsequent emergence of drug-resistant viruses will become increasingly important. Resistant virus selected for during treatment may subsequently be transmitted to newly infected individuals, undermining the effectiveness of currently recommended or available first-line ART.[183] A recent comprehensive assessment of transmitted drug resistance (TDR) reported a significant rise in prevalence of predominantly non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated resistance mutations since ART rollout in east and southern Africa.[184] The highest TDR levels (9-13%) have been detected in East Africa.[185, 186] As NNRTIs are the cornerstone of standard first-line ART in sub-Saharan Africa, reduced susceptibility to this drug class is especially worrisome in view of the limited availability of alternative first-line drug options.

Mathematical modeling is an important tool to inform policy makers about the potential consequences in terms of HIV drug resistance as a result of increased ART coverage in sub-Saharan Africa. Models of HIV transmission have been used to predict emergence of TDR,[21, 187-189] but these models have not examined the impact of earlier treatment initiation. In this study we used a compartmental mathematical model to predict whether initiation of ART at different immunological thresholds and the availability of second-line ART have an effect on transmission of drug-class specific resistance in East Africa. Specifically, we examined whether the number of new HIV infections averted by early ART initiation offsets a potential rise in TDR.

METHODS

Study design and population

To predict time trends of TDR our model included resistance data from PharmAccess African Studies to Evaluate Resistance (PASER). This comprised two distinct observational studies on transmitted (PASER-Surveillance) and acquired (PASER-Monitoring) drug resistance conducted in Kampala, Uganda and Mombasa, Kenya (Table 1). PASER-Monitoring used a prospective cohort that assessed HIV drug resistance in individuals about to initiate first-line ART in 2007-2008 and 24 months thereafter.[190] Viral load and drug resistance testing were

not used to inform clinical decisions. PASER-Surveillance comprised two cross-sectional surveys among newly HIV-1 diagnosed, antiretroviral-naïve individuals attending voluntary counseling and testing sites in Kampala and Mombasa in 2009-2010.[185, 186] Specimens collected in the PASER studies were genotyped in two reference laboratories in Uganda, which participated in quality assessment schemes for genotypic drug resistance testing.

Table 1. *Characteristics of patients included in the PASER studies*

	Kampala, Uganda	Mombasa, Kenya
PASER-Surveillance cross-sectional survey among recently infected individuals		
Number of participants	77	81
Year of enrolment	2009-2010	2009-2010
Site Type	Voluntary Counseling and Testing	Voluntary Counseling and Testing
Age, years	22·0 (20·0-23·0)	23·4 (21·6-24·9)
Sex, female	54 (70·1)	71 (87·7)
CD4 cells/μL	417 (318·5-551·5)	400 (239-564)
Viral load, log_{10} c/ml	4·49 (3·96-5·28)	4·6 (4·2-5·1)
Any TDRM	6 (8·6)[a]	9 (13·2)[b]
NRTI mutation	2 (2·9)	1 (1·5)
NNRTI mutation	3 (4·3)	5 (7·4)
PI mutation	1 (1·4)	3 (4·4)
PASER-Monitoring longitudinal study among patients receiving first-line ART		
Number of participants	203	221
Year of enrolment	2007	2007-2008
Site Type	Government HIV clinic	Government general hospital
Age, yrs	36·0 (29·2-40·9)	36·4 (31·2-42·8)
Sex, female	113 (55·7)	131 (59·3)
Initial ART regimens		
Zidovudine-containing	122 (60·1)	171 (77·4)
Tenofovir-containing	81 (39·9)	3 (1·3)
Stavudine-containing	0	47 (21·3)
CD4 count at ART initiation, cells/μL	136 (40-206)	128 (63-197)
Viral load at baseline, log_{10} c/ml	5·4 (5·0-5·9) log_{10} c/ml	4·6 (4·1-5·4)
Previous ARV exposure	15 (7·4)	10 (4·5)
VL > 400 cps/ml at 12 months	25 (14·3)[c]	21 (11·6)[d]
Any DRM at 12 months	17 (77·3)[e]	6 (46·2)[f]
NRTI mutation	12 (54·6)	4 (30·8)
NNRTI mutation	14 (63·6)	4 (30·8)

PI mutation	1 (4·5)	1 (7·7)
VL > 400 cps/ml at 24 months	25 (15·5)[g]	20 (13·6)[h]
Any DRM at 24 months	15 (75·0)[i]	12 (70·6)[j]
NRTI mutation	11 (55·0)	10 (58·8)
NNRTI mutation	14 (70·0)	12 (70·6)
PI mutation	1 (5·0)	0

Data are presented as n (%) or median (IQR). [a]For n=70 with available genotype; [b]For n=68 with available genotype; [c]For n=175 retained in care; [d]For n=181 retained in care; [e]For n=22 with available genotype; [f]For n=13 with available genotype; [g]For n=161 retained in care; [h]For n=147 retained in care; [i]For n= 20 with available genotype; [j]For n=17 with available genotype. PASER, PharmAccess African Studies to Evaluate Resistance; ART, antiretroviral therapy; ARV, antiretroviral; TDRM, transmitted drug resistance mutations; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Model and calibration

A compartmental deterministic mathematical model was constructed which was described with a total of 77 ordinary differential equations and 123 parameters (Figure S1, Table S1). The model stratified disease progression into an acute stage, three chronic stages, and two AIDS stages. Three chronic stages were included to indicate previous (ART initiation at CD4 <200 cells/μL [191]),[182] current (CD4 <350 cells/μL),[182] and potential future treatment guidelines (CD4 <500 cells/μL).[192] Infectivity varied by stage of infection.[9, 55] Other key model parameters are summarized in Table 2. TDR was defined as the number of individuals infected with drug-resistant HIV over total number of HIV infected treatment-naïve individuals. In the Kampala model, mono therapy with zidovudine was available to a small number of individuals from 1991-1996, dual therapy with zidovudine/lamivudine was available to a small number of individuals from 1996-2000. Triple therapy started rollout in the model on a small scale from the year 2000 in both Kampala and Mombasa.

The model identified four sexual activity groups ranging in the number of new sexual partners per year.[193] Using Monte Carlo filtering techniques,[194] we parameterized the different sexual activity groups and only accepted the simulations that were associated with distinct HIV prevalence from country data[195, 196] and TDR prevalence by resistance class in the two PASER-Surveillance sites. For Kampala, this resulted in 1017 out of 50,000 simulations with HIV prevalence between 7·1-8·4% between 2005 and 2009 and TDR prevalence between 7·1-10% in 2009. For Mombasa, this resulted in 1247 out of 50,000 simulations with an HIV prevalence of 5·8-8·2% between 2006 and 2010, and TDR prevalence between 11·9-14·9% in 2009 (Figure S2).

Table 2. *Key Additional Model Parameters**

Description	**Estimate or Range****	**Reference**
Disease stages duration		[8, 11]
Acute stage	10-16 weeks	
Chronic stage >500 cells/μL	0·87-1 year	
Chronic stage 350-500 cells/μL	2·9-3·1 years	
Chronic stage 200-350 cells/μL	3·6-3·9 years	
AIDS stage***	6-12 months	
Final AIDS stage***	7-13 months	
Infectivity		[9, 55]
Acute stage	27-43 times that of chronic stage	
Chronic stage (all)	10% per year	
AIDS stage***	3-5 times higher than chronic stage	
Final AIDS stage***	0%	
Proportion of people in sexual risk groups		Model Calibration
Highest	1·5-2·5%	
2nd	10-20%	
3rd	20-30%	
Lowest	47·5-68·5%	
Number of partners per year in each sexual risk		Model Calibration
Highest	9-14	
2nd	1·7-3	
3rd	0·12-0·22	
Lowest	0·04-0·06	
Mortality rates per year		[197]
Population	0·02	
Chronic HIV stage	0·098	
AIDS stage	0·63	
On treatment during chronic stage, first year	0·02-0·098	
On treatment during chronic stage, 12+ months	0·02-0·05	
On treatment during AIDS stage, first year	0·03-0·3	
On treatment during AIDS stage, 12+ months	0·03-0·06	
HIV Test Rate		
Baseline	10-30%	Model Calibration
Rate of being tested in the acute stage of HIV	Half of the test rate	Assumption****
Rate of being tested in the chronic stage of HIV	test rate	Model Calibration
Rate of being tested in the AIDS stage	test rate + 10%	
Linkage to care from test to treat	75-100%	Model Calibration
Reduction in transmissibility of those patients on	90-100%	[7, 43, 46]

Percentage of people that go to second line after continued virological failure during first two years on treatment Kampala, Uganda, on zidovudine-based regimen on tenofovir-based regimen	33-50% 33-66%	PASER-Monitoring, Kampala
Percentage of those who go onto second-line not due to resistance in the first 12 months	1·5-3%	[198]
*For a complete table of parameters, please see Table S3. **All ranges are uniformly distributed ***Two AIDS stages were included because during the final months before death, patients have limited sexual activity **** Due to window phase of antibody-based test		

Sensitivity analysis

Sensitivity analyses using recursive partitioning[199, 200] were conducted to determine the most influential parameters on both TDR prevalence and number of acute infections in Kampala and Mombasa, respectively (Figure S4).

Data and additional parameters

The PASER-Monitoring data from ARV-naïve patients about to start HIV treatment were used as parameters in the model regarding regimens being prescribed and resistance patterns. In 2008-9, approximately 40% of individuals from PASER-Monitoring in Kampala were receiving tenofovir-containing regimens, and 60% zidovudine-containing regimens, both combined with emtricitabine or lamivudine and efavirenz or nevirapine. In Mombasa, just 1% of individuals were on tenofovir-containing regimens, and all others were on zidovudine or stavudine-containing regimens (Table 1). We assumed that stavudine would be phased out and replaced by zidovudine in Mombasa. We also evaluated the impact of instead replacing stavudine by tenofovir in a sensitivity analysis. Specific drug resistance mutations were assumed to be selected for by tenofovir (i.e. K65R) and zidovudine (i.e. thymidine analogue mutations [TAMs]), for lamivudine and emtricitabine (i.e. M184V), and as well as efavirenz and nevirapine (i.e. NNRTI-specific mutations). Individuals were classified as receiving either a zidovudine-containing or tenofovir-containing regimens, and within these regimens, there were different probabilities of acquiring the signature mutations of zidovudine/tenofovir as well as the M184V or NNRTI-specific mutations. The model also included second-line treatment which consisted of a ritonavir-boosted protease inhibitor (PI) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). Each different regimen (zidovudine-, tenofovir-, or PI-based) was assumed to have a different likelihood of transmitting acquired drug resistant mutations onwards to a susceptible individual.[201] In our model, patients with an acquired drug resistant virus could either pass on a NRTI mutation (divided further into a TAM, M184V, or K65R), NNRTI mutation, or PI mutation. Drug resistance mutations have a

reduced fitness as compared to a wild-type virus that is susceptible to antiretroviral drugs for those with an acquired resistance mutation.[164] The fitness cost can result in a lower viral load. Because viral load is the key parameter explaining transmission,[167] drug resistant viruses are less easily transmitted. A specific fitness cost for K65R, PI and TAMs was estimated by reductions in replication capacity in the literature.[201, 202] The fitness cost for the M184V and NNRTI mutations was estimated directly from PASER data as there were a sufficient number of patients who acquired these mutations while on treatment. We calculated the fitness cost using a published formula by taking the difference between baseline viral load and viral load after treatment failure with the respective resistance mutation.[203] We then took the intra-quartile range of the fitness costs from the transformed PASER data as the parameter values (Table S2). The estimates from the PASER data were in line with the literature.[204, 205] Reversion to wild-type after infection with a drug resistant virus was also considered (Table S3).

As a baseline scenario, we calculated the TDR prevalence for ART initiation at <200 CD4 cells/μL (including 20% of patients with CD4 200-350 cells/μL to represent the current treatment situation). We then predicted the effect on TDR prevalence of ART initiation at CD4 <350 and <500 cells/μL. The total number of people accessing treatment depends on the HIV testing and retention rate, both of which were calibrated in the model. We also investigated the impact of increasing access to second-line therapy. In the model, we assume that second-line is only limitedly available. In accordance with PASER data, the proportions of people who switch to second-line therapy after continued virological failure in Kampala and Mombasa is 33-66% and 15-30% respectively during the first two years on therapy, as is assumed to not be available thereafter. We expected an increased availability of second line regimens and viral load testing in the future. Accordingly, we increased the proportions of people who switch to second-line therapy after continued virological failure in Kampala and Mombasa up to 80-100% for the entire duration of antiretroviral treatment. We then determined the overall and mutation-specific TDR prevalence over 10 years for all immunological ART initiation cut-offs. Full model description including equations can be found in the Text S1 of the supplement.

In order to investigate whether the prevention of new infections by earlier initiation of ART offsets rising TDR, we calculated the total number of new HIV infections averted for each additional case infected with drug resistant HIV.

RESULTS

Impact of ART on the HIV epidemic

Figure 1A shows the effect of earlier first-line ART initiation on estimated HIV prevalence in Kampala and Mombasa. Although the HIV prevalence remains relatively stable when treatment is initiated at <200 or <350 CD4 cells/μL due to reduced mortality of infected individuals, a decline in HIV prevalence is expected when treatment is initiated at <500 CD4 cells/μL. HIV incidence is expected to drop in both cities when treatment is initiated at <350 and <500 CD4 cells/μL (Figure 1B). The decrease in HIV incidence is also reflected in the proportion of infections that can be averted at particular immunological thresholds of ART initiation. Compared to initiating ART at CD4 <200 cells/μL, initiating ART at CD4 <350 cells/μL averts a median of 12·6% (Interquartile range (IQR) 11·3%-13·7%) of infections over 10 years in Kampala and averts a median of 11·6% (IQR 10·3%-13·0%) of infections in Mombasa. Initiating ART at CD4 <500 cells/μL averts a median of 28·8% (IQR 26·0%-31·4%) and a median of 26·3% (IQR 23·2%-29·5%) in Kampala and Mombasa, respectively.

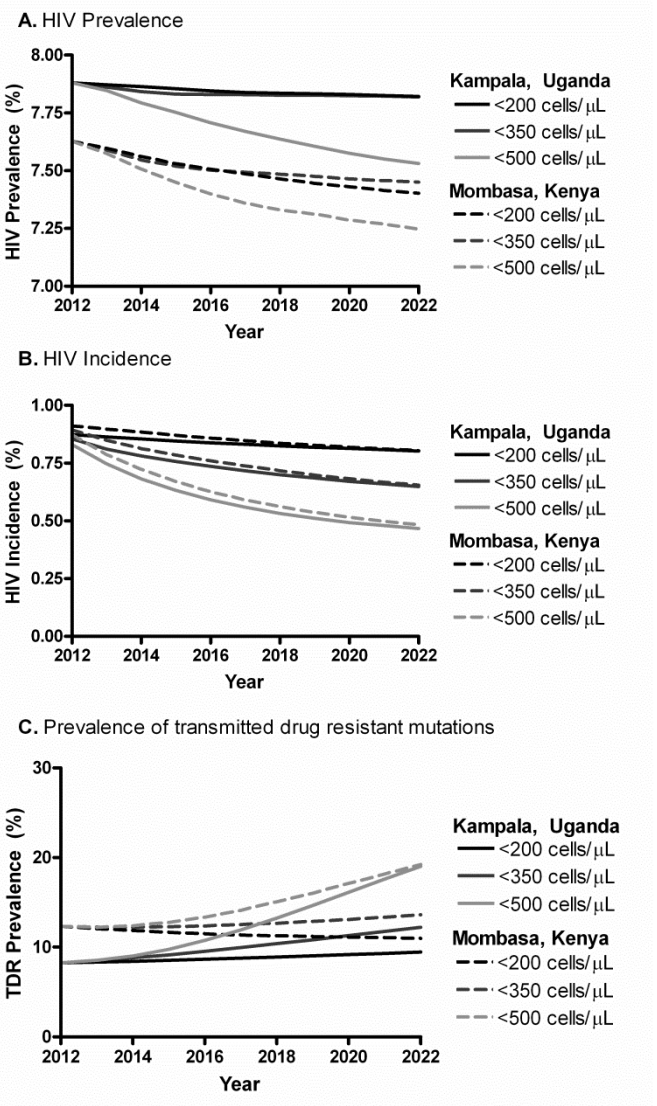


Figure 1. *Yearly median of HIV Prevalence, incidence, and overall transmitted drug resistance prevalence from 2012-2022 when initiating treatment at CD4<200 cells/μL, <350 cells/μL, and <500 cells/μL in Kampala, Uganda, and Mombasa, Kenya*

Prevention of new infections and increase of TDR

When treatment is initiated at CD4 <350 cells/μL, a median of 18 (IQR 11-31) infections in Kampala and 46 (IQR 30-83) infections in Mombasa will be averted for every additional case infected with drug-resistant virus. Similarly, when treatment is initiated at CD4 <500 cells/μL, the estimated number of infections averted per additional case of TDR is a median of 22 (IQR 17-35) in Kampala and 32 (IQR 21-57) in Mombasa. The larger number of infections averted

in Mombasa as compared to Kampala is in line with the smaller TDR increase predicted in Mombasa.

Evolution of overall TDR prevalence

Figure 1C shows that expanding access to ART by initiating treatment at higher CD4-counts is expected to increase TDR prevalence in both Kampala and Mombasa. Between 2012 and 2022, the estimated TDR prevalence in Kampala increases from a median of 8·3% (IQR 7·7%-9·0%) to a median of 9·4% (IQR 8·4%-10·5%), 12·2% (IQR 10·9%-13·8%) and to 19·0 % (IQR 16·5%-21·8%) when initiating ART at CD4<200, <350 or <500 cells/μL, respectively. During the same period, the estimated TDR prevalence in Mombasa remains a median of 12·3% (IQR 11·7%-13·1%) when starting ART at CD4 <200 cells/μL, but increases to a median of 13·6% (IQR 12·5%-14·9%) when starting at CD4 <350 cells/μL and to a median of 19·2% (IQR 17·1%-21·5%) when starting at CD4 <500 cells/μL.

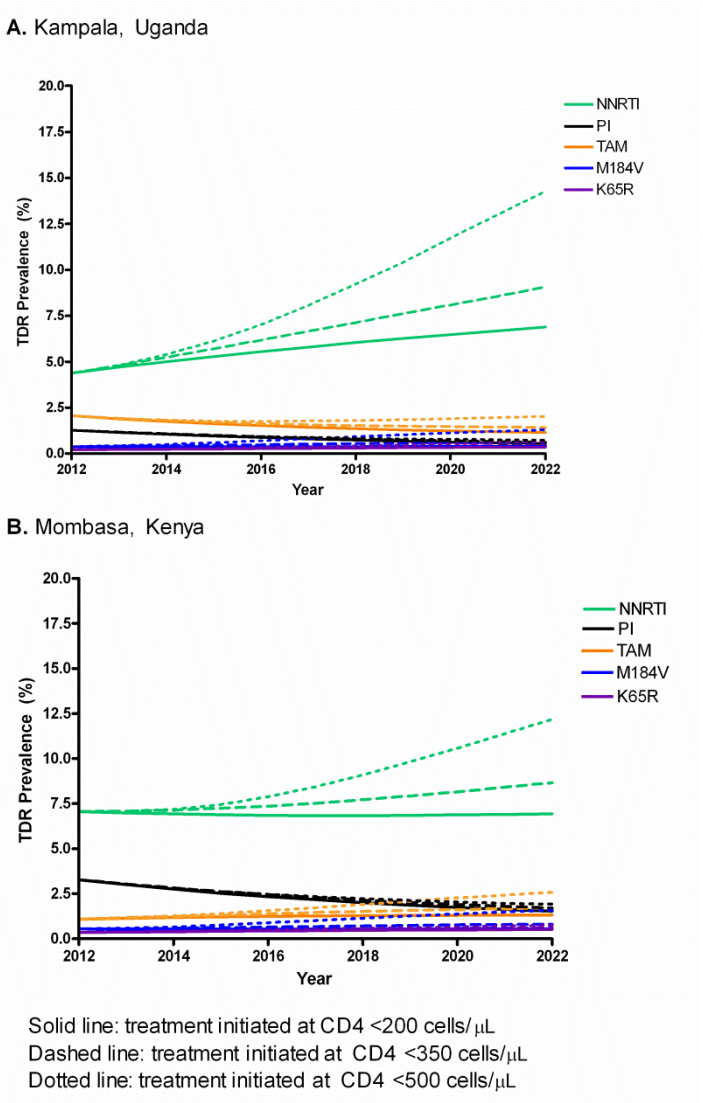


Figure 2. *Yearly median of transmitted drug resistant mutation prevalence by mutation, from 2012-2022 when starting treatment at CD4<200 cells/μL, <350 cells/μL, and <500 cells/μL in Kampala, Uganda, and Mombasa, Kenya*

Drug resistance by drug class and mutation

In both settings, current TDR is predominantly characterized by resistance to NNRTIs. According to our modeling results, NNRTI mutations are predicted to continue to comprise the majority of the future prevalence of TDR (Figure 2A and B). In Kampala, the prevalence of transmitted NNRTI resistance is estimated to rise over the next ten years from a median of 4·4% (IQR 3·8%-4·9%) to a median of 6·9% (IQR 6·0%-7·9%) when initiating at CD4 <200 cells/μL. An increase to a median of 9·1% (IQR 7·8%-10·5%) when initiating treatment at CD4 <350 cells/μL is predicted, and to 14·3% (IQR 11·9%-16·6%) when initiating at CD4 <500

cells/μL. In Mombasa, NNRTI resistance is estimated to remain stable (median 7·1%; IQR 6·3%-7·7% in 2012 to median 6·9%; IQR 6·0%-7·9% in 2022) when initiating ART at CD4 <200 cells/μL, but to increase to a median of 8·7% (IQR 7·6%-9·7%) when initiating at a CD4 count of <350 and to 12·2% (IQR 10·9%-13·7%) when starting at <500.

With respect to the NRTI class, in Kampala, estimated prevalence of TAMs decrease between 2012 and 2022, regardless of the immunological threshold used. In contrast, the TAM prevalence in Mombasa is estimated to slightly increase over the same period. A sensitivity analysis in which stavudine was replaced by tenofovir instead of zidovudine yielded similar results (Figure S4). Transmitted M184V increases in both Kampala and Mombasa when treatment is initiated at CD4 <500 cells/μL, although the prevalence was predicted to remain <2% in both areas. In both cities, PI resistance decreases over time, irrespective of immunological threshold used to initiate therapy. Transmitted K65R will increase slightly at all immunological thresholds but will remain <1% between 2012 and 2022 in both settings.

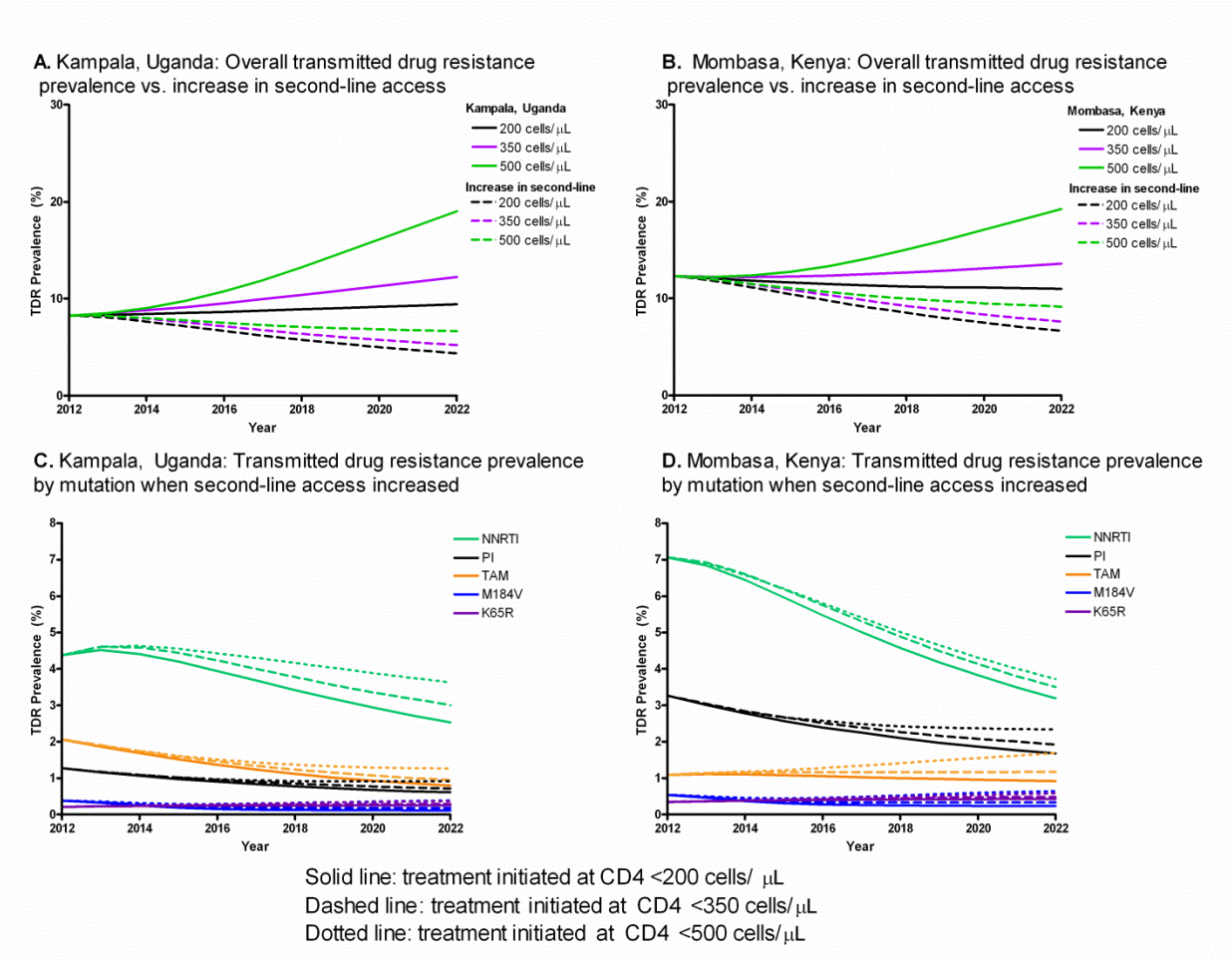
Increasing access to second-line

If access to virological monitoring and second-line treatment increases in parallel to the further scale-up of first-line ART, TDR is not expected to increase at any of the immunological thresholds used for ART initiation. In the scenario where 80-100% of individuals with prolonged virological failure are appropriately switched to second-line boosted PI therapy, the level of TDR is expected to decline in both locations at all immunological thresholds to below the 2012 TDR level. Increasing access to boosted PIs will either reduce or stabilize TDR for all drug classes (Figure 3A-D).

Sensitivity analysis

In the models for both Kampala and Mombasa, higher test rates (greater than 22.5% and 21.4% respectively) was the strongest predictor for a reduction in new infections. This is likely due to the fact that more individuals will get into care sooner, and thus spend a greater amount of time with a suppressed virus. In both Kampala and Mombasa, transmitted drug resistance depends most strongly on the rate of reversion of a drug resistant mutation in a treatment-naïve individual to a wild type virus. This is because if revertancy is slower, a patient is more likely to infect another person with a resistant virus instead of a wild type virus. (See Figure S3)

Figure 3. *Yearly median of transmitted drug resistant mutation prevalence by mutation when increasing access to second-line treatment for those with continued virological failure to 80-100% from 2012-2022 when starting treatment at CD4<200 cells/μL, <350 cells/μL, and <500 cells/μL in Kampala, Uganda, and Mombasa, Kenya*



DISCUSSION

We have modeled the impact of ART initiation at different immunological thresholds on the prevalence of TDR in two East African settings over the next ten years. This is the first model to show that averted HIV infections due to the expansion of antiretroviral treatment eligibility offset the risk of increased TDR. We predict that the number of infections that will be averted by earlier ART initiation will far exceed the number of infections with a drug resistant virus. When the current WHO treatment guidelines of ART initiation at CD4<350 cells/μL are fully implemented in these two settings, TDR prevalence is expected to increase slightly. Expanding treatment by initiating ART at CD4 <500 cells/μL will lead to an increasing TDR prevalence. TDR mutations associated with the NNRTI drug class, the cornerstone of current first-line regimens,[206] are expected to drive the TDR rise. Importantly, if switches from first- to second-line occur for all patients necessitating a switch, then the overall TDR prevalence, including NNRTI resistance, will decrease in the next ten years. This implies that

wider access to virological monitoring and boosted PIs for second-line therapy will preserve the effectiveness of NNRTI-based first-line treatment in all scenarios.

Current and predicted TDR is predominantly due to NNRTI resistance. This finding corroborates a recent meta-analysis of TDR which estimated an increase of predominantly NNRTI-related resistance of 29% per year in East Africa.[184] This can be explained by the low genetic barrier of NNRTIs for HIV drug resistance as only a single amino acid substitution is sufficient for high level resistance.[15] In addition, transmitted NNRTI-associated mutations persist for a prolonged period of time.[207] Transmission of NNRTI resistance can have important clinical ramifications as their presence is associated with an increased risk of virological failure of standard first-line treatment and for further selection of drug resistance after treatment initiation.[183] Our modeling study suggests that this can be prevented by increasing access to boosted PIs in second-line ART. Timely switches to second-line regimens are only possible when routine virological monitoring, i.e. at 6- or 12-monthly intervals, is implemented. In agreement, a recent model of HIV transmission predicted that routine virological monitoring in patients on ART can reduce TDR.[21] For this purpose, cheap point-of-care viral load assays should be developed.[21, 184]

This analysis models the changes in treatment initiation guidelines, and thus even when the treatment initiation threshold changes, many individuals still initiate therapy late in infection. When treatment is initiated at CD4 <500 cells/µL not all individuals initiate treatment early due to test rates and retention of the respective settings. In the model, once treatment at CD4 <500 cells/µL is fully scaled up in 2013, 43% of individuals initiate treatment between CD4 350-500, 38% initiate between CD4 200-350, and 19% initiate when CD4 is <200. In 2022, 49% of individuals initiate between 350-500, 34% initiate between 200-350, and 17% initiate at CD4 <200.

Our mathematical model has several strengths. To our knowledge, our model is the first to examine the impact of initiating ART at different immunological thresholds, including at CD4 <500 cells/µL, on the prevalence of TDR in sub-Saharan Africa. This is particularly relevant in light of increased interest for early initiation of ART as a means to prevent new infections. We have demonstrated that the number of new infections prevented by earlier ART initiation far outweighs the expected number of infections with drug-resistant virus. Second, our analysis predicts future levels of HIV drug resistance in sub-Saharan Africa in terms of the presence of specific mutations to particular drugs, accounting for variation in transmissibility between individual mutations. A small number of mathematical HIV transmission models have examined the impact of antiretroviral drugs on transmitted drug resistance in sub-Saharan Africa.[21, 187-189] Almost all previous models used overall TDR rates to describe HIV drug resistance.[187-189] One model used a classification of HIV drug resistance similar to ours, but only reported overall TDR.[21] Lastly, this model combines data on transmitted and acquired HIV drug resistance from the same geographic areas and time period, collected within the same research project. This is important as resistance acquired

during treatment constitutes the pool of variants that can be transmitted within a population. The TDR predictions were largely similar for the two distinct geographic settings even though these two settings have a different history of antiretroviral roll-out. In Uganda, antiretroviral drugs became available at least five years ahead of neighboring countries, including limited-scale distribution of mono and dual NRTI-based therapies.[208] This may account for the higher initial rate of TAMs observed in Kampala, but our analysis shows that it is unlikely to impact future rates of TDR.

This study has some potential limitations. First, the data on acquired resistance do not exceed 24 months of follow-up. Data on HIV drug resistance beyond 24 months of ART in resource-limited settings is scarce. Nonetheless, the PASER-Monitoring study provides the most accurate empirical data on acquired resistance patterns currently available in Africa. Second, we did not incorporate the type of ART monitoring to guide switching, i.e. clinical, immunological or virological, as a variable in our model. Instead, based on PASER-Monitoring data we noted that in Kampala 33-66% and in Mombasa 15-30% of patients with virological failure were appropriately switched to second-line during the first two years on HIV treatment. Third, baseline HIV test rates were assumed to be 10-30% of the populations. Increasing HIV testing uptake is likely to lead to greater numbers of people initiating ART at higher CD4 counts, although this poses logistical challenges for implementation. Fourth, we assumed that drug regimen use would remain constant for the next ten years, as it is difficult to make predictions about future drug substitutions. We did, however, account for the fact that stavudine is likely to be phased out. We assumed that stavudine would be replaced by zidovudine in Mombasa, or instead by tenofovir in a sensitivity analysis, with comparable results. Finally, costs are not included in this analysis as we do not have comprehensive costing data for these study sites. Second-line treatment is expensive and using second-line to limit drug resistance can increase costs. Conversely, second-line treatment can also result in reduced HIV transmission (as less resistance emerges) which can be cost saving due to the substantial lifetime costs associated with a new infection.

Infections averted is a commonly used metric in modeling studies to quantify the impact of an intervention on a population. The ratio of infections averted to TDR gained has been recently described,[209] and can quantify infections averted versus gains in TDR. These metrics cannot be validated in large prospective cohort studies, as it is not known how many infections would have occurred in absence of an intervention. The ratio of infections averted to transmitted drug resistance gained does not, however, take into account all potential benefits or detriments of increased treatment. One potential detriment could be higher mortality of those individuals with resistance to first-line or to second-line treatment. Data from resource rich settings show that there is limited impact of drug resistance on mortality.[210, 211] Although no data is available, resistance could increase mortality in resource limited settings as treatment options are limited.

With regard to our modeling strategy, we assumed that individuals could only be infected with a wild type virus or a virus containing a single class of resistance mutation, as the PASER-Surveillance data from Kampala and Mombasa showed this. While most transmitted drug resistance is transmission of a virus containing a single resistance mutation, it has been described that in approximately 20% of the time, a virus containing >1 resistance mutation is transmitted. But, importantly, this usually involves mutations from the same class. Transmission of resistance involving more than one class is rare in sub-Saharan Africa.[212] Our assumption that only a single mutation can be transmitted therefore is in agreement with epidemiological studies on transmission of drug resistant HIV.[212 213] In our model, we also assumed a closed population for both cities. We have calibrated the model to the closed population, thus our predictions on the closed populations should be accurate. For this analysis, we do not calculate the number of deaths averted or person-years lived, thus our results should not be influenced by this assumption.

In conclusion, expansion of antiretroviral treatment eligibility will lead to increased TDR, but this is not expected to offset the preventative benefit of controlling the HIV epidemic. Transmitted NNRTI resistance can potentially have a profound impact on the effectiveness of first-line treatment. Importantly, we have demonstrated that further increase of NNRTI resistance can be avoided by increasing access to second-line boosted PI regimens. Therefore, as ART is scaled-up, efforts should be made to make virological monitoring and effective second-line therapy available. Transmitted drug resistance should not be a reason to withhold early initiation of ART as averted HIV infections due to expanded treatment eligibility are predicted to offset the risk of increased transmitted resistance.

ACKNOWLEDGEMENTS

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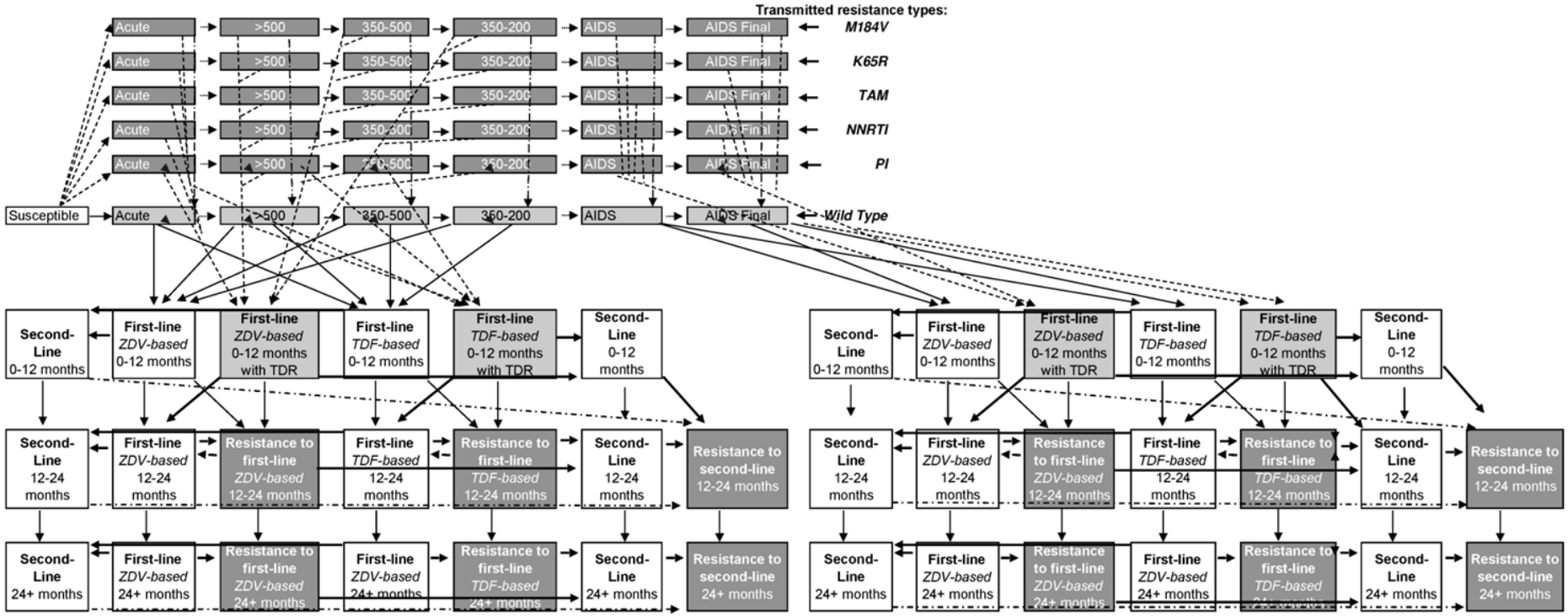
Supplement: Chapter 3

Figure S1. *Structure of the compartmental deterministic model, full description on next page:*



Structure of the model, continued. The figure is a schematic representation of the dynamic process by which individuals become infected with HIV or resistant HIV due to contact with someone with a transmitted or acquired resistant virus, are given treatment. The force of infection is the rate by which susceptible individuals become infected. Without treatment, infected patients progress through six stages: the recent stage, the chronic stage (divided into CD4 counts of >500, 350-500, and 200-350 cells/μL), an AIDS stage in which patients have a limited level of sexual activity and the final AIDS stage in which patients have no sexual activity.

Individuals in the dark grey boxes are carrying a particular drug resistant virus and can pass on that virus to a susceptible individual. Individuals are in light grey boxes when they can contribute a wild-type virus to a susceptible individual (and the light grey boxes on treatment have a reduced infectiousness, but not quite as reduced as with individuals without resistant virus upon treatment initiation). Individuals on treatment (white boxes on bottom) move through three different periods defined by the time since start of antiretroviral drug therapy and the disease stage in which treatment was started. These periods and disease stages were included as mortality depends on time since start of treatment and the CD4 count at start of treatment.

All boxes have different mortalities. All boxes (except the ones with susceptible individuals) contribute to the force of infection, but all with different infectivity. The mathematical equations are listed on page 3 of the web appendix.

Table S1. *Model equation labels and parameter values*

Model Equation Labels			
Variable Label	***Description***		
k	*HIV infection stages*		
k=1	Acute Stage		
k=2	Chronic stage >500 cells/μL		
k=3	Chronic stage 350-500 cells/μL		
k=4	Chronic stage 200-350 cells/μL		
k=5	AIDS stage		
k=6	Final AIDS stage		
	Virus type		
WT	Wild type		
R	*Resistant virus type*		
R=1	M184V-containing virus		
R=2	K65R-containing virus		
R=3	TAM-containing virus		
R=4	NNRTI-containing virus		

R=5	PI-containing virus		
Variable Label	***Description***		
l	*Treatment Initiation*		
l=1	Treatment initiated when CD4 >200 cells/µL		
l=2	Treatment initiated when CD4 <200 cells/µL		
m	*Treatment stages*		
m=1	0-12 months on treatment		
m=2	12-24 months on treatment		
m=3	24+ months on treatment		
Tx	*Type of therapy*		
Tx=1	Zidovudine-based therapy		
Tx=2	Tenofovir-based therapy		
2nd	Second-line protease inhibitor-based therapy		
b	*Resistance to first-line therapy*		
b=1	Not resistant to first-line		
b=2	Resistant to first-line		
2ndR	*Resistance to second-line therapy*		
λ	*Variables involved in the Force of Infection*		
Model parameters, descriptions and values assessed.			
Variable Label	***Description***	***Parameter Range Assessed***	***Source***
i	Sexual Activity Group		
	Proportion of people in sexual risk groups		
i=1	Highest	1.5-2.5%	Model Calibration
i=2	2nd	10-20%	
i=3	3rd	20-30%	
i=4	Lowest	47.5-68.5%	
γ_k	*HIV infection duration by stage k, k=1..6*		[8, 11]
γ_1	Acute Stage	10-16 weeks	
γ_2	Chronic stage >500 cells/µL	0.87-1 year	
γ_3	Chronic stage 350-500 cells/µL	2.9-3.1 years	
γ_4	Chronic stage 200-350 cells/µL	3.6-3.9 years	
γ_5	AIDS stage	6-12 months	
γ_6	Final AIDS stage	7-13 months	
μ	*Yearly Mortality rate*		[197]

μ	Mortality rate general population	0.02	
μ_k	Mortality rate untreated HIV infection, k=1..6		
μ_1	Mortality during acute infection	0.098	
μ_2	Mortality during chronic infection (CD4 >500 cells/µL)	0.098	
μ_3	Mortality during chronic infection (CD4 350-500 cells/µL)	0.098	
μ_4	Mortality during chronic infection (CD4 200-350 cells/µL)	0.098	
μ_5, μ_6	Mortality during AIDS stage (CD4 <200 cells/µL)	0.63	
$\mu_{l,m}$	Mortality rate treatment patients in infection stage *l* and treatment stage *m (l=1..2, m=1..3)*		[197]
$\mu_{1,1}$	Mortality rate 0-12 months on treatment, initiated when CD4 >200 cells/µL	0.02-0.098	
$\mu_{1,2}$	Mortality rate 12-24 months on treatment, initiated when CD4 >200 cells/µL	0.02-0.05	
$\mu_{1,3}$	Mortality rate 24+ months on treatment, initiated when CD4 >200 cells/µL	0.02-0.05	
$\mu_{2,1}$	Mortality rate 0-12 months on treatment, initiated when CD4 <200 cells/µL	0.03-0.3	
$\mu_{2,2}$	Mortality rate 12-24 months on treatment, initiated when CD4 <200 cells/µL	0.03-0.06	
$\mu_{2,3}$	Mortality rate 24+ months on treatment, initiated when CD4 <200 cells/µL	0.03-0.06	
η_k	Proportion of patients who successfully initiate therapy (product of test rate, retention, and ART initiation threshold, *k*=1..6*)*	Model Calibration	
η_1	Acute stage: Initiate at CD4 <200 cells/µL	0	
	Acute stage: Initiate at CD4 <350 cells/µL	0	
	Acute stage: Initiate at CD4 <500 cells/µL	0	
η_2	Chronic infection (CD4 >500 cells/µL): Initiate at CD4 <200 cells/µL	0	
	Chronic infection (CD4 >500 cells/µL): Initiate at CD4 <350 cells/µL	0	
	Chronic infection (CD4 >500 cells/µL): Initiate at CD4 <500 cells/µL	0	
η_3	Chronic infection (CD4 350-500 cells/µL): Initiate at CD4 <200 cells/µL	0	
	Chronic infection (CD4 350-500 cells/µL): Initiate at CD4 <350 cells/µL	0	
	Chronic infection (CD4 350-500 cells/µL):	0.075-0.3	

	Initiate at CD4 <500 cells/μL		
η_4	Chronic infection (CD4 200-350 cells/μL): Initiate at CD4 <200 cells/μL	0	
	Chronic infection (CD4 200-350 cells/μL): Initiate at CD4 <350 cells/μL	0.075-0.3	
	Chronic infection (CD4 200-350 cells/μL): Initiate at CD4 <500 cells/μL	0.075-0.3	
η_5, η_6	AIDS Stage (CD4 <200 cells/μL): Initiate at CD4 <200 cells/μL	0.075-0.3	
	AIDS Stage (CD4 <200 cells/μL): Initiate at CD4 <350 cells/μL	0.075-0.3	
	AIDS Stage (CD4 <200 cells/μL): Initiate at CD4 <500 cells/μL	0.075-0.3	
ρ_k^R	Proportion of individuals who have reverted from a resistant virus, *R*, to a wild-type virus by stage *k*, *R*=1..5, *k*=1..6		[207]
ρ_1^1	Reversion from M184V-containing virus to wild type during acute stage	38-98%	
ρ_2^1	Reversion from M184V-containing virus to wild type during chronic stage (CD4 >500 cells/μL)	94-100%	
ρ_3^1	Reversion from M184V-containing virus to wild type during chronic stage (CD4 350-500 cells/μL)	100%	
ρ_4^1	Reversion from M184V-containing virus to wild type during chronic stage (CD4 200-350 cells/μL)	100%	
ρ_5^1	Reversion from M184V-containing virus to wild type during AIDS stage	100%	
ρ_6^1	Reversion from M184V-containing virus to wild type during final AIDS stage	100%	
ρ_1^2	Reversion from K65R-containing virus to wild type during acute stage	0-2%	
ρ_2^2	Reversion from K65R-containing virus to wild type during chronic stage (CD4 >500 cells/μL)	0-4%	
ρ_3^2	Reversion from K65R-containing virus to wild type during chronic stage (CD4 350-500 cells/μL)	0-10%	
ρ_4^2	Reversion from K65R-containing virus to wild type during chronic stage (CD4 200-350 cells/μL)	1-16%	
ρ_5^2	Reversion from K65R-containing virus to wild type during AIDS stage	0%	
ρ_6^2	Reversion from K65R-containing virus to wild	0%	

	type during final AIDS stage		
ρ_1^3	Reversion from TAM-containing virus to wild type during acute stage	1-7%	
ρ_2^3	Reversion from TAM-containing virus to wild type during chronic stage (CD4 >500 cells/μL)	4-14%	
ρ_3^3	Reversion from TAM-containing virus to wild type during chronic stage (CD4 350-500 cells/μL)	9-29%	
ρ_4^3	Reversion from TAM-containing virus to wild type during chronic stage (CD4 200-350 cells/μL)	12-42%	
ρ_5^3	Reversion from TAM-containing virus to wild type during AIDS stage	0%	
ρ_6^3	Reversion from TAM-containing virus to wild type during final AIDS stage	0%	
ρ_1^4	Reversion from NNRTI-containing virus to wild type during acute stage	0-2%	
ρ_2^4	Reversion from NNRTI-containing virus to wild type during chronic stage (CD4 >500 cells/μL)	1-7%	
ρ_3^4	Reversion from NNRTI-containing virus to wild type during chronic stage (CD4 350-500 cells/μL)	3-17%	
ρ_4^4	Reversion from NNRTI-containing virus to wild type during chronic stage (CD4 200-350 cells/μL)	6-25%	
ρ_5^4	Reversion from NNRTI-containing virus to wild type during AIDS stage	0%	
ρ_6^4	Reversion from NNRTI-containing virus to wild type during final AIDS stage	0%	
ρ_1^5	Reversion from PI-containing virus to wild type during acute stage	1-4%	
ρ_2^5	Reversion from PI-containing virus to wild type during chronic stage (CD4 >500 cells/μL)	2-8%	
ρ_3^5	Reversion from PI-containing virus to wild type during chronic stage (CD4 350-500 cells/μL)	4-24%	
ρ_4^5	Reversion from PI-containing virus to wild type during chronic stage (CD4 200-350 cells/μL)	8-36%	
ρ_5^5	Reversion from PI-containing virus to wild type during AIDS stage	0%	
ρ_6^5	Reversion from PI-containing virus to wild type during final AIDS stage	0%	
ψ_{Tx}	Proportion of individuals assigned to a		

	particular first-line regimen *Tx, Tx*=1..2		
ψ_1	Proportion of individuals starting a zidovudine-based regimen, Kampala	60%	
	Proportion of individuals starting a zidovudine-based regimen, Mombasa	99%	
ψ_2	Proportion of individuals starting a tenofovir-based regimen, Kampala	40%	
	Proportion of individuals starting a tenofovir-based regimen, Mombasa	1%	
$\Phi_{m,b}$	Proportion of individuals on first-line treatment who go to second-line treatment, *m*=1..3, *b*=1..2		
	Kampala		
$\Phi_{1,1}$	Individuals on zidovudine-based therapy for 0-12 months who go to second-line (due to toxicity)	1.5-3%	[198]
$\Phi_{2,1}$	Individuals on zidovudine-based therapy for 12-24 months who go to second-line	33-50%	PASER-M Data
$\Phi_{3,1}$	Individuals on zidovudine-based therapy for 24+ months who go to second-line	0%	PASER-M Data
$\Phi_{1,2}$	Individuals on tenofovir-based therapy for 0-12 months who go to second-line (due to toxicity)	1.5-3%	[198]
$\Phi_{2,2}$	Individuals on tenofovir-based therapy for 12-24 months who go to second-line	33-66%	PASER-M Data
$\Phi_{3,2}$	Individuals on tenofovir-based therapy for 24+ months who go to second-line	0%	PASER-M Data
	Mombasa		
$\Phi_{1,1}$	Individuals on zidovudine-based therapy for 0-12 months who go to second-line (due to toxicity)	1.5-3%	[198]
$\Phi_{2,1}$	Individuals on zidovudine-based therapy for 12-24 months who go to second-line	17.4-34.2%	PASER-M Data
$\Phi_{3,1}$	Individuals on zidovudine-based therapy for 24+ months who go to second-line	0%	PASER-M Data
$\Phi_{1,2}$	Individuals on tenofovir-based therapy for 0-12 months who go to second-line (due to toxicity)	1.5-3%	[198]
$\Phi_{2,2}$	Individuals on tenofovir-based therapy for 12-24 months who go to second-line	20-30%	PASER-M Data
$\Phi_{3,2}$	Individuals on tenofovir-based therapy for 24+ months who go to second-line	0%	PASER-M Data
$\xi_{m,b}^{Tx}$	The rate of acquired resistance after *m* time, on first-line treatment *Tx*, *m*=1..3, *b*=1..2,		[214, 215], PASER-M

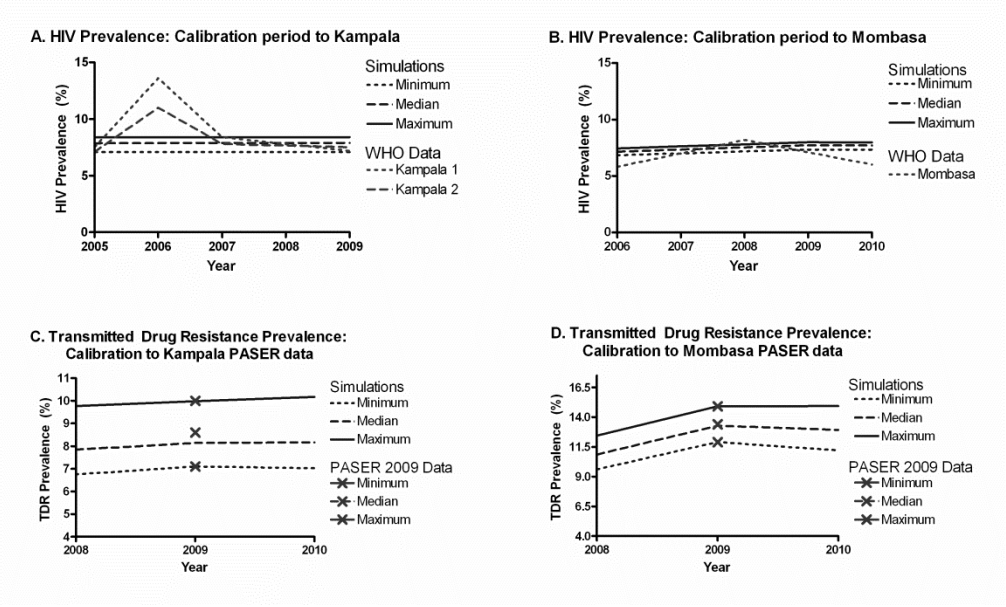
	Tx=1..2		Data
	Kampala		
$\xi_{1,b}^{1}$	Acquired resistance after 0-12 months on zidovudine-based therapy	10%	
$\xi_{2,b}^{1}$	Acquired resistance after 12-24 months on zidovudine-based therapy	8.3%	
$\xi_{3,b}^{1}$	Acquired resistance after 24+ months on zidovudine-based therapy	0-1%	
$\xi_{1,b}^{2}$	Acquired resistance after 0-12 months on tenofovir-based therapy	6.0%	
$\xi_{2,b}^{2}$	Acquired resistance after 12-24 months on tenofovir-based therapy	4.7%	
$\xi_{3,b}^{2}$	Acquired resistance after 24+ months on tenofovir-based therapy	0-1%	
	Mombasa		
$\xi_{1,b}^{1}$	Acquired resistance after 0-12 months on zidovudine-based therapy	7.2%	
$\xi_{2,b}^{1}$	Acquired resistance after 12-24 months on zidovudine-based therapy	8.2%	
$\xi_{3,b}^{1}$	Acquired resistance after 24+ months on zidovudine-based therapy	0-1%	
$\xi_{1,b}^{2}$	Acquired resistance after 0-12 months on tenofovir-based therapy	6.0%	
$\xi_{2,b}^{2}$	Acquired resistance after 12-24 months on tenofovir-based therapy	7.0%	
$\xi_{3,b}^{2}$	Acquired resistance after 24+ months on tenofovir-based therapy	0-1%	
ξ_{m}^{2nd}	The rate of acquired resistance to second-line therapy after *m* time, *m*=1..3		[216]
ξ_{1}^{2nd}	Acquired resistance after 0-12 months on second-line PI-based therapy	4-6%	
ξ_{2}^{2nd}	Acquired resistance after 12-24 months on second-line PI-based therapy	3-5%	
ξ_{3}^{2nd}	Acquired resistance after 24+ months on second-line PI-based therapy	0-0.1%	
ν^{Tx}	The rate at which individuals who acquired resistance to first-line therapy become successfully re-suppressed on first-line therapy, *Tx*=1..2		PASER-M Data
	Kampala		
ν^{1}	Resuppression on first-line after acquired resistance to zidovudine-based therapy, 12-24 months on treatment	8.3-33.3%	

ν^2	Resuppression on first-line after acquired resistance to tenofovir-based therapy, 12-24 months on treatment	16-49.3%	
	Mombasa		
ν^1	Resuppression on first-line after acquired resistance to zidovudine-based therapy, 12-24 months on treatment	7.7-30.7%	
ν^2	Resuppression on first-line after acquired resistance to tenofovir-based therapy, 12-24 months on treatment	40-65%	
α	The reduction in infectiousness on people on treatment	90-100%	[7, 43, 46]
θ^{Tx}	The proportion of individuals infected with a drug resistant virus that become successfully suppressed on first-line, Tx=1..2		PASER-M Data
	Kampala		
θ^1	Proportion of individuals infected with a drug resistant virus who are successfully suppressed on zidovudine after 12 months	70-82%	
θ^2	Proportion of individuals infected with a drug resistant virus who are successfully suppressed on tenofovir after 12 months	90-94%	
	Mombasa		
θ^1	Proportion of individuals infected with a drug resistant virus who are successfully suppressed on zidovudine after 12 months	78.4-92.8%	
θ^2	Proportion of individuals infected with a drug resistant virus who are successfully suppressed on tenofovir after 12 months	82-94%	
	Parameters used in Force of Infection (λ)		
β_k	The infectiousness of an individual in a given stage of infection, not on treatment, k=1..6		[9, 55]
β_1	Infectiousness during acute stage	27-43 times chronic stage	
β_2	Infectiousness during chronic stage (CD4 >500 cells/μL)	10%/year	
β_3	Infectiousness during chronic stage (CD4 350-500 cells/μL)	10%/year	
β_4	Infectiousness during chronic stage (CD4 200-350 cells/μL)	10%/year	
β_5	Infectiousness during AIDS stage	3-5 times chronic	

		stage	
β_6	Infectiousness during final AIDS stage (no longer sexually active)	0%	
τ_R^{TX}	The proportion of patients who acquire a specific drug resistant virus, *R*, depending on the first-line treatment, Tx, R=1..5, Tx=1..2		PASER-M Data
τ_1^1	The proportion of patients who acquired an M184V mutation on a zidovudine-based therapy	33-43%	
τ_2^1	The proportion of patients who acquired a K65R mutation on a zidovudine-based therapy	0-3%	
τ_3^1	The proportion of patients who acquired a TAM on a zidovudine-based therapy	3-6%	
τ_4^1	The proportion of patients who acquired a mutation to NNRTIs on a zidovudine-based therapy	43-63%	
τ_5^1	The proportion of patients who acquired a mutation to PIs on a zidovudine-based therapy	0%	
τ_1^2	The proportion of patients who acquired an M184V mutation on a tenofovir-based therapy	17-36%	
τ_2^2	The proportion of patients who acquired a K65R mutation on a tenofovir-based therapy	0-10%	
τ_3^2	The proportion of patients who acquired a TAM on a tenofovir-based therapy	0%	
τ_4^2	The proportion of patients who acquired a mutation to NNRTIs on a tenofovir-based therapy	54-84%	
τ_5^2	The proportion of patients who acquired a mutation to PIs on a tenofovir-based therapy	0%	
τ_R^{2nd}	The proportion of patients who acquire a specific drug resistant virus, *R*, to second-line treatment, *R*=1..5		PASER-M Data
τ_1^{2nd}	The proportion of patients who acquired an M184V mutation on a second line PI-based therapy	57-71%	
τ_2^{2nd}	The proportion of patients who acquired a K65R mutation on a second line PI-based therapy	0-10%	
τ_3^{2nd}	The proportion of patients who acquired a TAM on a second line PI-based therapy	7-21%	

τ_4^{2nd}	The proportion of patients who acquired a mutation to NNRTIs on a second line PI-based therapy	0%	
τ_5^{2nd}	The proportion of patients who acquired a mutation to PIs on a second line PI-based therapy	7-21%	
ζ_R	The fitness cost of a particular mutation *R* based on viral replication capacities of viruses that were acquired to first- or second-line therapy, *R*=1..5		
ζ_1	The fitness cost of M184V-containing virus	60-70%	PASER-M Data
ζ_2	The fitness cost of K65R-containing virus	45-60%	[202]
ζ_3	The fitness cost of a TAM-containing virus	0-20%	[201]
ζ_4	The fitness cost of a virus containing a mutation to NNRTIs	30-70%	PASER-M Data
ζ_5	The fitness cost of a virus containing a mutation to PIs	0-20%	[201]
ε	Sexual mixing assortativity	0.38-0.54	Model Calibration
i	Sexual activity groups, number of new sexual partners per year	Model Calibration	
i=1	Highest	9-14	
i=2	2nd	1.7-3	
i=3	3rd	0.12-0.22	
i=4	Lowest	0.04-0.06	

Figure S2. *Model Calibration to HIV prevalence and transmitted drug resistance prevalence*

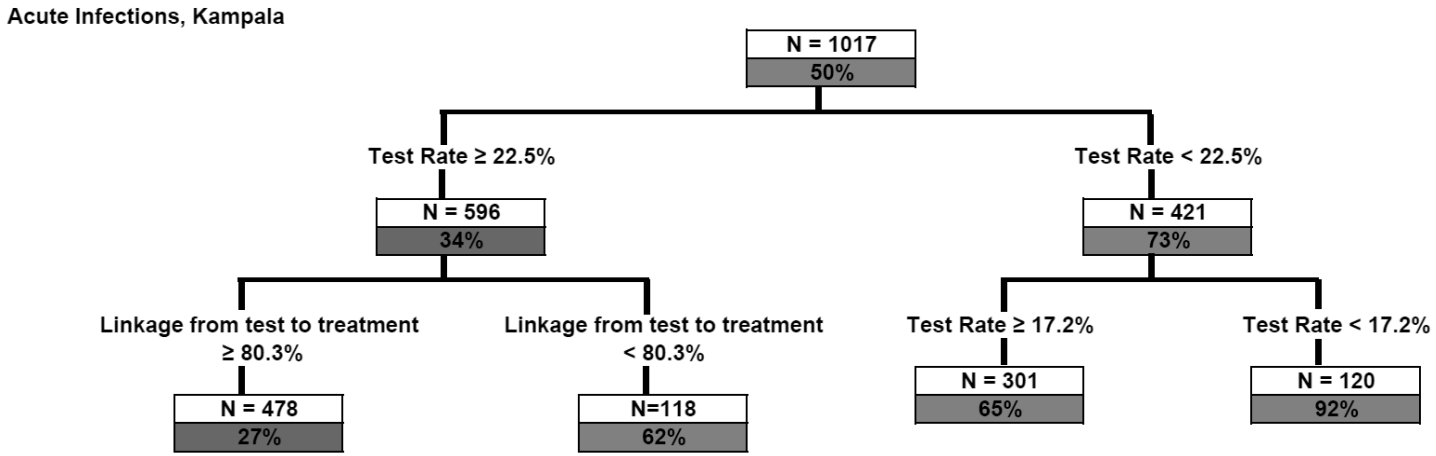


Figures S2A & S2B show the time period over which the model was calibrated. The WHO data from Uganda had two sites in Kampala in which HIV prevalence was estimated, hence two lines: Kampala 1 and Kampala 2[195]. There was one prevalence estimate for Mombasa[196]. We use the transmitted drug resistance prevalence point estimate for 2009 from the PASER data for Kampala and Mombasa respectively (Figures S2C and S2D).

Figure S3: *Sensitivity analysis: recursive partitioning* [199, 200]

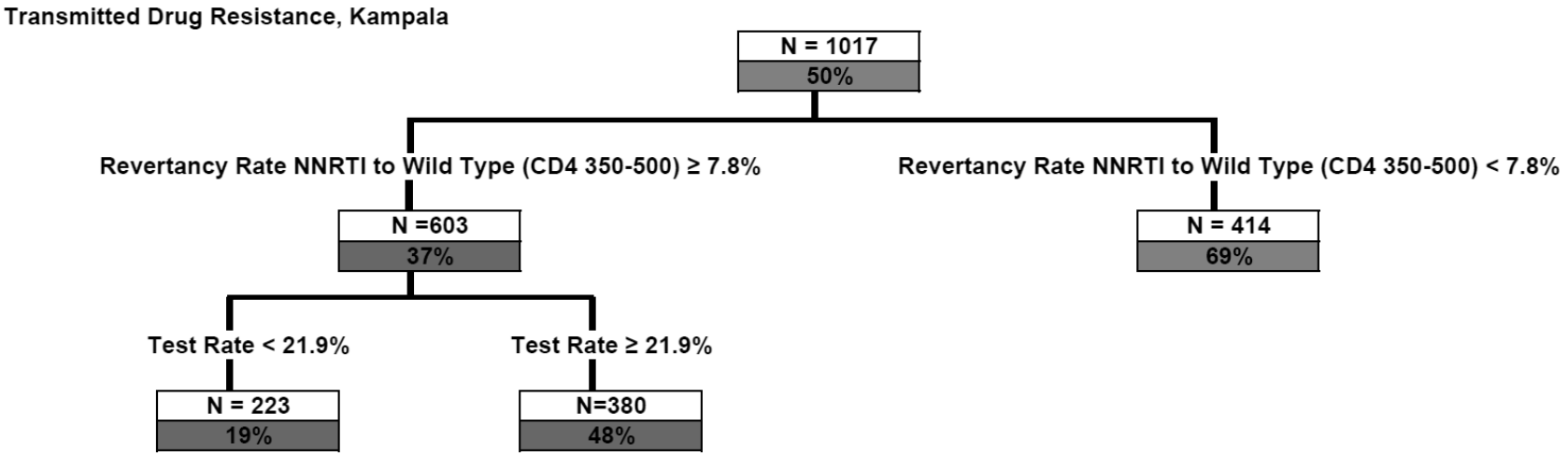
The N in the following recursive partitioning trees represents the number of simulations that fulfill all of the given criteria for a branch in the tree. The percentage represents the percent of simulations which are greater than the median number of acute infections or greater than the median transmitted drug resistance prevalence, respectively. The percentages highlighted in red represent branches of the tree which 50% or more of the simulations resulted in a higher-than-median number of acute infections or higher-than median transmitted drug resistance prevalence, respectively. The percentages highlighted in green represent branches of the tree which 50% or less of the simulations resulted in a higher-than-median number of acute infections or higher-than median transmitted drug resistance prevalence, respectively. Observations for which less than 100 simulations were found were not included.

3a. Recursive partitioning, simulations which lead to an above or below median number of acute infections (a median of 30,810 acute infections over 10 years), Kampala, Uganda



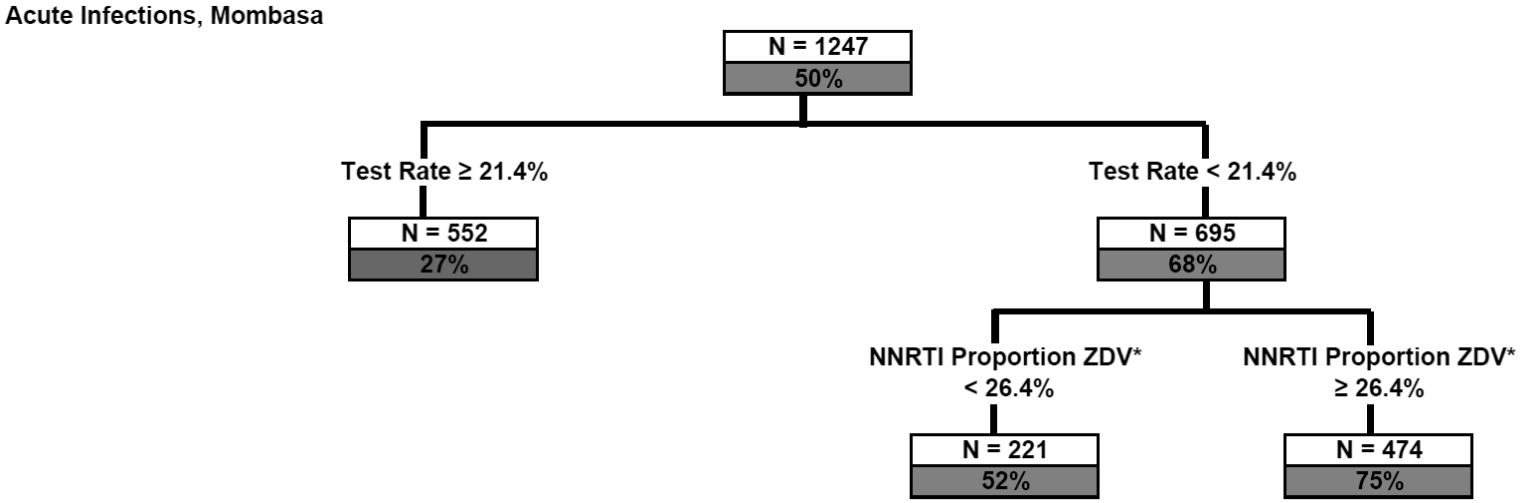
3a description. In Kampala, a yearly test rate of >22.5% is the strongest predictor for a reduction in new infections. This is likely due to the fact that more individuals will get into care sooner, and thus spend a greater amount of time with a suppressed virus.

3b. Recursive partitioning, simulations which lead to above or below median transmitted drug resistance prevalence (a median of 9.4% after 10 years), Kampala, Uganda



3b description. In Kampala, transmitted drug resistance depends most strongly on revertancy. This is because if revertancy is slower, a patient is more likely to infect another person with a resistant virus. After revertancy, the prevalence of transmitted drug resistance depends on the test rate. This is due to the fact that if the test rate is higher, more people will go onto treatment who may then develop resistance. This therefore increases the pool of patients with acquired drug resistance who can then transmit their virus.

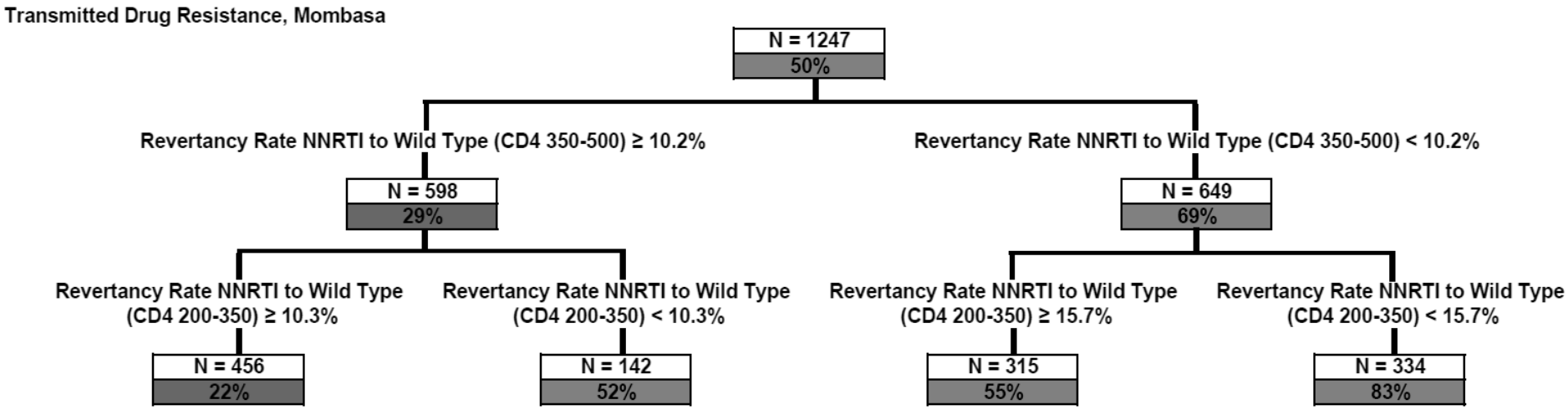
3c. Recursive partitioning, simulations which lead to an above or below median number of acute infections (a median of 15,075 acute infections over 10 years), Mombasa, Kenya



*Proportion of people failing on zidovudine- based therapy that acquire a resistance mutation to NNRTIs

3c description. In Mombasa, a yearly test rate of >21.4% is the strongest predictor for a reduction in new infections. This is likely due to the fact that more individuals will get into care sooner, and thus spend a greater amount of time with a suppressed virus.

3d. Recursive partitioning, simulations which lead to above or below median transmitted drug resistance prevalence (a median of 11.0% after 10 years), Mombasa, Kenya



3d. description. In Mombasa, transmitted drug resistance depends most strongly on revertancy. This is because if revertancy is slower, a patient is more likely to infect another person with a resistant virus. After revertancy, the prevalence of transmitted drug resistance depends on the test rate. This is due to the fact that if the test rate is higher, more people will go onto treatment who may then develop resistance. This therefore increases the pool of patients with acquired drug resistance who can then transmit their virus.

Table S2. *Acquired resistance mutations*, proportion to which they will contribute to transmitted drug resistance (TDR)*

	Proportions**				
	Tenofovir-based regimen	**Zidovudine-based regimen**	**Second-line, boosted protease inhibitor**	**Fitness Cost**	**Reference**
M184V	17-36%	33-43%	57-71%	60-70%	PASER-M***[204]
K65R	0-10%	0-3%	0-10%	45-60%	[202]
TAM	0%	3-6%	7-21%	0-20%	[201]
NNRTI	54-84%	46-63%	0%	30-70%	PASER-M***,[205]
PI	0%	0%	7-21%	0-20%	[201]

**Patients can only transmit a single resistance mutation, as most viruses that transmit only contain one resistance mutation[217]*

***Ranges from PASER data and Gallant et al. 2006[215], Pozniak et al., 2006[214], and Molina et al., 2008[216]*

***Interquartile range of reduction in infectivity to respective mutations in PASER-M cohort from Kampala & Mombasa: We used viral load measurements at treatment initiation, and a viral load measurement again upon treatment failure with respective mutation present. We then calculated the fitness cost (a proxy for reduction in infectivity) of the viruses which acquired the M184V and K65R mutations using a published formula.[203] The results were in line with current literature.[204, 205]

Table S2 description: For this analysis, we assume that a person failing treatment can go on to transmit a drug resistant virus containing a single mutation. To illustrate how this table can be interpreted, the following is how resistance to a tenofovir-based regimen is handled. Based on our PASER-M data, 17-36% of patients who fail first line tenofovir-containing therapy will go on to acquire an M184V mutation. Between 0-10% will acquire a K65R mutation, and 54-84% of patients will acquire a mutation to NNRTIs. Each of these resistant viruses also has an associated fitness cost. Therefore, a person failing a tenofovir-based regimen will go on to transmit an M184V-containing virus 5.1%-14.4% of the time (17-36% multiplied by 1 minus the extremes of the fitness cost range, 30-40%); they will go on to transmit a K65R-containing virus 0-5.5% of the time (0-10% multiplied by 1 minus the extremes of the fitness cost range, 40-55%); and they will go on to transmit a virus carrying

resistance to NNRTIs 16.2-58.8% of the time (54-84% multiplied by 1 minus the extremes of the fitness cost range, 30-70%).

Table S3. *Rate of reversion to wild-type HIV-1 after being infected with a drug-resistant HIV virus, by each stage of infection*

	Mutation				
Stage of infection	**M184V**	**K65R**	**TAM**	**NNRTI**	**PI**
Acute Stage	38-98%*	0-2%	1-7%	0-2%	1-4%
CD4 >500 cells/µL	94-100%	0-4%	4-14%	1-7%	2-8%
CD4 350-500 cells/µL	100%	0-10%	9-29%	3-17%	4-24%
CD4 200-350 cells/µL	100%	1-16%	12-42%	6-25%	8-36%
CD4 <200 cells/µL	100%	0%	0%	0%	0%

*All ranges follow a uniform distribution and are based on Jain et al. 2011[207], and model calibration

Text S1. *Model Description and equations*

The model is seeded in 1972 with one infected individual. The state variables and HIV transmission equations for the model are shown below. There are four activity classes *i* based on the partner acquisition rate change: class 1 in which individuals have 9-14 partners per year, class 2 with 1.7-3 partners, class 3 with 0.12-0.22 and class 4 with 0.04-0.06.

The model included six HIV infection stages *k*: class 1 is the acute stage, class 2 is the chronic stage where CD4 count is >500 cells/µL, class 3 is the chronic stage where CD4 count is 350-500 cells/µL, class 4 is the chronic stage where CD4 count is 200-350 cells/µL, class 5 is the pre-final AIDS stage in which individuals have limited sexual activity. Class 6 is the final AIDS stage in which patients do not have any sexual intercourse [9].

During treatment, the model includes two infection stages *l*: class 1 are individuals who were in the recent or chronic stage before start of treatment, class 2 are patients who were in one of the AIDS stage before antiretroviral therapy was initiated.

A proportion of individuals are infected with a wild type virus, *WT*, or a resistant virus *R*. There are five types of *R*, a person is infected with an M184V-containing virus where *R*=1, a K65R-containing virus where *R*=2, a TAM-containing virus where *R*=3, an NNRTI-containing virus where *R*=4, and a PI-containing virus where *R*=5.

Patients progress through three treatment stages *m*: The first two treatment stages occur, respectively, during the first 12 months (stage 1) and 12-24 of treatment (stage 2). Patients receiving antiretrovirals for more than 24 months are in stage 3. Patients can be on one of two first-line therapies, either a zidovudine-based regimen (*Tx*=1) or a tenofovir-based regimen (*Tx*=2). There are two states of resistance to first-line therapy, those not resistant *b*=1 and those resistant *b*=2.

The population used is the catchment area where the PASER data was collected in each city, 161,000 in Mombasa, and 336,000 in Kampala.

State variables

E_i = Entry rate susceptible individuals, i=1..4

S_i = Susceptible individuals, i=1..4

$I_{i,k}^{WT}$ = HIV infected individuals infected with a wild-type virus, not on treatment, i=1..4, k=1..6

$I_{i,k}^{R}$ = HIV infected individuals infected with a resistant virus, *R*, not on treatment, i=1..4, k=1..6, *R*=1..5

$I_{i,l,m,b}^{Tx}$ = HIV infected individuals on first-line treatment, *Tx*, i=1..4, l=1..2, m=1..3, b=1..2

$I_{i,l,m}^{2nd,Tx}$ = HIV infected individuals on second-line treatment, coming from first-line therapy *Tx*, i=1..4, l=1..2, m=1..3

$I_{i,l,m}^{2ndR}$ = HIV infected individuals resistant to second-line treatment

Other variables

λ_i^{total} = Total (wild-type + resistant) force of infection, *i*=1..4

λ_i^{WT} = Force of infection of wild-type virus, *i*=1..4

λ_i^{R} = Force of infection of resistant viruses, *i*=1..4, *R*=1..5

N_i = Number of individuals in sexual activity class *i*, *i*=1..4

μ = Mortality general population

μ_k = Mortality untreated HIV infected patients in infection stage *k, k*=1..6

$\mu_{l,m}$ = Mortality treated patients in infection stage *l* and treatment stages *m, l*=1..2, *m*=1..3

γ_k = HIV infection progression rate by stage *k*, *k*=1..6

η_k = Proportion of patients who successfully initiate therapy (product of test rate, retention, and ART initiation threshold), *k*=1..6

ρ_k^R = Proportion of individuals who have reverted from a resistant virus, *R*, to a wild-type virus by stage *k*, *R*=1..5, *k*=1..6

ψ_{Tx} = Proportion of infected individuals who go on treatment *Tx*, *Tx*=1..2

$\phi_{m,b}$ = Proportion of individuals on first-line treatment who go to second-line treatment, *m*=1..3, *b*=1..2

$\xi_{m,b}^{Tx}$ = The rate of acquired resistance after *m* time, on first-line treatment *Tx*, *m*=1..3, *b*=1..2, *Tx*=1..2

ξ_m^{2nd} = The rate of acquired resistance to second-line therapy after *m* time, *m*=1..3

ν^{Tx} = The rate at which individuals who acquired resistance to first-line therapy become successfully re-suppressed on first-line therapy, *Tx*=1..2

α = The reduction in infectiousness on people on treatment

ϑ^{Tx} = The proportion of individuals infected with a drug resistant virus that become successfully suppressed on first-line, *Tx*=1..2

β_k = The infectiousness of an individual in a given stage of infection, not on treatment, *k*=1..6

τ_R^{Tx} = The proportion of patients who acquire a specific drug resistant virus, *R*, depending on the first-line treatment, *Tx*, *R*=1..5, *Tx*=1..2

τ_R^{2nd} = The proportion of patients who acquire a specific drug resistant virus, *R*, to second-line treatment, *R*=1..5

ζ_R = The fitness cost of a particular mutation *R* based on viral replication capacities of viruses that were acquired to first- or second-line therapy, *R*=1..5

Ordinary Differential Equations

(1) $E_i = population - S_i - I_{i,k}^{WT} - I_{i,k}^{R} - I_{i,l,m,b}^{Tx} - I_{i,l,m}^{2nd,Tx} - I_{i,l,m}^{2ndR}$

(2) $S_i = E_i - S_i(\lambda_i^{total} + \mu)$

(3) $I_{i,1}^{WT} = \lambda_i^{WT} * S_i + (\sum_{R=1}^{5}(I_{i,1}^{R} * \rho_1^{R})) - I_{i,1}^{WT}(\gamma_1 + \eta_1 + \mu_1)$

(4) $I_{i,k}^{WT} = \gamma_{k-1} * I_{i,k-1}^{WT} + (\sum_{R=1}^{5}(I_{i,k}^{R} * \rho_k^{R})) - I_{i,k}^{WT}(\gamma_k + \eta_k + \mu_k)$
$k = 2..5$

(5) $I_{i,6}^{WT} = \gamma_5 * I_{i,5}^{WT} + (\sum_{R=1}^{5}(I_{i,6}^{R} * \rho_6^{R})) - I_{i,6}^{WT}(\gamma_6 + \eta_6 + \mu_6)$

(6) $I_{i,1}^{R} = \lambda_i^{R} * S_i - I_{i,1}^{R}(\gamma_1 + \eta_1 + \rho_1^{R} + \mu_1)$

(7) $I_{i,k}^{R} = \gamma_{k-1} * I_{i,k-1}^{R} - I_{i,k}^{R}(\gamma_k + \eta_k + \rho_k^{R} + \mu_k)$
$k = 2..5$

(8) $I_{i,6}^{R} = \gamma_5 * I_{i,5}^{R} - I_{i,6}^{R}(\eta_6 + \rho_6^{R} + \mu_6)$

(9) $I_{i,1,1,1}^{Tx} = (\sum_{k=1}^{4}(\eta_k * \psi_{Tx} * I_{i,k}^{WT})) - I_{i,1,1,1}^{Tx}(1 + \xi_{1,1}^{Tx} + \phi_{1,1} + \mu_{1,1})$

(10) $I_{i,2,1,1}^{Tx} = (\sum_{k=5}^{6}(\eta_k * \psi_{Tx} * I_{i,k}^{WT})) - I_{i,2,1,1}^{Tx}(1 + \xi_{1,1}^{Tx} + \phi_{1,1} + \mu_{2,1})$

(11) $I_{i,l,2,1}^{Tx} = (\sum_{b=1}^{2} I_{l,1,b}^{Tx}) + \nu^{Tx} * I_{i,l,2,2}^{Tx} + \vartheta^{Tx} * I_{i,l,1,2}^{Tx} - I_{i,l,2,1}^{Tx}(1 + \xi_{2,1}^{Tx} + \phi_{2,1} + \mu_{l,2})$

(12) $I_{i,l,3,1}^{Tx} = I_{i,l,2,1}^{Tx} - I_{i,l,3,1}^{Tx}(\xi_{3,1}^{Tx} + \phi_{3,1} + \mu_{l,3})$

(13) $I_{i,1,1,2}^{Tx} = (\sum_{k=1}^{4}(\sum_{R=1}^{5}(\eta_k * \psi_{Tx} * I_{i,k}^{R}))) - I_{i,1,1,2}^{Tx}(1 + \xi_{1,2}^{Tx} + \phi_{1,2} + \vartheta^{Tx} + \mu_{1,1})$

(14) $I_{i,2,1,2}^{Tx} = (\sum_{k=5}^{6}(\sum_{R=1}^{5}(\eta_k * \psi_{Tx} * I_{i,k}^{R}))) - I_{i,2,1,2}^{Tx}(1 + \xi_{1,2}^{Tx} + \phi_{1,2} + \vartheta^{Tx} + \mu_{2,1})$

(13) $I_{i,l,2,2}^{Tx} = (\sum_{b=1}^{2}(\xi_{1,b}^{Tx} * I_{i,l,1,b}^{Tx})) + \xi_{1,2}^{Tx} * I_{i,l,2,1}^{Tx} - I_{i,l,2,2}^{Tx}(1 + \nu^{Tx} + \phi_{2,2} + \mu_{l,2})$

(14) $I_{i,l,3,2}^{Tx} = I_{i,l,2,2}^{Tx} + \xi_{3,1}^{Tx} * I_{i,l,3,1}^{Tx} - I_{i,l,3,2}^{Tx}(\phi_{3,2} + \mu_{l,3})$

(15) $I_{i,l,1}^{2nd,b} = (\sum_{Tx=1}^{2}(I_{i,l,1,b}^{Tx} * \phi_{1,b})) - I_{i,l,1}^{2nd,Tx}(1+\xi_1^{2nd}+\mu_{l,1})$

(16) $I_{i,l,2}^{2nd,b} = I_{i,l,1}^{2nd,b} + (\sum_{Tx=1}^{2}(I_{i,l,2,b}^{Tx} * \phi_{2,b})) - I_{i,l,2}^{2nd,b}(1+\xi_2^{2nd}+\mu_{l,2})$

(17) $I_{i,l,3}^{2nd,b} = I_{i,l,2}^{2nd,b} + (\sum_{Tx=1}^{2}(I_{i,l,3,b}^{Tx} * \phi_{3,b})) - I_{i,l,3}^{2nd,b}(\xi_3^{2nd}+\mu_{l,3})$

(18) $I_{i,l,2}^{2ndR} = (\sum_{b=1}^{2}(\sum_{m=1}^{2}(I_{i,l,m}^{2nd,b} * \xi_m^{2nd}))) - I_{i,l,2}^{2ndR}(1+\mu_{l,2})$

(19) $I_{i,l,3}^{2ndR} = I_{i,l,2}^{2ndR} + (\sum_{b=1}^{2}(I_{i,l,3}^{2nd,b} * \xi_3^{2nd})) - I_{i,l,3}^{2ndR}(\mu_{l,3})$

Force of infection

The equation for the force of infection includes a mixing matrix $M_{i,j}$ for infected individuals, with a different infectiousness for each stage of infection, $\beta_{i,k}$. The elements of this matrix are *i,j* and represent the probability that an individual with *i* new partnerships per year will form a new partnership with a member who has *j* new partners. The rate at which the sexual partner changes for individuals in each sexual activity group *i* is expressed as c_i. The values of the matrix depend on the degree of mixing ε. This degree can be fully assortative (ε=1), where partnerships are only formed within the same activity class. Or fully random (ε=0), where partnerships are randomly formed between different activity classes [193].

(20) $M_{i,j} = \varepsilon\delta + \dfrac{(1-\varepsilon)c_j N_j}{\sum_{i=1}^{4} c_i N_i}$

Where δ = 1 when *i* = *j*, and δ = 0 when *i* ≠ *j*.

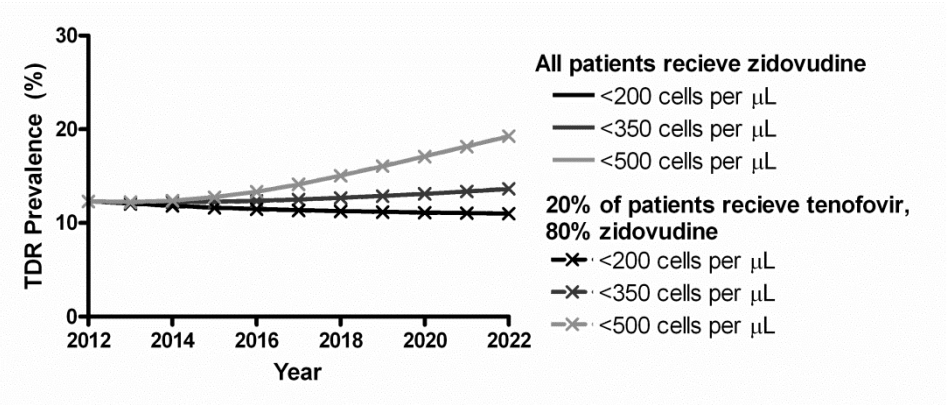
(21) $\lambda_i^{total} = \lambda_i^{WT} + \lambda_i^{R}$

(22)
$$\lambda_i^{WT} = c_i \sum_{j=1}^{4} \frac{M_{i,j}}{N_j}\Big(\sum_{k=1}^{6} I_{i,k}^{WT}\beta_k + \sum_{Tx=1}^{2}\Big(\sum_{l=1}^{2}\Big(\sum_{m=1}^{3}\alpha I_{i,l,m,1}^{Tx}\beta_2\Big)\Big)$$
$$+\sum_{Tx=1}^{2}\Big(\sum_{l=1}^{2}(\alpha I_{i,l,1,2}^{Tx}\beta_2)\Big) + \sum_{b=1}^{2}\Big(\sum_{l=1}^{2}\Big(\sum_{m=1}^{3}\alpha I_{i,l,m}^{2nd,b}\beta_2\Big)\Big)$$

(22)
$$\lambda_i^{R} = c_i \sum_{j=1}^{4} \frac{M_{i,j}}{N_j}\Big(\sum_{R=1}^{5}\Big(\Big(\sum_{k=1}^{6} I_{i,k}^{R}\beta_k\Big) + \Big(\sum_{Tx=1}^{2}\Big(\sum_{l=1}^{2}\Big(\sum_{m=1}^{3}\alpha\zeta_R\tau_R^{Tx} I_{i,l,m,2}^{Tx}\beta_2\Big)\Big)\Big)\Big)$$
$$+\Big(\sum_{l=1}^{2}\Big(\sum_{m=2}^{3}(\alpha\zeta_R\tau_R^{2nd} I_{i,l,m}^{2ndR}\beta_2)\Big)\Big)\Big)$$

In which λ_i^{total} is the force of infection due to contact with an infected person. Similarly, λ_i^T is the force of infection due to contact with a person with a wild-type virus, on treatment or not, and λ_i^R is the force of infection due to contact with a person with a resistant virus *R*, either due to acquired or transmitted resistance. λ_i^R is the contribution to transmitted resistant viruses to each of the five resistant categories *R* (M184V, K65R, TAMs, NNRTI, and PI resistance).

Figure S4. *Sensitivity analysis of having all patients in Mombasa, Kenya, on zidovudine, or moving 20% to tenofovir in 2012 the other 80% remaining on zidovudine, when initiating treatment at CD4<200 cells/μL, <350 cells/μL, and <500 cells/μL*



Chapter 4

Increasing the use of second-line therapy is a cost-effective approach to prevent the spread of drug resistant HIV: a mathematical modelling study

Brooke E. Nichols, Kim C.E. Sigaloff, Cissy Kityo, Raph L. Hamers, Rob Baltussen, Silvia Bertagnolio, Michael R. Jordan, Timothy B. Hallett, Charles A. B. Boucher, Tobias F. Rinke de Wit, David A.M.C. van de Vijver

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ABSTRACT

Background Earlier antiretroviral therapy initiation reduces HIV-1 incidence. This benefit may be offset by increased transmitted drug resistance, which could limit future HIV treatment options. We analyse the epidemiological impact and cost-effectiveness of strategies to reduce transmitted drug resistance.

Methods We develop a deterministic mathematical model representing Kampala, Uganda to predict the prevalence of transmitted drug resistance over a 10-year period. We then compare the impact on transmitted drug resistance and cost-effectiveness of: (1) introduction of pre-therapy genotyping (2) doubling use of second-line treatment to 80% (50-90%) of patients with confirmed virological failure on first-line ART and (3) increasing viral load monitoring from yearly to twice yearly. An intervention can be considered cost-effective if it costs less than three times the gross domestic product per capita per quality adjusted life year gained, or less than $3,420 in Uganda.

Results The prevalence of transmitted drug resistance is predicted to rise from 6.7% (Interquartile range [IQR] 6.2-7.2%) in 2014, to 6.8% (IQR 6.1-7.6%), 10.0% (IQR 8.9-11.5%) and 11.1% (IQR 9.7-13.0%) in 2024 if treatment is initiated at a CD4<350, <500, or immediately, respectively. The absolute number of transmitted drug resistance cases is predicted to decrease 4.4-8.1% when treating earlier compared to treating at CD4<350 due to the preventative effects of earlier treatment. Most cases of transmitted drug resistance can be averted by increasing second-line treatment (additional 7.1-10.2% reduction), followed by increased viral load monitoring (<2.7%) and pre-therapy genotyping (<1.0%). Only increasing second-line treatment is cost-effective, ranging from $1,612-$2,234 (IQR $450-dominated) per quality adjusted life year gained.

Conclusions While earlier treatment initiation will result in a predicted increase in the proportion of patients infected with drug-resistant HIV, the absolute numbers of patients infected with drug-resistant HIV is predicted to decrease. Increasing use of second-line treatment to all patients with confirmed failure on first-line therapy is a cost-effective approach to reduce transmitted drug resistance. Improving access to second-line antiretroviral therapy is therefore a major priority.

INTRODUCTION

In 2012, an estimated 2.4 million people became newly infected with HIV-1 globally.[218] Alongside behaviour change, male circumcision, and condom use, the need for additional HIV prevention strategies remains. The initiation of antiretroviral therapy (ART) at a CD4 cell count between 350-550 cells/µl has the potential to prevent 96% of new infections as compared to treatment initiation at CD4 <250 cells/µl among sero-discordant couples.[7, 219] In addition, a 41% reduction in mortality and opportunistic infections has been observed in individuals initiating ART at higher CD4 cell counts.[7] The World Health Organization (WHO) has recently revised its treatment guidelines and now recommends treatment initiation at CD4 <500 cells/µl.[14, 219]

There is concern that earlier ART initiation (i.e. at higher CD4 cell counts) may result in increased emergence and subsequent transmission of drug resistant HIV.[20] This could in turn jeopardize the effectiveness of future HIV treatment, particularly in the context of restricted drug availability in many resource-limited countries. In a previous study, we predicted that as more individuals initiate ART early, far more new infections are averted than drug-resistant infections are gained.[20] Despite the predicted reduction in new drug resistant infections, strategies to minimize drug resistance will remain essential to preserve the effectiveness of currently available drugs.

There are several ART program-level strategies that can help mitigate the emergence and transmission of drug resistance (TDR).[19-21] WHO has recently recommended monitoring patients by measuring plasma HIV RNA level, or viral load testing, which can reduce TDR if implemented at regular intervals (every 6 or 12 monthly). Viral load testing can reduce the emergence of HIV drug resistance by early identification of patients with virological failure, prompting intensified adherence counselling and switch to second-line ART as necessary, thereby minimizing emergence of HIV drug resistance.[19, 21] Second, prompt switching to a protease-inhibitor (PI) based second-line regimen of individuals experiencing virological failure has been associated with a reduced risk for drug resistance.[20, 22] Finally, pre-therapy genotypic resistance testing to select a fully active regimens guide may mitigate acquired drug resistance.[23, 24] These three strategies carry additional costs however and are not routinely available in sub-Saharan Africa.

Mathematical modelling in combination with cost-effectiveness analyses can be used to help inform policy makers about ways to prevent new HIV infections while simultaneously minimizing TDR, at the lowest possible cost. The aim of this analysis was to determine the most cost-effective of strategy that can be used to prevent the spread of TDR in settings with similar characteristics of Kampala, Uganda.

METHODS

Study design and population

We used a previously published compartmental deterministic mathematical model[20] based on an urban population in Kampala, Uganda. To predict time trends of TDR our model included drug resistance data from the PharmAccess African Studies to Evaluate Resistance (PASER) on transmitted[185] and acquired[23, 220] drug resistance in Kampala, Uganda.

Model and calibration

The model has been extended to incorporate population growth of the catchment area of the Joint Clinical Research Centre (JCRC), further expansion of ART and different patient monitoring strategies that can be used to reduce drug resistance. Using Monte Carlo filtering techniques,[194] we accepted 1,438 of 515,000 simulations that were associated with a specified TDR prevalence,[195] proportion of mutations observed in TDR, HIV prevalence, and population size (Table S1 shows the values used for calibration). The model calibration to the population size and HIV prevalence is shown in the supplement (Figure S1,S2). All reported results are the median and interquartile range (IQR) of the accepted simulations.

At the JCRC, the HIV test rate is relatively low, as approximately 50% of individuals are tested with and initiate ART at CD4 counts <200 cells/µl. Therefore, even if immediate treatment was recommended upon diagnosis, we would expect no more than 10% of individuals to initiate at a CD4 threshold of >500 cells/µl (Figure S3 shows this proportion of treatment initiation over time) assuming no change in the rate of HIV testing. Yearly viral load measurements and twice yearly CD4 cell counts are obtained for all patients on ART. After a detectable viral load, adherence counselling is provided, and thereafter a second viral load measurement is obtained. Pre-therapy genotypic testing is not provided.

In accordance with PASER-Monitoring data, the proportion of people who switch to second-line therapy with confirmed virological failure (defined as a plasma HIV RNA value of ≥1000 copies/mL) after adherence counselling during the first two years on therapy is 33-66% of those on tenofovir-based regimens and 33-50% of those on zidovudine-based regimens.[20] This resulted in approximately 3.5% of patients switching to second-line therapy after one year.[20] Of the individuals with virological failure during the second year of antiretroviral treatment, a median of 33% (range 16%-48%) had viral resuppression on their tenofovir-based regimens, and a median of 10% (range 8%-21%) on zidovudine-based regimens.[20] We assumed that these percentages of switching to second-line and resuppression on first-line would persist beyond two years on therapy. This would result in many individuals failing on first-line therapy to be switched to second-line over several years. Higher rates of switching to second-line would result in individuals switching earlier after initial virological failure, on average. The switch rate at the JCRC is not CD4 cell count-dependent. Approximately 40% of individuals receive tenofovir-containing regimens at the JCRC, and 60% zidovudine-

containing regimens, both combined with emtricitabine or lamivudine and efavirenz or nevirapine.[20] Table 1 shows the key assumptions for this model.

Table 1. *Key Model Parameters*[20]

Description	**Estimate or Range***	**Reference**
Disease stages duration		[8, 11]
Acute stage	10-16 weeks	
Chronic stage >500 cells/μL	0·87-1 year	
Chronic stage 350-500	2·9-3·1 years	
Chronic stage 200-350	3·6-3·9 years	
AIDS stage**	6-12 months	
Final AIDS stage**	7-13 months	
Infectivity		[9, 55]
Acute stage	27-43 times	
Chronic stage (all)	10% per year	
AIDS stage**	3-5 times	
Final AIDS stage**	0%	
Proportion of people in sexual		Model
Highest	1·5-2·5%	
2nd	10-20%	
3rd	20-30%	
Lowest	47·5-68·5%	
Number of partners per year in		Model
Highest	9-14	
2nd	1·7-3	
3rd	0·12-0·22	
Lowest	0·04-0·06	
Mortality rates per year		[197]
Population	0·02	
Chronic HIV stage	0·098	
AIDS stage	0·63	
On treatment during chronic stage, first year	0·02-0·098	
On treatment during chronic stage, 12+ months	0·02-0·05	
On treatment during AIDS stage, first year	0·03-0·3	
On treatment during AIDS	0·03-0·06	
HIV Test Rate		
Baseline	10-30%	Model
Rate of being tested in the acute stage of HIV	Half of the test rate	Assumption***
Rate of being tested in the	test rate	Model
Rate of being tested in the AIDS stage	test rate + 10%	

Linkage to care from test to treat	75-100%	Model
Reduction in transmissibility of	90-100%	[7, 43, 46]
Percentage of people that go to second line after continued virological failure, yearly after 12 months on treatment:		
Percentage of those who go onto second-line not due to resistance in the first 12 months	1·5-3%	[198]
*All ranges are uniformly distributed **Two AIDS stages were included because during the final months before death, patients have limited sexual activity *** Due to window phase of antibody-based test		

Baseline Scenarios

Three baseline scenarios, treatment initiation at CD4 <350 cells/µl, CD4 <500 cells/µl and immediate treatment upon diagnosis, were considered in this analysis. In our baseline scenarios, we assume yearly viral load monitoring for patients on treatment. We assumed that these monitoring approaches and switching rates from first- to second-line described above would persist unchanged. The laboratory monitoring and/or the increase in the use of second-line were subsequently evaluated for each treatment initiation threshold.

Strategies to reduce TDR

At each CD4 initiation threshold we evaluated scenarios in which we altered three patient monitoring strategies in order to reduce TDR. All strategies were modelled to be implemented in 2014, scaled-up linearly until 2016, and implemented until 2024. The first strategy is increased viral load monitoring every six months (instead of the current practice of yearly viral load measurements). We also evaluated the scenario where the biannual viral load measurements are provided for just the first two years on treatment. In the scenarios that evaluate biannual viral load alone, there is no increased access to second-line treatment but the yearly rate of resuppression on first-line is doubled.

Second, we evaluated a scenario with increased switch rate to second-line treatment. In this scenario, individuals with virological failure on first-line therapy after a yearly viral load measurement and do not achieve viral resuppression on first-line ART after adherence counselling (median resuppression rate 17.7%; range 8.3%-49.3%) are switched to a second-line regimen after a confirmatory viral load test. Those who do not achieve viral resuppression on first-line ART after adherence counselling are then switched to second-line therapy (median 82.3%; range 50.7-91.7%). This scenario was also combined with biannual viral load testing.

Third, a scenario was evaluated where pre-therapy genotyping is performed for all individuals. Based on the resistance profile, a fully-active first-line regimen then prescribed.

Cost-effectiveness analysis

Each compartment in our deterministic model was assigned a range of cost and quality adjusted life year (QALY) depending on the intervention (Table 2 shows key costs, and Tables S2-S4 show detailed costs and QALY assumptions).[222] Rates of HIV clinical monitoring tests were taken from the JCRC's standard practice (Table S5). Local costs for hospitalization of HIV infected persons, opportunistic infections, HIV testing, and ART, were all taken into account. Generally, a health-related intervention can be considered very cost-effective at a cost less than the gross domestic product (GDP) per capita ($1,140 in Uganda in 2012[223]) per QALY, and cost-effective if less than three times the GDP per capita ($3,420) per QALY gained.[224, 225] We calculated both the average cost-effectiveness ratios (ACERs) where we compared each scenario to baseline, and the incremental cost-effectiveness ratios (ICERs) where we compared each scenario to the next least-costly scenario.[226] Patient monitoring strategies were compared within each respective treatment initiation threshold (CD4 <350 cells/µl, <500 cells/µl, and immediate treatment). All costs and QALYs have been discounted yearly at the standard of 3%.[36, 227]

Table 2. *Key Cost Parameters**

Description	**Estimate****
Cost of testing negative for HIV per test ***	$6
Cost of testing positive for HIV per test***	$21
Cost of an outpatient visit in the hospital†	$16
Cost of first inpatient day in the hospital†	$24
Cost of subsequent inpatient day in the hospital†	$8
Cost of zidovudine-based treatment, per year	$108
Cost of tenofovir-based treatment, per year	$223
Cost of boosted protease inhibitor-based treatment, per year (second-line therapy)	$268
Cost of a CD4 cell count‡	$30
Cost of a viral load test‡	$71
Cost of pre-therapy genotypic testing‡	$159
Exchange rate, Ugandan Shilling to USD over year 2012	2500:1
*All costs collected from the Joint Clinical Research Centre in Kampala, Uganda.	
**All costs are log-normally distributed +/- 10% of the listed cost [221]	
***Includes costs of HIV tests, outpatient staff, laboratory personnel	
†Includes costs related to infrastructure, nurses, doctors, and other hospital personnel ‡Includes the price of an outpatient visit, costs of respective test, and laboratory personnel	

Sensitivity analysis

We performed a univariate sensitivity analysis of cost-effectiveness of second-line at each treatment initiation threshold. Six key input variables - cost of viral load testing, cost of CD4 cell count testing, cost of antiretroviral drugs, prevalence of transmitted drug resistance,

cost discounting, and QALY discounting - were considered to identify the sensitivity of our model. To evaluate whether the costs of viral load monitoring or pre-therapy genotyping influenced the cost-effectiveness of the scenarios including those tests, we calculated the ICERs for those scenarios with a reduction in the price of each up to 90%.

Availability of second-line treatment is limited throughout sub-Saharan Africa. Access to second-line at the JCRC is, however, high. Therefore, we also performed a sensitivity analysis in which we assumed that second-line treatment is only limitedly available, as might be more representative for other African sites. We modelled this limited availability by reducing the number of people switching to second-line by 50-70% (thus on average, 8.8% of all patients on second-line treatment at 10 years in the limited second-line scenario, compared to 22% in the full scale-up of second-line, when treating at CD4 <350 cells/µl). We then calculated the impact on levels of TDR as well as the cost-effectiveness of switching all individuals with confirmed virological failure on first-line therapy to second-line therapy.

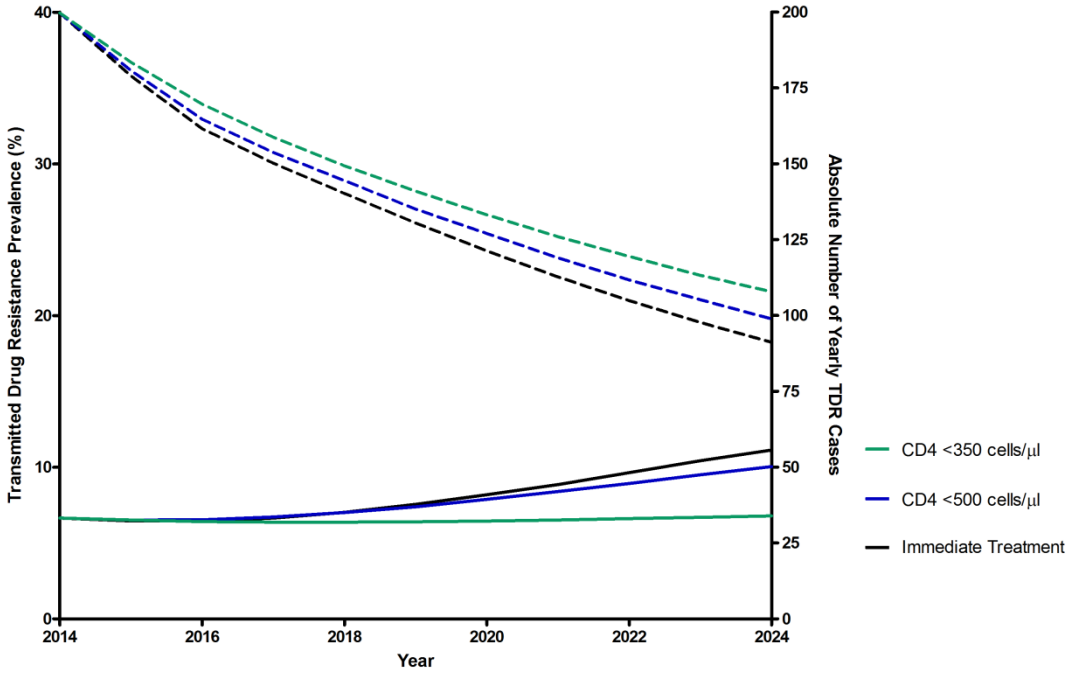
RESULTS

Impact of ART on transmitted drug resistance

The prevalence of TDR is predicted to rise at all CD4 initiation thresholds (Figure 1). In 2014, the prevalence of TDR is predicted to rise from 6.7% (IQR 6.2-7.2%), to 6.8% (IQR 6.1-7.6%), 10.0% (IQR 8.9-11.5%) and 11.1% (IQR 9.7-13.0%) in 2024 if the treatment initiation threshold is CD4 cells <350 cells/µl, <500 cells/µl, and irrespective of CD4 cell count, respectively.

The absolute number of TDR infections is predicted to decrease, however, compared to initiating treatment at CD4 <350 cells/µl due to decreasing HIV incidence. Initiating treatment at a CD4 count of <500 cells/µl and treating immediately averts 61 or 4.4% (IQR 44-81 or 3.3%-5.5%) and 110 or 8.1% (IQR 87-142 or 6.6%-9.4%) of TDR infections, respectively, as compared to initiating ART at CD4 <350 cells/µl. TDR is predicted to be primarily due to NNRTIs, followed closely by resistance to PIs (Figure S4).

Figure 1. *Yearly transmitted drug resistance prevalence (solid lines) and absolute number of yearly TDR cases (dashed lines) by CD4 treatment initiation thresholds of <350, <500 CD4 cells/μl, and immediate treatment over 10 years*



Epidemiological impact of strategies to reduce drug resistance

Biannual viral load monitoring

Biannual viral load monitoring had a modest impact on preventing new TDR infections (Figure 2). No more than 2.7% of TDR was predicted to be averted over 10 years at any treatment initiation threshold. The two viral load strategies (in which 6-monthly viral loads were available for the first two years on therapy both with and without additional access to second-line) had minimal impact on TDR, averting <1.0% of TDR over the coming 10 years.

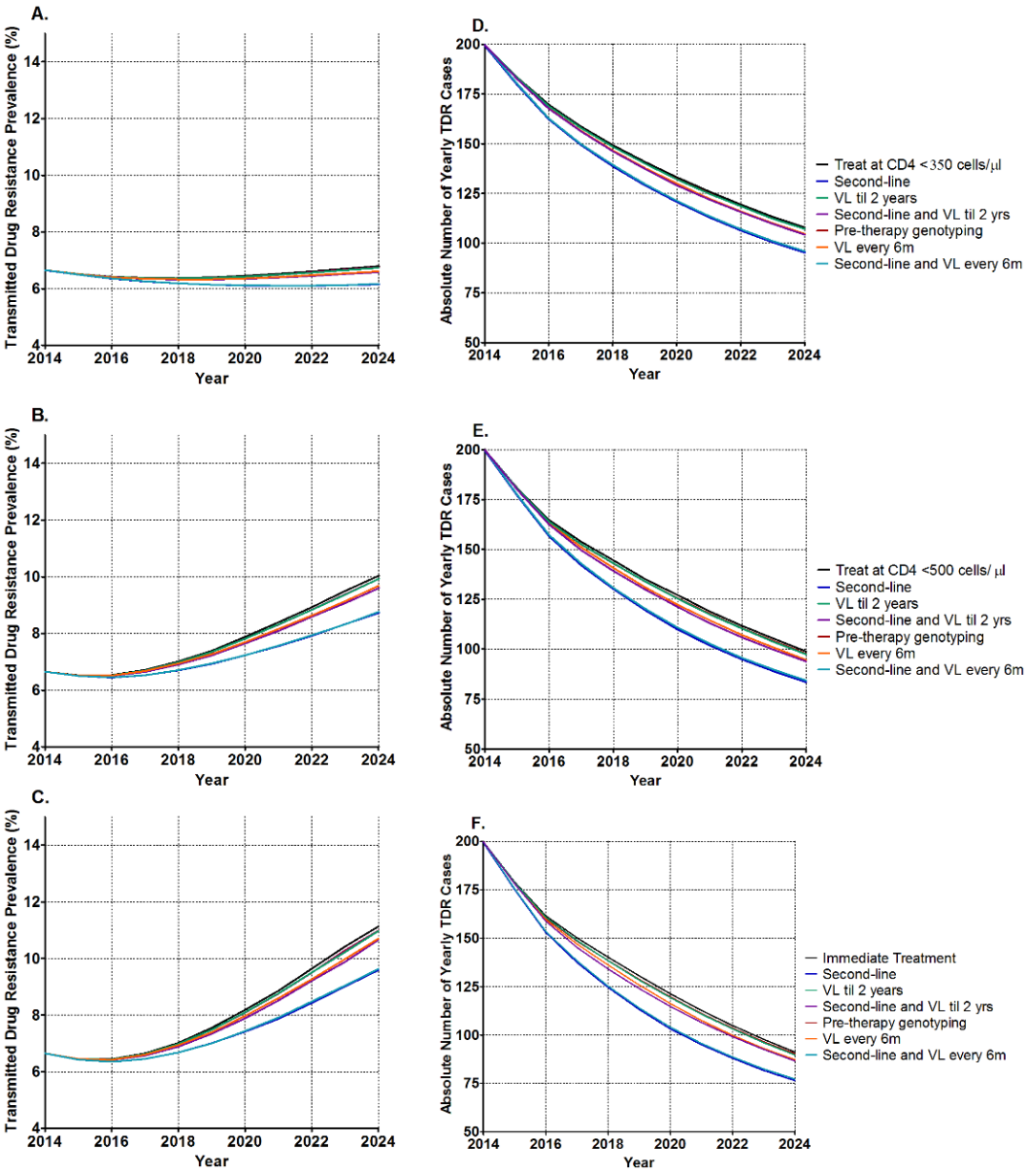
Increase in second-line

Increasing the use of second-line ART has the largest impact on averting drug resistant infections (Figure 2). The largest effect of increased access to second-line was predicted when ART is initiated at time of diagnosis (averting 10.2% of TDR, IQR 8.5%-12.0%), followed by treatment initiation at CD4 cell counts <500 cells/μl (9.4%, IQR 7.8%-11.2%), and at <350 cells/μl (7.1%, IQR 5.8%-8.5%), compared to the respective baseline scenarios at each treatment initiation threshold. Combining biannual viral load testing for the duration of ART with increased use of second-line ART did not greatly increase the impact on TDR compared to increasing use of second-line ART alone.

Pre-therapy genotyping

Pre-therapy genotyping had only a limited impact on preventing spread of drug resistant HIV, averting a maximum of 1.0% of TDR over 10 years (Figure 2).

Figure 2.*Yearly transmitted drug resistance prevalence (A-C) and absolute number (D-F) of yearly TDR cases by antiretroviral treatment initiation threshold, by patient monitoring strategy, over a period of 10 years. Panel A & D refer to when all monitoring strategies are implemented in combination with treatment initiation at CD4 <350 cells/µl, Panel B & E in combination with treatment initiation at CD4 <500 cells/µl, and Panel C & F in combination with immediate treatment.*



VL= viral load testing

Cost-effectiveness of strategies to reduce drug resistance

Increasing use of second-line treatment was the only strategy that was considered cost-effective in our analysis, with an incremental cost effectiveness ratio ranging between $1,612 and $2,234 per QALY gained depending on the treatment initiation threshold (Table 3). All other scenarios were dominated by increasing use of second-line, as all scenarios were more costly and less effective than second-line alone.

Sensitivity analysis

Our sensitivity analysis indicated that the cost of ART, viral load and CD4 cell count testing increased the cost-effectiveness ratios so that increasing second-line use was no longer cost-effective (Figure S5). Three parameters, cost and QALY discounting and TDR prevalence, did not change the overall outcome that increasing use of second-line is considered cost-effective when treating at all thresholds for the ranges tested.

Even when the cost of pre-therapy genotyping was reduced by 90%, the scenario of implementing pre-therapy genotyping was still dominated by other strategies at every treatment initiation threshold. Likewise, a 90% reduction in the price of viral load testing alone did not change the cost-effectiveness outcomes of any of the strategies associated to increased viral load testing. This is likely because viral load tests are also used in the baseline scenarios, so the incremental difference in the scenarios with biannual viral loads is limited.

Under the more realistic assumption that second-line treatment is limitedly used, switching all individuals with confirmed virological failure that persist even after adherence counselling is still considered cost-effective when initiating treatment at CD4 <350 (ICER $1,437, IQR $643-$3,882) and CD4 <500 ($1,681, $488-$8,491) and very cost-effective when initiating treatment immediately ($563, $433-$792). It should also be noted that when second-line treatment is limitedly used, the prevalence of TDR is predicted to be as high as 30% in 10 years with immediate treatment, highlighting the importance of second-line use (Figure S6).

Table 3. *Cost-effectiveness of strategies to reduce transmitted drug resistance by treatment initiation threshold. Within each treatment initiation stratum, average and incremental cost-effectiveness ratios are calculated based on the total additional cost and QALYs gained.*

Intervention	Total Cost (Millions USD)	QALYs Gained	Infections Averted	Average Cost- Effectiveness Ratio	Incremental Cost-Effectiveness Ratio	Conclusion
Treatment at CD4 <350	33.8 (31.6-36.0)					
Increase second line	34.0 (31.7-36.2)	81 (-199-351)	104 (83-130)	$1,925 ($450-Dominated)	$1,925 ($450-Dominated)	Cost-Effective
Viral Load every 6 months, for first two years on treatment	34.1 (31.8-36.4)	3 (-250-280)	9 (6-12)	$95,417 ($1,077-Dominated)	Dominated ($725-Dominated)	Dominated
Viral Load every 6 months, for first two years on treatment & increased 2nd line	34.2 (31.9-36.4)	29 (-234-287)	31 (23-40)	$11,602 ($1,216-Dominated)	Dominated ($908-Dominated)	Dominated
Pre-therapy Genotyping	34.6 (32.3-37.0)	3 (-285-273)	7 (5-10)	$329,018 ($3,014-Dominated)	Dominated ($3,387-Dominated)	Dominated
Continual Viral Load every 6 months	38.4 (35.9-41.0)	16 (-258-297)	25 (18-34)	$283,020 ($15,844-Dominated)	Dominated ($24,765-Dominated)	Dominated
Continual Viral Load every 6 months & increased 2nd line	38.5 (35.9-41.1)	75 (-170-329)	98 (75-126)	$64,539 ($13,884-Dominated)	Dominated ($18,177-Dominated)	Dominated
Treatment at CD4 <500	38.5 (36.0-41.3)					
Increase second line	38.7 (36.2-41.5)	87 (-190-375)	132 (105-165)	$2,234 ($505-Dominated)	$2,234 ($505-Dominated)	Cost-Effective
Viral Load every 6 months, for first two years on treatment	38.9 (36.4-41.7)	-12 (-302-288)	12 (8-18)	Dominated ($1,431-Dominated)	Dominated	Dominated

Viral Load every 6 months, for first two years on treatment & increased 2nd line	39.0 (36.5-41.8)	26 (-277-318)	43 (33-56)	$18,337 ($1,473-Dominated)	Dominated ($1,290-Dominated)	Dominated
Pre-therapy Genotyping	39.6 (37.1-42.5)	-18 (-298-309)	13 (9-17)	Dominated ($3,734-Dominated)	Dominated	Dominated
Continual Viral Load every 6 months	44.0 (41.1-47.1)	2 (-290-310)	33 (24-43)	Dominated ($28,250-Dominated)	Dominated	Dominated
Continual Viral Load every 6 months & increased 2nd line	44.0 (41.2-47.2)	70 (-208-366)	122 (95-157)	$72,975 ($15,593-Dominated)	Dominated ($21,720-Dominated)	Dominated
Treat Immediately	39.9 (37.4-42.9)					
Increase second line	40.1 (37.5-43.0)	121 (-165-406)	137 (109-169)	$1,612 ($463-Dominated)	$1,612 ($463-Dominated)	Cost-Effective
Viral Load every 6 months, for first two years on treatment	40.4 (37.7-43.4)	17 (-292-331)	13 (9-19)	$25,767 ($1,276-Dominated)	Dominated ($1,315-Dominated)	Dominated
Viral Load every 6 months, for first two years on treatment & increased 2nd line	40.4 (37.8-43.4)	33 (-276-344)	46 (34-58)	$15,100 ($1,517-Dominated)	Dominated ($1,544-Dominated)	Dominated
Pre-therapy Genotyping	41.2 (38.5-44.2)	18 (-329-341)	14 (10-19)	$69,252 ($3,620-Dominated)	Dominated ($4,541-Dominated)	Dominated
Continual Viral Load every 6 months	45.6 (42.7-49.0)	19 (-276-320)	34 (25-45)	$292,107 ($17,550-Dominated)	Dominated ($27,785-Dominated)	Dominated
Continual Viral Load every 6 months & increased 2nd line	45.8 (42.8-49.1)	81 (-212-355)	127 (97-160)	$69,140 ($16,409-Dominated)	Dominated ($20,685-Dominated)	Dominated

DISCUSSION

This mathematical model of the Kampala, Uganda setting predicts that the prevalence of TDR will rise from 6.7% up to between 6.8% and 11.1% over the coming decade. The absolute number of TDR cases is predicted to decline due to the preventative effects of earlier treatment. Among three patient monitoring strategies assessed in this analysis, the most TDR infections can be averted by increasing use of second-line treatment. Pre-therapy genotyping and twice yearly viral load monitoring are costly with limited health benefits at a population level, and therefore should not be prioritized in ART program implementation.

We found that increased use of boosted PI-based second-line treatment is the only the cost-effective approach for reducing TDR. Compared to NNRTIs, boosted PIs have a higher genetic barrier (a higher number of mutations are required to overcome drug selective pressure) for the development of drug resistance.[15] Consequently, use of PIs is associated with a lower probability of resistance development during treatment and subsequent transmission of resistance to others.[216] At the JCRC, yearly viral load monitoring is already common practice, as recommended by the WHO.[14] No additional laboratory monitoring is therefore necessary to implement increased use of second-line treatment in this setting.

Increasing viral load testing to more than once per year has a limited impact on TDR prevalence. This is in agreement with data from literature that showed that the risk of virological failure reduces with increased time of virological suppression.[228, 229] Combining increased use of second-line treatment with twice-yearly viral load resulted in fewer QALYs gained than increased use of second-line treatment alone. This is due to the fact that increased viral load monitoring will also increase resuppression on first-line therapy.[230] However, the vast majority of resuppressed patients in our dataset went on to fail on first-line therapy again after one year. Therefore, the increased resuppression rate result in two time periods of a patient failing on first-line therapy instead of one time period. Our model assigns slightly lower QALYs to the time individuals spend failing on therapy compared to being successfully suppressed on therapy (see Table S2). Therefore, more resuppression on first-line, as with viral load testing every 6 months, will lead to more instances of viral failure on first-line and therefore slightly lower QALYs on a population level over time. Once individuals are on a boosted PI-based second-line regimen, the likelihood of failure decreases significantly, due to the high genetic barrier.[15] Thus, viral load determination remains of key importance for monitoring ART, but increasing its frequency to twice-yearly is not cost-effective or greatly impact TDR.

Pre-therapy genotyping had little added benefit on a population level and is very expensive. Pre-therapy genotyping would potentially have a larger impact on TDR and be most cost-effective if the baseline prevalence of TDR were higher in the modelled scenarios. Indeed, the simulations with the lowest ACERs of pre-therapy genotyping were the simulations in which TDR was the highest (data not shown).

Previous studies have investigated the impact and/or cost-effectiveness of laboratory-based patient monitoring compared to symptom-based patient monitoring.[231-235] The majority have predicted that laboratory-based monitoring was cost-effective or cost-saving, but depends largely on test costs.[231-233, 235] One study found that viral load testing every 12 months is more cost-saving than viral load testing every 6 months, in agreement with our results of viral load every 6 months being cost-ineffective.[235] Just two studies incorporated the preventative effects of laboratory-monitoring techniques on HIV transmission with cost-effectiveness analyses, and found that regular viral load monitoring was highly cost-effective and even cost-saving.[231, 233] A study by Phillips et al. evaluated virological monitoring while taking into account both drug resistance and HIV transmission.[21] This study concluded that viral load tests every six months would reduce TDR by about 50% compared to clinical monitoring. These results cannot be compared to ours, as our baseline scenario included yearly viral load measurements.

Our mathematical model and cost-effectiveness analysis has several strengths. To our knowledge, our model is the first to include multiple ART intervention strategies into a population-level model that accounts for HIV transmission dynamics, TDR, and cost-effectiveness simultaneously within one dynamic model. Second, our model is also the first to demonstrate the cost-effectiveness of second-line treatment at several treatment initiation thresholds, and the consequences on TDR if second-line is only limitedly available. Third, this model combines data on transmitted and acquired HIV drug resistance from the same geographic areas and time period, collected within the same research project. Finally, comprehensive cost data was also collected and utilized from the same study site.

This study has some potential limitations. First, data on HIV drug resistance beyond 24 months of ART in resource-limited settings is scarce. While data from high-income countries shows that acquired resistance after two years on therapy diminishes or reaches steady-state,[236, 237] it could be that acquired resistance after 24 months is as high as 12-24 month acquired resistance rates. If this were the case, it could be that we underestimated future TDR prevalence. Based on our model output it is unlikely that the outcomes of the different patient monitoring strategies would contradict our results. Second, our predictions rely on the reasonable assumption that drugs used as first-line will remain constant over the coming 10 years, although ART guidelines are subject to change. Third, the cost of second-line is relatively low at the JCRC ($268 per year) compared to tenofovir-based first-line ($223 per year). When the costs of second-line are increased to $466 per year, twice that of a tenofovir-based regimen, increased second-line is no longer considered cost-effective. All other scenarios, however, continue to be dominated by increased second-line. It is therefore of the utmost importance to keep the cost of PI-based second-line drugs as low as possible.

We modelled a setting where second-line is widely used and viral load testing is performed annually. Availability of yearly viral load testing and second-line use is not mirrored across

sub-Saharan Africa. We have reported that increased use of second-line is cost-effective when viral load testing is already in place. We cannot say, however, how cost-effective increased second-line use would be in the absence of viral load testing. We attempted to address this issue by modelling a 50-70% reduction in second-line use, and found that that the cost-effectiveness of second-line became stronger or even cost-saving. We could not reliably model absence of viral load monitoring, as we do not have data to accurately calibrate the model for such an analysis and wanted our model to reflect available data.

CONCLUSIONS

While the prevalence of TDR is predicted to increase with ART initiation at higher CD4 cell count thresholds, the incident cases with TDR are predicted to decrease. Increasing the number of individuals who switch directly to second-line after confirmed first-line failure, in a setting where annual viral load monitoring is already in place, is both cost-effective and reduces TDR at all treatment initiation thresholds. Our observations are particularly relevant in light of the 2013 WHO guidelines which recommend treatment initiation at CD4 <500 cells/μl.[14] With the increasing rollout of first-line treatment, it is imperative to simultaneously expand access to yearly viral load testing coupled with affordable second-line ART, in order to facilitate appropriate switching to second-line ART.

ACKNOWLEDGEMENTS

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Supplement: Chapter 4

Table S1. *Variables used to calibrate and accept simulations using the Monte Carlo filtering technique*

Parameter used to accept simulations	Values Accepted	Source
Transmitted Drug Resistance (TDR) Prevalence	7.1%-10% in 2009	[185]
Proportion of mutations that make up TDR*	7-27% resistance to protease inhibitors 23-43% thymidine analogue mutations (TAMs, encoding for resistance to zidovudine and stavudine) 40-60% resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs)	[185]
HIV Prevalence	7.1%-8.4% between 2005 and 2009	[20, 195]
JCRC catchment area population	300,000-372,000 in 2012	Local Data

* The M184V (associated with resistance to lamivudine or emtricitabine) and K65R mutations (associated with tenofovir resistance) were also included in the model, but were not calibrated specifically to the model as these mutations were not observed in the PASER-Surveillance data [185].

Figure S1. *Simulations of HIV prevalence 1992-2010; Compared to Ugandan HIV Prevalence Data*

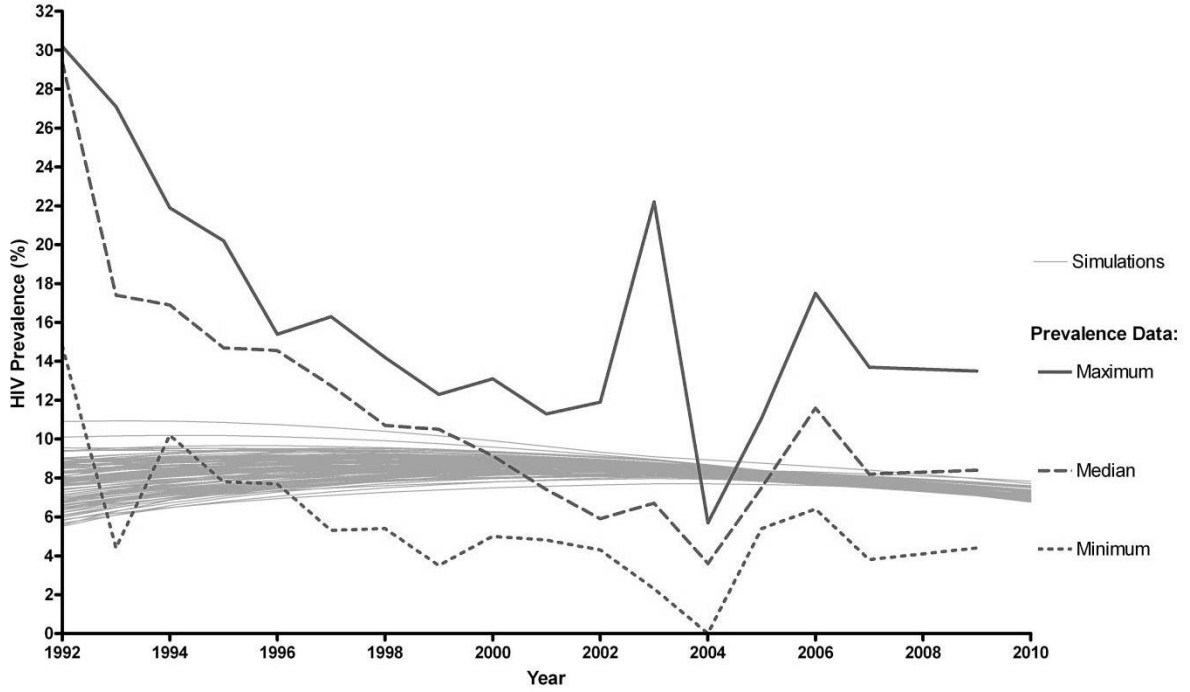
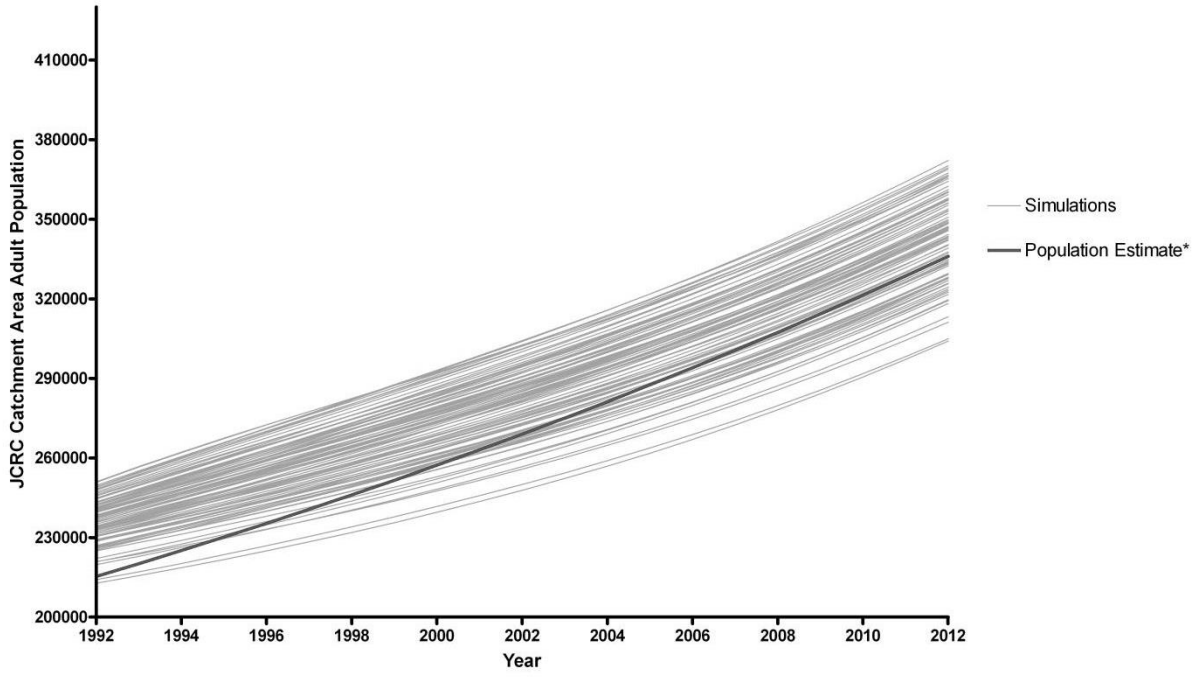


Figure S2. *Simulations of HIV population 1992-2012; Joint Research Clinical Centre Catchment Area Population, Kampala, Uganda*



*Based on the historic population growth rates of Uganda

Figure S3. *Proportions of CD4 cell count at treatment initiation by treatment initiation guideline*

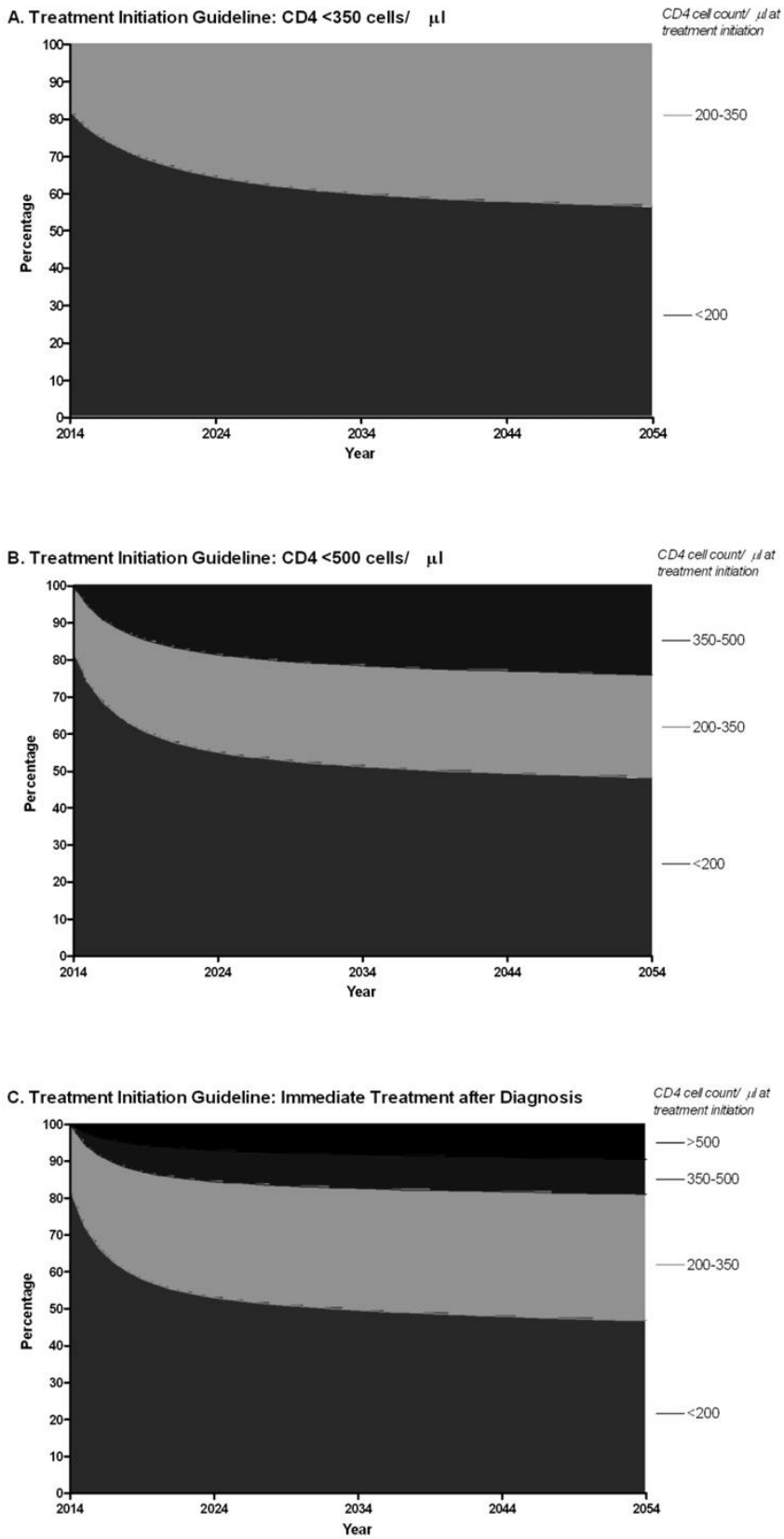


Table S2. *Assumed utility weightings for QALYs*

Status	**Utility Weight***
Susceptible	1.0
Acutely infected	0.94
Chronically infected	0.94
Infected early AIDS stage	0.82
Infected late AIDS stage	0.7
Infected on treatment	0.94
Resistant/failing on treatment	0.82-0.94 (assumption)

*Weights based on a pooled analysis by Tengs and Lin (2002) [222]

Table S3. *Costs used in treating opportunistic infections, per unit**

Drug	**Unit**	**Cost, USD**
Acyclovir	200mg	$0.20
Azithromycin	500mg	$1.07
Amphotericin B	50mg	$14.00
Ceftriaxone	2g	$4.00
Ciprofloxacin	500mg	$0.20
Fluconazole	200mg	$0.40
RHZ	150/75/400mg	$0.24
RHZE	150/75/400/275mg	$0.48

*All costs collected from the Joint Clinical Research Centre, Kampala, Uganda

Table S4. *Costs used in diagnosing opportunistic infections and monitoring HIV, per test*

Test/Supply	**Cost, USD***
Antigen test	$16.80
Biopsy	$23.60
Complete Blood Count	$5.00
CD4 Test	$14.00
Chest X-ray	$6.00
CSF Analysis	$19.20
Liver function	$26.00
Lumbar puncture	$40.00
Renal function	$20.40
Skin biopsy	$23.60
Stool exam	$12.00
Swab & culture	$12.00
Sputum	$14.40
Urine analysis	$12.00
Viral load test	$55.00

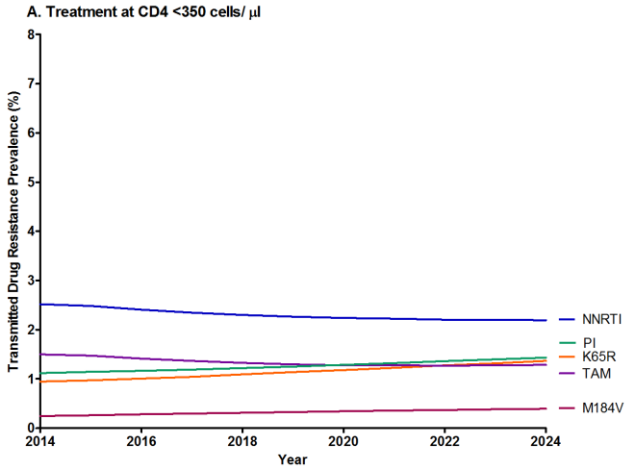
*All costs collected from the Joint Clinical Research Centre, Kampala, Uganda; costs are inclusive of laboratory and hospital personnel (and exclusive cost of outpatient visit)

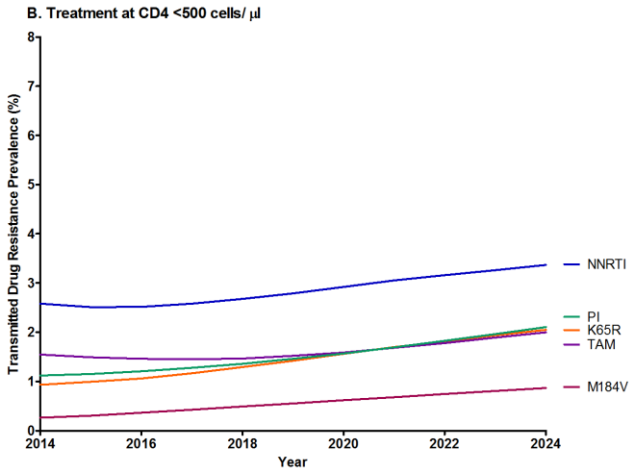
Table S5. *Opportunistic infection rates hospitalization & treatment assumptions**

Opportunistic Infections (OIs)	Percent Hospitalized	Duration of Hospitalization	Drugs used to treat disease:	Additional lab tests needed
Herpes Zoster	0%	N/A	Acyclovir, 5x200mg, 7 days	-
Diarrhea	20%	5 days	Ciprofloxacin, 2x500mg, 5 days	Renal function, stool exam
Tuberculosis	30%	7 days	RHZE 2 months, RHZ 4 months	Chest X-ray, sputum, liver function
Pneumonia	30%	7 days	Ceftriaxone,1x2g, 7 days	-
Oral Candida	0%	N/A	Fluconazole, 1x200mg, 7 days	-
Genital Ulcers	10%	-	Acyclovir, 4x200mg, 14 days	Swab & culture
Esophageal Candida	10%	7 days	Fluconazole, 1x200mg, 7 days	-
Extra Pulmonary TB	50%	10 days	RHZE 2 months, RHZ 10 months	Chest X-ray, sputum, liver function
Cryptococcal Meningitis	100%	17.5 days	Amphotericin B, 1x50mg, 14 days	Lumbar puncture, CSF analysis, antigen test
Kaposi's Sarcoma-Cutaneous	20%	6 days	Start ART	Skin biopsy
Herpes Simplex	10%	7 days	Acyclovir, 4x200mg, 10 days	Swab & culture
Kaposi's Sarcoma-Visceral	100%	7 days	Start ART	Biopsy
Urethritis	40%	7 days	Azithromycin, 1x2g, 7 days	Urine analysis

*Based on expert opinion of one treating physician and head nurse at the Joint Clinical Research Centre in Kampala, Uganda

Figure S4. *Yearly transmitted drug resistance prevalence separated out by the following resistance mutation or class: a TAM mutation, M184V mutation, K65R mutation, or resistance to NNRTIs, PIs. Panel A is when treatment is initiated at a CD4 count <350 cells/µl, Panel B at CD4 <500 cells/µl, and Panel C is when treatment is initiated immediately.*





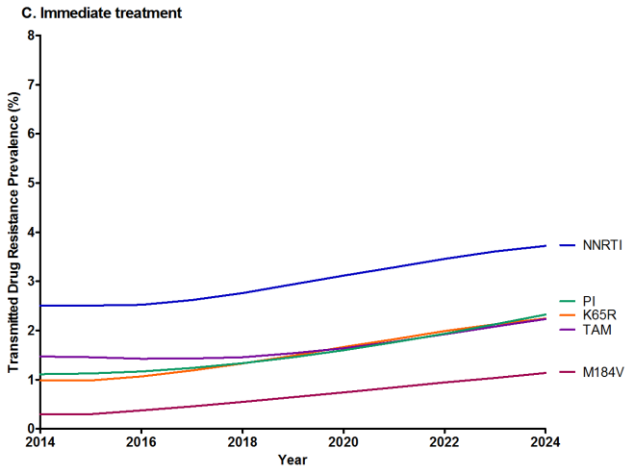
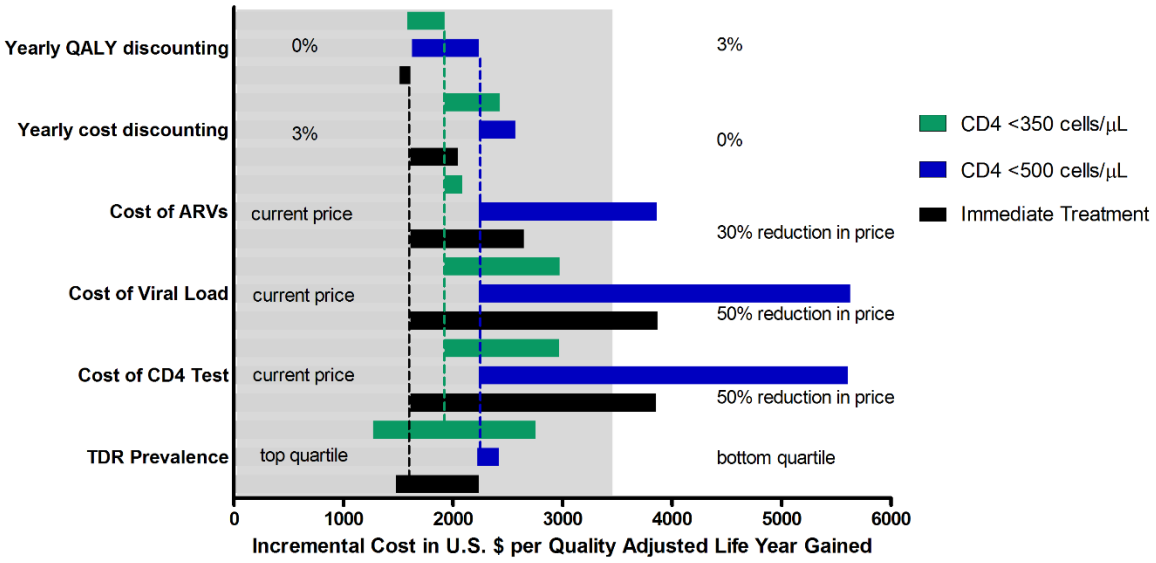
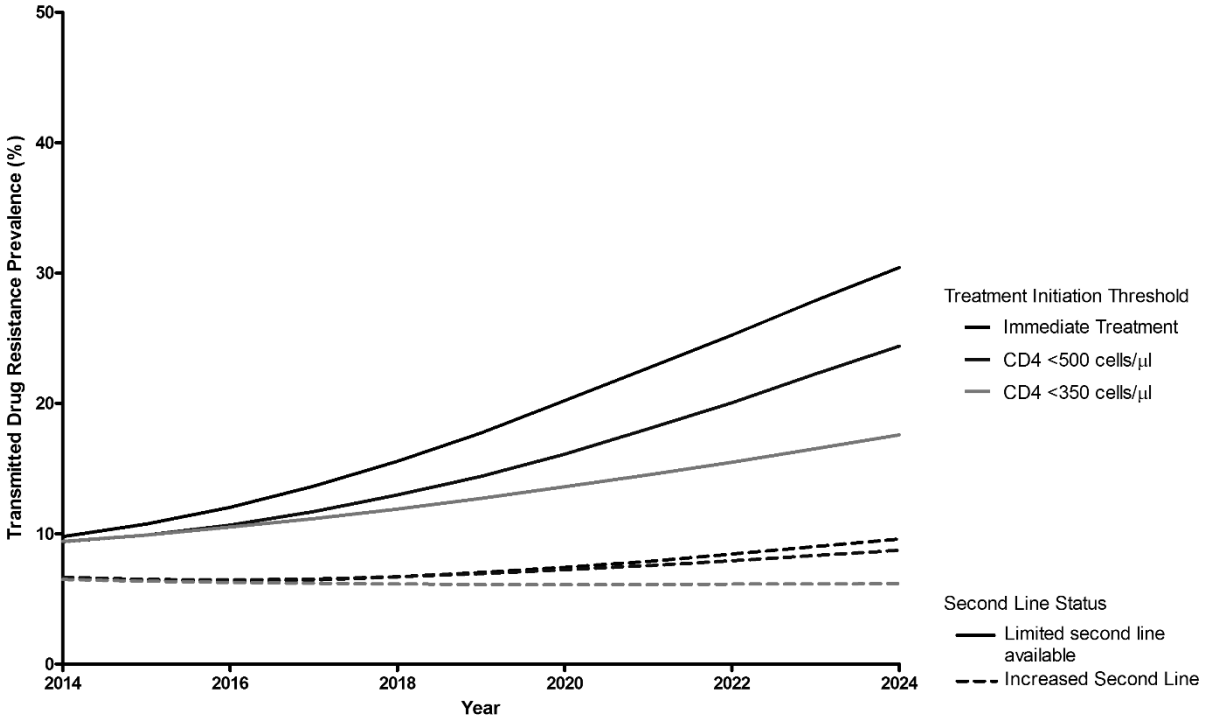


Figure S5. *One-way sensitivity analyses of the incremental cost-effectiveness of increasing use of second-line treatment at three different treatment initiation thresholds over 10 years.*



This diagram summarizes the results of a series of one-way sensitivity analyses on the incremental cost-effectiveness of increasing use of second-line treatment at three different treatment initiation thresholds. Each horizontal bar represents the full range of cost-effectiveness ratios produced by varying a given model parameter across its plausible range. The vertical dotted lines represent the incremental cost-effectiveness ratio at each treatment initiation threshold ($1,612 per quality adjusted life year for immediate treatment, $2,234 per quality adjusted life year gained when treating at CD4 <500 cells/μl, and $1,925 per quality adjusted life year gained when treating at CD4 <350 cells/μl). The gray area represents the values that can be considered cost-effective.

Figure S6. *Sensitivity analysis: transmitted drug resistance prevalence by treatment initiation threshold when second-line treatment is limitedly available (solid line) versus scaled up to 80-100% (dashed line)*



Chapter 5

Partner notification for reduction of HIV-1 transmission among men who have sex with men: a mathematical modeling study

Brooke E Nichols, Hannelore M Götz, Eric C van Gorp, Annelies Verbon, Casper Rokx, Charles AB Boucher, David AMC van de Vijver

Part II

Pre-exposure Prophylaxis

Chapter 6

Cost-effectiveness of Pre-Exposure Prophylaxis (PrEP) in preventing HIV-1 infections in rural Zambia: a modeling study

Brooke E Nichols, Charles AB Boucher, Janneke H van Dijk, Phil E Thuma, Jan L Nouwen, Rob Baltussen, Janneke van de Wijgert, Peter MA Sloot, David AMC van de Vijver

PLoS One 2013; 8(3):e59549

ABSTRACT

Background Pre-exposure prophylaxis (PrEP) with tenofovir and emtricitabine effectively prevents new HIV infections. The optimal scenario for implementing PrEP where most infections are averted at the lowest cost is unknown. We determined the impact of different PrEP strategies on averting new infections, prevalence, drug resistance and cost-effectiveness in Macha, a rural setting in Zambia.

Methods A deterministic mathematical model of HIV transmission was constructed using data from the Macha epidemic (antenatal prevalence 7.7%). Antiretroviral therapy is started at CD4<350 cells/mm^3. We compared the number of infections averted, cost-effectiveness, and potential emergence of drug resistance of two ends of the prioritization spectrum: prioritizing PrEP to half of the most sexually active individuals (5-15% of the total population), versus randomly putting 40-60% of the total population on PrEP.

Results Prioritizing PrEP to individuals with the highest sexual activity resulted in more infections averted than a non-prioritized strategy over ten years (31% and 23% reduction in new infections respectively), and also a lower HIV prevalence after ten years (5.7%, 6.4% respectively). The strategy was very cost-effective at $323 per quality adjusted life year gained and appeared to be both less costly and more effective than the non-prioritized strategy. The prevalence of drug resistance due to PrEP was as high as 11.6% when all assumed breakthrough infections resulted in resistance, and as low as 1.3% when 10% of breakthrough infections resulted in resistance in both our prioritized and non-prioritized scenarios.

Conclusions Even in settings with low test rates and treatment retention, the use of PrEP can still be a useful strategy in averting infections. Our model has shown that PrEP is a cost-effective strategy for reducing HIV incidence, even when adherence is suboptimal and prioritization is imperfect.

INTRODUCTION

Despite extensive prevention efforts there were 2.6 million new HIV infections in 2009 globally.[6] While the annual number of new infections has been decreasing since 1997, there is still an urgent need for more effective prevention strategies in addition to use of condoms and behavior change. Pre-exposure prophylaxis (PrEP) with daily oral tenofovir and emtricitabine has been shown to be efficacious in preventing HIV infections.[28, 272, 273] In the recent Partner's PrEP study among African heterosexual serodiscordant couples, daily PrEP was shown to prevent 73% of infections over three years of follow-up compared to the control arm.[272] Similarly, the TDF-2 trial among heterosexual men and women in Botswana showed that daily PrEP prevented 62% of infections over a median of 1.1 years compared to the control arm.[273] In the recent iPrEx study, daily PrEP was shown to prevent 44% of infections over a median of 1.2 years compared to the control arm in a highly sexually active cohort of men who have sex with men (MSM).[28] The FEM-PrEP trial, among heterosexual African women did not, however, find a protective effect of PrEP, likely due to poor adherence.[32]

It is unknown who should receive PrEP so that most infections are averted at the lowest cost. The cost-effectiveness of PrEP has not been established for a low-income country such as Zambia. Two hypothetical PrEP distribution scenarios could be utilized. First, PrEP could be given to more sexually active individuals, potentially by identifying a seronegative partner in a serodiscordant relationship or people with sexually transmitted infections (STIs) and their partners. Another hypothetical approach could be to randomly assign PrEP to individuals regardless of level of sexual activity in order to avert infections.

The drugs used in PrEP regimens are the same as those recommended for first-line treatment regimens. A critical issue in PrEP use is therefore the development of HIV drug resistance in the population. Potential risks associated with using the same drugs for both prevention and for treatment can be illustrated by the use of nevirapine for prevention of mother-to-child transmission.[33] Recent maternal use of nevirapine for prevention of mother-to-child-transmission was associated with a higher probability of virological failure in the mothers receiving nevirapine as part of their first-line regimen.[154]

Our objective is to use mathematical modeling to explore the possibilities of daily oral PrEP optimization using realistic data collected in the rural HIV clinic at the Macha Mission Hospital in Zambia. Rural settings such as Macha often face more barriers to treatment, such as large travel distances to clinics and fewer financial resources available.[274] Particularly in these settings, optimized PrEP strategies can be of great additional value from both a public health and economic perspective. We therefore evaluated the impact of hypothetical scenarios in which PrEP is prioritized to individuals with the highest sexual activity or is distributed randomly. We could therefore determine cost-effectiveness at both ends of the PrEP distribution spectrum, from where PrEP is given to those at highest risk of becoming

infected, to giving PrEP to individuals regardless of risk. We additionally aimed to evaluate the risk for resistance development.

METHODS

Setting and population

Our model is based on the rural population of Macha, Zambia and using data from the HIV Clinic at Macha Hospital. Macha is located in the Southern Province of Zambia, and approximately 80 km away from the nearest town, Choma.[274] The hospital serves as a district-level referral hospital for rural health centers within an 80 km radius, with 90,000 persons that are aged 12 years and over in the Macha Hospital catchment area.[274] The antenatal prevalence between 2002[275] and 2009 [local data] was stable around 7.7%. Macha Hospital has provided care to over 7500 HIV-infected adults and children since 2005 through the Government of Zambia's antiretroviral treatment program, with additional support from the President's Emergency Plan for AIDS Relief (PEPFAR) through the non-governmental organization, AidsRelief.[274] Since the start of the clinic in 2005, treatment is implemented according to WHO guidelines, initially at CD4 <200 cells/mm^3, and at CD4 <350 cells/mm^3 since 2010. The HIV pharmacy is well-stocked and treatment is readily available for all diagnosed patients who drop below the treatment threshold.

Model and assumptions

A compartmental deterministic mathematical model was constructed and parameters were chosen to represent the Macha setting (Table 1). Our model stratifies disease progression into an acute stage, a chronic stage and two AIDS stages (Figure S1). Two AIDS stages are included because during the final months before death, patients will have limited sexual activity and are therefore assumed not to transmit HIV.[9, 12] The acute stage has a duration that ranged between 10 and 16 weeks.[8] The combined duration of the acute stage and the chronic stage is 8.5-8.7 years.[9, 276] The pre-final AIDS stage ranged between 6 and 12 months.[9, 12] Compared to the chronic stage, it was assumed that infectivity was 27-43 times higher in the acute stage[55] and 3-5 times higher in the AIDS stage[9, 12] (Table 1).

Individuals that test positive for HIV can reduce their risk behavior,[42, 277, 278] largely due to a reduction in acquisition of new partners.[277] Based on recent work done in neighboring Zimbabwe, it is assumed in our model that patients will reduce the acquisition of new partners by 0-40%.[279]

Model Description and Validation

Following earlier model's methods for defining risk structure,[187, 280] the model identifies four sexual activity groups ranging in the number of new sexual partners per year.[193] Data about the proportion of individuals in a particular sexual activity group and their number of new

Table 1. *Model Parameters*

Description	Estimate or Range*	Reference
Test rate	10-20%	Macha, Zambia
Rate of being tested in the acute stage of HIV	50% of the test rate	Assumption**
Rate of being tested in the chronic stage of HIV	test rate	Macha, Zambia
Rate of being tested in the AIDS stage	test rate + 10%	Macha, Zambia
Disease stages duration		[8, 9, 12, 276]
Acute stage	10-16 weeks	
Chronic stage	8.31-8.43 years	
AIDS stage	6-12 months	
Final AIDS stage	7-13 months	
Proportion of people in sexual risk groups		Model Calibration
*Highest****	1.0%-2.9%	
*2nd****	15.1%-24.0%	
3rd	10%	
Lowest	63.1%-73.9%	
Number of partners per year in each sexual risk group		Model Calibration
*Highest****	7-31	
*2nd****	1.5-2.6	
3rd	0.1	
Lowest	0.03	
Mortality rates per year		[197]
Population	0.02	
Chronic HIV stage	0.098	
AIDS stage	0.63	
On treatment during chronic stage, first 3 months	0.05-0.098	
On treatment during chronic stage, second 3 months	0.03-0.06	
On treatment during chronic stage, 6+ month	0.02-0.05	
On treatment during AIDS stage, first 3 months	0.1-0.3	
On treatment during AIDS stage, second 3 months	0.05-0.12	
On treatment during AIDS stage, 6+ month	0.03-0.06	
Linkage to care from test to treat	70%	Macha, Zambia
Proportion of people on PrEP		
Non-prioritized PrEP	40-60%†	Assumption
Prioritized PrEP (approximately half of highest two sexual risk groups)	5-15%‡	Assumption

Effectiveness of PrEP *Moderate Adherence* *High Adherence*	 20-60% 50-90%	[28, 272, 273]
Reduction in transmissibility of those patients on treatment	90-100%	[7, 43, 46]
Rate of resistance among those infected despite use of PrEP	10%, 50%, 100%	Assumption
Rate of discontinuation of PrEP (not due to resistance)	4-5%	[215]
Number of HIV tests per year on PrEP	1-4	Assumption
Number of HIV clinic visits in first year	8	Macha, Zambia
Number of yearly HIV clinic visits after first year	4	Macha, Zambia
Costs		
Cost of PrEP per year (TDF/FTC) (§)	$126 ($137.12)	[281, 282]
Cost of testing negative for HIV per test (§)	$1 ($3.78)	Macha, Zambia, [282]
Cost of testing positive for HIV per test (§)	$3.84 ($9.4)	Macha, Zambia, [282]
Cost of an inpatient day in the hospital	$10.27	[282]
Cost of an outpatient visit in the hospital	$2.78	[282]
Cost of treatment per year (TDF/FTC+EFV) (§)	$194 ($243)	[281]
Cost of a CD4 Count test (§)	$31-$39 ($34-$42)	Macha, Zambia, [282]

Cost discounting rate per year	3%	
Exchange rate, Zambian Kwacha to USD over year 2011	3845:1	

*All ranges are uniformly distributed, except where indicated
** Due to window phase of antibody-based test
***Not uniformly distributed, see figure S2
† Not uniformly distributed, median 43% over 10 years;
‡ Not uniformly distributed, median 12% over 10 years;
§Comprehensive costs, including costs of outpatient visits, additional laboratory tests, laboratory personnel

partners are not available. Using the Monte Carlo filtering techniques[283] we parameterized the different sexual activity groups and only accepted the 1795 simulations that were associated with a prevalence of 7.7% (±0.05%) from 2002 until 2009 in accordance with Macha. Monte Carlo filtering allowed us to test the impact of PrEP over a wide range of sexual activities, as a wide variety of sexual risk group combinations resulted in the appropriate HIV prevalence (Table 1).

In summary, the highest sexual activity group had an average of 13 new partners per year and made up on average just 2% of the population, representing a core group of highly

sexually active individuals. This group is instrumental in determining the peak of the epidemic. Only simulations where this group was small and their number of partners were high allowed the epidemic to peak appropriately. The second highest sexual activity group had on average 2 new partners per year and made up a more substantial 18% of the population, representing individuals whom are not in steady or monogamous relationships. This is the group is an important factor in determining where the equilibrium of the epidemic is reached. The only simulations that were accepted into the analysis were the ones in which this group allowed the epidemic to reach an equilibrium prevalence of 7.7% (±0.05%) from 2002-2009 in accordance with Macha data. The two lowest groups had <1 new sexual partner per year, representing individuals in long term relationships or marriages. The final distribution of proportion of sexual activity groups and number of new partners per year are given in Figure S2. Other variables used to calibrate the model included: transmissibility during the acute stage of infection, transmissibility during the AIDS stage of infection, the rate at which individuals moved from acute to chronic infection, rate at which individuals move from the AIDS stage to the AIDS final stage, and the rate of mixing between sexual risk groups (epsilon). Full model description including equations can be found in the Text S1.

HIV testing

Approximately 10% of individuals aged 12 and older undergo an HIV-test yearly in Macha. In our model, we studied the impact on the HIV-epidemic of test rates that were ranged randomly between the current level and a double proportion of 20%.[284] We assumed different test rates for different stages of disease progression (Table 1).

Treatment

After a positive HIV-test, 70% of individuals are retained in care. Treatment is then started at CD4 <350 cells/mm^3. In the AIDS stage, there is therefore immediate treatment after diagnosis. Additionally it takes approximately 4 years to progress from infection to CD4 <350 cells/mm^3 [11]. Treatment reduces the infectivity by 90-100% as compared to the chronic stage.[7, 43, 46]

Scenario Assumptions

Baseline: Our baseline in this model is the current practice in Macha (i.e. test rate 10-20%, retention 70% and start of treatment at CD4 <350 cells/mm^3).

Non-Prioritized versus Prioritized PrEP distribution: We examined the impact of two hypothetical scenarios where PrEP is perfectly and imperfectly prioritized to represent both ends of the prioritization spectrum. In the first hypothetical scenario, we examined the impact of completely perfect prioritization by assigning approximately half of the individuals in the two highest sexual activity groups, 5-15% of the population (4,500-13,500 individuals), to receive PrEP. We assigned just half of the highest sexual activity groups, as identifying those groups completely would likely not be feasible. In the second hypothetical scenario

where PrEP is imperfectly prioritized, PrEP is assigned to half of the population in a non-prioritized manner by assigning PrEP to 40-60% of the population at random (36,000-54,000 individuals). Time to reach PrEP coverage was 1-2 years.

PrEP adherence: Adherence is key in PrEP use as illustrated by all recent PrEP studies.[28, 32, 272, 273] Since it is unknown what level of adherence would be expected in Macha, we examined a high population-level adherence scenario and ranged PrEP effectiveness from 50%-90%, derived from the highly adherent in recent PrEP trials,[28, 272, 273] and a moderate population-level PrEP adherence scenario, where effectiveness ranged from 20%-60%.

Drug resistance: Rates of drug resistance due to PrEP are currently unknown. Drug resistance may emerge in individuals who become infected with HIV despite the use of PrEP. It is unknown how rapidly resistance will emerge after PrEP failure. We therefore evaluated a scenario with low resistance development, where resistance develops in 10% of breakthrough infections (infections despite the use of PrEP). We also evaluated a moderate resistance and high resistance scenario, where resistance emerges in 50% and 100% of breakthrough infections respectively. The prevalence of drug resistance is expressed as the proportion of individuals with a resistant virus over the total number of infections in the population.

Cost-effectiveness analysis

In order to evaluate the feasibility of the range in PrEP implementations, we conducted a cost-effectiveness analysis. Each compartment in our deterministic model was assigned a range of cost and quality adjusted life year (QALY) depending on the intervention (Table 1, and Tables S1-S3). A QALY of 1 means one year of life lived in perfect health. As our base, a susceptible person not on PrEP was considered to have no reduction in health-related quality of life. Rates of HIV clinical tests were taken from Macha's standard practice, including the different types of tests and how frequently they are administered. Costs and rates for hospitalization of HIV infected persons, opportunistic infections (Table S4), HIV testing, and treatment, were all taken into account using costs from Macha and the WHO-CHOICE costing database.[282] Current ARV costs were taken from the 2011 Clinton Health Access Initiative negotiated prices.[281] An intervention is said to be cost-effective if it costs less than three times the gross national income (GNI) per capita ($3210 in Zambia[285]) per QALY gained. An intervention is defined as very cost-effective at a cost up to one times the GNI per capital ($1070 in Zambia[285]) per QALY.[224, 225] We calculated both the average cost-effectiveness ratios where we compared each scenario to baseline, and the incremental cost-effectiveness ratios where we compared each scenario to the next least-costly scenario.[226] We follow methodological guidelines on cost-effectiveness analysis[226], and only consider the latter as meaningful for making optimal resource allocation decisions. All costs have been discounted yearly (converting future costs into present terms) at the standard of 3%.

Sensitivity Analysis

We performed one-way deterministic sensitivity analysis of cost-effectiveness where our baseline model for comparison was the prioritized PrEP model with moderate PrEP adherence. Eight key input variables, HIV prevalence, PrEP efficacy, proportion of people in highest two sexual activity groups on PrEP, number of HIV tests per year for those on PrEP, cost of antiretroviral drugs, total costs depending on the exchange rate, cost and QALY discounting were considered to identify the sensitivity of our model. We also determined the amount of additional money that could be spent on infrastructure and programmatic costs of implementing prioritized PrEP and have the intervention still be (very) cost-effective.

Ethics Statement

Written informed consent was obtained from the study participants. Ethical approval was granted by the University of Zambia Biomedical Research Ethical Committee in 2008 before data collection began.

RESULTS

Baseline Scenario: Start of Treatment at CD4<350 cells/mm^3

The impact of treatment alone under the current guidelines of treatment at CD4 <350 cells/mm^3 reduces incidence, showing an 18% decline in new infections over 10 years. The prevalence remained stable at 7.7% after 10 years, as treatment dramatically reduces mortality and patients therefore remain alive.

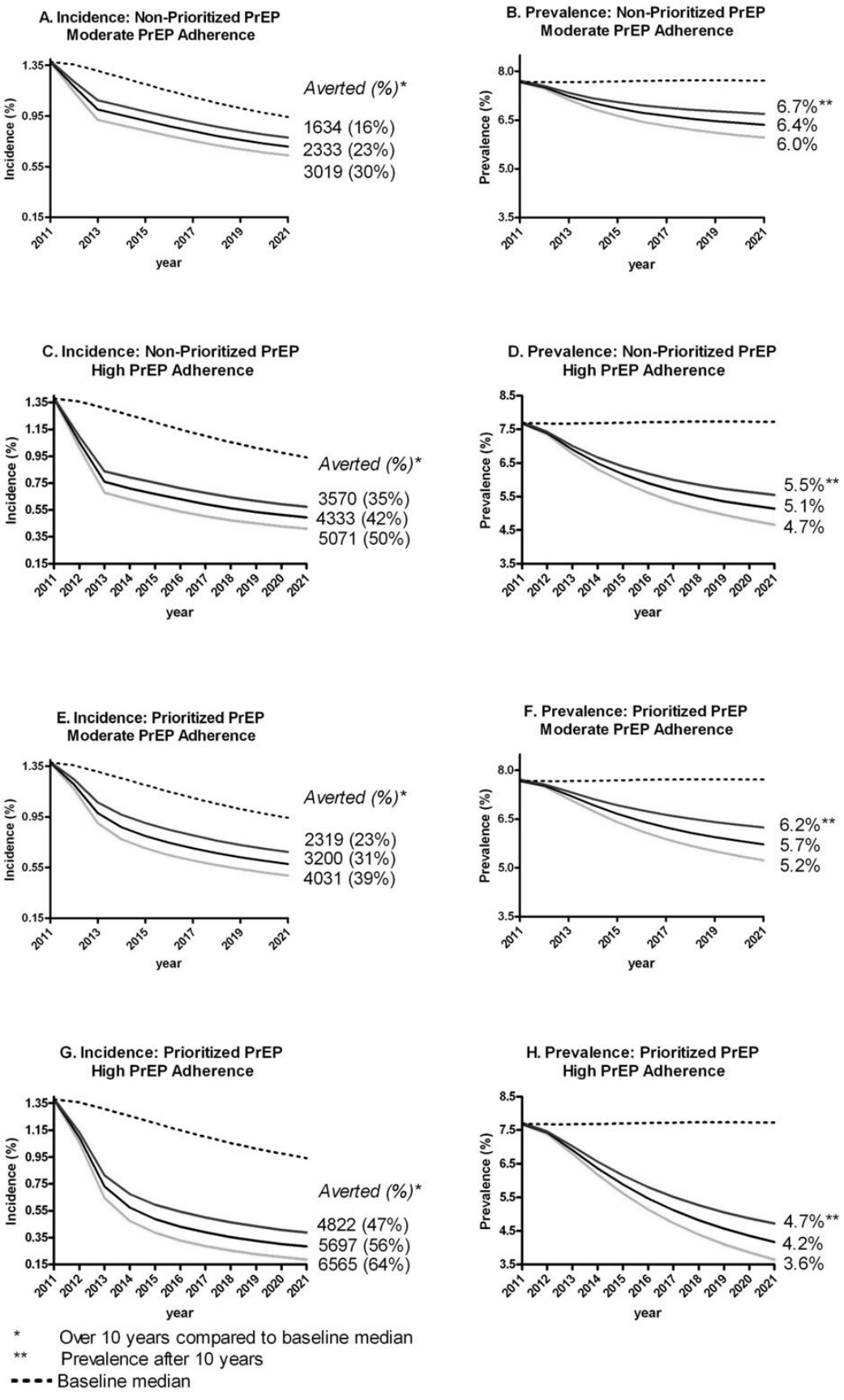
Prioritized versus Non-Prioritized PrEP

Compared to our baseline scenario of starting treatment at CD4 <350 cells/mm^3, prioritizing PrEP will result in 3200 infections averted over 10 years (31% reduction; interquartile range (IQR) 23%-39%), whereas a non-prioritized PrEP strategy will result in just 2333 infections averted (23% reduction; IQR: 16-30%) (Figure 1A, 1E). The prevalence in the prioritized approach is lower after 10 years, at 5.7% (IQR: 5.2%-6.2%), compared to a prevalence of 6.4% (IQR: 6.0%-6.7%) in the non-prioritized strategy (Figure 1B, 1F).

Impact of adherence

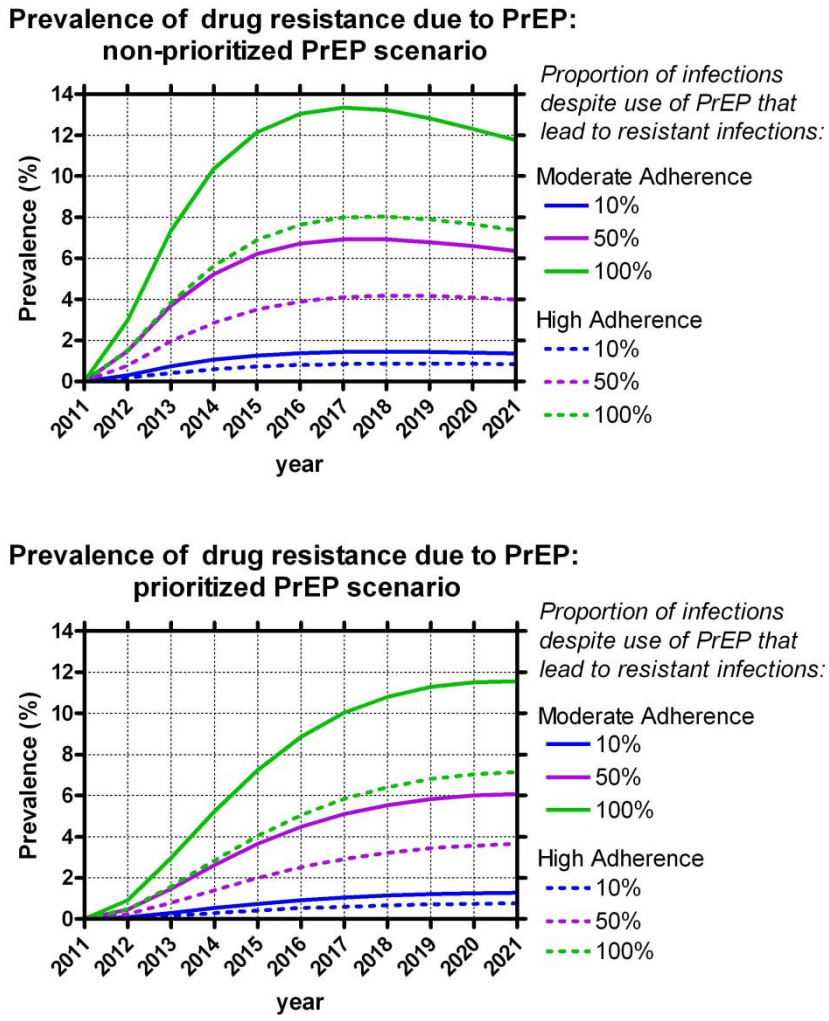
As expected, high PrEP adherence had a strong impact on the HIV epidemic as compared to moderate PrEP adherence in both the prioritized and non-prioritized strategies. The impact, however, was stronger than expected. In the non-prioritized strategy, compared to baseline, an estimated 4333 infections (42% reduction; IQR: 35%-50%) were averted with high

Figure 1. *Prioritizing highest sexual risk groups versus a non-prioritized PrEP strategy, incidence and prevalence.*



adherence to PrEP (Figure 1C), 2000 more than with moderate adherence. In the prioritized strategy, compared to baseline, an estimated 5697 infections (56% reduction; IQR: 47%-64%) were averted with high adherence to PrEP (Figure 1G), almost 2500 more than with moderate adherence. High adherence also has a strong impact on the HIV prevalence after 10 years of the intervention, with a median prevalence of 5.1% (IQR: 4.7%-5.5%) in the non-prioritized strategy and 4.2% (IQR: 3.6%-4.7%) in the prioritized strategy (Figure 1D, 1H).

Figure 2. *Prevalence of drug resistance due to PrEP over 10 years.*



Drug resistance and PrEP

Investigating the impact of PrEP on resistance development showed that when 100% of breakthrough infections developed a drug resistant virus with moderate adherence, the prevalence of drug resistance due to PrEP was strikingly high. In the prioritized PrEP scenario, there was an 11.6% (IQR 10.3%-12.8%) prevalence of drug resistance due to PrEP alone after 10 years (Figure 2). Assuming a 50% and 10% drug resistance rate among PrEP users resulted in a 6.1% (IQR 5.3%-6.8%) and 1.3% (IQR 1.1%-1.4%) drug resistance prevalence due to PrEP after 10 years. The results were almost identical in our non-prioritized scenario.

Adherence, however, appears to strongly impact the prevalence of drug resistance due to PrEP. With high adherence, the drug resistance due to PrEP was 7.1% (IQR 5.3%-8.8%) in the prioritized scenario, approximately 4% lower than in the moderate adherence scenario, assuming a 100% drug resistance rate among PrEP users. Assuming a 50% and 10% drug resistance rate among PrEP users resulted in a 3.7% (IQR 2.6%-4.6%) and 0.8% (IQR 0.5%-1.0%) drug resistance prevalence due to PrEP after 10 years in the prioritized scenario. The results were again almost identical in our non-prioritized scenario with high adherence.

Cost-effectiveness

We evaluated the cost-effectiveness of the prioritized and non-prioritized PrEP interventions compared with the baseline (Table 2). Our baseline scenario cost $4.3 million (IQR: $3.8-$4.7 million) over 10 years. Of that amount, approximately 54% would be covered under PEPFAR as long as PEPFAR continues. A total of 10222 infections would be expected over 10 years.

The prioritized PrEP strategy cost an additional $11.5 million (IQR: $11.1-$13.4 million) compared to the baseline strategy. A median of 36,216 QALYs would be gained (IQR: 26,174, 45,690) with the prioritized scenario over 10 years.

The non-prioritized PrEP strategy cost an additional $43.9 million (IQR: $41.4, $46.0 million) compared to baseline. A median of 23,571 QALYs would be gained (IQR: 15,680, 31,764) with the non-prioritized scenario over 10 years.

Based on the interpretation of average cost-effectiveness ratios only, both strategies can be considered (very) cost-effective. However, the interpretation of incremental costs and effects of the prioritized PrEP strategy as compared to the non-prioritized strategy reveals that the former strategy is both less costly and more effective, and 'dominates' the latter. This means that the non-prioritized PrEP strategy cannot be considered economically attractive. The incremental cost-effectiveness ratio of the prioritized PrEP strategy is $323 per QALY (IQR: $257, $428) and this strategy can thus be considered very cost-effective.

Sensitivity Analysis

One-way sensitivity analyses (Figure 3) highlighted the eight key input parameters of our model. Even when just 10% of the highest two sexual activity groups are prioritized for PrEP (2% of the total population, or 1,800 individuals), the cost per QALY is actually lower than when approximately half of the two highest sexual activity groups are prioritized, at only $177 per QALY. This shows that targeting just a small fraction of those individuals in a higher sexual activity group would be optimal from a cost-effectiveness perspective.

It appears that PrEP will be more cost-effective in regions with higher HIV prevalence at $161 per QALY in a region with a prevalence of 15%. In contrast, prioritized PrEP is no longer very cost-effective for a prevalence of 1%, at $2062 per QALY. The remainder of the parameters-- frequency of HIV testing on PrEP, PrEP effectiveness (as controlled by adherence[28]), cost of ARVs, cost and QALY discounting rate, and exchange rate-- did not result in large differences in cost-effectiveness from our baseline prioritized model.

Table 2. *Cost-effectiveness of PrEP interventions, and additional money available for programmatic costs in each intervention over 10 years for the intervention to remain very cost-effective, or cost-effective*

		Total Effects					*Amount that can be spent and still have the intervention be:*	
Intervention	**Total cost in $ Millions (*) (IQR**)**	**Infections averted (% averted) (IQR)**	**QALYs gained (IQR)**	**Average Cost-Effectiveness Ratio**	**Incremental Cost-Effectiveness Ratio†**	**Conclusion**	**Very Cost-Effective in $ Millions (IQR)**	**Cost-Effective in $ Millions (IQR)**
Baseline, standard care, no PrEP	4.3 (54%) *(3.8, 4.7)*	-	-	-	-	-	-	-
Non-prioritized PrEP, PrEP randomly distributed	48.2 (4%) *(45.7, 50.3)*	2333 (23%) *(16%, 30%)*	23571 (15680, 31764)	$1843 ($1386, $2724)	Dominated‡	-	-	-
Prioritized PrEP to most sexually active	15.8 (13%) *(14.7, 16.9)*	3200 (31%) *(23%, 39%)*	36216 (26174, 45690)	$323 ($257, $428)	$323 ($257, $428)	Very Cost-Effective	25.2 (16.2, 33.2)	98.4 (69.4, 124.9)

*Percentage of total costs that are currently covered under PEPFAR –primarily ARV treatment.
** IQR: Interquartile range
† When non-prioritized PrEP is compared to prioritized PrEP
‡ Less effective and more costly than prioritized PrEP

If implemented, the prioritized PrEP strategy could spend an additional $25.2 million over 10 years on infrastructure and programmatic costs and remain very cost-effective ($94.8 million to remain cost-effective) (Table 2).

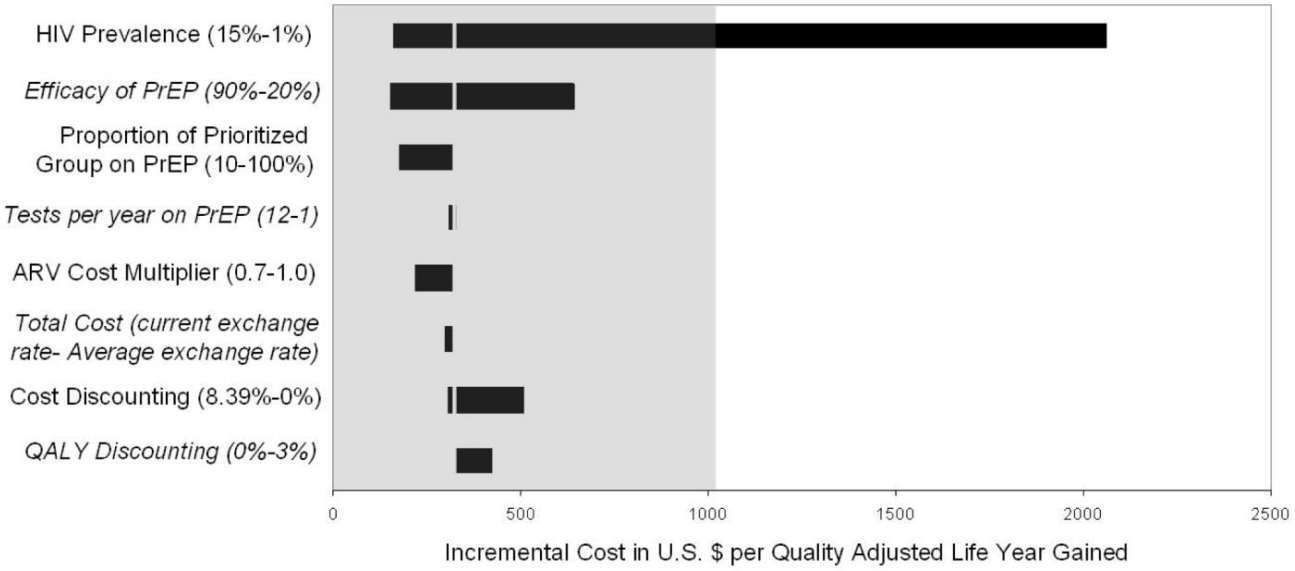


Figure 3. This diagram summarizes the results of a series of one-way sensitivity analyses on the incremental cost-effectiveness of pre-exposure prophylaxis. Each horizontal bar represents the full range of cost-effectiveness ratios produced by varying a given model parameter across its entire plausible range, as described in the methods. The vertical line represents the prioritized PrEP strategy incremental cost-effectiveness estimate ($323 per quality adjusted life year). The grey area of the diagram represents the point to which the given parameters are very cost-effective (at a point of $1070 per quality adjusted life year).

DISCUSSION

Our model has shown that PrEP is a cost-effective strategy for reducing HIV incidence, even when prioritized imperfectly and distributed regardless of risk of acquiring HIV. If PrEP can be perfectly prioritized to the most sexually active individuals, it is a very cost-effective prevention method and averts 31% of infections averted over 10 years at $323 per QALY. Even when prioritizing just a small fraction of the highly sexually active, PrEP is very cost-effective at $177 per QALY gained.

The prevalence of drug resistance due to PrEP could be high. It is therefore important to closely monitor patients who become infected despite the use of PrEP for resistance. Drug resistance is, however, much lower when adherence to PrEP is higher.

A strength of our study is access to cost and epidemiologic data from Macha, a rural setting in Zambia. Access to this dataset enables us to make reliable predictions about the potential implementation of PrEP. Another strength is that there is limited migration into and out of Macha as transportation and mobility are limited. Migration can have a major impact on a

local HIV epidemic, and also on a mathematical model attempting to capture HIV dynamics in a population. The population in Macha has, however, remained fairly stable over time.

A limitation of our modeling approach is that highly sexually active individuals are difficult to identify. Nonetheless, we found that cost-effectiveness remained the same if only 10% of the high sexual activity groups could be prioritized (2% of the total population). Health care providers could begin with prioritizing those individuals who present with STI symptoms at clinics, or are identified as the seronegative partner in a serodiscordant relationship. Over a wide spectrum of adherence and PrEP prioritization, we predict that PrEP will reduce HIV incidence and will be cost-effective.

Our model does not take into account administrative program costs[286], as they would vary widely depending on the precise intervention used. We have also not included indirect costs, as these are very difficult to quantify. We have instead shown the additional amount that could be spent on those costs and retain cost-effectiveness. The government of Zambia or donors could invest an additional $25,200,000 over 10 years in the implementation of prioritized PrEP, and have it remain very cost-effective.

Previous models have shown the potential impact of PrEP. A model by Pretorius *et al.* evaluated cost-effectiveness in a generalized South African epidemic.[287] When all individuals were assigned to receive PrEP, they showed a decrease in incidence in 2025 of about 40% compared to their baseline. This is approximately in line with our findings, albeit a bit low considering that we assigned PrEP to half of our population.

A model by Abbas *et al*. investigated the factors influencing the emergence and spread of HIV drug resistance arising from PrEP rollout, based on a general mature epidemic in sub-Saharan Africa.[288] In their PrEP scenario analyses, the largest decrease in infections was achieved with a non-prioritized strategy (31% in an optimistic scenario, similar to our "high adherence" scenario; 7% in realistic, similar to our "moderate adherence") and the smallest decrease with the prioritized-by-activity strategy (8% in optimistic, 3% in realistic). The benefits of PrEP in this model were much lower than estimates from our model. Reasons for this could be their definitions of optimistic and realistic, as well as the level of protection offered from PrEP.

In iPrEx, HIV drug resistance due to PrEP was not a major issue,[28] likely due to monthly monitoring of participants for seroconversion. The only resistance found was in those with a false negative HIV test at randomization and started PrEP. The study by Abbas *et al.* has also examined the emergence of drug resistance due to PrEP in a heterosexual sub-Saharan epidemic.[288] In agreement with our results, the Abbas model has shown that there is not much difference in the prevalence of drug resistance in a non-prioritized or prioritized PrEP scenario, but that higher PrEP adherence would result in less drug resistance. The total prevalence of resistance in their optimistic scenario was about 1.9-2.5% and 9.2-9.9% in

their realistic scenario. If we had evaluated the same measure of drug resistance, these figures are likely lower than ours.

Several prevention strategies using antiretroviral drugs have been shown to be effective in reducing new infections with HIV. These strategies include antiretrovirals for prevention of mother-to-child transmission,[154, 155] topical tenofovir as an intra-vaginally applied microbicide[34] and earlier start of treatment as prevention.[7] Our baseline model looks at the impact of starting treatment at a CD4 count of <350 cells/mm^3, and found that starting treatment at that cutoff is already an intervention. Incidence was reduced by more than 30% after 10 years.

iPrEx is the first study to be published looking at the efficacy of PrEP, and was investigating an MSM community with high numbers of sexual contacts. Results on the effectiveness of PrEP in heterosexuals have also been reported.[32, 272, 273] FEM-PrEP trial had enrolled 1,951 African women to investigate the efficacy of TDF/FTC as PrEP, and was recently discontinued due to lack of an effect, likely due to adherence.[32] Two studies, however, found more encouraging results. The Partner's PrEP study of 4,758 serodiscordant couples based in Kenya and Uganda found a 73% reduction in risk of the participants on TDF/FTC compared to placebo.[272] Similarly, the CDC's Botswana-based TDF2 study found a 63% reduction in risk of those assigned to receive daily PrEP.[273] Adherence to PrEP is key as the highly adherent in both iPrEx and Partner's PrEP appeared to have the same level of high PrEP efficacy, showing that PrEP works similarly irrespective of MSM or heterosexual transmission.

Even in settings with low test rates and treatment retention, the use of PrEP can still be a useful strategy in averting infections. Our model has shown that PrEP is a cost-effective strategy for reducing HIV incidence, even when adherence is suboptimal and prioritization is imperfect. Particularly in high prevalence settings, prioritizing PrEP to high sexual activity groups could be a cost-effective way to curb the epidemic. Effective ways to prioritize high sexual activity groups in a heterosexual epidemic and maximize adherence should be investigated further in order to increase the numbers of infections averted and cost-effectiveness.

ACKNOWLEDGEMENTS

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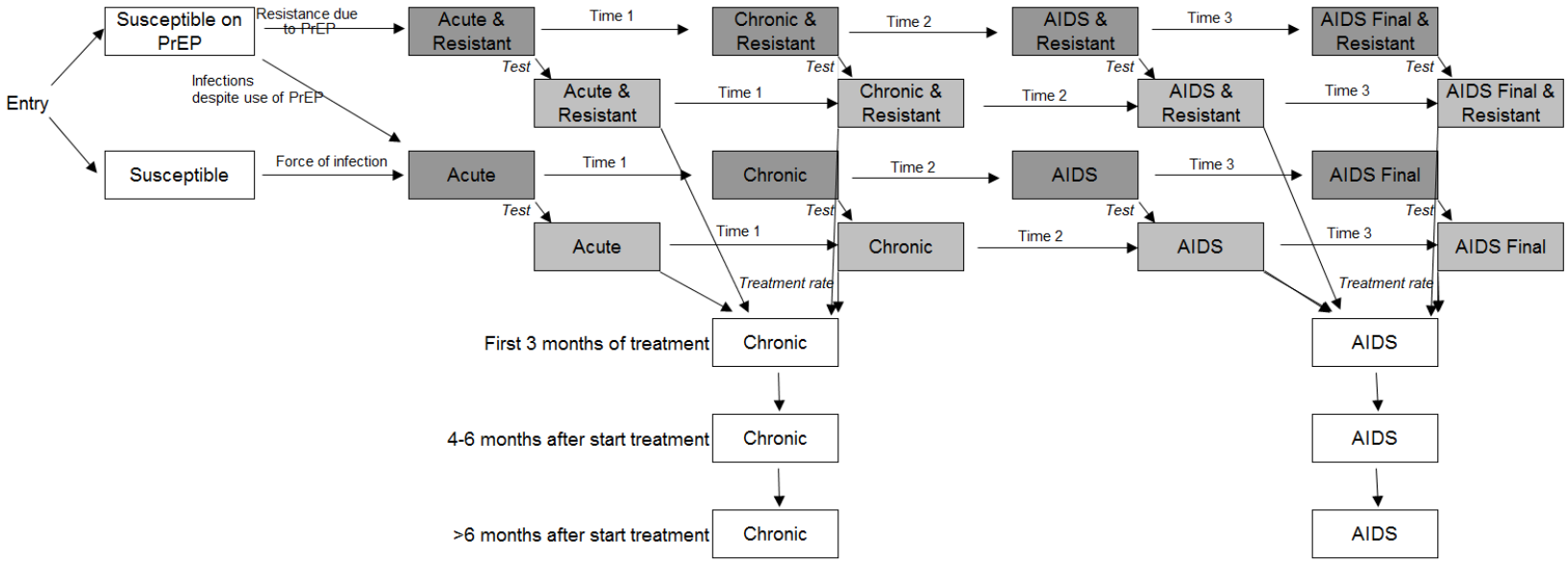
Supplement: Chapter 6

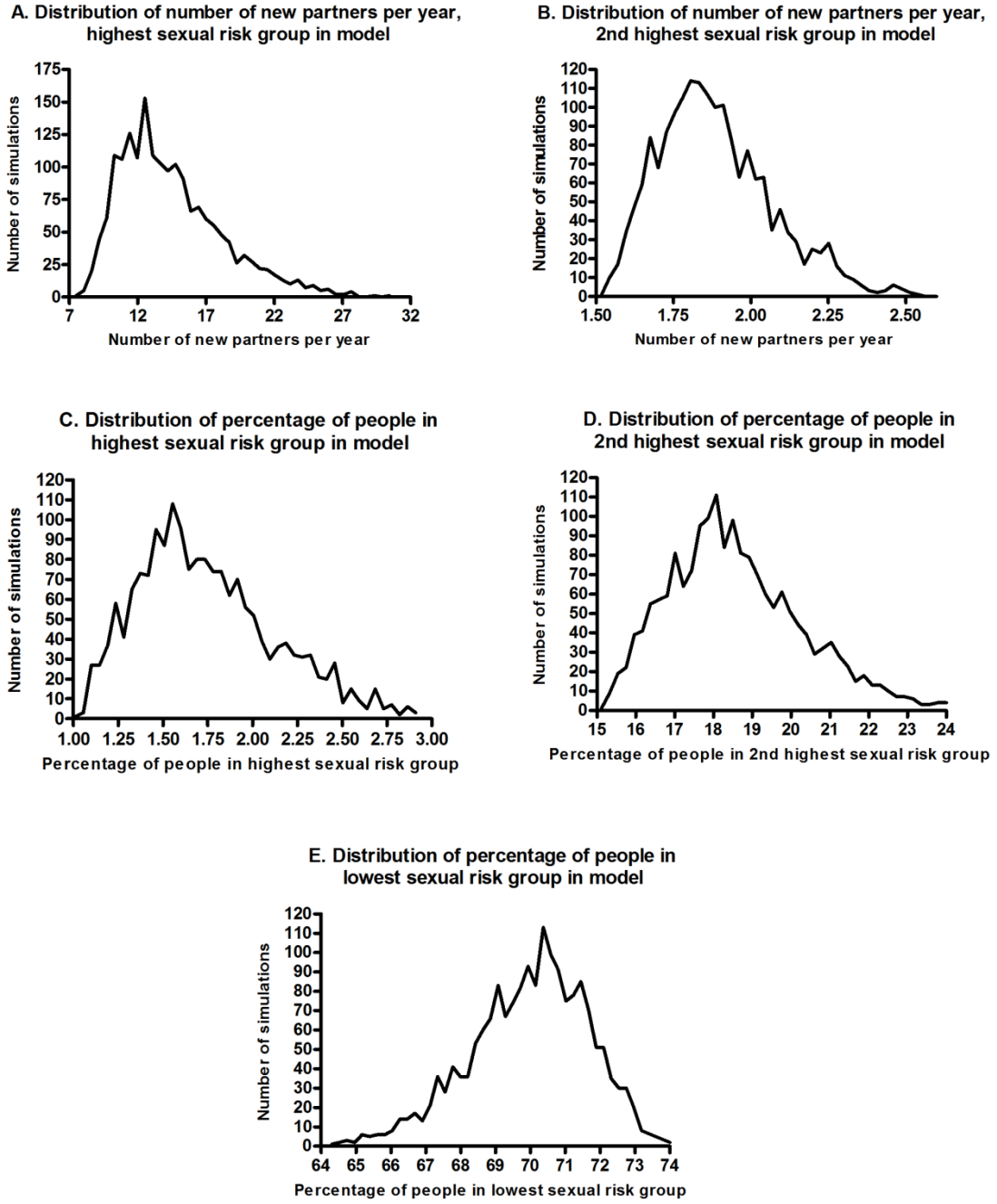
Figure S1. *Structure of the compartmental deterministic model, full description on next page:*



1: *Structure of the model, continued*. The figure is a schematic representation of the dynamic process by which individuals become infected with HIV or resistant HIV due to PrEP, become tested and are given treatment. A proportion of individuals on PrEP will develop a drug resistant virus due to PrEP use, and will progress through infection with a resistant virus. The force of infection is the rate by which susceptible individuals, on PrEP or not, become infected. Without treatment, infected patients progress through four stages: the acute stage, the chronic stage, an AIDS stage in which patients have a limited level of sexual activity and the final AIDS stage in which patients have no sexual activity. Individuals in the dark grey boxes have not been diagnosed with HIV and did not adapt their risk behavior. After testing positive for HIV, individuals move to a light grey box with the corresponding disease stage and adapt their behavior. Individuals on treatment (white boxes on bottom) move through three different periods defined by the time since start of antiretroviral drug therapy and the disease stage in which treatment was started. These periods and disease stages were included as mortality depends on time since start of treatment and the CD4 count at start of treatment.

All boxes have different mortalities. All boxes (except the ones with susceptible individuals) contribute to the force of infection, but all with different infectivity. The mathematical equations are listed in Text S1. Parameters and ranges can be found in Table 1, as well as in Tables S1-S4.

Figure S2: Distributions of sexual activity groups*



*Distribution not shown for 3rd highest sexual risk group, as this was fixed at 10% of the population with 0.1 new partners per year. The number of new sexual partners per year for the lowest sexual risk group was also fixed at 0.03 new partners per year.

Text S1. *Model Description and equations*

The state variables and HIV transmission equations for the model are shown below. There are four activity classes *i* based on the partner acquisition rate change: class 1 in which individuals have 7-31 partners per year, class 2 with 1.5-2.6 partners, class 3 with 0.1 and class 4 with 0.03.

The model included four HIV infection stages *k*: class 1 is the acute stage, class 2 is the chronic stage, class 3 is the pre-final AIDS stage in which individuals have limited sexual activity. Class 4 is the final AIDS stage in which patients do not have any sexual intercourse [9].

During treatment, the model includes two infection stages *l*: class 1 are individuals who were in the recent or chronic stage before start of treatment, class 2 are patients who were in one of the AIDS stage before antiretroviral therapy was initiated.

A proportion of individuals can be assigned to receive pre-exposure prophylaxis (PrEP) or not (ω). Of those that are assigned PrEP, a proportion will develop resistance due to PrEP (α). The model includes two states of drug resistance *r*, state 1 is infected with a non-resistant virus, state 2 has a resistant virus due to PrEP use.

Patients progress through three treatment stages *m*: The first two treatment stages occur, respectively, during the first three months (stage 1) and months four to six after start of treatment (stage 2). Patients receiving antiretrovirals for more than six months are in stage 3.

State variables

E_i = Entry rate susceptible individuals, i=1..4

S_i = Susceptible individuals, i=1..4

S_i^P = Susceptible individuals on PrEP, i=1..4

$I_{i,k,r}^U$ = HIV infected individuals, unaware of their infection, i=1..4, k=1..4, r=1..2

$I_{i,k,r}^T$ = HIV infected individuals who tested positive for HIV, i=1..4, k=1..4, r=1..2

$I_{i,l,m}^{Rx}$ = Infected individuals receiving treatment, i=1..4, l=1..2, m=1..3

Other variables

$\lambda_{i,k}$ = Force of infection, i=1..4, k=1..4

$\lambda_{i,k}^P$ = Force of infection, with use of PrEP, i=1..4, k=1..4

N_i = Number of individuals in sexual activity class i, i=1..4

μ = Mortality general population

μ_k = Mortality untreated HIV infected patients in infection stage *k,* k=1..4

$\mu_{l,m}^{Rx}$ = Mortality treated patients in treatment stages *l* and *m,* l=1..3, m=1,2

γ_k = HIV infection progression rate by stage k, k=1..4

τ_k = Proportion of patients tested for HIV in stage k, k=1..4

RX_k = Proportion of patients starting treatment in progression stage k, k=1..4

ρ = Proportion of patients that are retained in care

α = Rate of development of HIV-resistant virus due to PrEP use

ω = Proportion of patients on PrEP

d = Rate of discontinuation of antiretroviral treatment

φ = Effectiveness of PrEP

ψ = Reduction in transmissibility of breakthrough infection

Ordinary Differential Equations

(1) $E_i = 90,000 - S_i - S_i^P - I_{i,k,r}^U - I_{i,k,r}^T - I_{l,m}^{Rx}$

(2) $S_i = E_i(1-\omega) - S_i \sum_{k=1}^{4} \lambda_{i,k} - S_i \mu$

(3) $S_i^P = E_i(\omega) - S_i^P \sum_{k=1}^{4} \lambda_{i,k}^P - S_i^P \mu$

(4) $I_{i,1,1}^U = S_i \sum_{k=1}^{4} \lambda_{i,k} + S_i^P (\sum_{k=1}^{4} \lambda_{i,k}^P)(1-\alpha) - I_{i,1,1}^U(\mu_1 + \gamma_1 + \tau_1)$

(5) $I_{i,1,2}^U = S_i^P (\sum_{k=1}^{4} \lambda_{i,k}^P)\alpha - I_{i,1,2}^U(\mu_1 + \gamma_1 + \tau_1)$

(6) $I_{i,k,r}^U = \gamma_{k-1} I_{i,k-1,r}^U - I_{i,k,r}^U(\mu_k + \gamma_k + \tau_k)$
$k = 2,3$

(7) $I_{i,4,r}^U = \gamma_3 I_{i,3,r}^U - I_{i,4,r}^U(\mu_4 + \tau_4)$

(8) $I_{i,1,r}^T = I_{i,1,r}^U \tau_1 - I_{i,1,r}^T(\mu_1 + \gamma_1 + \rho RX_1)$

(9) $I_{i,k,r}^T = I_{i,k,r}^U \tau_k + \gamma_{k-1} I_{i,k-1,r}^T - I_{i,k,r}^T(\mu_k + \gamma_k + \rho RX_k)$
$k = 2,3$

(10) $I_{i,4,r}^T = I_{i,4,r}^U \tau_4 + \gamma_3 I_{i,3,r}^T - I_{i,4,r}^T(\mu_4 + \rho RX_4)$

(11) $I_{i,1,1}^{Rx} = \mathrm{r}\,(I_{i,1,r}^T * RX_1 + I_{i,2,r}^T * RX_2) - I_{i,1,1}^{Rx}(4 + d + \mu_{1,1}^{Rx})$

(12) $I_{i,2,1}^{Rx} = \rho(I_{i,3,r}^T RX_3 + I_{i,4,r}^T RX_4) - I_{i,2,1}^{Rx}(4 + d + \mu_{2,1}^{Rx})$

(13) $I_{i,l,2}^{Rx} = 4I_{i,l,1}^{Rx} - I_{i,l,2}^{Rx}(4 + d + \mu_{l,2}^{Rx})$

(14) $I_{i,l,3}^{Rx} = 4I_{i,l,2}^{Rx} - I_{i,l,3}^{Rx}(d + \mu_{l,3}^{Rx})$

Force of infection

The equation for the force of infection includes a mixing matrix $M_{i,k}^{U}$ for patients unaware of their infection and a matrix $M_{i,k}^{T}$ for patients aware of their infection, with a different infectiousness for each stage, $\beta_{i,k}$. The elements of this matrix are *i,k* and represent the probability that an individual with *i* new partnerships per year will form a new partnership with a member who has *k* new partners. The rate at which the sexual partner changes for individuals in each sexual activity group *i* is expressed as c_i. The values of the matrix depend on the degree of mixing ε. This degree can be fully assortative (ε=1), where partnerships are only formed within the same activity class. Or fully random (ε=0), where partnerships are randomly formed between different activity classes [193].

(15) $$M_{i,k}^{U} = \varepsilon\delta + \frac{(1-\varepsilon)c_k N_k}{\sum_{i=1}^{4} c_i N_i}$$

(16) $$M_{i,k}^{T} = \varepsilon\delta + \frac{(1-\varepsilon)(1-\zeta)c_k N_k}{\sum_{i=1}^{4} (1-\zeta)c_i N_i}$$

Where δ = 1 when *i = k*, and δ = 0 when *i ≠ k*. Furthermore, ζ is the proportional reduction in acquisition of new partnerships after patients become aware of their infection. ζ ranges between 0 and 40% for k=1,2 and ζ = 0 for k=3,4.

(17) $$\lambda_{i,k} = \lambda_{i,k}^{U} + \lambda_{i,k}^{T} + \lambda_{i,k}^{RX}$$

(18) $$\lambda_{i,k}^{P} = (1-\varphi)(\lambda_{i,k}^{U} + \lambda_{i,k}^{T} + \lambda_{i,k}^{RX})$$

(19) $$\lambda_{i,1}^{U} = (1-\psi)c_i \frac{M_{i,1}^{U}}{N_1}(\beta_{i,1} I_{i,1}^{U})$$

(20) $$\lambda_{i,k}^{U} = c_i \sum_{k=2}^{4} \frac{M_{i,k}^{U}}{N_k}(\beta_{i,k} I_{i,k}^{U})$$
$$k = 2,3,4$$

(21) $$\lambda_{i,1}^{T} = (1-\psi)(1-\zeta)c_i \frac{M_{i,1}^{T}}{N_1}(\beta_{i,1} I_{i,1}^{T})$$

(22) $$\lambda_{i,k}^{T} = (1-\zeta)c_i \sum_{k=2}^{4} \frac{M_{i,k}^{T}}{N_k}(\beta_{i,k} I_{i,k}^{T})$$
$$k = 2,3,4$$

(23) $$\lambda_{i,k}^{RX} = (1-\zeta)c_i \sum_{k=1}^{4} \frac{M_{i,k}^{T}}{N_k}(\beta_{i,k} I_{l,m}^{RX})$$

In which $\lambda_{i,k}^{U}$ is the force of infection due to contact with patients unaware of their infection. Similarly, $\lambda_{i,k}^{T}$ and $\lambda_{i,k}^{RX}$ are the forces of infection due to contacts with patients tested positive for HIV and patients receiving treatment. Additionally, $\lambda_{i,k}^{P}$ is the force of infection due to contact of people on PrEP with all infected patients.

Table S1. *Assumed utility weightings for QALYs*

Status	**Utility Weight***
Susceptible	1.0
Susceptible on PrEP	98-100%: 1.0 0-2%: 0.9-1.0**
Acutely infected	0.94
Chronically infected	0.94
Infected early AIDS stage	0.82
Infected late AIDS stage	0.7
Infected on treatment	0.94
*Weights based on a pooled analysis by Tengs and Lin (2002) [222] **0-2% will suffer from renal failure on these ARVs[289], which could result in a reduction in quality of life, or go unnoticed.	

Table S2. *Costs used in treating opportunistic infections, per unit*

Drug	**Unit**	**Cost, USD**	**Source**
Aciclovir	200mg	$0.014	Macha, Zambia
Amoxicillin	250mg	$0.037	Macha, Zambia
Amphotericin B	50mg	$6.12	Macha, Zambia
Ciprofloxacin	250mg	$0.029	Macha, Zambia
Doxycycline	100mg	$0.011	Macha, Zambia
Fluconazole	200mg	$0.125	Macha, Zambia
RHE	150/75/400mg	$0.025	[290]
RHZE	150/75/400/275mg	$0.06	[290]

Table S3. *Costs used in diagnosing opportunistic infections and monitoring HIV, per test*

Test/Supply	**Cost, USD***
Antigen test	$0.82
CD4 Test	$31-$39
Chest X-ray film	$0.83
Creatinine test	$0.15
Hepatitis B	$1.87
Lumbar puncture	$2.78
Microscope slide	$0.03
RPR	$0.16
Cost of lab personnel, per minute	$0.007
*All costs taken from Macha, Zambia	

Table S4. *Opportunistic infection rates* and hospitalization & treatment assumptions***

Opportunistic Infections (OIs), observed in Macha dataset	Rate of OI			Percent Hospitalized	Duration of Hospitalization	Drugs used to treat disease:	Additional lab tests needed
	Chronic	AIDS	On Treatment				
Herpes Zoster	2.00%	6.40%	4.10%	5-15%	7 days	Aciclovir, 5x800mg, 7 days	-
Diarrhea	0.46%	3.10%	2.10%	5-10%	3-7 days	Ciprofloxacin, 2x500mg 3-5 days	-
Tuberculosis	0.92%	3.10%	2.20%	90-100%	14 days	RHZE 2 months, RHZ 4 months	Chest X-ray, 3 acid-fast bacillus (AFB) smears
Pneumonia	1.00%	2.20%	1.20%	75-85%	5-7 days	Amoxicillin, 4x1000mg, 7 days	-
Oral Candida	0.46%	2.40%	1.80%	0%	-	Fluconazole, 1x100mg, 7 days	-
Genital Ulcers	0.31%	1.40%	1.10%	0%	-	Doxycycline, 2x100mg, 7 days	Rapid plasma reagin (RPR)
Esophageal Candida	0.00%	0.15%	0.15%	20-30%	5-7 days	Fluconazole, 1x200mg, 7-14 days	-
Extra Pulmonary TB	0.15%	0.69%	0.38%	90-100%	14-21 days	RHZE 2 months, RHZ 10 months	Chest X-ray, 3 AFB smears
Cryptococcal Meningitis	0.08%	0.23%	0.08%	100%	21-28 days	Amphotericin B, 2x50mg, 14 days; Fluconazole, 1x400mg, 14-365 days	Antigen test, lumbar puncture
Kaposi's Sarcoma-Cutaneous	0.00%	0.23%	0.23%	20-40%	7 days	Start ART	-
Herpes Simplex	0.08%	0.46%	0.46%	0%	-	Aciclovir, 3x400mg, 5-10 days	-
Kaposi's Sarcoma- Visceral	0.00%	0.08%	0.00%	80-90%	14-28 days	Start ART	-
Urethritis	0.08%	0.08%	0.08%	0%	-	Doxycycline, 2x100mg, 7 days	-

*Based on data from Macha

**Based on expert opinion of three physicians, one in Macha, two from Erasmus MC

Chapter 7

Pre-Exposure Prophylaxis will have a limited impact on HIV-1 drug resistance in sub-Saharan Africa: A comparison of mathematical models

David A.M.C. van de Vijver, Brooke E. Nichols, Ume L. Abbas, Charles A.B. Boucher, Valentina Cambiano, Jeffrey W. Eaton, Robert Glaubius, Katrina Lythgoe, John Mellors, Andrew Phillips, Kim C. Sigaloff, Timothy B. Hallett

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ABSTRACT

Background Preexposure prophylaxis (PrEP) with tenofovir and emtricitabine can prevent new HIV-1 infections, but there is a concern that use of PrEP could increase HIV drug resistance resulting in loss of treatment options. We compared standardized outcomes from three independent mathematical models simulating the impact of PrEP on HIV transmission and drug resistance in sub-Saharan African countries.

Methods All models assume that people using PrEP receive an HIV test every 3-6 months. The models vary in structure and parameter choices for PrEP coverage, effectiveness of PrEP (at different adherence levels) and the rate with which HIV drug resistance emerges and is transmitted.

Results The models predict that the use of PrEP in conjunction with antiretroviral therapy will result in a lower prevalence of HIV than when only antiretroviral therapy is used. With or without PrEP, all models suggest that HIV drug resistance will increase over the next 20 years due to antiretroviral therapy. PrEP will increase the absolute prevalence of drug resistance in the total population by less than 0.5% and amongst infected individuals by at most 7%. Twenty years after the introduction of PrEP, the majority of drug-resistant infections is due to antiretroviral therapy (50-63% across models), whereas 40-50% will be due to transmission of drug resistance, and less than 4% to the use of PrEP.

Conclusion HIV drug resistance resulting from antiretroviral therapy is predicted to far exceed that resulting from PrEP. Concern over drug resistance should not be a reason to limit the use of PrEP.

INTRODUCTION

In 2011, an estimated 2.5 million people became infected with HIV-1.[291] Alongside behavior change, male circumcision, and condom use, there is an urgent need for novel HIV prevention strategies. Daily oral pre-exposure prophylaxis (PrEP) with tenofovir and emtricitabine can prevent 44-75% of new HIV infections.[28, 272, 273] Two studies have found no protective effect of PrEP on prevention of new infections, but this was probably due to limited adherence.[32, 292]

The use of PrEP can result in the emergence and spread of drug resistance[33] if individuals on PrEP are infected with HIV before, or while taking PrEP. Only a single point mutation in the viral genome is required for resistance to tenofovir (K65R), and another single point mutation is required for resistance to emtricitabine (M184V).[33] Drug resistance can therefore quickly emerge in HIV infected individuals that use PrEP. Indeed, resistance was shown to develop in most patients who started PrEP in the trials whilst also having an unrecognized acute infection.[28, 32, 272, 273] However, in those individuals that became infected following assignment to PrEP, resistance developed in only a few, perhaps due to suboptimal adherence.[28, 272, 273]

There is a concern that the preventive benefits of PrEP could be offset in the long-term by an increase in drug resistance to commonly prescribed antiretroviral drug regimens.[293] The World Health Organization (WHO) recommends the use of tenofovir in first-line regimens. In addition, any first-line regimen is recommended to include lamivudine or emtricitabine,[108] which have comparable resistance profiles. The concern over resistance is highlighted by the US food and drug administration (FDA) that approved PrEP under the condition that drug resistance is evaluated in viral isolates from individuals that become infected while using PrEP.[294]

Determining the impact of PrEP on the development of drug resistance requires prospective epidemiological studies. These studies would have to be unfeasibly large, expensive, and time consuming. Mathematical modeling has therefore been used to predict if PrEP can increase drug resistance in infected populations.[288, 295-297] However, these mathematical models can make diverse predictions. This heterogeneity can be the result of differences in assumptions used in reconstructing HIV transmission and drug resistance, differences in the risk behavior structure, differences in the setting being modeled, or simply differences in the way the question is posed and the results articulated.

We compared standardized outcomes from three independent mathematical models that determined the impact of PrEP on HIV transmission and drug resistance in areas in sub-Saharan Africa where antiretroviral therapy (ART) is available. The outcomes of the models were standardized so that differences in results could not be due to differences in the way the results were articulated.

METHODS

Study design

We reviewed PubMed for mathematical models that studied the impact of PrEP in the presence of antiretroviral therapy on HIV drug resistance in sub-Saharan Africa (Keywords: PrEP, resistance, model). We also reviewed the proceedings of the main HIV conferences for similar models (the conferences considered were the Conference on Retroviruses and Opportunistic Infections -CROI, the meeting of the International AIDS Society- IAS and the AIDS meeting). Three groups agreed to participate in the model comparison exercise. The models included are (i) the Synthesis Transmission Model,[21, 298] (ii) the South African Transmission Model,[296] and (iii) the Macha Transmission Model[297] (Table 1). The Synthesis Transmission model reports that PrEP will not increase the number of people living with a drug resistant virus.[21, 298] The other models used a different metric and find that drug resistance can increase amongst infected individuals after PrEP implementation.[296, 297]

Mathematical models

The Synthesis Transmission Model is an individual-based stochastic model that simulates the HIV epidemic in Sub-Saharan Africa starting in the 1980s and incorporates age (range 15 to 65 years), gender, condom-less sex, CD4 count, specific antiretroviral drugs and resistance. For this model comparison, the model was calibrated to the HIV epidemic in South-Africa. The overall adult HIV prevalence was 15.4% in 2013, when PrEP is introduced. Availability of ART starts in 2003 with initiating therapy in those with WHO stage 4 or CD4 cell count<200 cells/µl. After 2010, the model assumes that ART is initiated at a CD4 count<350 cells/µl.[21] PrEP introduction in the model was implemented in the form of a program targeting sero-discordant couples currently having condom-less sex.

The South African Transmission Model is a deterministic mathematical model that simulates the HIV epidemic in the adult population (15-49 year-olds) of South Africa. The model assumes an HIV prevalence of 17% at the end of 2003 when roll-out of ART was started. The model assumes a treatment eligibility threshold of CD4< 200 cells/µl until the end of 2009 when the threshold changes to CD4<350 cells/µl. The model is stratified according to gender, sexual activity level, stage of HIV-infection, drug resistance, and use of ART or PrEP. In this comparison, we use the base-case scenario.[296]

The Macha Transmission Model is a deterministic mathematical model that focuses on Macha, a rural area in southern Zambia. The model assumes an HIV prevalence of 7.7% from 2002 until 2009. Treatment is started in patients with a CD4 count<350 cells/µl. The model is stratified according to sexual activity level, stage of HIV-infection, drug resistance due to PrEP, and use of ART or PrEP.[297] For this model comparison, the model was extended to simulate acquired resistance due to ART based on previously reported data.[220]

Assumptions of the models regarding PrEP

The models assume that PrEP becomes available in areas where antiretroviral drugs have already been used for HIV treatment for 8 to 10 years. All models assume that people receiving PrEP will be tested for HIV at intervals between three and six months (Table 1).

The models use different assumptions about the uptake of a future PrEP intervention. The Synthesis Transmission Model assumes that eventually 5% of the entire uninfected population will use PrEP. The South African Transmission Model and the Macha Transmission Model assume that 30% and 15% of the uninfected population, respectively, will receive PrEP once it is rolled out.

The models assume that PrEP has a high efficacy in preventing infection with HIV and that the effectiveness of PrEP in daily practice depends on adherence.[28, 272, 273] The Synthesis Transmission Model assumes that PrEP prevents all infections with HIV when a patient is fully adherent. When patients are partially adherent, the model assumes that percentage reduction in effectiveness of PrEP is equivalent to the percentage of PrEP doses taken.[28] The South African Transmission Model also assumes that the effectiveness of PrEP depends on adherence, but used the efficacy of the Partners PrEP study.[272] The South African Transmission Model and the Macha Transmission Model assume an average PrEP effectiveness of 75%[296] and 44%,[28] respectively.

Assumptions of the models regarding drug resistance

The outcomes of the models are standardized according to three important events that contribute to drug resistance: acquired resistance due to treatment with antiretroviral drugs, transmission of drug resistant HIV at the time of infection and acquired drug resistance due to the use of PrEP whilst infected. In the following paragraphs we discuss the assumptions (summarized in Table 1) made in the different models regarding these events.

The Synthesis Transmission Model assumes that drug resistance due to PrEP is characterized by the M184V and/or K65R mutations.[21, 298] The other models do not specifically represent different drug-resistance mutations but assume that resistance due to PrEP results from the M184V mutation, as was previously reported.[28, 272, 273]

Epidemiological studies report wide variations in the risk of acquired drug resistance during treatment.[120, 213, 299] The proportion of people on ART in whom acquired resistance developed by the end of the first year was 7% in the Synthesis Transmission Model, 16% in the South African Transmission Model[19, 300] and 7% in the Macha Transmission Model.[220] All models assume that the risk of acquired resistance gradually decreases after one year of ART.

The models all assume that transmission of drug resistant HIV depends on the plasma HIV RNA viral load. The Synthesis Transmission Model assumes that the risk of transmitting wild-

Table 1. *Comparison of mathematical models and key assumptions*

Model name	Synthesis Transmission Model	South-African Transmission Model	Macha HIV Transmission Model
Setting and structure of the models			
Model authors	Valentina Cambiano, Deenan Pillay, Jens Lundgren, Geoff Garnett, Andrew Phillips	Ume Abbas, Robert Glaubius, John Mellors	Brooke Nichols, Charles Boucher, Jan Nouwen, Janneke van Dijk, Phil Thuma, David van de Vijver
Target population for PrEP	Sero-discordant couples having unprotected sex in sub-Saharan Africa	South African population, aged 15-49 years	Catchment area of rural Macha mission hospital, Zambia
Structure	Individual-based stochastic	Deterministic	Deterministic
HIV related parameters			
Prevalence (years)	15.4% (2013)	17% (2004)	7.7% (2002 – 2009)
Transmission	Depends on plasma HIV-1 RNA viral load	Probability in chronic stage is 0.0017 per sex act, 10-fold increase during acute stage, 3-fold during final stage/AIDS	10% per partnership per year, 4.9 fold increase in acute stage and 4.3 fold during AIDS stage [9]
CD4 count at start of treatment	Before 2010 <200 cells/µl; 2010 and later <350 cells/µl	Before 2010 <200 cells/µl; 2010 and later <350 cells/µl	<350 cells/µl
PrEP related parameters			
Coverage	5% (couples)	30%	15%
Implementation of PrEP	10 years after roll-out of antiretroviral therapy	8 years after roll-out of antiretroviral therapy	8 years after roll-out of antiretroviral therapy
HIV testing for those on PrEP	Every 3 months	Every 6 months	Every 6 months
Transmission reduction due to PrEP	Depends on adherence taken from iPrex.[28] PrEP had a 100%	Depends on adherence. Taken from Partners PrEP. [272] PrEP has 90%	Depends on adherence. An average value of 40% was taken [28]

	efficacy when a patient was fully adherent. Otherwise, the level of protection depended on the level of adherence. The distribution of the level of adherence was taken from iPrEX	efficacy when a patient has taken PrEP. 88% of persons receiving PrEP took the drugs 95% of the time, 12% took the drugs 1% of the time.	
Drug resistance			
Acquired resistance on treatment	6.6% during first year, 8.9% after two years, 10.9% after three years, up to 29.8% after 20 years	16% during first year, 5% show virological failure after one year with 60% of those developing resistance	7% during the first year, additional 3% during the second year [220] and then additional 0.5% per year
Acquired resistance on PrEP	Depends on adherence and ranges between 25% and 44% after three months on PrEP	Depends on adherence, 33% resistance within one month on average	A pessimistic scenario was taken in which resistance always emerged
Transmission of drug resistance	Depends on plasma HIV-1 RNA viral load, M184V reduced by 80% and K65R by 30%	75% probability relative to wild-type in case of acquired and 100% in case of transmitted ART or PrEP resistance.	50% probability as compared to wild-type
Effectiveness of PrEP in preventing infection against resistant virus	0-50% efficacy relative to wild-type (dependent on presence of M184V and/or K65R)	25% efficacy relative to wild-type	50% efficacy relative to wild-type
Reversion of resistance after PrEP removal	M184V reverts back to wild-type at a rate of 0.8 per three months , K65R at a rate of 0.2 per three months	PrEP resistance reverts on average after 1.5 months	A pessimistic scenario was taken in which reversion was assumed to not occur
Impact on future treatment after PrEP failure	Diminished (dependent on presence of specific mutations)	Diminished	Diminished

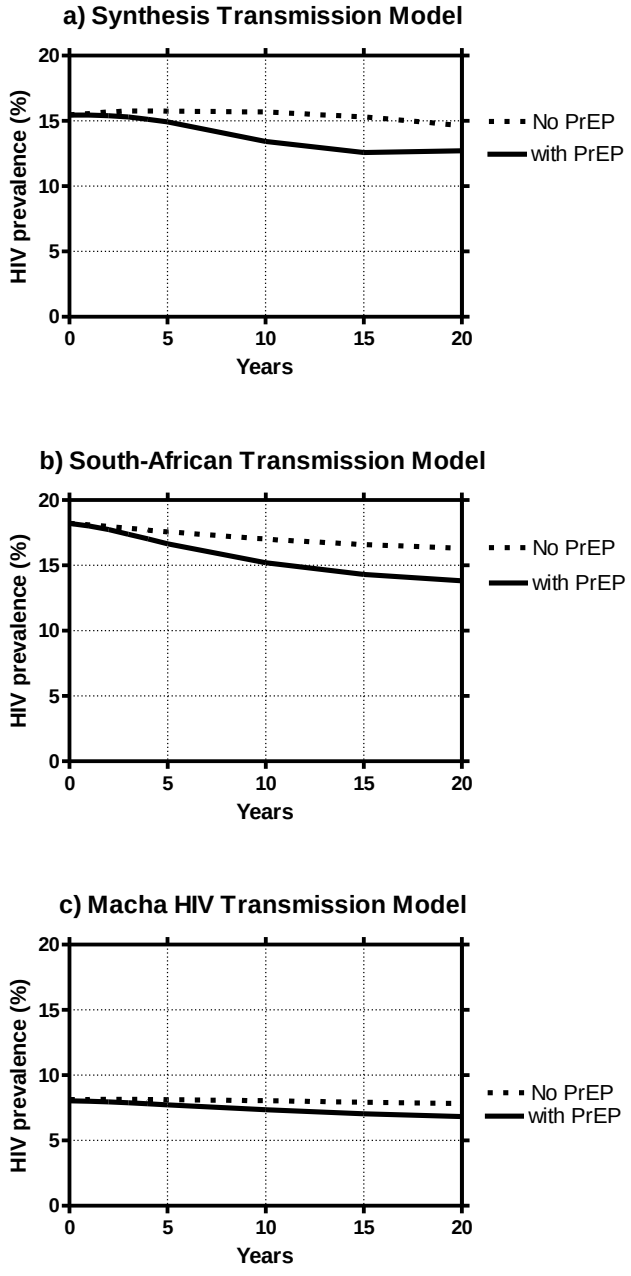
type or drug resistant HIV is the same for a given plasma HIV RNA viral load. However, because individuals with drug resistant virus are more likely to be on antiretroviral drugs, they are less likely to transmit because they have a lower plasma HIV RNA viral load.[167] Given that a person with a virus containing the M184V mutation is the source of a new infection, the probability that this mutation is transmitted is 20%; the corresponding figure for K65R is 70%.[166, 301] The South African Transmission Model assumes that drug resistant virus acquired during treatment has a reduced fitness on average[164] and is therefore 25% less transmissible[167] than wild-type virus. Conversely, a virus with transmitted drug resistance is assumed to be equally transmissible as wild-type virus. The Macha Transmission Model assumes that resistance to PrEP involves the M184V mutation which is associated with 50% lower plasma HIV RNA level as compared to a wild-type virus[165] and is assumed to be 50% less transmissible.[181] In addition, all of the models assume residual virological efficacy of antiretrovirals against drug resistant viruses,[302] resulting in partial effectiveness of PrEP in preventing infection with a resistant virus. In particular, the Synthesis Transmission Model assumes a partial effectiveness of PrEP against a drug resistant virus (in the presence of K65R or M184V) that is 50% lower than the effectiveness of PrEP against a wild-type virus. PrEP is assumed not effective against a virus containing both the K65R and the M184V mutations. Similarly, the South Africa Transmission Model and the Macha Transmission Model assume that drug resistance reduces the effectiveness of 75% and 50%, respectively.[181]

The assumptions relating to the emergence of drug resistance amongst persons who continue or start using PrEP after becoming infected differ for the three models. Emergence of drug resistance in the Synthesis Transmission Model depends on number of active drugs, viral load and adherence. It is assumed that continued use of PrEP after infection results in the emergence of drug resistance in 25-44% of patients after three months with the risk continuing at the same rate thereafter. The South African Transmission Model assumes that drug resistance will emerge in 33% of persons on average after one month of inappropriate use of PrEP after becoming infected and with the same risk thereafter. The Macha Transmission Model uses a worst-case scenario meaning that resistance will always develop after PrEP failure.

The Synthesis Transmission Model and the South African Transmission Model assume that once PrEP is stopped, the virus can revert to a majority variant that is not resistant to antiretroviral drugs while off ART. There is evidence that the M184V mutation, which is the most frequently observed in PrEP failure, can revert within weeks to a wild-type virus that is susceptible to antiretroviral treatment.[207] The Synthesis Transmission Model assumes that M184V reverts to a wild-type virus at a rate of 80% per three months. This rate is comparable to the South Africa Transmission Model that assumes that reversion takes places after an average of 1.5 months. The Macha Transmission Model follows a worst-case scenario assuming that reversion will not occur. The other models assume that after reversion, drug resistance remains present in a minority of viruses[303] resulting in an increased likelihood of developing HIV drug resistance after start of ART initiation.

Output metrics

To enable comparison between the models, each model simulated two strategies over twenty years: In the first strategy ART was provided and in the second strategy both PrEP and ART were provided. The key outputs of the models for comparison were the prevalence of HIV in the general population, the prevalence of HIV-drug resistance in the general population, the proportion of infected individuals with resistant infections, and the source of drug-resistant infection.



RESULTS

Impact of ART and PrEP on the prevalence of HIV

All models assume that access to ART will increase in the next twenty years and that ART can prevent new HIV infections.[7] Baseline model projections suggest that if PrEP is not implemented, HIV will decrease by a modest amount without PrEP: by almost 2% in the South-African Transmission Model and by less than 1% in the two other models (Figure 1).

All models find that availability of PrEP will result in greater decreases in HIV prevalence as compared to a situation where PrEP is not available. The greatest decrease is predicted in the South African Transmission Model

Figure 1. *Prevalence of HIV-1 in the next twenty years.*
The graphs show a comparison of the prevalence of HIV in the coming twenty years when pre-exposure prophylaxis (PrEP) is available (solid line) and when PrEP is not available (dashed line). Antiretroviral drugs are available for treatment of HIV, irrespective whether PrEP is available or not. Implementation of PrEP starts in year 0.

(from 18.2% prevalence at implementation of PrEP to 13.8% after twenty years) (Figure 1b). Smaller reductions in HIV prevalence are reported by the Synthesis Transmission Model which reports a decrease from 15.5% to 12.7% (Figure 1a) and the Macha Transmission Model which finds a reduction from 8.0% to 6.8% (Figure 1c). Results from previous models have suggested implementing PrEP in addition to ART can result in a reduction in the prevalence of HIV compared to the use of ART alone.[287, 304] The larger decrease in HIV prevalence reported by the South African transmission model therefore seems to be ascribed to the greater proportion of uninfected individuals (30%) that are assumed to receive PrEP in this model as compared to the other models (PrEP coverage of 5% in the Synthesis Transmission Model 15% and the Macha Transmission Model) (Table 1).

Impact of ART and PrEP on HIV drug resistance

All of the models find that HIV drug resistance in the general population will increase in the next twenty years, and to fairly similar levels regardless of whether PrEP is used or not (Figure 2). In the Synthesis Transmission Model the population prevalence of drug resistance (measured as the proportion of drug resistance in the total population) will increase from less than 1% to approximately 4% in the next 20 years (Figure 2a). In the South-African Transmission Model the population prevalence will increase from about 1% to just over 2% (Figure 2b) and in the Macha Transmission Model the population prevalence of resistance will rise from about 1% but will remain at less than 2% (Figure 2c). The comparatively large increase observed in the Synthesis Transmission Model might be due to the higher long term probability of acquiring resistance during treatment assumed in this model which reaches a prevalence of 29.8% after twenty years (Table 1). Notably, all models suggest that PrEP will only have a modest impact on the population prevalence of HIV drug resistance with an increase of at most 0.34% (or an additional 34 individuals infected with a drug resistant virus out of 10,000 individuals) as found in the Macha Transmission Model (Figure 2c). Similarly, the South African Transmission Model predicts an increase of 0.18%. The Synthesis Transmission Model predicts that PrEP will result in a 0.29% reduction in the population prevalence of HIV drug resistance, which is ascribed to prevention of new HIV infections due to PrEP.

In addition, the models predict that the prevalence of HIV drug resistance amongst those infected will increase over the next twenty years with and without the use of PrEP (Figure 2d-f). The largest increase is observed in the Synthesis Transmission Model which predicts that, without PrEP, the prevalence of infected patients carrying a drug resistant virus will increase over the next twenty years from 4% to 29%, when PrEP is not available, or to 32% when PrEP is used (Figure 2d). Drug resistance in the South-African Transmission Model is predicted to rise from 5% to 14% when PrEP is not available, and from 5% to 17% if PrEP is used (Figure 2e). In the Macha Transmission Model resistance is predicted to increase from 13% to 18% if PrEP is not implemented, but to about 25% if PrEP is used (Figure 2f). The relatively large discrepancy between the level of drug resistance in infected individuals with

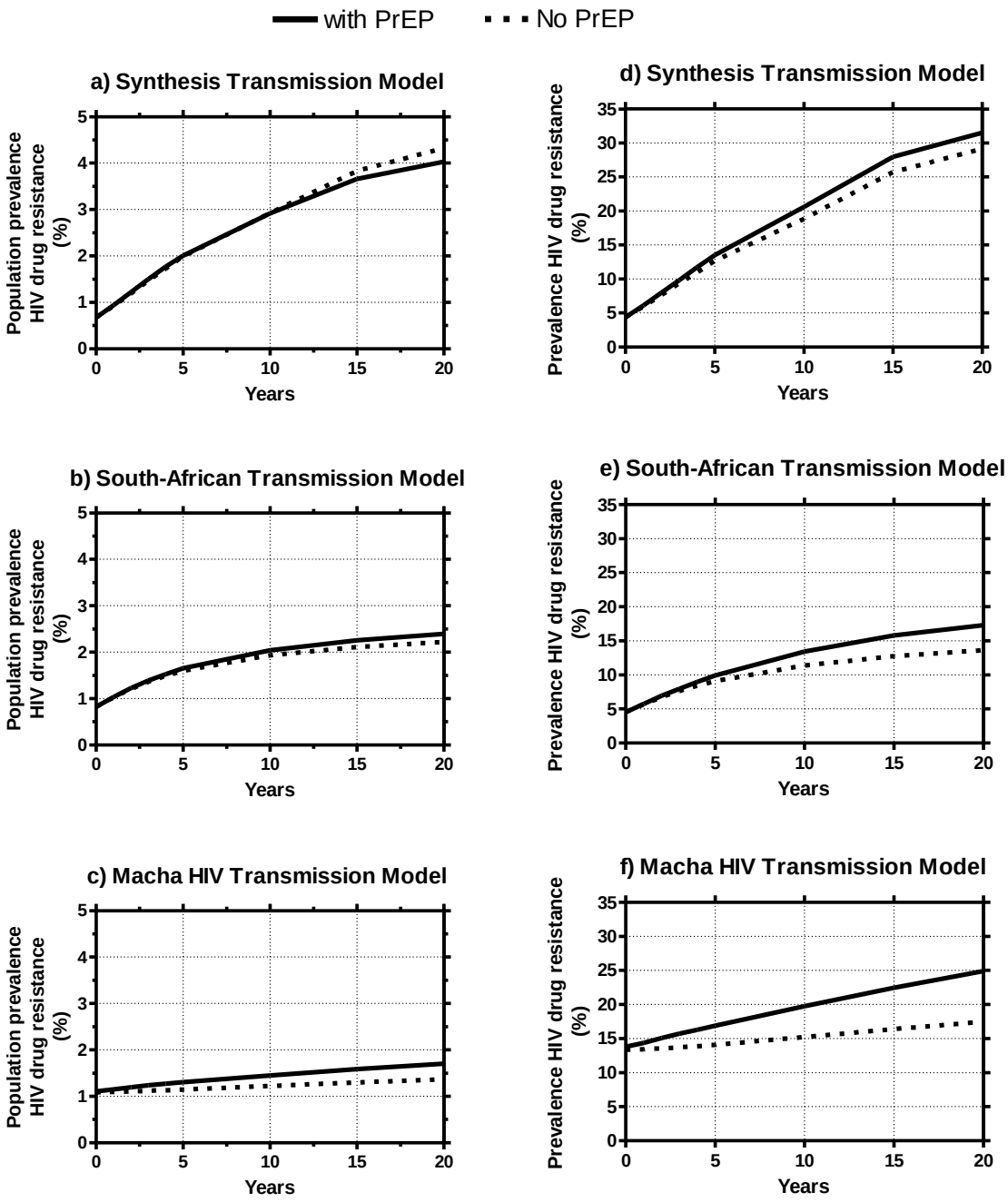


Figure 2. *Prevalence of HIV-1 drug resistance in the next twenty years*
Figures a, b and c show the population prevalence of HIV-1 drug resistance (measured as the proportion of the total population that is infected with a drug resistant virus) when pre-exposure prophylaxis (PrEP) is available (solid line) and when PrEP is not available (dashed line). Figures d, e and f show the prevalence of HIV-1 drug resistance amongst individuals infected with HIV-1 when pre-exposure prophylaxis (PrEP) is available (solid line) and when PrEP is not available (dashed line). Antiretroviral drugs are available for treatment of HIV, irrespective whether PrEP is available or not. Implementation of PrEP starts in year 0.

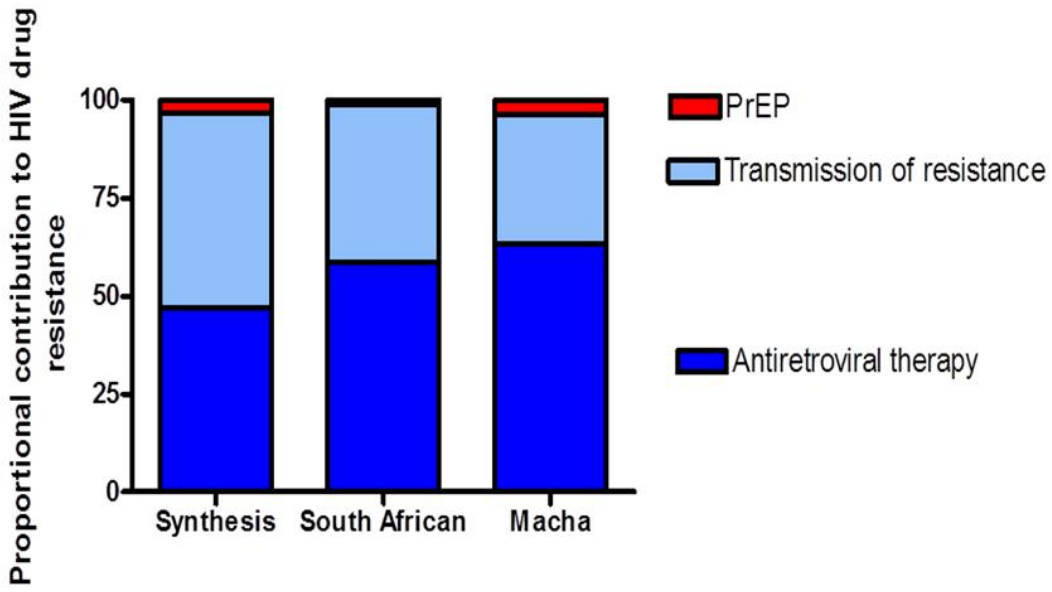
and without PrEP in the Macha Transmission Model is due to the assumption that the virus all individuals that become infected whilst using PrEP will develop drug resistance .

Conversely, the other models assumed that acquiring resistance due to PrEP depends on adherence and that not all individuals will acquire a resistant virus (Table 1).

Factors contributing to HIV drug resistance

Figure 3 shows the proportional contribution of the three different factors that contribute to HIV drug resistance after 20 years. Of all persons living with a drug-resistant HIV infection after twenty years, the majority (50-63% across models) is due to drug resistance arising from combination ART for treatment of HIV. Transmission of resistance is the cause of drug resistance in 40-50% of individuals across models. The cause of resistance in the remainder of persons living with a drug-resistant infection (less than 4%) can be directly attributed to the acquisition of resistance whilst infected and using PrEP.

Figure 3. *Proportional contribution of events contributing to HIV-1 drug resistance twenty years after the introduction of pre-exposure prophylaxis (PrEP)*



DISCUSSION

We compared three independently developed mathematical models that predicted the impact of the implementation of PrEP on HIV drug resistance in sub-Saharan Africa. To facilitate the comparison, the models were re-analyzed to report common outcomes. The models represented different generalized HIV epidemic settings and different PrEP intervention strategies. Despite these differences, all models predict that the prevalence of drug resistance will increase in the coming twenty years due to increased acquired and transmitted resistance. But, importantly, PrEP is predicted to have a limited impact on future levels of drug resistance and just a small proportion (less than 4%) of resistant infections are predicted to be directly attributable to PrEP. This result was consistently found in models with high and low PrEP coverage.

The models made different assumptions regarding the acquisition, loss and transmission of drug resistance and the effectiveness of PrEP, which reflects the existing uncertainty about these processes. Nevertheless, the relative consistency between the models is reassuring and shows that PrEP is not likely to have a major impact on future levels of drug resistance.

The models included in this comparison have several limitations. First, the risk of acquired resistance due to antiretroviral treatment in sub-Saharan Africa used in the models was based on available data from the literature.[19, 213, 220, 300] This risk for resistance has generally been collected in settings where laboratory monitoring techniques (estimation of plasma HIV RNA load and genotypic resistance tests) were not routinely available. Previous studies have shown that availability of such laboratory monitoring techniques is associated with a reduction in the incidence of drug resistance.[19, 213] This reduction can be due to a reduced accumulation of drug resistance associated mutations as virological failure is identified in a timely manner. In addition, patients experiencing virological failure can be advised to improve adherence which may then reduce the risk of resistance. If laboratory techniques become widely available in the coming years, then the risk of acquired drug resistance is expected to decrease and therefore the proportion of drug resistance due to PrEP could increase. The absolute number of drug resistant infections that can be ascribed to PrEP would, however, be expected to remain limited; and more frequent monitoring of persons on PrEP for breakthrough infection would be expected to further limit resistance.

Our standardized model comparison used a simple classification of drug resistance. As such, a distinction between particular drug resistance associated mutations or resistance to particular classes of antiretroviral drugs was not considered.

The mathematical models assume that individuals with an undiagnosed acute infection can start using PrEP. However, the models did not assume that resistance will develop faster if PrEP is used during the acute stage compared to if PrEP is used during chronic infection. Randomized clinical trials have found that resistance due to PrEP is predominantly found among patients who start PrEP with an unrecognized acute infection,[28, 32, 272, 273] suggesting that drug resistance mutations when using PrEP are potentiated by high viral replication. The resultant underestimation of the contribution of PrEP to drug resistance in the models compared here is likely to be small since the acute stage has a brief duration of 10-16 weeks[8] meaning that few people will start PrEP in this phase of infection.

The purpose of this model comparison is to highlight the potential contribution of PrEP to resistance, given this has been a major issue in the FDA approval of PrEP and in public health arguments concerning PrEP.[293, 294, 305] Therefore, the simulated interventions were simplified to enable comparison between models, and the results should not be taken as our prediction or recommendation for how to scale-up PrEP. The comparison did not standardize and simulate the roll-out of antiretroviral drugs, adherence to antiretroviral treatment, particular antiretroviral drug treatment or the availability of viral load monitoring.

In conclusion, drug resistance will always be a risk with the use of antiretroviral drugs. Drug resistance due to ART and transmission of drug resistance will, however, far exceed drug resistance due to PrEP. Expanding access to antiretroviral drugs will require careful planning so that most infections can be averted at the lowest cost. However, with good monitoring of persons initiating and remaining on PrEP, drug resistance should not be a reason to withhold PrEP.

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DvdV, UA, CB, VC, JE, KL, JM and TH conceived the study. VC and AP contributed data from the Synthesis Transmission Model. UA, RG and JM contributed data from the South-Africa Transmission Model. DvdV, BN, CB and KS contributed data from the Macha Transmission Model. DvdV and BN analyzed the combined data from all models. DvdV and BN wrote the first draft of the manuscript and UA, CB, VC, JE, RG, KL, JM, AP, KS and TH contributed to data interpretation and development of the manuscript. All authors contributed to subsequent drafts and reviewed and approved the final manuscript.

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Part III

Treatment as Prevention versus Pre-exposure Prophylaxis

Chapter 8

Cost-Effectiveness of PrEP in HIV/AIDS Control in Zambia - a Stochastic League Approach

Brooke E Nichols, Rob Baltussen, Janneke H van Dijk, Phil E Thuma, Jan L Nouwen, Charles AB Boucher, David AMC van de Vijver

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ABSTRACT

Background Earlier ART initiation and pre-exposure prophylaxis (PrEP) prevent HIV, though at a substantial cost. We use mathematical modeling to compare the cost-effectiveness and economic affordability of antiretroviral-based prevention strategies in rural Macha, Zambia.

Methods We compare the epidemiological impact and cost-effectiveness over 40 years of a baseline scenario (treatment initiation at CD4<350 cells/µl) with treatment initiation at CD4<500 cells/µl, and PrEP (prioritized to the most sexually active, or non-prioritized). A strategy is cost-effective when the incremental cost-effectiveness ratio (ICER) is <$3480 (<3 times Zambian per capita GDP). Stochastic league tables then predict the optimal intervention per budget level.

Results All scenarios will reduce the prevalence from 6.2% (interquartile range 5.8%-6.6%) in 2014 to about 1% after 40 years. Compared to the baseline, 16% of infections will be averted with prioritized PrEP plus treatment at CD4<350, 34% with treatment at CD4<500, and 59% with non-prioritized PrEP plus treatment at CD4<500. Only treating at CD4<500 is cost-effective: ICER of $62 ($46-$75). Non-prioritized PrEP plus treating at CD4<500 is borderline cost-effective: ICER of $5,861 ($3,959-$8,483). Initiating treatment at CD4<500 requires a budget increase from $20 million to $25 million over 40 years, with a 96.7% probability of being the optimal intervention. PrEP should only be considered when the budget exceeds $180 million.

Conclusion Treatment initiation at CD4<500 is a cost-effective HIV prevention approach that will require a modest increase in budget. Although adding PrEP will avert more infections, it is not economically feasible as it requires a ten-fold increase in budget.

INTRODUCTION

In 2011, 2.5 million individuals became newly infected with HIV.[306] Every person that becomes infected will need costly lifelong treatment. The treatment of currently infected individuals is already very costly, so ways in which to prevent new infections is important in order to keep costs under control.

It has been shown that daily oral antiretroviral drugs can prevent sexual transmission of HIV-1 in two ways.[7, 43] One strategy is to give daily pre-exposure prophylaxis (PrEP) with the antiretroviral drugs tenofovir and emtricitabine to uninfected individuals in order to prevent HIV infection. Daily PrEP efficacy has been shown to be as high as 44-75% when adherence is high.[28, 272, 273] Some studies, however, failed to show an impact of PrEP, likely due to sub-optimal adherence.[32] Another strategy is earlier initiation of antiretroviral treatment among individuals that are infected with HIV-1 as prevention. As compared to delayed antiretroviral treatment at a CD4 cell count of <250 cells/µl, initiating antiretroviral treatment between CD4 350-550 cells/µl led to a 96% reduction in HIV transmission from a patient to their uninfected partner.[7] Importantly, this approach of "treatment-as-prevention" also provides clinical benefits as patients starting treatment at higher CD4 counts have a reduced risk for opportunistic infections and death.[7, 13, 98] Based on these benefits of earlier ART initiation, the WHO has now moved from recommending treatment at CD4 <350 cells/µl to treating earlier in infection at CD4 <500 cells/µl.[14] The resources needed to implement treatment at CD4 <500 cells/ul, however, are substantial. In many resource limited settings, however, not all HIV patients eligible for treatment under the former guidelines receive care due to late diagnosis of HIV infection and poor linkage to- and retention in- care.[218, 307, 308] Thus the resources needed to fully implement treatment at the earlier immunologic threshold of CD4 <500 cells/µl are substantial.

Treatment as prevention has been estimated to eliminate the epidemic when all patients are diagnosed early in infection and placed immediately on treatment.[48, 309] In practice, however, approximately 70% of patients in studies from Zambia are diagnosed with a CD4 count below 350 cells/µl[310] and thus would not be able to initiate treatment early (CD4 350-550 cells/µl)[7]. Even if individuals are diagnosed in time, there are still problems with linkage to- and retention in- pre-ART care, resulting in individuals not initiating treatment on time.[297] Although PrEP is less effective than treatment as prevention, PrEP can still play a role in preventing infections, particularly among high-risk individuals.[311]

Stochastic league tables (SLT) are an innovative approach to report on the cost-effectiveness of HIV/AIDS interventions in the context of uncertainty around the costs and effects estimates, and especially future funding. Previous cost-effectiveness analyses typically identify whether interventions are cost-effective compared to some international threshold.[282, 297] In this paper, we improve on this approach by using stochastic league tables. First, we identify the optimal mix of interventions by reference to an explicit budget level, and thereby avoid the use of cost-effectiveness thresholds. Second, we move away

from deterministic approaches to cost-effectiveness analyses that report uncertainty ranges around a mean – instead we use a bootstrapping procedure in which we calculate the probability that an intervention is included in this optimal mix. Third, given the uncertainty about HIV funding, we determine the optimal mix of interventions for different budget levels. Given that international funding has stagnated or declined in recent years while the absolute number of HIV-infected individuals increases,[312] this type of analysis is essential as costs will have to be taken on by country health systems.

We aim to evaluate the epidemic impact and cost-effectiveness of PrEP and treatment as prevention, and their combinations in the context of a previously described mathematical model of the HIV epidemic in the rural setting of Macha, Zambia. We aim to introduce SLT to the HIV field, and use it to assess what mix of interventions is most efficient at different budget levels.[297] We also report standard cost-effectiveness ratios to indicate the differences between the two scenarios.

METHODS

Setting and Population

Our model is based on the rural population of Macha, Zambia and uses data from the HIV Clinic at Macha Mission Hospital in the Southern Province of Zambia.[274, 297] The hospital serves as a district-level referral hospital for rural health centers within an 80 km radius, with approximately 90,000 persons that are aged 12 years and over in the Macha Mission Hospital catchment area as of 2011.[274] The antenatal prevalence between 2002[275] and 2009 was stable around 7.7%, and declined to below 5% in 2010 [local data]. Since the start of the ART clinic in 2005, treatment is implemented according to WHO guidelines, initially at CD4 <200 cells/µl, and at CD4 <350 cells/µl since 2010.

Mathematical Model

A previously described deterministic mathematical model was constructed and parameters were chosen to represent Macha.[236, 297] Compared to the published model, the current model has now been adapted to incorporate population growth, updated HIV prevalence data from Macha, and treatment rollout in line with the treatment rollout experienced in Macha. Using Monte Carlo filtering techniques[283] we accepted 539 of 85,000 simulations that were associated with an HIV prevalence of 7.7% (6.7%-8.7%) from 2002 until 2009, and a decreasing prevalence between 2009 and 2010 in accordance with Macha data (where a prevalence of <5% were observed for 2010 and 2011). The accepted simulations also had to have an adult population (aged 12 and over) of 90,000 (80,000-100,000) in 2007, and an extrapolated adult population of 96,000 (86,000-106,000) in 2012. After 40 years the

population is predicted to be 197,000 (IQR 186,000-208,000). The model calibration to the population and HIV prevalence is shown in Figures S1 and S2 respectively.

Baseline scenario

Our baseline scenario is the current practice in Macha, with an annual population HIV test rate of 10-20%, which leads to approximately 50% of patients initiating ART with a CD4 <200 cells/μl.[297] Therefore, not all individuals are diagnosed before their CD4 count reaches the treatment initiation threshold. After a positive HIV-test, 70% of individuals are retained in care.[297] Treatment is then started at CD4 <350 cells/μl. Patients who then initiate treatment have a reduced infectivity between 90-100%.[7, 43, 46] We assumed that all these variables remained constant over the 40-year period.

Intervention Scenarios

In this analysis, we evaluated the costs and effects associated with a change in treatment guidelines to initiate treatment at CD4 <500 cells/μl (in line with the new WHO guidelines[14]). We also evaluated the costs and effects of two hypothetical PrEP scenarios. Both PrEP scenarios assumed that treatment would continue at CD4 <350 cells/μl. We also evaluated both PrEP scenarios combined with a treatment initiation threshold of CD4 <500 cells/μl. All interventions are implemented in 2014, scale up linearly over 1-2 years, and are implemented until 2054.

Non-Prioritized versus Prioritized PrEP distribution

It is not known how PrEP will be implemented in daily practice. We therefore examined the impact of two hypothetical scenarios where PrEP is perfectly and imperfectly prioritized to represent both ends of the prioritization spectrum.[297] In the first hypothetical scenario, we examined the impact of perfect prioritization by assigning approximately half of the individuals in the two highest sexual activity groups, 5-15% of the population, to receive PrEP. We assigned PrEP to just half of the highest sexual activity groups, as identifying those groups completely would not be feasible. In the second hypothetical scenario where PrEP is imperfectly prioritized, PrEP is assigned to 40-60% of the population at random. For these analyses, we assumed moderate population-level PrEP adherence, where effectiveness ranged from 20%-60%.[28]

Early Treatment Initiation

For this scenario, the treatment initiation threshold is CD4 <500 cells/μl. The test rate and retention in care remain the same as in the baseline scenario,[297] thus individuals may still be diagnosed and initiate treatment late in infection. With these test and retention rates, there will still be approximately 20% of patients who are diagnosed with a CD4 cell count between 350 and 500 and therefore initiate treatment early in this scenario.

PrEP Combined with Early Treatment

For the combination scenarios, we looked at the impact of expanding the treatment initiation threshold to CD4 <500 cells/µl combined with prioritized and non-prioritized PrEP respectively.

Cost-effectiveness analysis

Standard cost-effectiveness analysis typically identifies a single cost-effectiveness ratio for an intervention (with an uncertainty range), which is then compared to a cost-effectiveness threshold. The World Health Organization suggests that interventions are cost-effective if they cost less than three times the gross national income (GNI) per capita (Three times GNI in Zambia is $3480)[285] per quality-adjusted life year (QALY) gained. Decisions are then made upon the incremental cost-effectiveness ratio (ICER) where each scenario is compared to the next least-costly scenario.[36] The stochastic league table method is preferable however, as the analysis calculates the probability of selection of an intervention, and then calculates this probability for different budget levels. This probability reflects the likelihood that an intervention is the most economically attractive option. Using this method, no comparison of results to an arbitrary cost-effectiveness threshold is required, and thus could be more suitable tool for resource prioritization in diverse settings.

The construction of stochastic league tables requires four steps.[38] Firstly, using Monte Carlo simulations, random draws are taken from estimated distributions of total costs and effects for all interventions, defined *a priori*. The distribution of effects is taken directly from the output of the 539 model simulations. To reflect uncertainty, costs are here assumed to be log-normally distributed,[221] with a standard deviation of +/-10% of the cost values collected in Macha to represent small potential variations in price. We defined uncertainty around 11 variables of quantities and prices (for a table of full ranges and distributions of costs and effects used, see Table S1 and S2). The covariance is assumed to be zero. The conclusions are not dependent on these assumptions. Random draws are then taken from these distributions for all interventions. We then determine the average cost of the baseline scenario to treat HIV and opportunistic infections in Macha. We estimate this based on current HIV treatment costs collected from Macha combined with the results from our mathematical model.

The second step is to determine the optimal mix of interventions for given levels of resource availability (at increments of $100,000 in this analysis) for mutually exclusive interventions.[38, 313] The baseline intervention is then evaluated according to its average cost-effectiveness ratio (versus doing nothing), while the cost-effectiveness of others in the mutually exclusive set are evaluated incremental to the baseline intervention.[38]

Third, this process is repeated 10,000 times to provide 10,000 estimates of the optimal mix of interventions.[38] *P* represents the number of times an intervention is included in the optimal mix, and *P*/10000 is the probability that the intervention is included. Thus *P* is the

proportion of samples for which the intervention is estimated to be optimal based on the sample average and incremental cost-effectiveness ratios.[38]

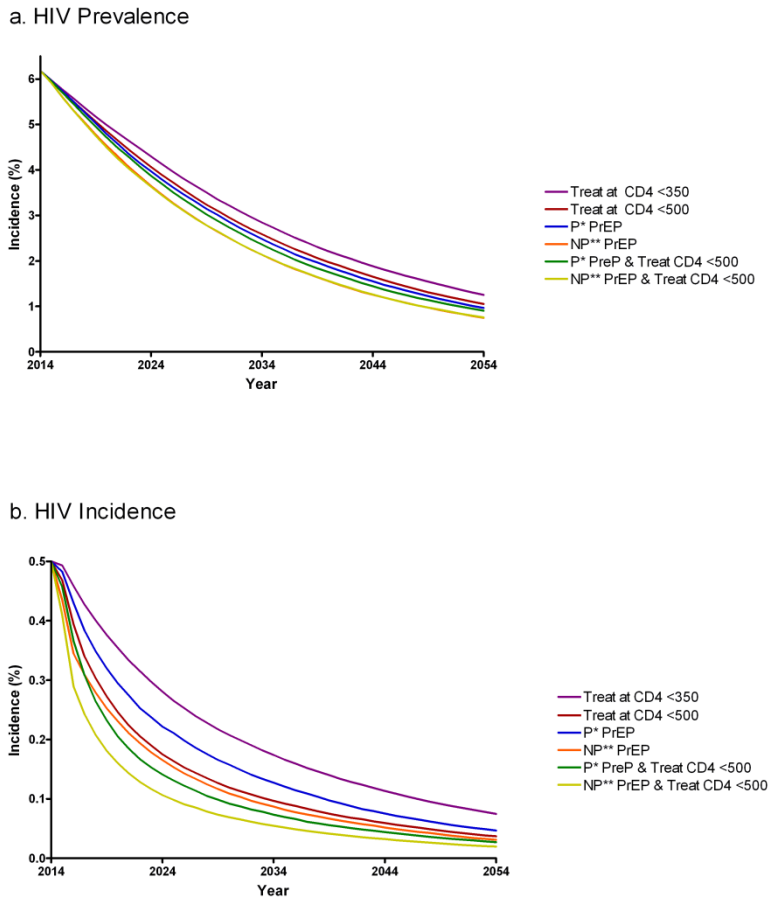
Fourth, the procedure is repeated for varying levels of resource availability to reveal the 'resource expansion path', showing the probability that each intervention will be included at different levels of resource availability (in increments of $100,000).[38] Decision-makers can use this information to prioritize interventions should more resources become available for HIV prevention. The probability that a more expensive alternative will be included increases with resource availability.[38] We present results from the current budget up to a twelve-fold increase of the current budget for illustrative purposes.

In order to evaluate the long term effects of treatment and PrEP interventions, we conducted the analysis over a 40 year time horizon. Each scenario was run in our mathematical model. All model outputs used to populate the stochastic league analysis can be found in Table S1. Costs have been discounted appropriately to implement interventions beginning in 2014, and discounted at an annual rate of 3% thereafter (a table of cost used for this analysis can be found in Table S2). QALY estimates were then multiplied by the number of people in each disease state at each time point and were discounted at an annual rate of 3% to get a total number of QALYs expected in the population over the 40 year time period (a table of QALY estimates can be found in Table S3).[36, 227] Stochastic league tables were generated with MCLeague Software (Version 1.1.1).

RESULTS

Impact of baseline scenario, treating at CD4 <350 cells/µl

Treating patients at a CD4 <350 cells/µl alone is predicted to strongly reduce the epidemic over the coming 40 years and is predicted to reduce prevalence from 6.2% (Interquartile range (IQR) 5.8%-6.6%) in 2014, down to 1.3% (IQR 0.9%-1.9%) in 2054 (Figure 1). In line with prevalence reduction, incidence is predicted to decline from 5 per 1000 susceptible individuals (IQR 4-5.9 per 1000 individuals) in 2014 down to 0.7 per 1000 individuals (IQR 0.4-1.4 per 1000 susceptible individuals) after 40 years (Figure 1).

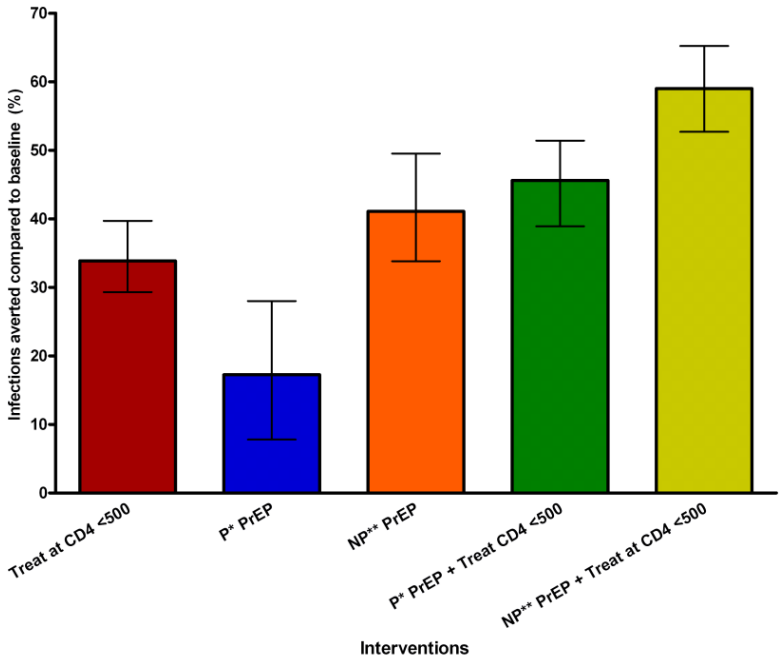


*P Prioritized PrEP to half of the most sexually active adult population
**NP Non-prioritized PrEP: PrEP to half of the adult population

***Figure 1**. HIV prevalence (a) and incidence (b) over 40 years in Macha, Zambia*

Impact of interventions

All interventions were predicted to reduce incidence even further as compared to the baseline scenario of treating at CD4 <350 cells/µl. The hypothetical prioritized PrEP scenario, where PrEP is prioritized to half of the most sexually active had the smallest impact on new HIV infections of all interventions evaluated, averting 16% (IQR 7.8%-28.0%) over 40 years, compared to treating at CD4 <350 cells/µl alone (Figure 2). The intervention with the greatest impact on new HIV infections was the hypothetical non-prioritized PrEP (giving PrEP to half of susceptible individuals) in combination with treatment initiation at CD4 <500 cells/µl, averting 59% of new infections (IQR 52.7%-65.2%) over 40 years compared to treating at CD4 <350 cells/µl.



*P Prioritized PrEP to half of the most sexually active adult population
**NP Non-prioritized PrEP: PrEP to half of the adult population

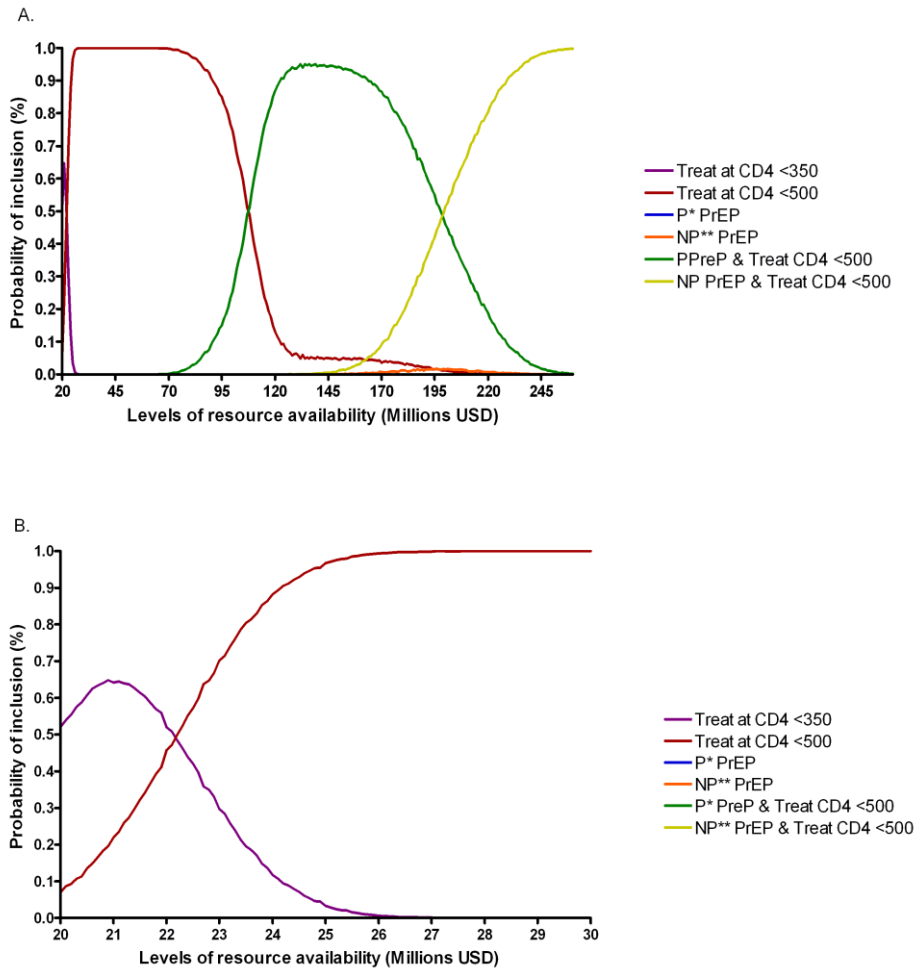
***Figure 2.** Cumulative median percentage of infections averted (and interquartile range) after 40 years of implementation by intervention, compared to the baseline of treating at CD4 <350 cells/µl*

Standard cost-effectiveness analysis

In the standard cost-effectiveness analysis, the only intervention that is cost-effective is initiating treatment in those with a CD4 <500 cells/µl at $62 per QALY gained (IQR $46-$75) after 40 years (Table 1). There was one strategy, non-prioritized PrEP and initiating treatment at CD4 <500 cells/µl, that straddled the standard cost-effectiveness threshold. The median ICER of this scenario is $5,861 (IQR $3,959, $8,483), which by definition is not cost-effective. However, 20.0% of simulations were considered cost-effective by the standard threshold with an ICER of <$3,480 per QALY gained.

Stochastic League Tables

We predict that it will cost on average $20,000,000 to treat HIV and opportunistic infections over the coming 40 years in Macha if treatment is continued at CD4 <350 cells/µl. Therefore, this is also the most likely economically attractive prevention scenario for the $20,000,000 budget. This scenario had a 52.0% probability of being included in the optimum mix of interventions. Initiating treatment at CD4 <500 cells/µl had a probability of being included of just 7.0%. In the remaining cases (41.0% of all random draws), costs of each possible option overrun the available resources and no intervention can be funded fully. This explains why the probabilities do not add up to 100% at low budget levels.



*P Prioritized PrEP to half of the most sexually active adult population
**NP Non-prioritized PrEP: PrEP to half of the adult population

***Figure 3**. Stochastic league curves for six HIV prevention interventions: probability of inclusion (%) in the optimum package of HIV prevention techniques, by 40 year available budget (B zoomed in version of A)*

For a $25,000,000 budget (25% increase in budget), changing the treatment initiation threshold to CD4 <500 cells/µl is the best intervention to support, with a 96.7% probability of being included in the optimum mix of interventions. Keeping the treatment initiation threshold at CD4 <350 cells/µl has a 3.3% probability of inclusion in the optimum mix of interventions. For budgets between $25 and $80 million (25%-400% increase in budget), the probability of including treatment at CD4 <500 cells/µl in the optimum mix of interventions is nearly 100%.

Only at much higher budget levels, greater than $110,000,000 (>550% increase in budget), is PrEP worth the economic investment. At a budget of $110,000,000 over 40 years, the most likely optimal HIV prevention mix includes prioritized PrEP in addition to initiating treatment at CD4 <500 cells/µl, with a probability of inclusion of 59.6%. The probability of inclusion of treatment at CD4 <500 cells/µl alone at this budget level is still 40.4%. At a budget of $200,000,000 (1000% increase in budget), the most likely optimal mix transitions to include non-prioritized PrEP in addition to initiating treatment at CD4 <500 cells/µl, with a probability of being included of 51.5%. At this budget level, the probability of including prioritized PrEP and treatment at CD4 <500 cells/µl is also high at 45.8%.

Prioritized PrEP would never be included as an optimal prevention strategy without simultaneously treating individuals with CD4 <500 cells/µl, as the probability of including prioritized PrEP in the absence of treating at CD4 <500 cells/µl optimal mix is 0 at all budget levels. The probability of including non-prioritized PrEP in the absence of expanded HIV eligibility criteria is very low (0.1%-1.7%), at 40-year budgets between $130-260 million.

DISCUSSION

We predict that the optimal mix of HIV interventions for small budget increases (>$3,000,000 over 40 years, or a 15% increase in budget) is to change the treatment initiation threshold to CD4 <500 cells/µl. Our analysis shows that PrEP should not be considered without also expanding the treatment eligibility criteria, as scenarios with PrEP in absence of expanded treatment were never included in the optimal mix of interventions at any budget level. The PrEP scenarios that do include expanded HIV eligibility criteria of CD4 <500 cells/µl should not be considered, however, unless the 40-year budget for HIV care and prevention in the setting is at least $110,000,000, or greater than a 550% increase in budget.

In our standard cost-effectiveness analysis, we found that non-prioritized PrEP in addition to changing the treatment initiation threshold to CD4 <500 cells/µl was considered cost-effective in 20% of simulations. It is important to note that the budget level in which this combination is included in the optimal mix of interventions is $200,000,000, or ten-times the cost of treating at CD4 <350 cells/µl alone. Thus, even though non-prioritized PrEP and

Table 1. *Cost-effectiveness of treatment at CD4 <500 cells/µl, PrEP interventions, and combinations thereof over 40 years*

Intervention	Total cost in $ Millions (IQR*)	Infections Averted (IQR)	QALYs gained (IQR)	Average Cost-Effectiveness Ratio (IQR)	Incremental Cost-Effectiveness Ratio (IQR)	Conclusion
Treatment available at CD4 <350 cells/µl, standard care, no PrEP	19.7 (17.5, 22.0)	-	-	-	-	-
Treatment available at CD4 <500 cells/µl	22.0 (19.8, 24.5)	3,388 (2,179, 5,329)	40,643 (29,353, 53,676)	$62 ($46, $75)	$62 ($46, $75)	Very cost-effective
Prioritized PrEP to most sexually active	75.9 (50.7, 113.1)	1,502 (740, 2,775)	13,611 (7,032, 24,305)	$4,103 ($2,890, $5,803)	Dominated**	Dominated**
Prioritized PrEP to most sexually active and Treatment available at CD4 <500 cells/µl	78.9 (53.8, 117.6)	4,494 (3,003, 6,935)	50,936 (38,117, 67,270)	$1,153 ($686, $1,756)	Weakly Dominated***	Weakly Dominated***
Non-prioritized PrEP, PrEP randomly distributed	170.1 (159.1, 182.4)	4,053 (2,480, 6,708)	40,318 (26,512, 61,199)	$3,730 ($2,454, $5,691)	Dominated**	Dominated**
Non-prioritized PrEP, PrEP randomly distributed and Treatment available at CD4 <500 cells/µl	173.6 (161.9, 185.8)	5,894 (3,832, 8,876)	67,835 (48,809, 89,899)	$2,253 ($1672, $3,188)	$5,861 ($3,959, $8,483)	Not cost-effective

* IQR: Interquartile range

** Less effective and more costly than the next least-expensive scenario

***Incremental cost-effectiveness ratio is higher than the next most effective program

initiating treatment at CD4 <500 cells/µl had borderline cost-effectiveness by standard cost-effectiveness analyses, the total cost to implement it would make it infeasible. This indicates the importance of explicitly referring to budget levels in economic analyses of health interventions.

Similar to previous modeling studies,[209, 314] we found that PrEP and earlier ART initiation thresholds both reduce incidence. In line with these studies, we predicted that the combination of PrEP and ART reduces incidence even further.[209, 314] Many studies have recently looked into the cost-effectiveness of oral daily PrEP in generalized epidemics,[287, 295, 315-317] and approximately half have found that PrEP can be cost-effective.[315-317] Of the two studies that found PrEP is not cost-effective, one assumed that individuals on PrEP would increase their number of partners,[295] and the other assumed changes in condom use.[287] These reasons are thought to be key drivers of those two cost-effectiveness results.[318] Other than the differences in changes of risk behavior, the differences in cost-effectiveness depended largely on the assumptions regarding PrEP adherence, coverage, and prioritization strategy.[318] In our study we assumed low to moderate PrEP adherence, as modeled by a 20-60% efficacy, we predicted that PrEP-only scenarios were not cost-effective. Given our assumption about relatively low efficacy, our PrEP-only scenarios fall in line with models by other groups.

Pretorius *et al.* used a population-based model to predict the cost-effectiveness of PrEP compared with and in combination with increasing treatment.[287] This model examines PrEP in the context of ART scale-up in the context of the South African epidemic. They have predicted that PrEP and "universal access to testing and treatment" would have a similar impact on incidence after 10 years, and the combination of the two would have the strongest impact. They have also predicted, however, that universal access to testing and treatment was cost-effective, while PrEP would need to cost more than five-times less than treatment to be more cost-effective than universal access to testing and treatment. Our model has shown similar results, and has the added value of putting the cost-effectiveness in the context of a budget.

Due to tightening budgets worldwide, ways in which to maximize HIV prevention in an affordable way are crucial. In addition, studies evaluating the impact and cost-effectiveness on HIV prevention of PrEP in the context of expanding ART guidelines are needed. The stochastic league table approach allows decision makers to see how to maximize effectiveness with potential budget increases, and put PrEP and treatment as prevention in the context of budget constraints. This approach also enables us to simultaneously take into account uncertainty regarding costs, quantities and effects, leading to comprehensive results. Another strength of our study is access to cost and epidemiologic data from Macha, Zambia, enabling us to make reliable predictions about the potential impact of expanded HIV eligibility criteria and PrEP implementation.

This study has some potential limitations. First, we have estimated what the cost of treating HIV and HIV-related conditions would be over 40 years based on current costs, though the true long-term costs are unknown. If the actual budget is lower than our calculation, it may be difficult to consider implementing any intervention other than treating at CD4 <350 cells/µl, and it could be difficult to fully implement that treatment guideline. If the actual budget is higher, then other interventions may be more effective at comparatively lower budget increases. Second, we have not taken into account the health system capacity or the programmatic costs associated with implementing an intervention. While there may be a budget to implement PrEP, there may not be the personnel available to implement the intervention. Third, programmatic costs could be substantial. We have left this out as it would depend on the specific plan of action chosen by decision makers for each intervention and would add further uncertainty into the model. Fourth, we have chosen the baseline scenario to initiate treatment at CD4 <350 cells/µl. We do this as even though the new WHO guidelines recommend initiating treatment between CD4 350 and 500 cells/µl, the guidelines first recommend prioritizing to individuals with CD4 <350 cells/µl.[14] Finally, more lab monitoring, such as regular viral load monitoring or resistance testing, could be implemented instead of or in addition to expanding the treatment eligibility criteria, but we have not incorporated different patient monitoring techniques into this analysis.[319] In the future, the stochastic league approach can be utilized to aid resource allocation decisions both between and within the realms of patient monitoring and HIV prevention. Our results should also be confirmed across settings in other validated mathematical models to allow for broader generalizability.

In conclusion, expanding treatment to treat those with CD4 <500 cells/µl is the optimal strategy for reducing the HIV epidemic with modest budget increases in a generalized epidemic. If PrEP is being used, it should only be implemented in combination with increased access to antiretroviral treatment in order to be considered. While strategies involving PrEP can be considered cost-effective using standard cost-effectiveness analyses, it is important to consider if a budget exists to implement PrEP, at what scale, and whether or not those funds could be more effective if allocated elsewhere.

ACKNOWLEDGEMENTS

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Supplement: Chapter 8

Figure S1. *Model calibration to Macha population*

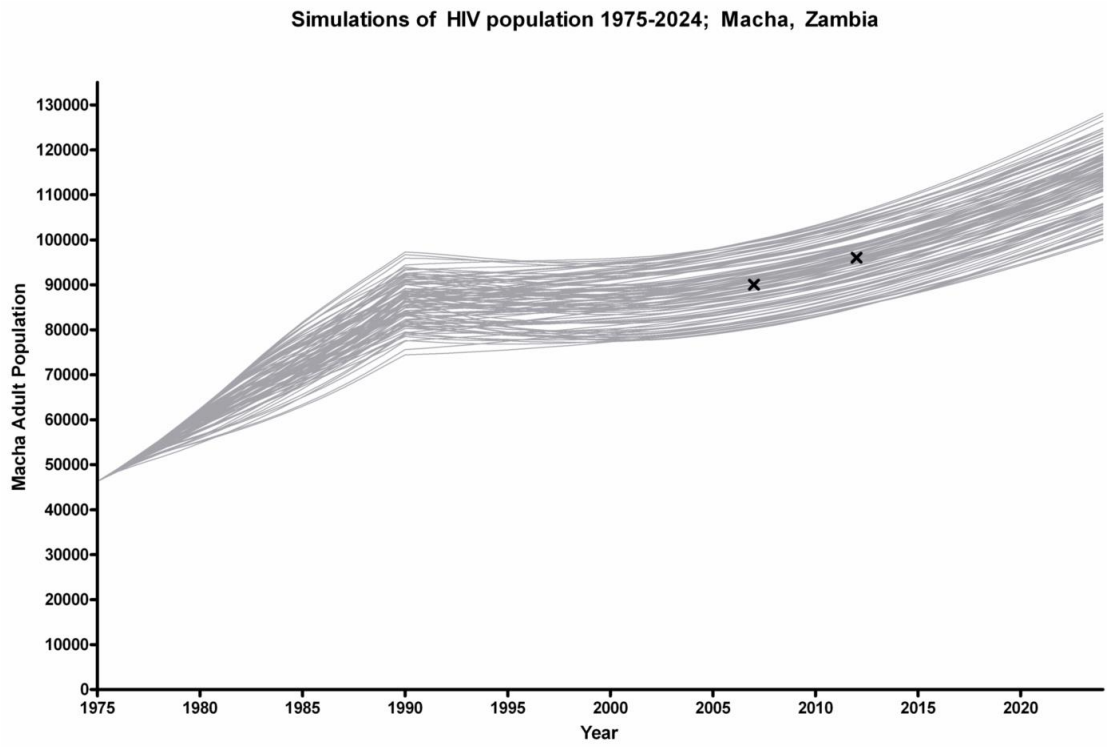

Figure S2. *Model calibration to HIV prevalence in Macha*

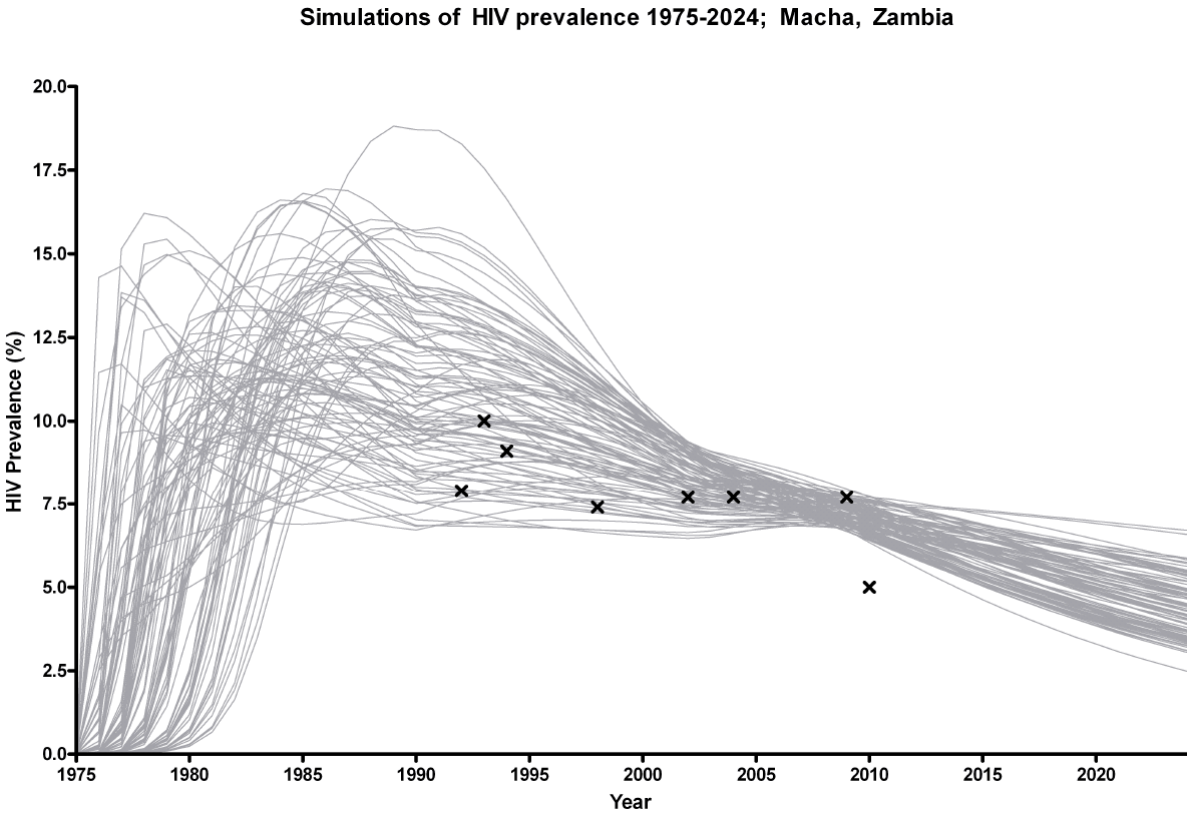

Table S1*: Quantity component to the stochastic league analyses for each of the six interventions, the quantities shown here are then multiplied by the costs to get the total population-level cost.*

	Number of person years spent in the following states (this is then multiplied by the cost of being in these states):					
Scenarios	PrEP	Acute infection (undiagnosed)	Chronic infection (undiagnosed)	AIDS (undiagnosed)	Acute infection & tested positive (in care, not on treatment)	Chronic infection & tested positive (in care, not on treatment)
Baseline, treat at CD4 <350 cells/uL	0	1793 (SD 41)*	20507 (SD 469)	2794 (SD 67)	42 (SD 1)	14733 (SD 201)
Treat at CD4 <500 cells/uL	0	1246 (SD 28)	15512 (SD 358)	2181 (SD 53)	25 (SD 0.5)	6991 (SD 76)
Prioritized PrEP	499,122 (SD 14,497)	1516 (SD 38)	17928 (SD 436)	2475 (SD 62)	36 (SD 1)	13472 (SD 191)
Non-Prioritized PrEP	1,141,078 (SD 4,967)	1093 (SD 21)	13960 (SD 280)	1980 (SD 42)	26 (SD 0.5)	11577 (SD 124)
Prioritized PrEP + treat at CD4 <500 cells/uL	504,720 (SD 14659)	1076 (SD 26)	13894 (SD 331)	1978 (SD 49)	22 (SD 0.5)	6566 (SD 73)
Non-prioritized PrEP + treat at CD4 <500 cells/uL	1,147,208 (SD 5113)	818 (SD 16)	11445 (SD 240)	1672 (SD 38)	17 (SD 0.5)	5921 (SD 53)

	Number of person years spent in the following states (this is then multiplied by the cost of being in these states):			*Number of:*		***Outcome*****
	AIDS & tested positive (in care, not on treatment)	Treatment (initiated during chronic stage)	Treatment (initiated during AIDS stage)	Negative HIV tests	Positive HIV tests	QALYS lived in the total population
Baseline, treat at CD4 <350 cells/uL	2886 (SD 32)	39296 (SD 394)	34041 (SD 187)	611951 (SD 7983)	11839 (SD 302)	3090413 (SD 8695)
Treat at CD4 <500 cells/uL	1928 (SD 17)	52519 (SD 495)	33885 (SD 186)	622160 (SD 8110)	7617 (SD 187)	3134497 (SD 8692)
Prioritized PrEP	2681 (SD 31)	37406 (SD 378)	34008 (SD 187)	513405 (SD 7210)	9710 (SD 284)	3108905 (SD 8710)
Non-Prioritized PrEP	2371 (SD 20)	34552 (SD 306)	33957 (SD 187)	391063 (SD 5064)	6532 (SD 137)	3138027 (SD 8647)
Prioritized PrEP + treat at CD4 <500 cells/uL	1836 (SD 16)	50287 (SD 480)	33870 (SD 186)	520627 (SD 7320)	6377 (SD 174)	3146423 (SD 8680)
Non-prioritized PrEP + treat at CD4 <500 cells/uL	1697 (SD 12)	46858 (SD 393)	33847 (SD 186)	395826 (SD 5181)	4562 (SD 94)	3165295 (SD 8658)

*All standard deviations represent the standard deviation of the 539 model simulations.

**This is the total effects of each respective intervention, and is thus not multiplied by any costs.

Table S2: Cost component to the stochastic league analyses for each of the six interventions, the costs shown here are then multiplied by the quantities to get the total population-level cost.

	Cost, 2012 USD (SD)*	**Cost Components**
Yearly costs		
PrEP	$134.36 (SD $13.40)	Twice yearly HIV tests**, one year of daily tenofovir & emtricitabine
Acute HIV infection (undiagnosed)	$1.73 (SD $0.17)	Cost of opportunistic infections**,†
Chronic HIV infection (undiagnosed)	$0.54 (SD $0.05)	Cost of opportunistic infections**,†
AIDS (undiagnosed)	$1.38 (SD $0.14)	Cost of opportunistic infections**,†
Acute infection & tested positive (in care, not on treatment)	$32.21 (SD $3.20)	Cost of opportunistic infections**,†, and CD4 test**
Chronic infection & tested positive (in care, not on treatment)	$37.25 (SD $3.70)	Cost of opportunistic infections**,†, and CD4 test**
AIDS & tested positive (in care, not on treatment)	$48.07 (SD $4.80)	Cost of opportunistic infections**,†, and CD4 test**
Treatment (initiated during chronic stage)	$221.00 (SD $22.10)	Cost of opportunistic infections**,†, CD4 test**, one year of treatment (tenofovir, emtricitabine, efavirenz), patient monitoring tests
Treatment (initiated during AIDS stage)	$229.52 (SD $23.00)	Cost of opportunistic infections**,†, CD4 test**, one year of treatment (tenofovir, emtricitabine, efavirenz), patient monitoring tests
One-time costs		
Testing negative for HIV (and not on PrEP)	$3.46 (SD $0.35)	Cost of HIV rapid test**
Testing positive for HIV	$40.81 (SD $4.10)	Cost of HIV rapid test**, HIV confirmatory test**, CD4 test**

* All costs follow a lognormal distribution

**Comprehensive costs, including costs of outpatient visits, additional laboratory tests, laboratory personnel.

† Rates of opportunistic infections differ by stage of HIV and treatment status. Full breakdown of opportunistic infections can be found in our previous publication.[297]

Table S3: Assumed utility weightings for QALYs[297]

Status	**Utility Weight***
Susceptible	1.0
Susceptible on PrEP	98-100%: 1.0 0-2%: 0.9-1.0**
Acutely infected	0.94
Chronically infected	0.94
Infected early AIDS stage	0.82
Infected late AIDS stage	0.7
Infected on treatment	0.94
*Weights based on a pooled analysis by Tengs and Lin (2002) [222] **0-2% will suffer from renal failure on these ARVs[289], which could result in a reduction in quality of life, or go unnoticed.	

Chapter 9

Discussion

Antiretroviral drugs can prevent new HIV infections.[7, 272, 273] Questions still remain, however, how an increase in the use of antiretroviral drugs will affect drug resistance. It is also not yet known what the most cost-effective way to use antiretroviral drugs to prevent HIV infections is. The overarching aim of this thesis is therefore to identify optimal antiretroviral-based strategies to prevent new HIV infections in terms of infections averted and costs incurred. This thesis addresses these concerns in three parts.

A discussion of the research aims, as outlined in chapter 1, are presented below:

1. **Evaluate the impact of treatment as prevention, PrEP, and partner notification on the epidemic in terms of infections averted and life-years saved using mathematical models**

In Kampala, Uganda, and Mombasa, Kenya, treatment as prevention is predicted to prevent infections (Chapter 3). Compared to initiating ART at CD4 cell count below 200 cells/µl, initiating ART at CD4 cell count below 350 cells/µl averts a median of 12.6% of infections over 10 years in Kampala and averts a median of 11.6% of infections in Mombasa. Initiating ART at CD4 cell count below 500 cells/µl averts a median of 28.8% and 26.3% in Kampala and Mombasa, respectively. In Macha, Zambia, treatment at a CD4 cell count of <500 compared to treatment at a CD4 cell count of <350 cells/µl is predicted to prevent approximately 34% of new infections over 40 years.

While the models and populations are quite different, the model based in East Africa and the one based in Zambia both predict a similar impact of earlier treatment initiation. The effectiveness of treatment as prevention could be improved with increased testing, linkage to care, and retention in care. In a side analysis of our model, when treating regardless of CD4 cell count and increased HIV testing in Macha, Zambia, up to 50% of infections can be prevented over 10 years (Chapter 6). This will not, however, lead to elimination of the epidemic, as has been shown in some modelling studies.[48, 320] Possible explanations why treatment as prevention will not lead to elimination of the epidemic include the role of the highly infectious acute stage of infection in disease transmission,[8, 280, 321] as well as poor linkage rates from testing to treatment.[297, 322]

We show that PrEP can prevent new infections (Chapter 6). The impact of a targeted PrEP strategy is modeled, where PrEP is given to those in the highest sexual risk groups, and a random PrEP strategy, where PrEP is given to approximately 50% of the population, regardless of risk. In this study, ART initiation is at a CD4 cell count of <350 cells/µl. PrEP is predicted prevent 23-31% of infections averted over 10 years. When we used an updated version of this model we find that the effect of PrEP over 40 years is somewhat attenuated, preventing between 16-41% (Chapter 8). A key limitation in our modeling of prioritized PrEP to the most sexually active is that the highest sexual risk groups in our model are artificial. Our model divides the population into four sexual risk groups which are then used to calibrate the model to the epidemic in Macha. We use this structure and calibration technique to estimate the sexual network as the true sexual mixing structure of a population is unknown.[283] The first group in our

model has the highest number of new partners per year (on average 13) and makes up just 2% of the population, the second group has on average 2 new partners per year, making up 18% of the population. The third and fourth groups has less than 1 new partner per year and represents people in long term relationships or marriages. The two groups with the highest number of new partners per year were the ones targeted for PrEP in our models. These most sexually active groups are hypothetical and do not directly refer to any easily identifiable group. The most at-risk individuals can be difficult to identify in practice. Models incorporating multiple specific risk sub-groups, such as sero-discordant couples, sex-workers, or people who frequent STI clinics, could help identify which groups should be targeted for PrEP to maximize its effectiveness.

PrEP and treatment as prevention are combined in one analysis (Chapter 8). We find that there is less than an additive effect between PrEP use and earlier treatment initiation: prioritized PrEP alone prevents 16% of new infections, treating at a CD4 cell count of <500 cells/µl alone prevents 34% of new infections, but when combined, only 45% are prevented. Non-prioritized PrEP alone prevents 42% of new infections, but when combined with earlier treatment, just 59% of new infections are prevented. This is likely due to an overlap of the interventions, or two different prevention techniques preventing the same infection, leading to inefficiency. There is less inefficiency with a combination of prioritized PrEP to the most sexually active and earlier treatment than with non-prioritized PrEP and earlier treatment. Thus, in order to maximize the effect of both PrEP and treatment as prevention, PrEP should be prioritized to those at highest sexual risk to maximize the efficiency of the preventative effect.

Finally, in order to maximize the preventative benefit of an earlier treatment initiation threshold, patients need to get into care earlier in infection at higher CD4 cell counts. This is a major challenge with treatment as prevention, even in resource-rich settings. In Europe, where infrastructure and healthcare systems are good, 44% of MSM on average are still diagnosed late with a CD4 cell count <350 cells/µl.[242] Models to date have modeled the effect of getting large numbers of individuals tested and into care, but have yet to model the challenges of getting people into care on time.[219, 309, 314, 320, 323, 324] One way to get patients into care earlier is through partner notification. If partners are notified, then can be diagnosed sooner and initiate treatment. We modeled the long-term impact of partner notification, supported by an online-partner notification system, among men who have sex with men (MSM) in the Netherlands (Chapter 5). The partner notification system, however, is not predicted to prevent many new infections, with <0.5% of infections prevented over 5 years. This small percentage of prevented infections can be attributed to the fact that most individuals who presented for HIV testing through notification had similar CD4 cell counts as those who presented for HIV testing without being notified. If partner notification could be used to target the partners of acutely infected patients, a larger impact may be observed. If partner notification can be used to get a larger percentage of patients into care, this will also increase the preventative effect. Other ways to get patients into care early should be further modeled and investigated. Mobile testing units have had successes in a broad variety of settings,[261-264] and could also be an important way to diagnose MSM at sex-clubs or parties in resource-rich settings, or heterosexuals in rural sub-

Saharan Africa. Both increasing awareness among general practitioners and efforts to normalize HIV testing can also be of importance, particular in resource-rich settings with low general HIV prevalence.[265-267] Many patients who were diagnosed late in infection had visited their general practitioner in the years before diagnosis with symptoms that could suggest an HIV infection. General practitioners that do more frequent HIV testing, especially among known at-risk populations such as MSM, can help to identify HIV. As such, increased HIV testing by general practitioners can lead to a reduction in the number of infected individuals who are diagnosed late.[266, 267]

In summary, this thesis has demonstrated that treatment as prevention, PrEP and partner notification can all prevent new infections (Chapters 3, 5, 6, 8).[7, 26, 272, 273] The magntitude by which the HIV epidemic is reduced does depend on the setting, the people that are targeted for a particular intervention, the CD4 treatment initiation threshold, linkage to care, patient retention, and the number of patients that can be identified early in their HIV infections.

2. Determine the impact of earlier antiretroviral treatment and PrEP on transmitted HIV drug resistance

One important consideration with the increasing usage of antiretroviral drugs for prevention is the development and further transmission of HIV drug resistance. This is particularly the case in sub-Saharan Africa where there are a limited number of antiretroviral drugs available for HIV treatment.

We addressed the impact of treatment as prevention in regards to infections averted and predicted rates of transmitted drug resistance in Mombasa, Kenya and Kampala, Uganda (Chapter 3) . When antiretroviral therapy is initiated at CD4 cell count below 350 cells/µl in these two settings, the prevalence of transmitted drug resistance is expected to increase slightly. Expanding treatment by initiating ART at CD4 cell count below 500 cells/µl will lead to an increasing prevalence of transmitted drug resistance from 8.3% and 12.3% to 19% and 19.2% over the coming 10 years in Kampala and Mombasa respectively. It is predicted, however, that the number of infections averted by earlier treatment initiation will far exceed the number of infections with a drug-resistant virus: between 18 and 46 infections averted due to the preventative impact of earlier treatment for every additional case of drug resistance that arises. We were able to show that that while prevalence of transmitted drug resistance is predicted to increase, the absolute number of transmitted drug resistance cases will decline with earlier treatment initiation (Chapter 4).

As the proportion of individuals infected with a drug resistant virus is predicted to increase, this will make treating HIV more difficult and complex over time. It is therefore still important to minimize transmitted drug resistance in order to preserve currently available antiretroviral regimens. There are several ART program-level strategies that can help mitigate the emergence and transmission of drug resistance (Chapter 4). Viral load testing can reduce the emergence of

HIV drug resistance by early identification of patients with virological failure, prompting intensified adherence counselling and switch to second-line ART as necessary, thereby minimizing emergence of HIV drug resistance.[21, 138] Second, prompt switching to a protease-inhibitor based second-line regimen of individuals experiencing virological failure has been associated with a reduced risk for drug resistance.[22, 325] Finally, pre-therapy genotypic resistance testing to select a fully active regimen may mitigate acquired drug resistance.[23, 24] Of these three patient monitoring strategies to reduce drug resistance, implementing yearly viral load testing and switching patients to second-line ART as soon as possible after confirmed failure is shown to prevent the most drug resistance: preventing approximately 10% of transmitted drug resistance cases over 10 years at all treatment thresholds.

One issue with the use of PrEP could be an increase in transmitted drug resistance. This could also have implications for treatment, as the drugs currently used as PrEP are also popular in first line antiretroviral treatment. We compared the results of three models of PrEP and drug resistance in sub-Saharan African countries (Chapter 7). The models predict that, even without PrEP, drug resistance will increase in the next 20 years due to antiretroviral therapy. When PrEP is added into the models, less than 4% of total resistance is attributed to PrEP, while 40-50% is due to transmission of resistance, and 50-63% is due to antiretroviral therapy 20 years after the introduction of PrEP. Therefore, it is concluded that drug resistance should not be a reason to limit the use of PrEP.

The potential for drug resistance should not, therefore, be a reason to withhold either earlier treatment initiation or PrEP. Yearly viral load testing and appropriate switching to second-line therapy should be rolled out simultaneously with earlier treatment initiation to minimize the development and transmission of drug resistance. Surveillance of drug resistance should be carried out in areas where earlier treatment and PrEP are implemented in order to monitor drug resistance.

3. Identify the cost-effectiveness of different antiretroviral-based prevention techniques and cost-effectiveness of methods that can reduce drug resistance.

New prevention techniques should only be implemented if they are both cost-effective and affordable. It is therefore essential to conduct cost-effectiveness analysis on antiretroviral-based prevention and monitoring strategies as they can be very costly. It is important to note that even if interventions are considered cost-effective, that does not mean that an intervention will save money. Large investments may need to be made up front before any benefits can be realized, an in many cases, cost-savings will not be achieved. Once money is spent, it cannot be spent elsewhere, either within HIV treatment and prevention, or on another disease. Identifying optimal investments to maximize health in a population by considering many options against each other simultaneously is ideal.

We found that PrEP is predicted to prevent up to 31% of new infections over 10 years, and that PrEP is considered cost-effective at $323 per quality adjusted life years gained when targeted to

the most sexually active individuals (Chapter 6). PrEP and treatment as prevention were combined in one model to investigate not only which prevention techniques are more cost-effective, but also to identify what prevention techniques are affordable in Macha, Zambia (Chapter 8). We find that, when treatment as prevention is added into the PrEP model, it is shown that PrEP alone is more costly and less effective in terms of prevented HIV infections than earlier treatment initiation at CD4 <500 cells/µl. Treatment as prevention is also shown to be the most affordable. With a small increase in budget (<25%), treating earlier in infection is the best way to maximize health in the population. It is shown that while a combination of PrEP and treatment as prevention is predicted to avert the largest number of infections, that it is not affordable. A combination of PrEP and earlier treatment initiation is only found to be the best way to maximize health in a population when there is a 9-fold increase in budget. If that large increase in budget was possible, it is likely that the money could better be spent elsewhere in the health sector to maximize health in the population.

There are several ways to increase the cost-effectiveness and affordability of antiretroviral-based prevention strategies by addressing general barriers to healthcare. Universal healthcare or a single payer system can be of importance in removing financial barriers to care, and thus increasing uptake to HIV-related care.[326] Access to healthcare services can also be improved for rural settings in particular. A main barrier to accessing healthcare can be the physical distance from a provider.[327, 328] Thus, programs to bring skilled healthcare workers to rural settings, or making transportation available for people in rural settings to get to a healthcare clinic, can be of importance.[327]

While this thesis has shown that PrEP is not cost-effective when compared to earlier treatment, PrEP could be more cost-effective in different formulations. Currently vaginal rings[98, 329-333] are being tested in randomized clinical trials for efficacy, and long-acting injectables are being tested for safety and acceptability.[334] These types of PrEP formulations would likely improve adherence, and thus efficacy of PrEP. It is also possible that they would be less costly than daily oral PrEP. PrEP may also be better suited to a more specialized group of at-risk individuals, and not just the most-sexually active, as has been modeled in this thesis. When results of the trials on different PrEP formulations are available, the cost-effectiveness of PrEP should be reassessed.

When treating earlier, it is essential to minimize drug resistance, as described in Aim 2. Of the three patient monitoring techniques investigated, increased use of boosted protease-inhibitor-based second-line treatment is shown to be the only cost-effective approach for reducing transmitted drug resistance in East Africa at between $1,612 and $2,234 per quality adjusted life year gained. Pre-therapy genotyping and twice yearly viral load monitoring are costly with limited health benefits at a population level. This is in line with current recommendations.[14] Unfortunately, yearly viral load monitoring and second-line therapy are not widely available in sub-Saharan Africa.[1]

Alternatives to the current viral load test should be implemented to reduce costs and increase feasibility. Viral load tests can be made more accessible in rural settings with the use of the dried blood spot.[335] There is also a reluctance to switch to second-line therapy after confirmed failure on first-line therapy.[336] Barriers to switching have included infrequent viral load monitoring, infrequent clinic visits, delayed clinic attendance, and clinical parameters, but inclination to switch differs largely by study site.[336] Barriers to switching should be further investigated. Addressing these barriers for switching in sub-Saharan Africa could help foster optimal monitoring and switching practices, which can in turn keep drug resistance to a minimum.

Finally, while the implementation of a partner notification system will not make a large impact in terms of infections averted, <0.5% infections prevented over 5 years, it is shown that that the system is still cost-effective with at €49,011 (IQR €47,688-€49,582) per quality adjusted life year gained over 5 years. As HIV is very expensive to treat in the Netherlands, any intervention that prevents even a small number of infections and is relatively cheap will likely be cost-effective. Since this system is easy to implement, and the burden lies primarily on the patient to contact their partners, it is recommended that partner notification be used throughout the Netherlands and in countries with similar epidemics. Other ways to get patients into care earlier should be investigated. If multiple methods can be tested (such as increased HIV testing at the general practitioner, and mobile HIV testing) and pared against each other in a stochastic league table analysis, as described in Chapter 8, a truly optimal strategy or combination of strategies for getting patients into care on time can be identified.

Critical assessment of models used and model developments throughout this thesis

A similar deterministic model structure was used throughout this thesis (See Chapter 1, Figure 3). This basic structure has been used in modeling studies of other research groups.[48, 309, 337] This modeling approach has the advantage of being transparent.[338] The boxes in the model all represent a disease state, and it is easy to visualize how people move from one box to another. The models in this thesis all use four different sexual risk groups of different sizes and differing sexual activity per group. As there is very limited and unreliable sexual behavior data, models have to rely on calibration of their sexual network to the current epidemic. As such, our model creates an approximate sexual network that results in the given prevalence or incidence that the model then matches. This similarity of results between studies in this thesis could in part be explained by the comparable model structures. Even when very different modeling structures were used to model the effect of treatment as prevention and PrEP, all models found that both interventions were effective.[219]

There are limitations to the models throughout this thesis. One limitation is assuming that there is sufficient availability of ART when initiating treatment at earlier CD4 cell counts. Stock outs of antiretroviral drugs, however, could be a real limitation in scaling up ART.[339] ART stock outs

could lead to patients dropping out of HIV care, or needing to switch to a sub-optimal regimen. Importantly, if patients are driven to non-adherence or treatment interruption due to ART stock outs, patients can acquire HIV drug resistance mutations and transmit their drug resistant virus to others.[340] If stock outs had been incorporated into the modeling of treatment as prevention, the predicted prevalence of transmitted drug resistance may have been higher than reported in this thesis. Stock outs could not be included in the models of this thesis however, as no data on stock outs were available for the regions that were modeled.

Another limitation of the modeling in this thesis is that the models project the current situations into the future. Therefore, if anything changes in HIV treatment, monitoring or prevention, then the exact predictions will be incorrect. Models are useful in predicting the direction of an epidemic or the direction of an effect of an intervention, but not for exact numbers or percentages.

Improvements have been made over time on the current models. The initial model presented in Chapter 6 was a model based in Macha, Zambia. In order to keep the model simple we assumed that the population size would remain constant over the duration of the model. We then used this model again in Chapter 8, but improved on the model by adding in population growth, and treatment rollout in line with the treatment rollout experienced in Macha, and new information that became available. This changed the sexual network dynamics behind the model, the HIV prevalence trend, and as such, altered our exact predictions. As a consequence, in Chapter 8 we predicted that PrEP would prevent fewer infections than in Chapter 6. In Chapter 8 we add in earlier treatment initiation to the prevention options, and find that PrEP is no longer cost-effective. When we add earlier treatment initiation to Chapter 6, we also find that earlier treatment initiation is both less expensive and more effective than PrEP alone. During the time of this PhD research, the CD4 cell count treatment initiation threshold has changed, thus also explaining the differences in thresholds used between chapters in this thesis. Before 2010, treatment was recommended at CD4 <200 cells/ul. From 2010-2013, treatment at CD4 <350 cells/ul was recommended, and since 2013, treatment at a CD4 cell count of <500 cells/ul is recommended. Therefore, while our exact estimates differ, our general conclusions of the models between chapters remain the same.

Similar improvements were made in the models between Chapter 3 and Chapter 4. The population was assumed to remain constant in Chapter 3, and population growth was incorporated in the model of Chapter 4. Also, additional drug resistance data was incorporated into the model in Chapter 4. In both studies, an increase in drug resistance is predicted when ART is initiated earlier, but the magnitude is diminished in Chapter 4 due to the inclusion of and calibration to additional data. In Chapter 3 a bigger influence of second-line is predicted than in Chapter 4. This is because the predicted transmitted drug resistance prevalence in Chapter 3 is much larger, and therefore can be reduced by a greater magnitude. As such, our general conclusions of the models between chapters remain the same.

The accuracy and reliability of models depends on the data that goes in. In all models we incorporate the most robust and up-to-date information available. The models on drug resistance in this thesis make use of the best currently available data on acquired and transmitted drug resistance in sub-Saharan Africa, resulting in reliable predictions. As more data becomes available, models from all chapters can continue to be improved.

Generalizability

The effect of treatment as prevention and PrEP was studied in African settings in this thesis. These results cannot easily be extrapolated to European settings without additional modeling work. The epidemics are very different: in Europe the HIV epidemic is mainly concentrated among MSM. MSM report a far greater number of sexual partners than heterosexuals.[341] As such, it could be that PrEP among MSM is even more cost-effective than in Africa, especially when targeted to the most sexually active MSM. On the other hand, earlier treatment initiation would probably be less cost-effective than in Africa. For one, the cost of treatment is much higher in Europe than in Africa. Secondly, the role of the acute stage in HIV transmission could play a greater role among European MSM due to higher sexual risk behavior than among African heterosexuals. If this were the case, the effectiveness of earlier treatment initiation could be diminished. Additionally, results regarding drug resistance cannot be generalized between Europe and Africa. This is because of differences in regimens used, differences in HIV monitoring strategies, and prior circulating resistance in Europe from the early years of HIV treatment.[342] Our results on drug resistance and treatment as prevention and PrEP could be extrapolated to other countries within sub-Saharan Africa that have similar treatment experience, however. The exact predictions may differ, but the direction of the predictions is likely to be similar.

Partner notification was studied among Dutch MSM. While these results are not directly generalizable to heterosexuals in sub-Saharan Africa, similar results could be expected if partner notification is tailored to each setting. Given the ubiquity of mobile phones in Africa, a mobile-phone based partner notification system, instead of the internet-based system developed for the Netherlands, could increase effectiveness.[343, 344] The cost-effectiveness ratio would likely be much lower in Africa, as the cost of HIV testing and treatment is lower, and the burden would still be primarily on the infected individual to contact their partners.

Conclusions and Future Research

Based on the contents of this thesis, the following is concluded:

1) Investing in treatment as prevention, as compared to PrEP, is a better way to maximize health in countries with a generalized HIV epidemic and limited budgets;

2) HIV drug resistance can be kept to a minimum by both ensuring the availability of yearly viral load monitoring and by prompt switching to protease-inhibitor-based second-line therapy after confirmed failure on first-line therapy;

3) Initiating HIV treatment earlier at higher CD4 cell counts will lead to increases in drug resistance. Due to the preventative impact of earlier treatment initiation however, far more infections are predicted to be averted than cases of drug resistance gained;

4) Online partner notification alone will have a small impact on the HIV epidemic, but is a cost-effective tool for getting HIV patients into care and on treatment earlier;

5) PrEP can prevent new infections. If PrEP is used as part of an HIV prevention strategy, it should be given to those at highest sexual risk, and is not predicted to contribute substantially to HIV drug resistance.

Since the start of this PhD research, earlier treatment initiation at a CD4 count of <500 cells/µl, is recommended by the World Health Organization for clinical benefit to the patient and in order to prevent new infections.[14] While earlier treatment is recommended, it is not yet widely implemented, and stock outs of ART occurred even under previous guidelines.[1, 339, 340] It is important not only to recommend earlier treatment, but to help realize the recommendation in daily practice. A parallel investment should be made in the scale up and use of yearly viral load monitoring as well as increasing the availability and use of second-line protease inhibitor drugs when indicated. Proper implementation of viral load monitoring and use of second-line protease inhibitor based treatment can help curb drug resistance that is predicted with treatment scale up.

PrEP has also since been approved for use by the Food and Drug Administration for HIV prevention.[345] PrEP has not been registered, however, by the European Medicines Agency, and has only been used limitedly in Africa, primarily as part of trials. As PrEP has been shown to prevent HIV infections, especially when adherent, a move should be made to register antiretrovirals for use as PrEP. PrEP can then be used for prevention among those who are at substantial risk for HIV infection.

Future studies should focus on identifying specific risk groups that would benefit most from PrEP to maximize its effectiveness. This could be, for example, individuals who have a known HIV-infected partner that is not yet on treatment, who have had to make use of post-exposure prophylaxis after sexual exposure, who have regular unprotected anonymous sex, women in HIV-endemic settings who want to protect themselves, or sex workers.

Future research should also focus on improving the cascade of care: identifying ways to get patients into care earlier and retaining patients in care. Without proper linkage to care and retention in care, treatment as prevention will have limited success, and there is a potential for increases in drug resistance.

Chapter 10

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Chapter 11

Summary

There are currently 35 million people living with HIV, and each year there are more than two million new HIV infections worldwide. HIV-infected patients will need lifelong treatment and care. HIV prevention is needed to reduce the number of new infections as, first and foremost, HIV is a very serious infection, and secondly HIV treatment is very expensive and should be kept economically sustainable. Early treatment initiation prevents new infections. When a patient is successfully suppressed on antiretroviral therapy, they are no longer infectious. Antiretroviral drugs can also be given to uninfected individuals to prevent infection, known as pre-exposure prophylaxis. The overarching aim of this thesis is to identify optimal antiretroviral-based strategies to prevent new HIV infections in terms of infections averted and costs incurred.

Within this thesis mathematical modeling and cost-effectiveness analysis have been utilized to address the following aims: 1) Evaluate the impact of treatment as prevention, pre-exposure prophylaxis (PrEP), and partner notification on the epidemic in terms of infections averted and life-years saved using mathematical models; 2) Determine the impact of earlier antiretroviral treatment and PrEP on transmitted HIV drug resistance; 3) Identify the cost-effectiveness of different antiretroviral-based prevention techniques and cost-effectiveness of methods that can reduce drug resistance.

Treatment as prevention, PrEP and partner notification are all predicted to prevent new infections (Chapters 3, 6, 7, 8). In Kampala, Uganda, and Mombasa, Kenya, treatment as prevention is predicted to prevent 29% and 26% respectively, over a 10 year period (Chapter 3). In Zambia, treatment as prevention is predicted to prevent 34% of new infections over 40 years, and PrEP alone is predicted to avert between 16%-42% (Chapter 8). When PrEP and treatment as prevention are combined, nearly 60% of infections are predicted to be averted over a 40 year period in Macha, Zambia. Among men who have sex with men (MSM) in the Netherlands, partner notification was predicted to avert only a small number of infections over 10 years, <0.1% (Chapter 5)

PrEP is shown to be cost-effective when ART is started at a CD4<350 cells/µl (Chapter 6) in Macha, Zambia. In the same analysis it is shown that the more that PrEP can be targeted to the most sexually active individuals, the more cost-effective it can be. In Chapter 8, however, when treatment as prevention is added into the PrEP model, it is shown that PrEP alone is more costly and less effective in terms of new HIV infections that are averted than earlier treatment initiation at CD4 <500 cells/µl. Treatment as prevention is also shown to be the most affordable. With a While the implementation of a partner notification system in the Netherlands was not predicted to make a large impact in terms of infections averted, it is shown that that the system is still cost-effective with at €49,011 (IQR €47,688-€49,582) per quality adjusted life year gained over 5 years. Since this system is easy to implement, and the burden lies primarily on the patient to contact their partners, it is recommended that partner notification be used throughout the Netherlands and in countries with similar epidemics.

There is fear that treatment as prevention will lead to increased drug resistance. Treatment as prevention was predicted to increase the prevalence of transmitted drug resistance (Chapter 3).

It is predicted, however, that the number of infections averted by earlier treatment initiation will far exceed the number of infections with a drug-resistant virus: between 18 and 46 infections averted due to the preventative impact of earlier treatment for every additional case of drug resistance that arises. In Chapter 4, it is shown that while prevalence of transmitted drug resistance is predicted to increase, the absolute number of transmitted drug resistance cases will decline with earlier treatment initiation. There are several ART program-level strategies that can help mitigate the emergence and transmission of drug resistance, including increased viral load monitoring, pre-therapy genotyping, and increased use of boosted protease-inhibitor-based second-line treatment (Chapter 4). Of the strategies modelled, increased use of boosted protease-inhibitor-based second-line treatment in combination with yearly viral load monitoring is shown to be the only cost-effective approach for reducing transmitted drug resistance in East Africa at between $1,612 and $2,234 per quality adjusted life year gained.

One issue with the use of PrEP could be an increase in transmitted drug resistance. In Chapter 7 the results of three models of PrEP and drug resistance in sub-Saharan African countries are compared. The models predict that, even without PrEP, drug resistance will increase in the next 20 years due to antiretroviral therapy. When PrEP is added into the models, less than 4% of total resistance is attributed to PrEP, while 40-50% is due to transmission of resistance, and 50-63% is due to antiretroviral therapy 20 years after the introduction of PrEP. Therefore, it is concluded that drug resistance should not be a reason to limit the use of PrEP.

Based on the contents of this thesis, the following is concluded: 1) Investing in treatment as prevention, as compared to PrEP, is a better way to maximize health in countries with a generalized HIV epidemic and limited budgets; 2) HIV drug resistance can be kept to a minimum by both ensuring the availability of yearly viral load monitoring and by prompt switching to protease-inhibitor-based second-line therapy after confirmed failure on first-line therapy; 3) Initiating HIV treatment at early CD4 cell counts will lead to increases in drug resistance. Due to the preventative impact of earlier treatment initiation however, far more infections are predicted to be averted than cases of drug resistance gained; 4) Online partner notification alone will have a small impact on the HIV epidemic, but is a cost-effective tool for getting HIV patients into care and on treatment earlier; 5) PrEP can prevent new infections. If PrEP is used as part of an HIV prevention strategy, it should be given to those at highest sexual risk, and is not predicted to contribute substantially to HIV drug resistance.

In conclusion, the use of antiretroviral drugs as prevention is a cost-effective method for curbing the HIV epidemic. Resistance can occur and increase as a result, but should not be a reason to withhold antiretroviral drugs.

Nederlandse Samenvatting

Er zijn momenteel wereldwijd 35 miljoen mensen geïnfecteerd met het humaan immunodeficiëntie virus (HIV). Elk jaar komen er twee miljoen nieuwe infecties bij. HIV is een zeer ernstige infectieziekte die zonder behandeling met HIV-remmers tot de dood zal leiden. Omdat geneesmiddelen die gebruikt worden om het HIV virus te remmen relatief duur zijn en deze levenslang moeten worden geslikt, is de behandeling van HIV momenteel een kostbare aangelegenheid. Recent onderzoek heeft aangetoond dat patiënten, die succesvol behandeld worden met HIV-remmers, nog maar een hele kleine kans hebben om hun seksuele partners met HIV te infecteren. Daarom is men gestart met het voorschrijven van HIV remmers bij mensen die zich in een vroeg stadium van de HIV infectie bevinden. Dit vroege behandelen heet behandeling ter preventie. Behandeling ter preventie kan alleen succesvol zijn als zoveel mogelijk patiënten vroeg starten met de behandeling. Helaas is van veel patiënten die zich in een vroeg stadium bevinden, vaak nog niet bekend dat ze geïnfecteerd zijn met HIV. Partnerwaarschuwing is een methode om het aantal patiënten sneller te diagnosticeren. Partnerwaarschuwing is het actief opsporen en uitvoeren van HIV-testen van partners van mensen bij wie recent een infectie is vastgesteld. Ook is aangetoond dat mensen die HIV-remmers gebruiken maar niet geïnfecteerd zijn, een sterk verminderd risico hebben om geïnfecteerd te raken met HIV. Dit preventieve gebruik van HIV remmers door mensen die niet geïnfecteerd zijn, wordt ook wel Pre-Expositie Profylaxe (PrEP) genoemd. Het algemene doel van dit proefschrift is om de beste strategie te vinden waarmee HIV-remmers kunnen worden toegepast voor preventie, zodat de meeste infecties kunnen worden voorkomen tegen zo laag mogelijke kosten.

In mijn proefschrift heb ik gebruik gemaakt van wiskundige modellen die voorspellen hoeveel infecties kunnen worden voorkomen door het gebruik van HIV-remmers. Met behulp van deze wiskundige modellen heb ik ook de kosteneffectiviteit berekend. In mijn proefschrift beantwoord ik de volgende vraagstellingen: 1) Hoeveel HIV-infecties kunnen voorkomen worden met behandeling ter preventie, PrEP en het waarschuwen van partners van patiënten van wie recent is vastgesteld dat ze HIV geïnfecteerd zijn? 2) Kan behandeling ter preventie en het gebruik van PrEP leiden tot meer nieuwe infecties met een geneesmiddelenresistent HIV? 3) Wat is de kosteneffectiviteit van de verschillende preventiestrategieën en hoe kan geneesmiddelenresistentie tegen HIV-remmers op een kosteneffectieve manier beperkt worden?

Behandeling ter preventie, PrEP en partnerwaarschuwing kunnen allemaal nieuwe infecties voorkomen (hoofdstuk 3, 6, 7 en 8). Over een periode van tien jaar, kan behandeling ter preventie in Kampala (Oeganda) en in Mombasa (Kenia) tussen de 25% en 30% van de nieuwe HIV infecties voorkomen (hoofdstuk 3). In Zambia, voorspel ik dat over een periode van 40 jaar, behandeling ter preventie 34% van de infecties voorkomt en PrEP tussen de 16% en 42% (hoofdstuk 8). Combinatie van zowel behandeling ter preventie en van PrEP is zeer effectief en voorkomt 60% van de HIV-infecties in Zambia. Partnerwaarschuwing bij mannen-die-seks-hebben-met-mannen (MSM) heeft in Nederland een kleine impact op het aantal nieuwe

infecties en voorkomt naar verwachting minder dan 0.1% van alle infecties over een periode van tien jaar (hoofdstuk 5).

PrEP is kosteneffectief in Zambia. De kosteneffectiviteit kan nog verder worden verhoogd als PrEP aan mensen wordt gegeven die op seksueel gebied het meest actief zijn (hoofdstuk 6). In hoofdstuk 8 laat ik zien dat in vergelijking met behandeling ter preventie, PrEP duurder is en minder HIV infecties voorkomt. Hoewel partnerwaarschuwing niet veel nieuwe infecties zal voorkomen is het wel kosteneffectief. Dit komt omdat de behandeling met HIV-remmers zeer kostbaar is.

In hoofdstuk 3 laat ik zien dat behandeling ter preventie in Afrika zal leiden tot een toename van het aantal nieuwe infecties met een geneesmiddelenresistent virus. Belangrijk hierbij is dat behandeling ter preventie wel zal leiden tot een veel sterkere afname van het aantal nieuwe infecties dan dat er nieuwe gevallen van infecties met resistente virussen bijkomen. Samengevat worden er tussen de 18 en 46 nieuwe infecties voorkomen voor iedere nieuwe infectie met een geneesmiddelenresistent virus. In hoofdstuk 4 laat ik zien dat resistentie op een kosteneffectieve wijze kan worden verminderd door het regelmatig meten van de virusdeeltjes in het plasma van patiënten die HIV-remmers gebruiken. Als dan blijkt dat de HIV-remmers die zo'n patiënt sinds het begin van de behandeling gebruikt niet werken (men noemt deze eerste behandeling de eerstelijns therapie) dan moet die worden vervangen door een andere behandeling, of ook wel tweedelijns therapie genoemd.

Geneesmiddelenresistentie kan ook een belangrijk nadeel zijn bij het gebruik van PrEP. De HIV-remmers die deel uitmaken van PrEP worden ook veel toegepast in de behandeling van HIV. Hoewel PrEP het risico op een HIV-infectie zeer sterk kan verminderen, kunnen gebruikers van PrEP toch nog geïnfecteerd raken. Er is een angst dat er resistentie kan ontstaan bij deze mensen die geïnfecteerd zijn geraakt, ondanks het gebruik van PrEP. Deze resistentie kan dan een nadelige invloed hebben op de latere behandeling en deze resistentie kan mogelijk overgedragen worden op andere mensen. Hoofdstuk 7 presenteert het resultaat van een vergelijking van drie onafhankelijke modellen in Afrika, ten zuiden van de Sahara. Deze modellen voorspellen allemaal dat geneesmiddelenresistentie in de komende 20 jaar sterk zal toenemen, omdat steeds meer mensen worden behandeld met HIV-remmers. Alle drie de modellen voorspellen dat over 20 jaar niet meer dan 4% van alle patiënten die een geneesmiddelenresistent virus bij zich dragen, toe is te schrijven aan PrEP. Geneesmiddelenresistentie lijkt daarom geen reden om PrEP niet te geven aan mensen die risico lopen op een HIV infectie.

Op grond van mijn proefschrift trek ik de volgende conclusies: 1) Investeren in behandeling ter preventie is, in vergelijking met PrEP, de beste methode om HIV te bestrijden in Afrika, ten zuiden van de Sahara, omdat zij een beperkt budget ter beschikking hebben, 2) De omvang van geneesmiddelenresistentie kan beperkt worden door jaarlijks vast te stellen hoeveel HIV-

deeltjes een behandelde patiënt in zijn plasma heeft. (Bij een patiënt die succesvol behandeld wordt is het aantal HIV-deeltjes gedaald tot onder de detectielimiet) Als blijkt dat de HIV-remmers niet goed meer werken moet men zo snel mogelijk een andere behandeling met HIV-remmers starten, 3) Het vroeger behandelen van HIV zal leiden tot een toename van geneesmiddelenresistentie en tot een afname van het aantal nieuwe HIV-infecties. Belangrijk is dat de toename in resistentie veel beperkter is dan de afname van het aantal nieuwe infecties, 4) Hoewel partnerwaarschuwing het aantal nieuwe infecties onder MSM in Nederland maar zeer beperkt zal laten afnemen, blijkt het wel een kosteneffectieve methode voor het opsporen van onbekende infecties, 5) PrEP kan nieuwe HIV-infecties voorkomen. PrEP moet aan de meest seksueel actieve mensen worden gegeven. PrEP heeft maar een heel beperkt effect op geneesmiddelenresistentie.

Samenvattend is de conclusie van mijn proefschrift dat HIV-remmers een kosteneffectieve methode is om de HIV epidemie in te dammen. Gebruik van HIV-remmers ter preventie zal leiden tot een toename van resistentie. Maar deze toename in resistentie is beperkt en weegt daarom niet op tegen de veel grotere beperking van de epidemie door HIV-remmers. Resistentie is daarom geen reden om geen HIV-remmers ter preventie te gebruiken.

Chapter 12

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How can someone promote without their (co)-promoters? Dank je wel mijn co-promotor, **David van de Vijver**, or Dr. Dave, MFD! Thank you for the opportunity to come to the Netherlands and do my PhD here, for keeping me up to date on the news, for keeping me informed about history, for editing my papers 2,394,202 (SD 10) times with me to make sure the papers reach their full potential, for letting me correct your English, for learning me (teaching me?) mathematical modeling, for fostering my coffee addiction, and for letting me steal bits of your candy acquisitions from the goodygoody box. I can always count on you to get excited about nerdy ideas & help me to solve modeling issues. Thank you **Charles Boucher** for helping me to think critically and for inspiring me to always take research a little bit further. Your ideas always help to push the limits of our research.

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And finally, my **little family**… First, my dear little monkey, **Matthijs**. There is nothing quite like your snuggles to get me through the day. Thank you for waking up so much during the night so I get more time to see you. You can always make me smile with your crazy noises, or laugh hysterically with your well-timed farts. I can no longer imagine what life was like without you.

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Chapter 13

About the Author

Curriculum Vitae

Brooke Nichols (Fokker) was born on August 3rd 1987 in New York, New York, USA. In 2005 she finished high school at Joel Barlow High School in Redding, CT, and began her undergraduate studies in International Relations, focused in International Health, at Mount Holyoke College in South Hadley, MA. In January 2009, she began her master's degree studies in epidemiology at the University of Massachusetts School of Public Health and Health Sciences in Amherst, MA. During her studies, she was a research assistant for the Proyecta Buena Salud study, investigating the epidemiology of stress and gestational diabetes in Latina women, and the Behaviors Affecting Baby and You (BABY) study, a randomized trial investigating the efficacy of an individually tailored 12-week physical activity intervention on the risk of developing gestational diabetes. She was also a teaching assistant for the graduate course Analysis of Epidemiologic Data. Brooke completed research projects in the summer of 2008 and 2009 in Lüderitz, Namibia. The focus of her research was the role of drinking establishments in HIV prevalence, as well as factors contributing to high HIV prevalence in migrant towns. She completed her masters studies with her thesis entitled *Density of Drinking Establishments and HIV Prevalence in a Migrant town in Namibia* based on her research project in Lüderitz.

In December, 2010 she began as a PhD student at the department of Viroscience in the Erasmus Medical Center in Rotterdam, the Netherlands, under supervision of Professor Charles Boucher and Dr. David van de Vijver. This project, focusing on the mathematical modeling and cost-effectiveness of antiretroviral-based HIV-1 prevention strategies, has resulted in the present thesis.

PhD Portfolio

Name: Brooke Elizabeth Nichols (Fokker)
Erasmus MC Department: Department of Viroscience
Research School: Post-graduate Molecular Medicine
PhD Period: 2010-2015
Promotor: Prof.dr. Charles A.B. Boucher
Copromotor: Dr. David A.M.C. van de Vijver

Education

2010-2015	PhD Program, Erasmus Medical Center, Rotterdam, the Netherlands. PhD thesis: Mathematical Modeling and Cost-Effectiveness of Antiretroviral-Based HIV-1 Prevention Strategies.
2009-2010	Master of Science, University of Massachusetts, Amherst, School of Public Health and Health Sciences, United States. Study: Epidemiology. Thesis: Density of Drinking Establishments and HIV Prevalence in a Migrant Town in Namibia.
2005-2009	Bachelor of Arts, Mount Holyoke College, South Hadley, Massachusetts, United States. Study: International Relations.

In-depth courses

Epidemiology and Control of Infectious Diseases, Imperial College, London	2011
Course in Virology, Erasmus MC	2012

Oral Presentations

15th Annual Resistance and Antiviral Therapy Meeting, London, United Kingdom	2011
10th European Meeting on HIV & Hepatitis, Barcelona, Spain	2012
19th International AIDS Conference, Washington DC, USA	2012
7th Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam	2013
8th Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam	2014

Poster Presentations

19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA	2012
20th Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, USA	2013
21st Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA	2014
22nd Conference on Retroviruses and Opportunistic Infections, Seattle, MA, USA	2015

Awards

Young Investigators Award: 19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA	2012
Young Investigators Award: 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, USA	2013
Young Investigators Award: 21st Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA	2014
Young Investigators Award: 22nd Conference on Retroviruses and Opportunistic Infections, Seattle, MA, USA	2015

List of Publications

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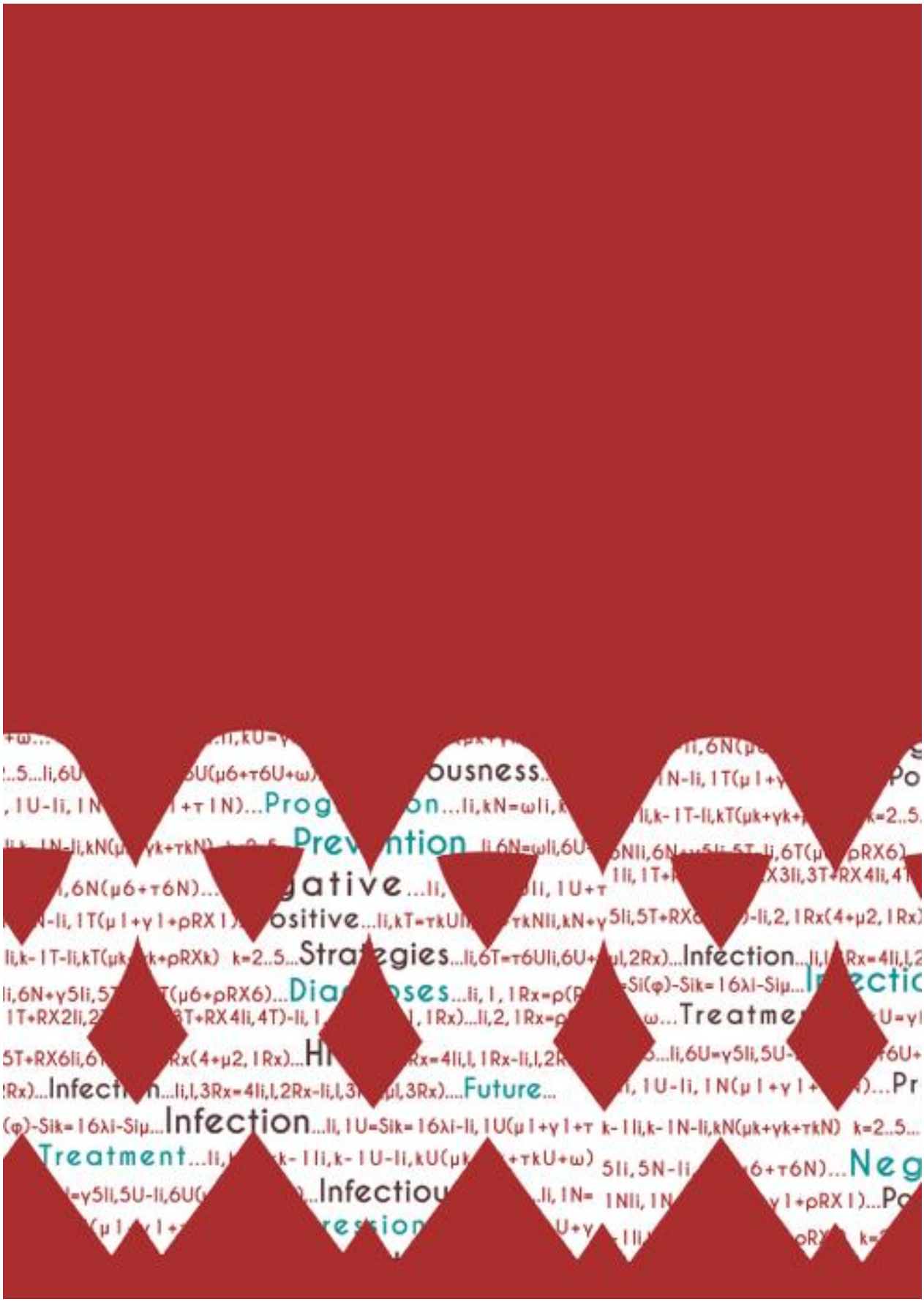
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