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Allocating Resources for HIV Prevention:
Determining an Optimal Intervention Scenario in Zambia

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Abstract

Allocating Resources for HIV Prevention:
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By Supriya Sarkar

A key strategy to end the HIV epidemic is the Fast-Track response, an international approach focused on the rapid scale-up of essential HIV prevention and treatment strategies. A component of this goal is the 90-90-90 targets, which aimed for 73% of people living with HIV (PLHIV) to be virally suppressed by 2020. Sub-Saharan Africa, a priority region for the response, is dependent on international funding for HIV programs, which has declined in recent years. With resource availability being tenuous, countries must scale-up HIV services in a cost-effective manner. In this dissertation, we focus on the HIV epidemic of Zambia to understand previous patterns in HIV care delays and to explore the potential epidemiologic and economic impacts of scaling-up HIV interventions.

In **Aim 1**, we used an electronic health record database to explore the care continuum to characterize the delays experienced by PLHIV after engaging in care. We found that half of PLHIV were considered eligible for treatment at their first clinical visit, but less than 10% were prescribed treatment immediately once they were deemed eligible. In **Aim 2**, we used agent-based modeling to estimate the impact of different HIV testing, treatment, and retention strategies on HIV incidence in Zambia. We found that the current standard of care could lead to a 40% reduction in HIV incidence by 2030. Interventions including 1) immediate treatment initiation after diagnosis (test-and-treat) and 2) couples voluntary counseling and testing (CVCT) amplified these results, leading to a 71% and 64% reduction in HIV incidence, respectively, over a ten-year period. In **Aim 3**, we calculated the cost-effectiveness of strategies that would prevent HIV in Zambia. We found that integrating CVCT with a test-and-treat approach could avert approximately 130,000 infections while saving $100 million over ten years.

We demonstrate the importance of scaling-up a test-and-treat approach, ensuring that all PLHIV have access to treatment, and the economic benefits of integrating cost-saving HIV interventions, such as CVCT into a test-and-treat setting. Our results will support policymakers in their decision-making process for allocating HIV resources as they face restrictive budgets and strive to achieve the Fast-Track goals.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 Background

1.1 Global Epidemiology of HIV/AIDS

HIV persists as a global challenge, despite the HIV epidemic shifting dramatically in the last several decades.[1, 2] Since the beginning of the epidemic in the early 1980s, over 70 million people have become infected and over 35 million have died as a result.[3] HIV incidence peaked at an estimated 3.7 million infections in 1997 before the introduction of antiretroviral therapy (ART). Increased ART access has fueled a rapid decline of incidence in the last 20 years, and expanded ART coverage has helped avert over 5 million infections with an 34% reduction in mortality between 2010 and 2017. [4, 5] The increase in HIV prevalence worldwide, however, is largely due to ART access. Global HIV prevalence increased from 31 million in 2002 to 35.3 million in 2012, as people on ART began to live longer lives.[1] As of 2017, however, approximately 37 million people globally were living with HIV/AIDS, with almost 2 million individuals being newly infected in that year and almost 1 million dying from AIDS-related illnesses.[6]

1.1.1 *Global Burden of Disease*

HIV continues to be a major contributor to the global burden of disease.[1, 7] Of the 38 million people living with HIV in 2019, 52.6% were women.[6] Although population risk factors differ by region, women of reproductive age tend to have the highest risk of HIV transmission in higher-prevalent settings. This is contrast to low HIV prevalent countries, where key populations (e.g., men who have sex with men (MSM), intravenous drug users, sex workers) tend to have the highest risk of acquiring infection.[8] Although there is heterogeneity in transmission and mortality by country,

there were more deaths among women aged 15-29 than men in the same age cohort, and more deaths among men aged 35 or older than women of similar age.

Individuals living with HIV are also at increased risk of acquiring other infectious diseases, including tuberculosis, cryptococcosis, hepatitis B and C viruses, and malaria.[9] For example, an estimated 39% of new tuberculosis cases occurred in individuals living with HIV and almost one-fifth of HIV-related deaths were attributed to tuberculosis-coinfection in 2015.[10] With ART use on the rise, HIV has been viewed as a manageable chronic illness, with many people living with HIV experiencing life expectancies similar to people who do not have HIV. Despite this, research has shown that a large proportion (18.5% – 53.0%) of people living with HIV die from cardiovascular disease, liver disease, and other malignancies, possibly from toxicity from prolonged ART use.[11]

These co-infections and long-term comorbidities contribute to the higher level treatment costs required, creating an economic burden on people affected by HIV as well as on national governments.[12] Since people of working age are most susceptible, HIV puts financial pressure on households due to premature mortality, lost income, and lifelong medical and healthcare costs. As a result, local and regional economies have suffered because of the lack of employment and unrealized profits.[13, 14]

1.1.2 Regional Epidemics

The epidemic varies significantly by region as aforementioned, with modes of transmission and risk factors differing by epidemic. In North America and Western Europe, where HIV prevalence

is approximately 0.5%, more men are affected by HIV (approximately 71% of people living with HIV in this region are men) and MSM are cited as a key population at risk.[2] The HIV epidemic in Asia is primary driven by heterosexual transmission, although injection drug use is an important risk factor, accounting for over a quarter of infections in China.[2] In sub-Saharan Africa, the main mode of transmission is unprotected heterosexual intercourse, with mother-to-child transmission (MTCT) also contributing as the epidemic in the region. Sub-Saharan Africa carries the largest burden of disease, with 25 million people living with HIV and accounting for two-thirds of the global total of new infections.[15-17]

1.2 HIV Epidemic in Sub-Saharan Africa

1.2.1 Recent Trends in Sub-Saharan Africa

Sub-Saharan Africa has seen one of the world's largest decline in HIV incidence in the last decade, with the number of new infections dropping by 30%. Scale-up and increased coverage of ART is predominantly responsible for this decline – studies have shown that in regions with high ART coverage (>30%) seronegative individuals were almost 40% less likely to acquire HIV than in regions with low ART coverage (<10%).[18] However, incidence still remains high, as 800,000 people were newly infected in 2017.[19]

Noticeable differences in HIV epidemiology exist throughout the region. The region has a total adult prevalence of 4.1%; however country-specific prevalence ranges from 0.1% in Somalia and 27.1% in Swaziland.[20, 21] HIV prevalence is generally lower in Eastern Africa than in Southern Africa; a definitive cause of this is uncertain, although a combination of actors may take a role,

including but not limited to: male circumcision rate, age at marriage, age at sexual debut, concordant sexual partners.[2]

1.2.2 Risk Factors in Sub-Saharan Africa

Heterosexual intercourse is the primary mode of transmission among adults coupled with a concomitant epidemic in children through vertical transmission. Among sub-Saharan couples in which one person is infected with HIV, two-thirds are in a discordant relationship[2] A large proportion of transmission may be related to being in a long-term partnership, although studies have found that half of the incidence is attributed to extra-partner sex.[22]

Women are disproportionately affected by the epidemic, and HIV prevalence is consistently higher in young women than in young men throughout the region. Young women consistently have higher prevalence rates than men and acquire HIV between five to seven years before their male peers.[19] Women may face this disproportionate vulnerability due to differences (compared to men) in age of sexual debut, engagement in transactional sex, sexually transmitted infections, and age disparate sex.[19]

The HIV epidemic in Sub-Saharan Africa is generally considered as a generalized one because of its presence in the general population. There is a paucity of data on key populations, such as MSM and injection drug users, due to criminal laws in many countries in the region. However, there is growing evidence that HIV prevalence and incidence is much higher in these groups than in the general population: one Kenyan study showed that incidence among men who have sex with

men exclusively is 3.7 times higher than men who have sex with both men and.[23] Sex work is also a key driver to the generalized epidemic; sex workers have a higher chance of acquiring infection, and prevalence is at least twice as high in this group than in the general population.[24]

1.2.3 HIV in Zambia

Zambia, a landlocked country of 17 million people in sub-Saharan Africa, has an adult HIV prevalence of 11.5%, the seventh highest in the world, with approximately 1.2 million people living with HIV.[6, 25] Although Zambia has experienced a reduction in HIV incidence of 24% in the last decade, prevalence has been relatively stable.

Similar to its neighboring countries, Zambia has a generalized epidemic. Geographical heterogeneity exists, as HIV prevalence ranges from 5.1% in Muchinga Province to 16.1% in Lusaka Province.[26] Women are disproportionately affected, with a 14.0% prevalence in adult women aged 15-49 compared to 8.9% prevalence in men of the same age. Adolescent girls and young women are especially at risk: early sexual debut (median: 17.3 years), early pregnancy (median: 19.1 years at first birth), and age disparate sex (women with partners 10+ years older: 7.2.[27, 28]

More than half (58.9%) of the Zambian adult population is in a stable relationship, or a married or cohabitating couple. A considerable fraction of these couples are HIV discordant, where one partner is HIV-negative and the other partner is HIV-positive.[22, 29, 30] An estimated 60.3% - 80.4% of all new heterosexual HIV infections occur through marriage or cohabitation. Men have

historically been thought to be the index case within a HIV discordant couple, but recent literature has shown that in close to half (40.3%) of stable heterosexual relationships in Zambia, the female partner is HIV-seropositive.[22, 31]

Among pregnant women attending antenatal care clinics, approximately 22% test HIV-positive (Stoner; 2016). A push to expand ART coverage among HIV+ pregnant women has been very successful in reducing mother-to-child transmission in Zambia; MTCT declined by half between 2007 and 2012.[32] However, over 7000 children were newly infected in 2017, illustrating that there is still work to be done to completely eliminate MTCT.[6]

1.3 HIV Care

The introduction and expansion of ART dramatically shifted the HIV epidemic curve with both HIV-related mortality and morbidity declining rapidly in the last few.[33] In Sub-Saharan Africa, over 7.5 million people initiated ART by 2014, representing a 50-fold increase in the decade prior.[34] The results of the landmark HPTN 052 study demonstrated a 96% decrease in transmission within serodiscordant couples where the HIV-infected partner was on early-ART.[35] Further studies confirmed that successful ART with viral suppression (e.g., undetectable viral load) could prevent HIV transmission to sexual partners.[36] These findings that ART could sustain a decrease in infections in sexual partners is very exciting; however, ART access alone cannot sustain population health improvements. Rather, lifelong retention in care, in parallel with increased access to ART, is needed to realize public health goals.

1.3.1 HIV Care Continuum

The progression between HIV testing to engagement in medical care and, ultimately, viral suppression in often portrayed in a framework known as the HIV care continuum, or HIV treatment cascade.[37] This model outlines the steps that an individual with HIV take from an initial diagnosis to achieving viral suppression. The framework varies between country contexts, but the most common components of the continuum include 1) HIV testing, 2) linkage or enrollment in HIV care, 3) CD4 testing, 4) retention in care, 5) treatment initiation, and 6) viral suppression.[33] This theoretical model characterizes patient engagement with a healthcare infrastructure, and the concept has been used to measure and evaluate HIV program progress in order to identify weaknesses and healthcare bottlenecks at each step.[34]

1.3.1.1 HIV Testing

The first step of the care continuum for individuals living with HIV is receiving a diagnosis and becoming aware of their status. Client-initiated (voluntary) as well as provider-initiated routine testing are two main service delivery approaches. In Zambia, providers offer HIV testing to all patients who are assessed for a sexually transmitted infection, antenatal care patients to facilitate prevention of horizontal transmission, and asymptomatic patients in HIV-relevant healthcare settings (e.g., injecting drug use treatment services, hospital emergencies).[38] According to UNAIDS, a quarter of individuals living with HIV globally do not know their status, precluding them from receiving necessary care, treatment, and their partners from receiving prevention services.[3] Lack of perceived risk, emotional burden of knowing one's status, and poor healthcare infrastructure are common barriers to HIV testing.

1.3.1.2 Linkage and Enrollment into HIV Care

Linkage to care is defined as the time between and an individual receiving one's positive HIV diagnosis and the first encounter with an HIV care provider.[39] This period of time is critical since initiating ART within three months of diagnosis is associated with higher probability of viral suppression.[37] In Zambia, only 67% of people receiving a positive HIV diagnosis are appropriately linked to care.[40] Delayed linkage to care or non-engagement of care is often associated with transportation costs, stigma, and lack of knowledge about HIV treatment.[41, 42]

1.3.1.3 CD4 Testing

CD4 count thresholds has historically been one of the defining eligibility criteria, along with World Health Organization (WHO) clinical disease stage, for initiating ART for individuals who have received a positive test result for HIV. In 2002, WHO guidelines stated that ART should be offered to the following: patients with severe symptoms (Stage 4), patients who are moderately symptomatic (Stage 3) and have a CD4 count of <300/mm^3, and asymptomatic or mildly symptomatic patients with a CD4 count of <200/mm^3.[43] WHO revised their treatment guideline in 2010, recommending that all HIV+ patients with a CD4 count of <350/mm^3 (as well as patients with Stage 3 or 4, irrespective of CD4 count). The impetus behind the 2010 updated guidelines was emerging evidence that initiating early treatment had benefits of reducing or avoiding immune function deterioration.[44] In 2013, WHO updated their guidelines once more, advocating for treatment for all individuals with HIV with a CD4 <500 cells/mm^3, regardless of WHO clinical disease stage, and lifelong ART for pregnant or breastfeeding women with HIV. The intention of 2013 guidelines was to expand ART coverage and to reduce HIV transmission.[45] WHO issued an

update to these guidelines in 2016, recommending that ART should be initiated in all individuals living with HIV, regardless of WHO clinical stage or CD4 cell count.[46] However, adhering to the most recent WHO recommendations has not been easy for many sub-Saharan contexts, where limited resources have not met overwhelming demand for treatment and priority has been given to individuals most at need.[47]

1.3.1.4 Retention in HIV Care

Retention in care in an HIV clinical context is loosely defined as "patients known to be alive and receiving highly active ART at the end of a follow-up period".[48] Retaining people living with HIV in care, however, is essential for both people who have initiated ART and those who have not yet become eligible for ART in order to achieve optimal health outcomes.[45] Many of the barriers discussed above (e.g., transportation, stigma, lack of perceived risk) with previous continuum steps as well as other risk factors (e.g., lack of financial resources, lack of familial support, clinic waiting times) contribute to the high loss to follow up (LTFU) rate in several settings, leading people who are receiving HIV treatment to become not adherent to medication after dropping out of care. Additionally, people who are ineligible for ART often discontinue care and return only after developing severe symptoms.[45]

1.3.1.5 Viral Suppression

Viral suppression is the final step of the continuum, as it is the ultimate goal for HIV treatment and public health efforts. People living with HIV are considered virally suppressed if their most recent viral load, measured within the last 12 months, is <200 copies/mL.[37] Once viral load

suppression is achieved, it must be sustained for the entirety of one's life.[49] Viral suppression is not only important to maintain the health of a patient with HIV but also in considerably minimizing the risk of transmission to a sexual partner. Globally, only 59% of people living with HIV are virally suppressed as of 2020[50].[51]

1.4 Global Efforts to Mitigate Epidemic

1.4.1 90-90-90 Targets

In 2014, UNAIDS called for an ambitious new target for HIV treatment scale-up in order for more people to achieve viral suppression and to end the AIDS epidemic by 2030. The three parts of the target are by 2020, 1) 90% of all people living with HIV will know their status, 2) 90% of all people with a diagnosed HIV infection will receive sustained ART, and 3) 90% of all people receiving antiretroviral therapy will have viral suppression. This idea was extended to 95-95-95, the targets to be reached by 2030. The idea behind the 90-90-90 strategy was that 72% of all people living with HIV globally would be virally suppressed if the target was achieved, and this could be enough to end the epidemic entirely by 2030.[52]

Once the strategy was announced, there was a substantial global effort in accelerating towards the 90-90-90 target. UNAIDS reported that in 2019 globally, 81% of people living with HIV know their status, 83% of people living with HIV who know their status are accessing ART, and 88% of people accessing ART were virally suppressed.[53] Much of the emphasis behind the 90-90-90 strategy has been on providing uninterrupted HIV treatment, and the progress made in the last several years reflect this. However, the largest and potentially most challenging gap remains at

the first part of the strategy – increasing the number of people living with HIV who know their status.[54]

1.4.2 90-90-90 Progress in Zambia

2019 data shows that 87% of people living with HIV are aware of their status, of which 89% are on HIV treatment.[6] Of those who are on treatment, 75% are virally suppressed. Zambia has recommended a test-and-treat strategy, which allows all people who test positive to start treatment and to link into ART care. Although the country has performed well in each of the target components; however only 53% of Zambians living with HIV are virally suppressed.[26]

1.5 HIV Prevention Interventions

The vast improvements made in HIV incidence reduction is in large part due to the implementation of various behavioral and biomedical interventions in the last few decades. Prevention programs have produced mixed results, with the efficacy of interventions vary widely.[55] The following is a short description of interventions that are currently being implemented in high-burden countries, such as Zambia.

1.5.1 HIV Counseling and Testing

HIV testing and counseling is often viewed as the entry into the treatment cascade for individuals who are diagnosed with HIV. Counseling was historically thought to provide risk-reduction benefits for individuals testing negative for HIV. An early clinical trial result showed that STI incidence, as a proxy for HIV incidence, was lower with counseling intervention compared to

didactic messages among HIV- participants.[56] More recent research has contradicted these findings; a 2013 study showed that risk-reduction counseling provided before and after HIV testing had no effect on STI acquisition among clinic patients compared to HIV testing with information (RR = 1.12; 0.94-1.33).[57] Despite these results and being resource-intensive, counseling continues to plays a large part in the testing process.[58]

1.5.2 Condom Distribution

The benefits of condom in preventing HIV transmission have been long-established, with consistent use of condoms resulting in an 80% reduction in HIV incidence.[59] Condoms have played a historic role in HIV prevention frameworks, with an estimated 45 million HIV infections averted through condom use in the past 30 years.[36, 60]

However, condom distribution and promotion has stalled, with coverage barely meeting 50% of the estimated need in East and Southern Africa. Additionally, condom use is low and inconsistent across high risk populations in this region. In Zambia, 37% of females and 50% of males who had more than one partner in the last year had used a condom during their last sexual intercourse.[61]

1.5.3 Voluntary Medical Male Circumcision (VMMC)

Male circumcision has been shown to reduce HIV transmission among men by 60% (Bailey, 2007; Gray, 2007). VMMC has been incorporated as one of the core components of the global HIV program since its adoption as a HIV prevention strategy by the WHO (Davis, 2018). VMMC is often heralded as a successful prevention strategy because it is a one-time biomedical intervention

with lifelong partial protection from HIV. WHO recommended an intensive VMMC scale-up in 14 sub-Saharan African countries, including Zambia, with a target goal of 80% coverage by 2016. VMMC was initially targeted towards men 15-49 years old in the general population; however, countries are now focusing on young men (ages 10-29) for maximum prevention impact and mean who are considered to be at higher risk.[62]

Since 2008, over 14.5 million circumcisions have been conducted in the 14 priority countries (1.4 million in Zambia) as a part of the global HIV prevention program.[63]

1.5.4 Antiretroviral Therapy

As discussed previously, ART can reduce HIV viral load to a level at which the virus is undetectable and risk of transmission is significantly reduced.[64] Antiretroviral treatment as prevention (TasP) refers to the use of ART, irrespective of CD4 count, to decrease risk of sexual transmission of HIV to a HIV-negative partner as a prevention strategy. Mathematical modeling studies have also been used to gauge the impact of ART significantly reducing the epidemic, with some studies projecting that "test and treat" could completely eliminate HIV.[65] In 2015, WHO removed all limitations on ART eligibility in their HIV guidelines and recommended that all people who have tested positive for HIV should initiate ART as soon after diagnosis as possible.[66] As a result, many high burden countries have adopted the "test and treat", or ART initiation for all, strategy into their national guidelines in the past few years, as Zambia did in 2017.[5] However, although 84% of low- and middle-income countries (LMICs) reported having incorporated test-

and-treat into their national policies, only 66% demonstrated full implementation of the strategy.[67]

1.5.5 Prevention of Mother-to-Child Transmission (PMTCT)

HIV transmission from an HIV-positive mother to her child during pregnancy, delivery, or breastfeeding is referred to as mother-to-child, or vertical, transmission. In the absence of interventions, the MTCT rate varies from 25%-42%; however, it has been greatly reduced (to less than 1% in some settings) in the advent of a targeted set of interventions, often referred to as PMTCT.[68] WHO and UNAIDS have recommended a 4-pronged PMTCT approach as follows: 1) primary prevention of HIV infection among women of child bearing age; 2) prevention of unintended pregnancies among HIV-positive women (i.e., contraception); 3) prevention of HIV transmission from HIV positive mothers to infants; and 4) provision of continuous care and treatment for infected mothers and their families.[69]

Programmatic efforts commonly focus on PMTCT Prongs 3 and 4.[70] WHO guidance recommends that HIV testing should be routine for pregnant women at their first antenatal care (ANC) visit. In 2013, WHO began recommending Option B+, a strategy that provides all HIV-positive pregnant women on lifelong ART irrespective of CD4 count. This approach removes the need to continually monitor CD4 counts, but it was initially thought to be financially unfeasible to implement in some developing countries.[46, 71]

Zambia has made great strides in reducing mother-to-child transmission of HIV, and the country immediately adopted Option B+ in 2013.[32, 72] Vertical HIV transmission rate dropped from 21% in 2009 to 6% in 2015, while ART coverage among HIV-positive pregnant women increased from 50% to 87% in the same timeframe.[72]

1.5.6 Couple's Voluntary Counseling and Testing (CVCT)

Although individual testing and counseling has not shown to have risk reduction benefits for individuals testing negative for HIV, such benefits have been shown for couples (i.e., sexual partners) who test together and mutually disclose their HIV status. Benefits are applicable to both seroconcordant (same HIV status) and serodiscordant (different HIV status) couples; some include: increased uptake and adherence to PMTCT for HIV-positive expectant mothers, HIV prevention within couples (e.g., consistent condom use), safer family planning and conception, increased chance of male circumcision, and increased uptake and adherence to ART.[73] WHO incorporated CVCT into their guidelines, strongly recommending that couples and partners should be offered voluntary HIV testing and counseling with support for mutual disclosure, in addition to couples in ANC settings and couples in which one individual has a known HIV status.[73] Moreover, multiple studies have shown that CVCT services are more cost-effective than individual testing services.[30]

In Zambia, like many other countries in the region, over half of adults ages 15-49 are married or cohabitating. In the capital city of Lusaka, almost a quarter of cohabitating couples are serodiscordant.[74] These statistics made Zambia an ideal setting to implement CVCT services. The

Zambian government has incorporated CVCT into their national guidelines; however, CVCT uptake is low and the service is often not available.[75]

1.6 HIV Funding and Resource Allocation

1.6.1 Overview

UNAIDS has reported that in order to meet the 90-90-90 targets in LMICs, an investment of approximately $26.2 billion would be required in 2020 globally; only $18.6 billion was made available in 2019, nearly 30% lower than what was required.[76] In East and Southern Africa, overall HIV funding had increased steadily between 2010 and 2018, after which the region experienced a 7% decrease is overall resources earmarked for HIV.[77]

Countries have increased their share of financial responsibility, with 42% of all HIV investments derived from domestic sources. However, the President's Emergency Plan for AIDS Relief (PEPFAR), the US initiative to support HIV/AIDS efforts abroad, and the Global Fund provide more than half the funding for the region.[78] The US, through PEPFAR, provides more money than any other single country towards the global effort against the HIV epidemic, with a total of $64 billion between 2004 and 2017.[79]

1.6.2 Trends

Despite donor government spending provide the majority of financial support towards HIV efforts in high burden areas, funding began to decrease for the first time in 2015 in five years, causing alarm that the primary global targets (e.g., 90-90-90) would not be reached. In 2016, total

disbursements decreased for 11 out or 14 foreign donors, with only three donors' contributions increasing or remaining flat. Although the US continues to be the largest donor to HIV efforts, the US funding request for PEPFAR dropped from $6.5 billion in 2014 to $5.2 billion in 2019.[80]

A 2016 UNAIDS report advocating for a fast-track approach called for the strengthening of prevention programs as for optimal allocation of available funding in light of the recent trend in donor assistance.[72, 81]

1.6.3 HIV Expenditures in Zambia

According to Zambia's most recent National AIDS Spending Assessment (NASA), over 90% of total HIV spending came from external (i.e., foreign assistance) sources. The vast majority of donor funding came from PEPFAR (89%). In 2018, PEPFAR spent more than $369 million in Zambia. Over 50% of the total PEPFAR budget in Zambia was earmarked for care and treatment services alone, while prevention programs received less than 8% of the budget.[82]

Total spending on ART in Zambia increased significantly from $23 million in 2005 to $125 million in 2012, while spending on other programs were relatively flat. Modeling studies have proposed that if funding decreases, ART spending should continue to be prioritized to provide treatment to the maximum number of HIV-positive individuals.[61]

1.7 Methods for Cost-Effectiveness Analyses and Epidemic Modeling

1.7.1 Resource Allocation

Resource allocation refers to the process in which resources, mainly financial, are distributed among competing programs. Evidence-based resource allocation in healthcare is defined as a strategy in which resources are spent to achieve the maximum health benefit based on the most currently available evidence. An evidence-based allocation strategy for national HIV programs take into consideration the local epidemic and cost-effectiveness of existing interventions.[83]

Studies have shown that many countries have historically not allocated HIV resources based on the latest evidence for a number of reasons, including lack of reliable data, contradictory results from various analyses, and political will. However, with the introduction and development of resource-efficiency and decision-making models in the last decade, countries have begun to align resources more closely to the results from these tools.[83, 84]

1.7.2 Existing Models for HIV Resource Allocation and Cost-Effectiveness Research

The three most widely used modeling tools that incorporate both program intervention and cost-effectiveness data are 1) the GOALS model, 2) the AIDS Epidemic Model (AEM), and 3) Optima. The objective of the analyses from each of these models is to compare intervention scenarios to assess the impact of different HIV intervention programs.[85]

Each of the three tools employ a dynamic compartmental model to project epidemic trends and the impact of various interventions. This type of model can simulate HIV transmission,

morbidity, and mortality among a standard population.[86] Each of the tools also incorporates the unit costs of various HIV interventions with the number of people who are reached by each intervention to determine the number of HIV infections averted and the number of HIV-related deaths averted.

The three models have similar structures, but there is some variability. The GOALS model and Optima are applied to either concentrated or generalized epidemics, while AEM has been designed to understand transmission in concentrated epidemics. Additionally, AEM and Optima have the capabilities to assess novel interventions, while GOALS considers only conventional interventions.[85, 87] None of these key resource allocation tools incorporate couples' testing and counseling despite it being a WHO-recommended intervention for high burden HIV settings.

1.7.3 Mathematical Models for Cost-Effectiveness Analyses

Mathematical models have been used in infectious disease epidemiology, including HIV epidemiology, to track the spread of disease within a population and to project population-level outcomes from individual-level inputs.[88, 89] Various types of mathematical models are used for resource allocation and cost-effectiveness studies because of their ability to predict disease incidence and prevalence over long time horizons and to evaluate the impact of interventions.[90, 91]

Compartmental models, such as the ones used in the resource allocation tools described above, are typically based on the classic *Susceptible – Infectious – Recovered* (SIR) framework, where

individuals within a population are categorized into different compartments based on their infection status. Individuals can belong to one compartment at a single point in time but are able to transition between compartments. This type of model can track the population, as a function of time, using a set of differential equations.[92] Compartmental models can be elaborated to include vital dynamics (birth and death rates) and population stratifications (e.g., age, risk status). Two assumptions that this type of model makes are: 1) individuals within a single compartments are identical and 2) transition rates between two compartments are proportional to the number of individuals in the initial compartment. The second assumption, based on the law of mass action, implies that individuals within a population become in contact with one another at random (i.e., homogenous mixing).[93, 94] Although compartmental models have been widely used in epidemiology, these assumptions often make these models restrictive and limiting in their use in answering certain problems.[95]

Agent-based models (ABMs), a type of computational modeling technique, can overcome some of these limitations. ABMs use an approach in which agents (e.g., individuals) with a set of characteristics are able to interact with one another and with their environment according to a predetermined set of rules.[96] These characteristics (e.g., age, probability of infection, geographic, infection status, sex, risk status, connections) are attributed to each individual; an individual's infection probability, along with interactions with other susceptible and infectious agents, ultimately determine the outcome of interest.[96]

ABMs have been increasingly used to model sexually transmitted diseases outbreaks, including HIV, since it is able to simulate sexual relationships between individuals and using specific characteristics to create a dynamic sexual network. An ABM is then able to simulate how a disease spreads through a network as well as simulate how interventions can disrupt the spread of disease. Because of this, ABMs have lent themselves to be useful in studies exploring the cost-effectiveness of various HIV interventions.[95, 97, 98] Despite the prolific use of ABMs in HIV cost-effectiveness studies, experts continue to rely more on compartmental models for resource allocation tools for HIV programming.

2 Summary

Sub-Saharan Africa has experienced a large reduction in new HIV infections in the last decade. Despite these advances, the decline in HIV incidence is slowing, and challenges in scaling up prevention services persist throughout the region. International donor assistance for HIV has declined recently, signaling the uncertainty of future global funding. To improve the efficiency of HIV prevention, allocating resources effectively is crucial to scaling up high-quality interventions to maximize HIV prevention.

The following dissertation details the HIV epidemic in Zambia, a sub-Saharan African country with a high HIV burden. Zambia has experienced an HIV epidemic driven primarily by heterosexual transmission, and most incident cases arise from transmission between married or cohabitating couples. Zambia has benefitted from the rapid scale-up of HIV interventions, including HIV testing, antiretroviral therapy (ART), voluntary medical male circumcision

(VMMC). At the same time, new prevention strategies such as ART initiation for all have been heralded for their remarkable clinical results in the reduction of HIV transmission, influencing governments, including Zambia, to adopt them into their HIV strategic planning.

Since HIV treatment greatly reduces viral transmission, a comprehensive understanding of HIV care is a critical driver for achieving prevention. The HIV care continuum is a framework that illustrates the series of steps from the time an individual receives a positive HIV diagnosis through the suppression of the virus with appropriate ART regimen; this framework is often used to identify gaps in HIV services.

Agent-based modeling has recently been used to evaluate drivers of the HIV epidemic and to estimate the effectiveness of HIV prevention strategies. An increasing number of studies have employed ABMs to predict the spread of HIV in a given population and to estimate the effectiveness of specific interventions. These models can track HIV transmission and are informed by epidemiological, behavioral, and clinical data. Modeling studies have also incorporated cost-effectiveness methods to inform how the various prevention interventions fit within national budgets. However, few studies have explored the cost-effectiveness and allocation of couples' testing and counseling (CVCT), a relatively inexpensive strategy in which couples in a sexual relationship receive HIV services simultaneously and which has been shown to reduce incident HIV infections.

3 Significance and Overview of Aims

The international HIV community has pledged to fast-track evidence-informed, high-quality services in order to end the AIDS epidemic by 2030. The foundation of this approach are the 90-90-90 targets, which aimed for 72% of people living with HIV to be virally suppressed by 2020. These targets have been measured using the HIV care continuum, a framework that is often used to highlight potential opportunities for intervention scale-up. The framework stages are most commonly measured cross-sectionally (e.g., proportion of HIV diagnosed people who are on ART at a given time). Cross-sectional continuums of care have limitations because they are unable to incorporate patient outcomes or care engagement and do not provide information on the average duration spent at each step. Longitudinal information that is lacking from traditional HIV continuum frameworks is critical for measuring HIV care success. However, this type of information is often difficult to obtain since many HIV patient cohorts are followed for no more than a few years. To date, there have only been a few studies that have analyzed large scale HIV surveillance data to understand patient outcomes and healthcare delays. In **Aim 1**, we characterized the historical distribution of time between states of the treatment cascade among people living with HIV in Zambia.

The 90-90-90 targets, measured using the HIV care continuum, has a large focus on achieving widespread viral suppression by using an ambitious test and treat strategy. Several countries, including Zambia, have widely adopted the 90-90-90 strategy but have focused primarily on the second "90" – increased access to ART. Emphasis on adequate testing and linking individuals with a positive HIV diagnosis, in tandem with treatment access, is essential to reduce HIV

incidence and to change the trajectory of the HIV epidemic. In Zambia, where the HIV epidemic is primarily driven by heterosexual transmission, interventions specifically targeting married and cohabitating partners are needed. Large scale-up of couples voluntary counseling and testing (CVCT), an innovative strategy that has shown to reduce HIV incidence among heterosexual couples, may help to halt the epidemic. In **Aim 2**, we sought to understand the impact of different HIV testing, treatment, and retention strategies on HIV incidence in Zambia.

The ambitious goals to end the HIV epidemic come at a cost. UNAIDS had estimated that over $26 billion was needed by 2020 to achieve the fast-track goals in low- and middle-income countries, and only $18.6 billion was available in 2019. As international commitment to funding the HIV response has begun to wane, scarce financial resources must be efficiently allocated in order to achieve these goals. Funding distribution among health programs and interventions in high HIV-prevalent countries, including Zambia, have not historically been aligned with geographic or risk prioritization. Cost-effectiveness of novel interventions have been evaluated in isolation and then compared to cost-effectiveness measures of existing strategies, an approach that negates the relative costs and impacts of these alternative options. More analyses of combination strategies are needed to understand how funds can be optimized across different interventions for decision-making. In **Aim 3**, we identified cost-effective and cost-saving scenarios of HIV prevention methods for the general population in Zambia.

4 Specific Aims

Aim 1. Characterize the distribution of time between states in the HIV treatment cascade among people living with HIV in Zambia

Hypothesis: *Estimated time intervals between various points of HIV care from longitudinal, observational studies in Zambia will differ from estimates from cross-sectional programmatic data*

Aim 2. Model the impact of various HIV testing, treatment, and care linkage strategies on HIV incidence among the general heterosexual population in Zambia

Hypothesis: *Interventions targeted towards heterosexual couples will substantially help to decrease HIV incidence over the next 10 - 30 years.*

Aim 3. Identify an optimal mix of HIV prevention methods for the general heterosexual population in Zambia given resource constraints

Hypothesis: *HIV prevention strategies that incorporate a national-level CVCT component will be more cost-effective than programs without this testing strategy.*

5 AIM 1

Application of Electronic Health Records to Estimate Wait Times Across the HIV Care Continuum in Zambia

Introduction

The HIV care cascade model has gained nearly universal acceptance in public health policy and practice.[99, 100] This framework dissects the complex healthcare system from HIV seroconversion to ART outcomes into discrete sequential steps: HIV testing, linkage to care, ART eligibility, ART retention, and viral suppression.[101] The care cascade, also known as the care continuum, has become the standard framework for identifying gaps in HIV care and is used globally to monitor and evaluate HIV/AIDS health system management.[102] It has served as the fundamental basis for global targets, in particular the United Nation's 90-90-90 strategy, which has called for substantial increases in HIV diagnosis, treatment, and viral suppression.[10, 52]

The care cascade has served as a significant tool in outlining benchmarks for appropriate HIV care and providing insights on HIV healthcare systems within and across countries. However, the implementation of this approach can be limiting. Although other frameworks describing the HIV care journey have been developed, the traditional and most commonly used HIV care cascade is structured in a linear fashion, as entry into each step is conditional on the previous step, missing one step results in an inability to benefit from ART.[100, 103] Since viral suppression has become an ultimate goal for treatment and prevention, it has become crucial to identify and to

ameliorate failure points along the cascade.[104] However, this cannot be done properly if patient cascade data is of poor quality and inadequately structured.[102]

HIV care continuums have customarily relied on cross-sectional data, which allows for up-to-date information about the proportion of people living with HIV (PLHIV) at each cascade step at specific point in time.[105, 106] Although this type of information is helpful for comparing progress of different HIV programs, cross-sectional analyses are more prone to biased inference since it is not able to take into account the time taken to transition from one cascade stage to the next or the changing composition of PLHIV between steps. A longitudinal framework for the cascade is a solution for this issue.[105, 107] Unlike a cross-sectional continuum, a longitudinal care cascade is able to provide insights on duration PLHIV experience while moving through the various cascade stages and on any loss-to-follow-up (LTFU) that may occur between treatment cascade steps.[108]

With an estimated 1.2 million PLHIV, Zambia has experienced a plateau in its success in decreasing HIV incidence. 77% of PLHIV are estimated to be virally suppressed, but there is limited information on the amount of time PLHIV stay within each stage prior to viral suppression.[6, 54] Overwhelming evidence shows that early ART initiation and sustained treatment are central to achieving viral suppression and preventing onward transmission, and this is information that can be relayed by longitudinal data. In this study, we use patient record data from a network of ART clinics in Zambia to characterize the time intervals experienced by PLHIV to transition between stages within the HIV care cascade.

Methods

Data Source

The data used for this analysis comes from The Center for Infectious Disease Research in Zambia (CIDRZ). CIDRZ is a Zambia-based nongovernmental organization funded by President's Emergency Plan for AIDS Relief (PEPFAR) to provide support to the Zambian Ministry of Health (MoH) in HIV care provision across four provinces: Lusaka, Western, Eastern, and Southern and three facility types: hospital, urban health center, rural health center). CIDRZ researchers conducted the Better Information for Health in Zambia (BetterInfo) study, which employed an innovative multi-stage sampling approach to estimate the entire population of patients on treatment as well as to enable comparisons across the four provinces and three health facility types through stratification. Details of the BetterInfo study methods have been previously published. In brief, the CIDRZ team selected two to ten facilities from each of the 12 strata (defined by facility type and province) using probabilities proportional to size, with a total of 32 MoH facilities. In each of the 32 facilities, the team enumerated all PLHIV on treatment who had at least one clinical visit between 2013 and 2015 and identified patients who were lost-to-follow-up, as defined as more than 90 days late for a clinic appointment. A simple random sample was selected from those who were deemed lost based on the above definition and were then traced to understand their outcomes (fallen out of care, mortality, switched clinics). [109, 110]

The BetterInfo study used patient data from SmartCare, a national electronic health record system established by the Zambian MoH to identify the clinic population, to enumerate the study cohort and to obtain clinical and socioeconomic data. SmartCare data was filtered to include adult

patients who were aged 18 or older at time of HIV care enrollment and had at least one HIV-related clinical interaction between 2000 and 2015. Among a random sample of patients who were deemed LTFU, intensive tracing was conducted to ascertain accurate patient status: transferred care to another clinic, disengaged from care, death. The BetterInfo investigators granted access to their SmartCare-derived database to conduct the analyses presented below.

Study Population

For this study, we restricted our analysis to include patients living with HIV who experienced their first HIV-related clinical visit between 2004 and 2015 at one of 32 CIDRZ-supported Zambian MoH health facilities in four provinces of Zambia: Lusaka, Western, Eastern, and Southern . Patient data before 2004 were excluded for primary analysis due to poor data quality. Patient data included, but was not limited to, demographics, medical history, clinic visit information and corresponding dates, and LTFU status.

Outcomes of Interest

Clinic visit types were recorded as one of the following: initial history and physical (IHP), ART initiation, ART eligibility, pharmacy visit, ART follow-up. Eligibility criteria for ART initiation was based on year and corresponding WHO guidance:

- 2004 – 2010: CD4 < 200 if WHO Stage 1 or 2; CD4 < 350 if WHO Stage 3; Stage 4
- 2011 – 2013: CD4 < 350; WHO Stage 3 or 4
- 2014 – 2015: CD4 < 500; pregnant or breastfeeding

We focused on patients' time spent within two specific stages of the care continuum: 1) time spent in formal HIV care before ART eligibility; 2) time spent while ART eligible prior to treatment initiation), with available visit types representing beginning and end points of the stages. Three specific clinical visits identified were: 1) the first documented clinical interaction, represented by the IHP visit, a proxy for when a patient entered formal HIV care; 2) a clinic visit for when a patient is deemed ART eligible, and 3) the first pharmacy visit, a proxy for when a patient initiates ART. We assumed that the clinical dates reflected a patient's experience within the different stages of the HIV care continuum.

Statistical Analysis

To determine the time that patients spent within each stage, we calculated the duration, in days, between the critical clinic visits described above. Since SmartCare data is primarily collected for medical record keeping and thus prone to some error in data entry, we ignored observations with inconsistencies in clinical visit history (e.g., if a patient's first ART initiation date preceded a treatment eligibility visit). We assumed that these errors were non-systematic and would not lead to biasing results. We then summarized the cascade stage durations for the entire patient population, as well as specific patient subgroups (i.e., province, sex, and facility type).

A data-fitting method was employed to choose a probability distribution that appropriately modeled the cascade stage duration and to quantify the parameters for the chosen distribution. We used functions from *fitdistrplus* in R (version 3.6.0), a general package that aims to help fitting

univariate parametric distributions to data by estimating distribution parameters by maximizing the likelihood function. Candidate distributions (Weibull, gamma, and log normal) were chosen based on the characteristics of the empirical data (Appendix).

We plot the density of the empirical data, the cumulative distribution function, and skewness and kurtosis plots in order to narrow down the distribution choices. We then fit the remaining possible distributions, to examine the theoretical density plot as well as the corresponding Q-Q plot and to compare it to our empirical data.

Results

185,688 patients with an HIV diagnosis were identified in the SmartCare database. Patients were excluded in the analysis if their IHP visit or first ART eligibility date preceded January 1, 2004, or if their ART eligibility date preceded the date of their IHP visit. Among the 160,925 patients remaining, 137,467 patients were included in the time to ART eligibility analysis while 104,561 patients were included in the time to ART initiation analysis (Figure 1). Inclusion was based on medical record completeness and lack of health record aberrations. We concluded from demographic comparisons that patients excluded from the analysis were not significantly different than those who were included.

Time Spent between HIV Care Enrollment and ART Eligibility

Among the 137,367 patients included in the analysis to explore the duration between HIV care enrollment and ART eligibility, 63.6% were female. More than half (54.7%) of the patients were

from Lusaka, while the remainder were split evenly across Eastern, Southern, and Western. The majority of patients (57.2%) accessed HIV care at urban health facilities, and over half (52.1%) had a CD4 count between 101 – 350 cells/mm^3 at the time of first clinical visit. Approximately a third of the patient population were enrolled in HIV care prior to June 1, 2010, while 41.2% and 22.3% enrolled between mid-2010 through 2013 and 2014 onwards, respectively (Table 5-1).

Female patients were more likely to be immediately eligible for ART at their first HIV care visit then male patients; however, the median wait time for ART eligibility experienced by female patients who were not immediately eligible (211 days; IQR: 16-819) was over twice the median wait time experienced by male patients (88 days; IQR: 6 – 430). Patients in Lusaka were more likely to be immediately eligible for ART at their first HIV clinical encounter. Among those who were not immediately eligible for treatment, patients from Western province had the shortest median wait time (59 days; IQR (6 – 595), while the median wait time for those in Eastern province was fivefold (311 days; IQR (7-987). This finding about Western province is particularly interesting, as both Western and Eastern provinces are vastly rural, especially compared to Lusaka Province, which is home to the country capital. As expected, among patients with CD4 counts less than 100 cells/mm^3 at care enrollment, the median time to ART eligibility was 6 days and the majority of these patients (62.3%) were deemed eligible for ART at their IHP visit.

Although this may have been expected, it is in line with the WHO guideline updates over the last 15 years, there was also a positive correlation with immediate ART eligibility and HIV care enrollment date; 32.2% of patients who enrolled in care before mid-2010 were deemed eligible for

ART at their first visit, while 66.2% who enrolled in HIV care in or after 2014 were automatically eligible for ART. In this same period of time, the median wait time decreased dramatically, from 293 days to 28 days (Table 5-2).

A Weibull distribution was chosen among Weibull, gamma, and lognormal distributions as it most closely fit the empirical data based on goodness-of-fit criteria (AIC and BIC) and a number of goodness-of-fit statistics: Kolmogorov-Smirnov statistic, Cramer-von Mises statistic, and Anderson-Darling statistic (Appendix Table 5-1). Density plots of Weibull distribution of wait time data between HIV care enrollment and ART eligibility by the factors described above are shown in Figure 5-2 through Figure 5-6. The parameters of each of the Weibull distributions are listed in Table 5-3.

Time Spent between ART Eligibility and ART Initiation

104,561 patients were included in the analysis exploring the wait time between ART eligibility and ART initiation. The demographics of this population subset are similar to that of the aforementioned analysis (Table 5-1). The differences in median wait times varied by sex, province, facility type, CD4 count at enrollment, and HIV care enrollment date; however, the median time was relatively similar within different groups. For example, while median time between ART eligibility and ART initiation for patients who enrolled prior to mid-2010 and from mid-2010 through 2013 was 28 days (IQR: 14-25) and 29 days (IQR: 15-74), respectively, patients who enrolled in care after 2013 experienced a median wait time of 26 days (IQR: 14-53). Time to ART initiation did vary by CD4 count at enrollment, with patients with lower CD4 counts

experiencing shorter time between being deemed ART eligible and initiating ART. However, a small proportion of patients with extremely low CD4 counts at enrollment immediately initiated treatment, especially compared to patients with CD4 counts higher than 500 cells/mm^3 (Table 5-4).

As previously done for time between care enrollment and ART eligibility, fit assessments were conducted on candidate distribution types (Weibull, gamma, and lognormal) using goodness-of-fit criteria and statistics. Based on the Akaike information criteria (AIC) and Bayesian information criteria (BIC) values, Weibull distribution was deemed to be the best fit of the empirical data. This was further evidenced by the results three goodness-of-fit tests (Kolmogorov-Smirnov, Cramer-von Mises, and Anderson-Darling) (Appendix Table 5-2).

Weibull curve best fit the empirical data, and the distribution parameters are listed in Table 5. The distribution of time between ART eligibility and ART initiation is illustrated in the density plots in Figures 5-7 through 5-11.

Discussion

We used a national electronic health record database to explore a part of the cascade of care from HIV care enrollment to ART initiation in order to understand the duration of the transition time experienced by people living with HIV. We found that over a 11-year period between 2004 and 2015, that almost half of all PLHIV were considered eligible for treatment at the first care enrollment visit but less than 10% were put on treatment immediately once they were deemed

ART eligible. The longitudinal nature of our analysis provides insights which would have been unlikely from a cross-sectional, facility-based analyses.

This study showed that transition time between earlier stages of the cascade (i.e., from HIV care enrollment to ART eligibility) tended to be more varied between and with-in groups than in later stages of the cascade (i.e., from ART eligibility to ART initiation). Although these findings may seem intuitive, as treatment eligibility has been historically dependent on national guidelines and current CD4 count, our results show large interquartile ranges among individuals with CD4 counts higher than 100 cells/mm^3. The median transition time and corresponding interquartile ranges decreased dramatically from 2010 to 2014, a reflection of the updated 2013 WHO guidelines recommending treatment for all individuals with a CD4 count of less than 500 cells/mm^3. Overall, patients spent approximately six months enrolled in HIV care before being considered eligible for ART. We were able to show that once patients were ART eligible, their median wait time to start treatment was approximately four weeks, a transition time that did not greatly vary between or with-in groups.

Measurement of HIV care cascade transition times is unique to longitudinal cascades, as it is able to provide meaningful implications of potential gaps and improvements in the healthcare system. Previous studies have shown that compared to cross-sectional HIV data, a longitudinal continuum can often provide additional insight in the form of person-time. For example, one study used simulated data to compare cross-sectional data to longitudinal data; the longitudinal metrics were able to reveal nuanced information about ART initiation and viral suppression

levels, which seemed to be much higher when relying solely on the cross-sectional data.[111] Another study based in KwaZulu-Natal also compared longitudinal and cross-sectional analyses and highlighted misleading conclusions of cross-sectional data.[102] Specifically, the authors were able to identify that linkage to HIV care was the most significant roadblock in the HIV cascade, a finding that was discovered based on the longitudinal analyses only.

Cross-sectional cascade data will always remain useful since its construction is resource efficient in terms of cost and labor, and thus it should be considered an alternative to inform decision-making.[102] However, individual-level longitudinal cascades may be an better option to use for reporting on HIV care engagement if sufficient resources are available. This study also adds to previous work analyzing longitudinal data to better understand the HIV care cascade. Similar studies have focused on the major challenges of earlier cascade transitions, strengthening our results regarding the long transition time between HIV care enrollment and ART eligibility.[102, 106]

A major limitation of this paper is that the available data only allowed us to analyze a subset of the cascade. A known challenge, particularly in achieving 90-90-90, is the transition between receiving an HIV positive diagnosis and enrolling into appropriate HIV care. The SmartCare dataset only provided information about patients once they enrolled in care, providing no information on the length of this transition time. Additionally, there was viral load information on an extremely small proportion (0.6%) of the patient population. Efforts to improve viral suppression, the third '90' of 90-90-90, have been successful in Zambia; however, information about the transition between ART initiation and viral suppression would help identify

characteristics of and target individuals who are less likely to achieve an undetectable viral load. Another potential limitation is our assumption that individuals who were excluded from our analysis due to missing data or health record errors were similar to the individuals who were included in our analysis. Future analysis could attempt to apply sophisticated missing data techniques in order to gain evidence for this assumption.

With Zambia's Ministry of Health 2017 recommendation that everyone with a positive HIV diagnosis start ART immediately, the goal is for the transition between HIV enrollment and ART eligibility will be completely eliminated and the transition time between diagnosis and ART initiation will reduce significant. However, until universal test and treat is nationally and successfully implemented, researchers should invest resources in more longitudinal cascade data and stakeholders should advocate for and improve upon interventions that help shorten these transition times.

Table 5-1. Patient Demographics

	Time to ART Eligibility Analysis (N = 137,367)	**Time to ART Initiation Analysis (N = 104,561)**
	% (n)	% (n)
Sex		
Female	63.6% (49,975)	61.2% (63,997)
Male	36.4% (87,392)	38.8% (40,564)
Province		
Eastern	14.8% (20,266)	13.0% (13,566)
Lusaka	54.7% (75,083)	57.7% (60,287)
Southern	15.4% (21,108)	13.9% (14,512)
Western	15.2% (20,910)	15.5% (16,196)
Facility Type		
Hospital	32.5% (44,676)	30.6% (32,035)
Rural	10.3% (14,117)	9.9% (10,386)
Urban	57.2% (78,574)	59.4% (62,140)
CD4 count at enrollment (cells/mm^3)		
Median		
<100	19.6% (23,180)	22.8% (21,284)
101 - 350	52.1% (61,523)	54.0% (50,500)
351 - 500	16.1% (18,999)	13.5% (12,605)
>500	12.1% (14,320)	9.7% (9,077)
Care Enrollment Date		
Prior to June 1, 2010	36.5% (50,064)	36.0% (37,653)
June 1 2010 - Dec 31, 2013	41.2% (56,611)	43.3% (45,271)
After Jan 1, 2014	22.3% (30,692)	20.7% (21,637)

Table 5-2. Time between HIV Care Enrollment and ART Eligibility

	Time between HIV Care Enrollment to ART Eligibility	
	Immediately eligible (%)	Median wait time in days (IQR)*
Sex		
Female	55.6%	211 (16 - 819)***
Male	44.2%	88 (6 - 430)
Province		
Eastern	42.7%	311 (7 - 987)***
Lusaka	57.7%	166 (14 - 583)
Southern	34.3%	163 (8 - 798)
Western	34.5%	59 (6 - 595)
Facility Type		
Hospital	38.6%	188 (12 - 833)***
Rural	39.3%	185 (16 - 694)
Urban	55.6%	163 (13 - 598)
CD4 count at enrollment		
<100	62.3%	6 (2 - 25)***
101 - 350	51.9%	36 (5 - 277)
351 - 500	28.2%	372 (141 - 905)
>500	32.8%	566 (211 - 1200)
Care Enrollment Date		
Prior to June 1, 2010	32.2%	293 (12 - 1289)***
June 1 2010 - Dec 31, 2013	52.9%	209 (21 - 584)
After Jan 1, 2014	66.2%	28 (5 - 108)
Overall	48.4%	176 (13 - 691)

* Among patients who were not immediately eligible
*** Indicates statistical significance

Table 5-3. Weibull Parameters for Distribution of Time between HIV Care Enrollment and ART Eligibility

	Weibull Parameters for Distribution of Time between HIV Care Enrollment and ART Eligibility			
	Shape	**Shape S.E.**	**Scale**	**S.E.**
Overall	0.513	0.002	287.406	2.215
Sex				
Male	0.482	0.003	179.056	2.636
Female	0.537	0.002	350.347	3.109
Province				
Eastern	0.688	0.005	527.630	7.475
Lusaka	0.524	0.002	258.904	2.920
Southern	0.478	0.003	282.921	5.292
Western	0.448	0.003	202.853	4.093
Facility Type				
Hospital	0.497	0.002	322.327	4.125
Rural	0.544	0.005	295.041	6.168
Urban	0.523	0.002	260.433	2.809
CD4 count at enrollment				
<100	0.603	0.005	18.569	0.350
101- 350	0.448	0.002	131.387	1.804
351- 500	0.826	0.006	581.559	6.329
>500	0.997	0.008	806.851	8.667
Care Enrollment Date (corresponding to WHO criteria changes)				
Prior to June 1, 2010	0.499	0.002	428.589	4.904
June 1 2010 - Dec 31, 2013	0.627	0.003	280.532	2.876
After Jan 1, 2014	0.626	0.005	54.237	0.899

Table 5-4. Time between ART Eligibility to ART Initiation

	Time between ART Eligibility to ART Initiation	
	Immediately on treatment (%)	Median wait time in days (IQR)
Sex		
Female	7.9%	28 (14 - 59)***
Male	9.9%	28 (14 - 55)
Province		
Eastern	15.3%	28 (14 - 70)***
Lusaka	7.6%	29 (15 - 63)
Southern	9.4%	20 (13 - 42)
Western	9.4%	24 (14 - 47)
Facility Type		
Hospital	10.9%	22 (14 - 46)***
Rural	10.5%	31 (16 - 76)
Urban	8.0%	28 (15 - 60)
CD4 count at enrollment		
<100	4.1%	24 (14 - 41)***
101 - 350	4.5%	28 (14 - 50)
351 - 500	9.2%	37 (18 - 120)
>500	18.3%	42 (19 - 143)
Care Enrollment Date		
Prior to June 1, 2010	5.5%	28 (14 - 52)***
June 1 2010 - Dec 31, 2013	7.2%	29 (15 - 74)
After Jan 1, 2014	19.3%	26 (14 - 43)
Overall	9.1%	28 (14 - 57)

* Among patients who did not initiate treatment immediately
*** Indicates statistical significance

Table 5-5. Weibull Parameters for Distribution of Time between ART Eligibility and ART Initiation

	Weibull Parameters for Distribution of Time between ART Eligibility and ART Initiation			
	Shape	**Shape S.E.**	**Scale**	**S.E.**
Overall	0.711	0.002	63.381	0.308
Sex				
Male	0.713	0.002	60.937	0.471
Female	0.711	0.002	64.964	0.405
Province				
Eastern	0.679	0.004	68.183	0.997
Lusaka	0.729	0.002	71.988	0.445
Southern	0.692	0.004	43.452	0.582
Western	0.726	0.004	49.425	0.597
Facility Type				
Hospital	0.683	0.003	49.931	0.460
Rural	0.696	0.005	79.549	1.260
Urban	0.734	0.002	68.239	0.414
CD4 count at enrollment				
<100	0.760	0.003	46.041	0.451
101- 350	0.741	0.002	57.634	0.377
351- 500	0.709	0.005	96.938	1.357
>500	0.680	0.006	110.013	1.997
Care Enrollment Date (corresponding to WHO criteria changes)				
<June 1, 2010	0.664	0.002	64.352	0.547
June 1 2010 - Dec 31, 2013	0.729	0.002	73.292	0.522
>Jan 1, 2014	0.973	0.005	40.604	0.335

Figure 5-1. Patient Flowchart

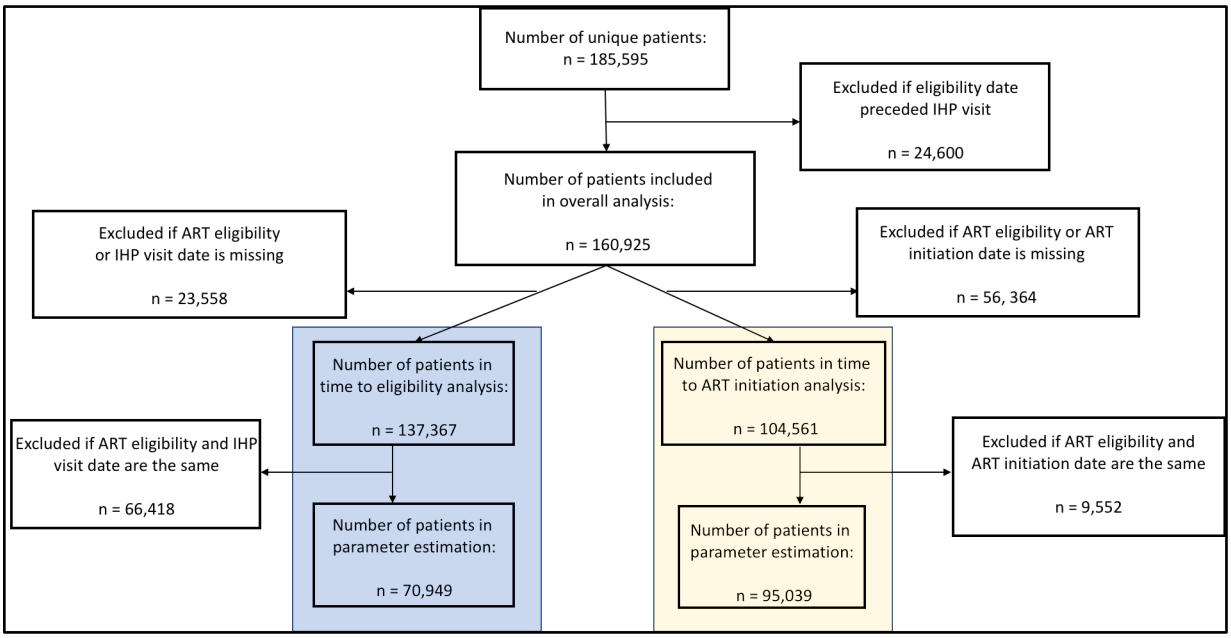


Figure 5-2. Density Plot and Median Time between HIV Care Enrollment and ART Eligibility, by Gender

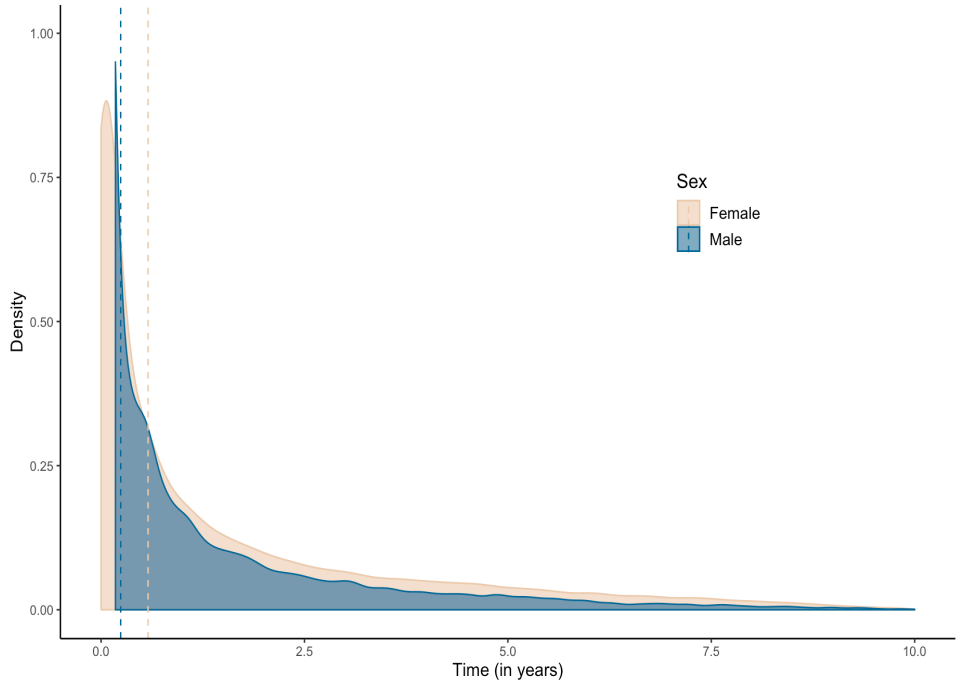


Figure 5-3. Density Plot and Median Time between HIV Care Enrollment and ART Eligibility, by Facility Type

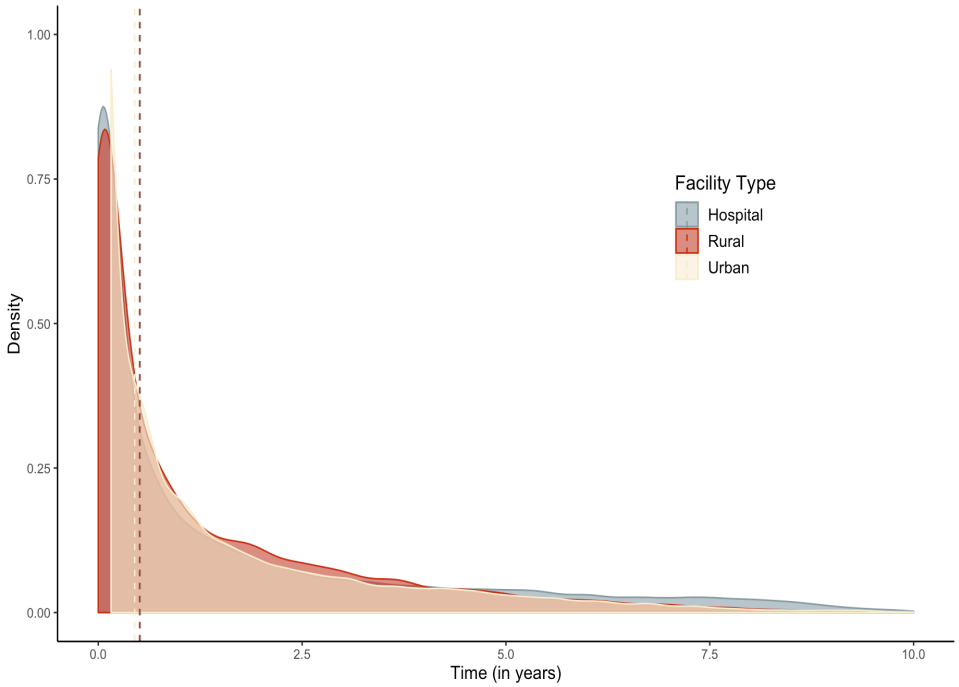


Figure 5-4. Density Plot and Median Time Between HIV Care Enrollment and ART Eligibility, by Province

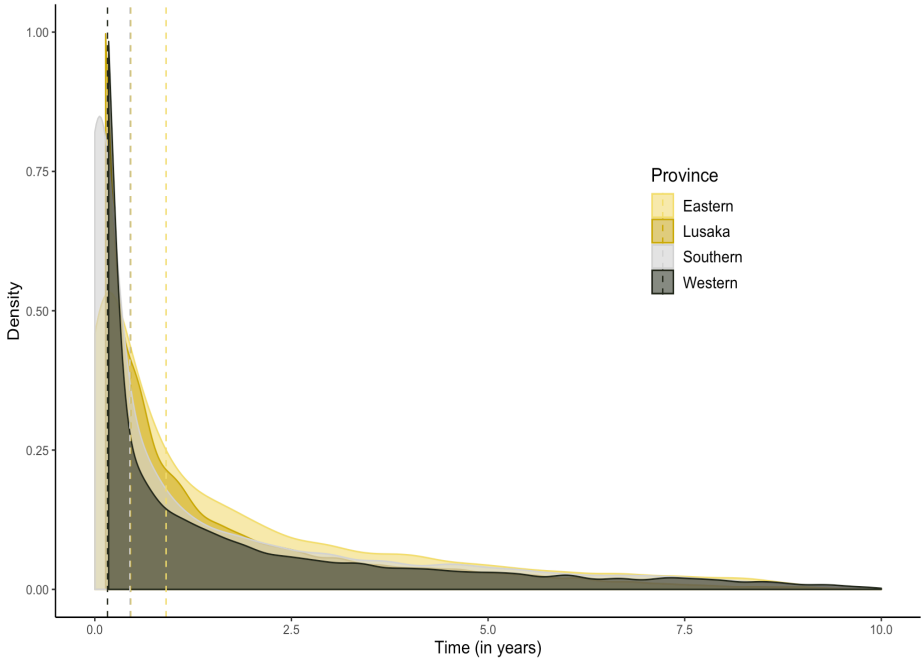


Figure 5-5. Density Plot and Median Time Between HIV Care Enrollment and ART Eligibility, by CD4 count at HIV Care Enrollment

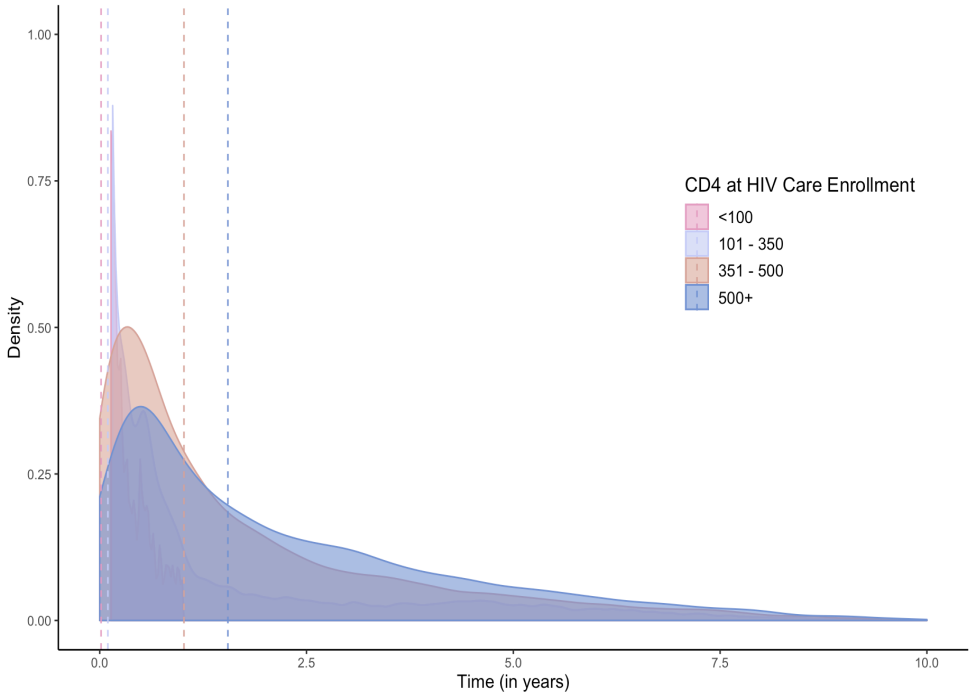


Figure 5-6. Density Plot and Median Time Between HIV Care Enrollment and ART Eligibility, by Enrollment Date

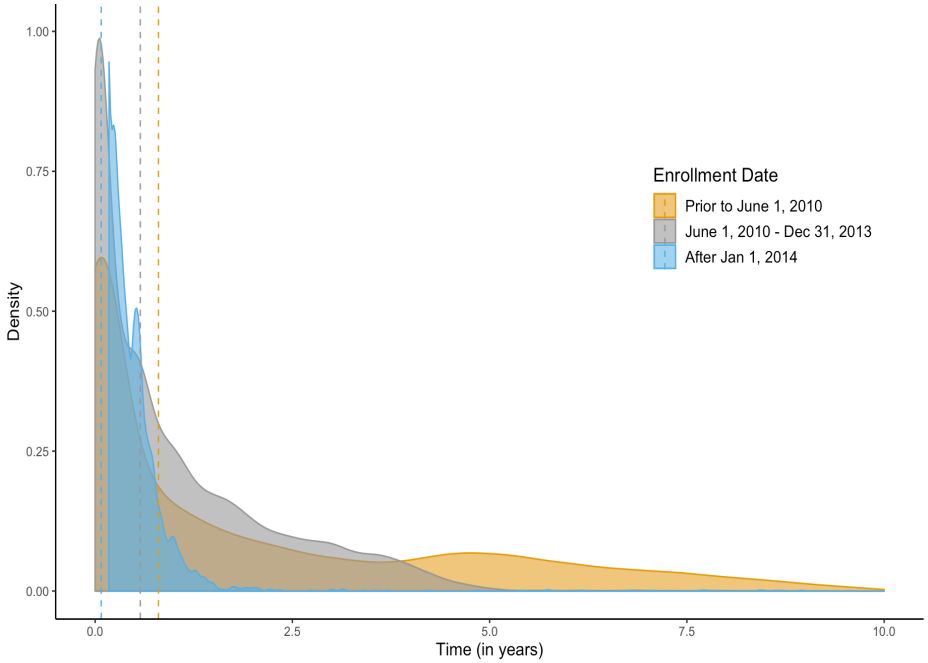


Figure 5-7. Density Plot and Median Time Between ART Eligibility and ART Initiation, by Gender

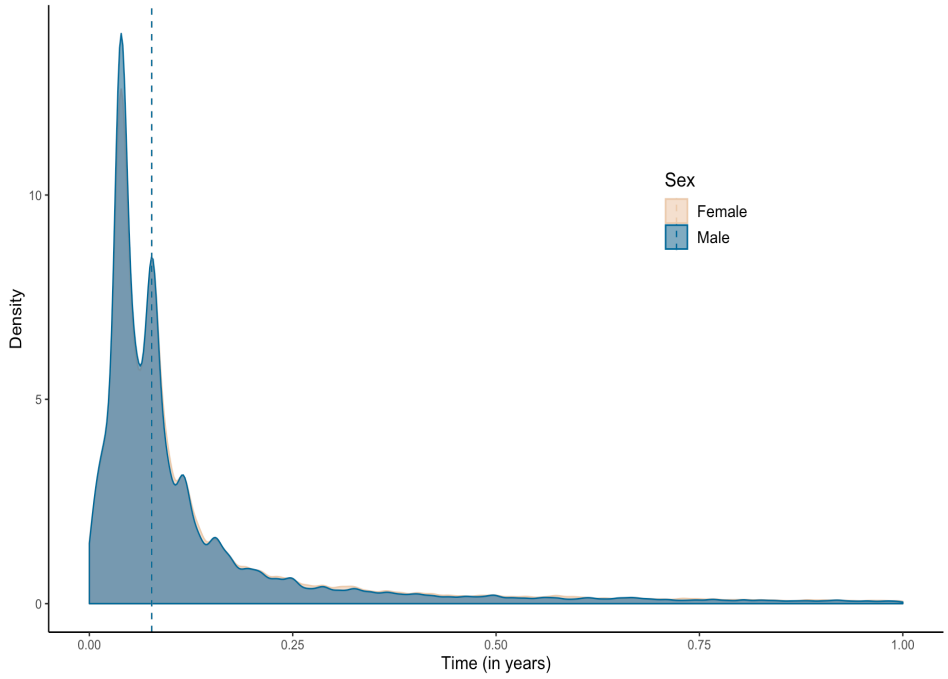


Figure 5-8. Density Plot and Median Time Between ART Eligibility and ART Initiation, by Province

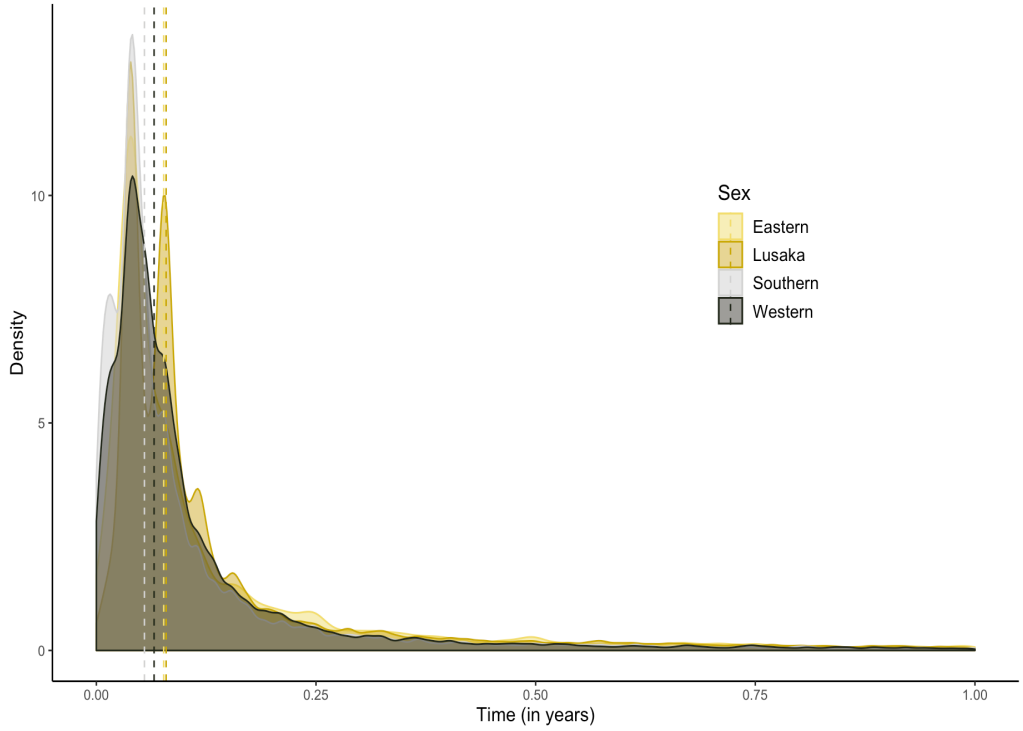


Figure 5-9. Density Plot and Median Time Between ART Eligibility and ART Initiation, by Facility Type

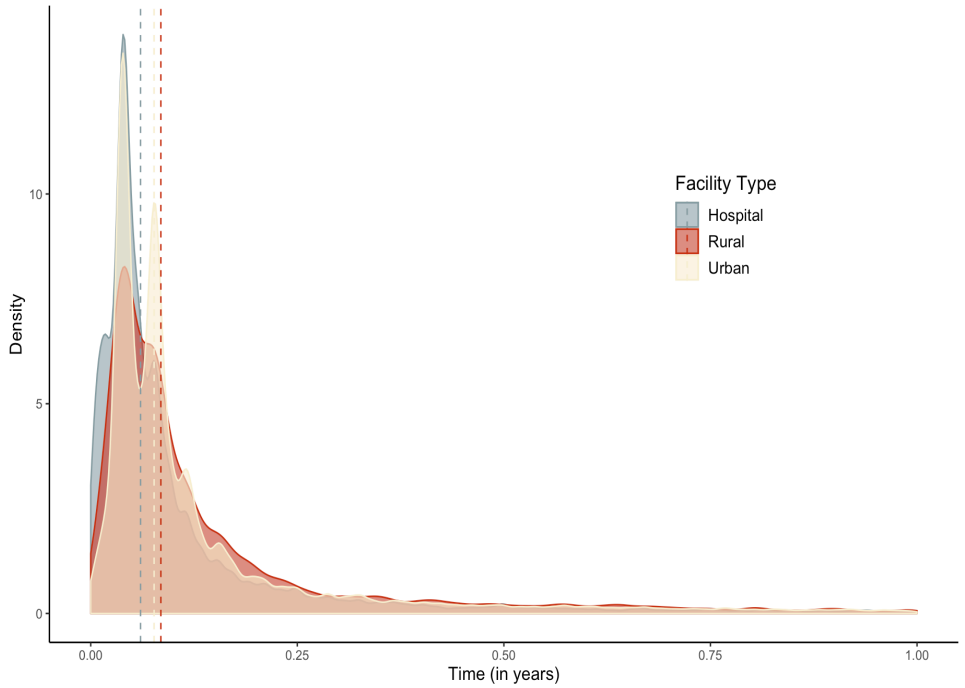


Figure 5-10. Density Plot and Median Time Between ART Eligibility and ART Initiation, by CD4 Count at HIV Care Enrollment

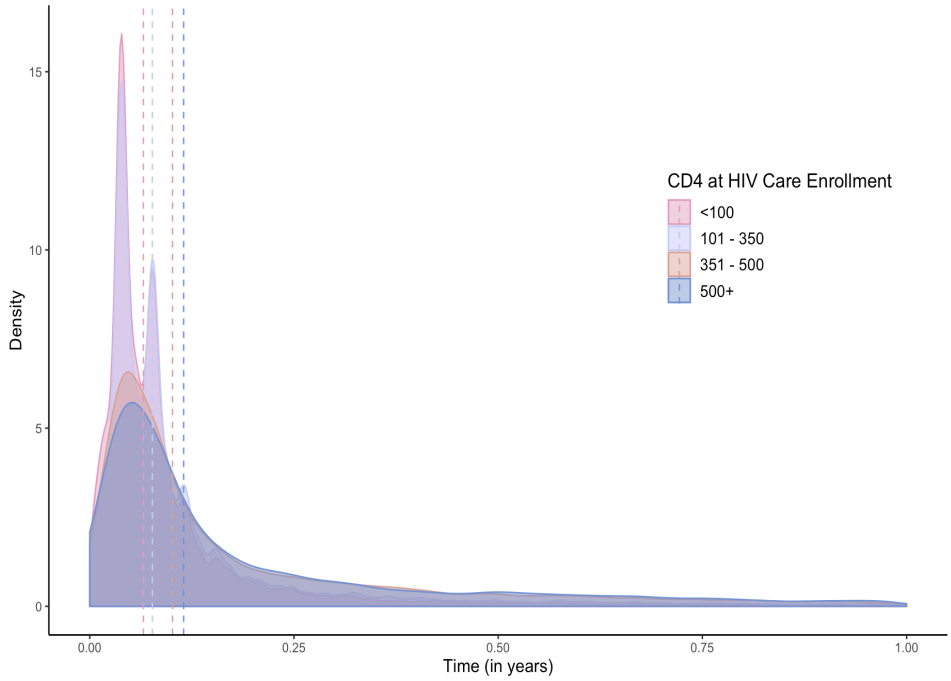
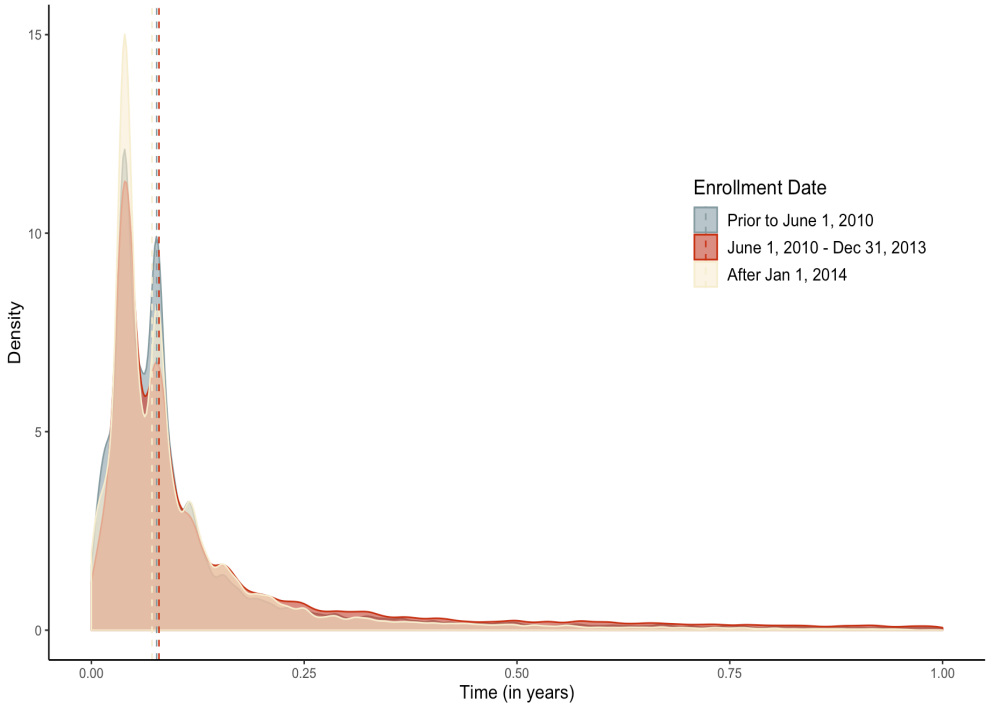
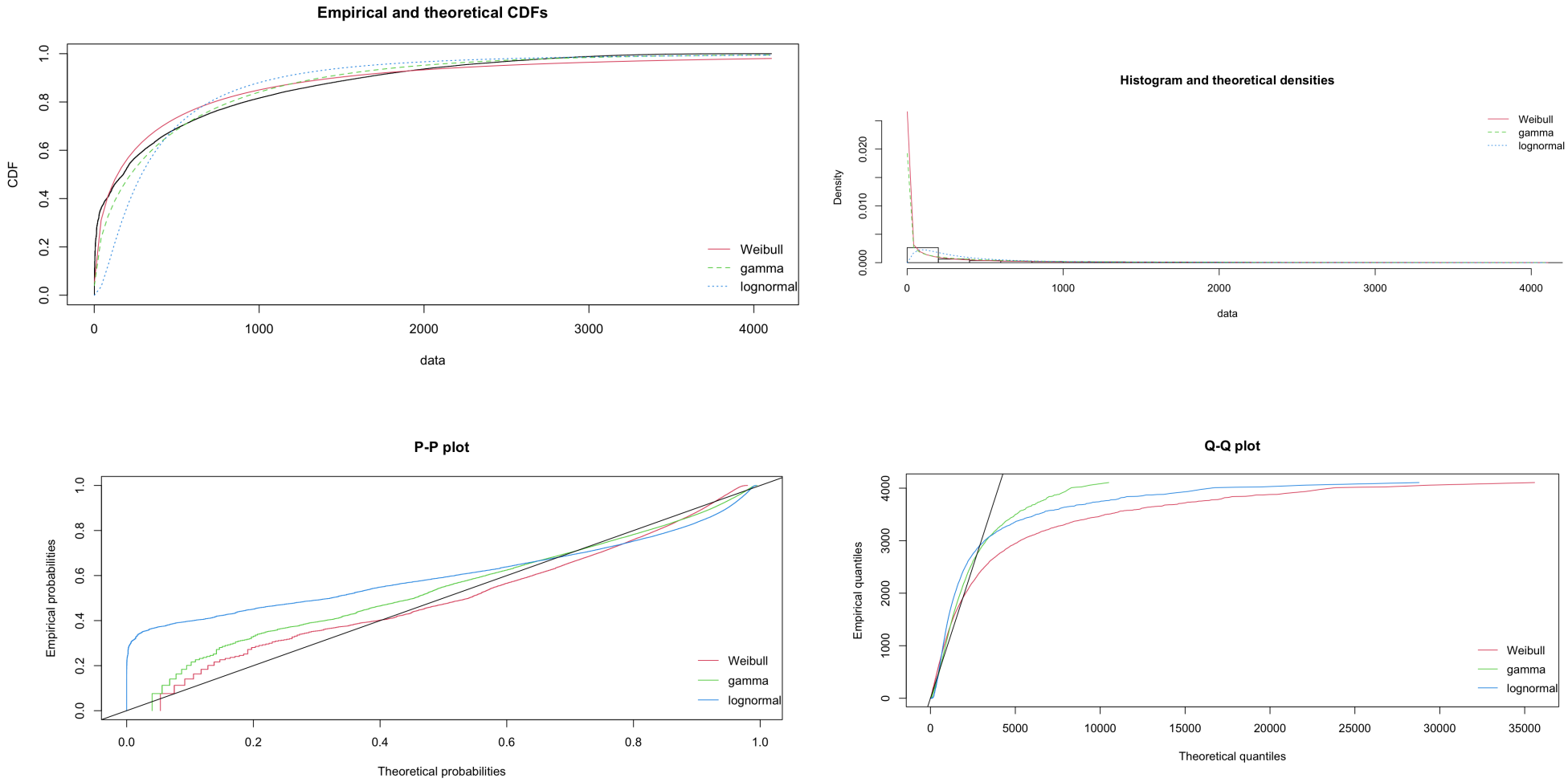


Figure 5-11. Density Plot and Median Time Between ART Eligibility and ART Initiation, by Enrollment Date



Chapter 5 Appendix

Appendix Figure 5-1. CDF, Density, P-P, and Q-Q Plots for Fitting Time to Eligibility Data



Appendix Table 5-1.Goodness-of-Fit Statistics and Criteria Comparing Distribution Types for Time to Eligibility

	Weibull	Gamma	Lognormal
Goodness-of-Fit Statistics			
Kolmogorov-Smirnov statistic	0.0432	0.1345	0.3264
Cramer-von Mises statistic	122.52941270	305.1168135	1.962150e+03
Anderson-Darling statistic	874.80267640	2098.3055315	5.228252e+04
Goodness-of-Fit Criteria			
Akaike's Information Criterion (AIC)	960,449.4	961,719.7	1,232,129
Bayesian Information Criterion (BIC)	960,467.8	961,738.1	1,232,147

Appendix Table 5-2. Goodness-of-Fit Statistics and Criteria Comparing Distribution Types for Time to ART Initiation

	Weibull	Gamma	Lognormal
Goodness-of-Fit Statistics			
Kolmogorov-Smirnov statistic	0.0438	0.0004	0.1292
Cramer-von Mises statistic	450.83	5,424.96	890.47
Anderson-Darling statistic	2371.67	24,394.83	4921.33
Goodness-of-Fit Criteria			
Akaike's Information Criterion (AIC)	976,544.3	1,007,770	1,101,382
Bayesian Information Criterion (BIC)	976,563.2	1,007,789	1,101,401

6 Aim 2

Understanding the Impact of Improved Testing, Treatment, and Retention on the HIV Epidemic in Zambia: A Modeling Study

Introduction

As of 2019, more than 20 million people were living with HIV (PLHIV) in Eastern and Southern Africa (ESA).[112] This figure, representing over half of the global HIV burden, has increased significantly in the past decade as antiretroviral therapy (ART) has become more accessible in the region and the life expectancy of PLHIV on treatment has approached that of the general population.[113] Expanded access to ART has been a driving factor in the strategy to control the HIV/AIDS epidemic, while increased testing and early ART initiation are paramount in decreasing HIV mortality, morbidity, and transmission.[114] During this same timeframe, the number of new infections in the region dropped 38%.[53, 112] Despite the significant progress in both HIV treatment and prevention, major challenges must be overcome before achieving the ultimate goal of ending the HIV/AIDS epidemic.[115]

In 2014, UNAIDS launched a fast-track response to rapidly scale up prevention and treatment services in order to meet 90-90-90 targets by 2020: 90% of PLHIV are aware of their status, 90% of PLHIV with a diagnosis are on treatment; and 90% of PLHIV on treatment have a suppressed viral load, with a further increase to 95-95-95 by 2030.[116] This global commitment to scale up HIV programs has increased the speed at which countries are progressing towards their 90-90-90

goals, especially in Eastern and Southern Africa. Based on 2019 UNAIDS data, the region as a whole has advanced steadily towards these targets, with 87% of PLHIV knowing their status, 83% of diagnosed PLHIV on treatment, and 90% of PLHIV on treatment who are virally suppressed.[112]

To achieve the first '90', access and uptake of HIV testing services (HTS) need to increase.[117] HTS are a critical step in HIV prevention as well as in the HIV treatment cascade.[118-120] Studies have shown that a substantial proportion of HIV transmission can be attributed to PLHIV who are undiagnosed.[119] Although there has been a dramatic scale-up of HTS over the last decade, a large fraction of PLHIV are still unaware of their positive status. HTS have traditionally been implemented via three different modalities. The first, known as voluntary counseling and testing (VCT), is an opt-in approach for individuals who actively seek HTS. The second, diagnostic counseling and testing (DCT), is a healthcare-initiated approach for individuals presenting with HIV-related symptoms or demonstrating other HIV-related risk factors. The third HTS strategy is provider-initiated testing and counseling (PITC), which is recommended by the World Health Organization (WHO) for high HIV burden areas. PITC is an opt-out approach in which any individuals seeking healthcare, regardless of reason, receives routine HIV testing.[121] PITC is highly effective in detecting infections earlier and therefore linking PLHIV to appropriate care earlier, as demonstrated by its impact on the decrease of mother-to-child transmission in antenatal care (ANC) settings. However, it has been underutilized for several reasons, including healthcare personnel shortages, inadequate healthcare provider training, and lack of provider experience with HTS.[117, 121, 122] In order to meet the first '90', innovative strategies are essential to address the underutilization of HTS.

Effort has been made to increase linkage to HIV care and treatment, which is essential in achieving the second '90'.[123] After many years of using CD4 count thresholds to determine ART eligibility, the WHO recommended test-and-treat guidelines in 2016.[124] Under these guidelines, any individual is eligible for ART after receiving a positive diagnosis for HIV. Results from clinical trials have shown that by initiating ART immediately after diagnosis, individuals experienced fewer HIV-related adverse outcomes, had improved rates of viral suppression, and were less likely to transmit HIV compared to patients who deferred ART.[124, 125] Though many countries have adopted a test-and-treat policy since the WHO introduced these guidelines, implementation in resource-limited settings, such as ESA, has been challenging due to the significant cost, infrastructure, and human resources required for treatment expansion.[126, 127]

Timely linkage to HIV care and ART initiation is intertwined with the third '90', which focuses on population-level viral suppression and is key to ending the epidemic. Randomized controlled trials and observational studies have shown that HIV transmission risk to sexual partners is closely associated with the viral load of PLHIV.[128, 129] Thus, if PLHIV on ART achieve viral suppression (i.e., undetectable viral load), the risk of HIV transmission is eliminated. This concept is referred to as treatment as prevention (TasP) or undetectable equals untransmittable (U=U).[130, 131]

Although ART coverage has been increasing in many countries since their adoption of a test-and-treat policy, long-term treatment outcomes, such as care retention, treatment adherence, and viral suppression, have not been thoroughly studied.[127] Additionally, there is currently no consensus

in the available literature on whether test-and-treat or enhanced adherence interventions significantly impact HIV incidence on a population level.[127, 132-134] As the second phase of the UNAIDS fast-track response begins, interventions should be targeted towards specific groups in order to alter the epidemic trajectory and decrease incidence.[135]

There is increasing evidence that the major factor driving the generalized HIV epidemic in sub-Saharan Africa (SSA) is HIV transmission within heterosexual cohabitating or married partners.[136-138] Studies have shown that in many ESA settings, over 80% of incident HIV infections in women occur through marriage or long-term partnerships.[139] Couples' voluntary counseling and testing (CVCT) is an HIV testing approach that the WHO has argued to be a feasible way to increase testing among people in an ongoing sexual relationship.[140] Several studies have demonstrated that CVCT could be an effective strategy in preventing HIV transmission in sub-Saharan Africa, where the vast majority of adults are in stable relationships, by increasing safe sex practices, such as increasing condom use among serodiscordant couples and decreasing condomless sex with outside partners, and increasing the uptake of treatment compared to individual-targeted interventions.[140-143] Although CVCT is a WHO-recommended testing strategy, it has not been universally incorporated into county-specific guidelines and uptake has remained around 25% in SSA.[140]

CVCT has been shown to have preventative and therapeutic effects on couples, regardless of serostatus.[30] Among seroconcordant negative couples, CVCT has been shown to help prevent HIV transmission through counseling and subsequent behavior modification. Among

seroconcordant positive couples, CVCT has led to behavior modification (e.g., reducing outside partners) as well as support for treatment initiation and adherence.[140, 144] CVCT's greatest effect has been seen among serodiscordant couples; one study showed that HIV incidence among serodiscordant couples dramatically declined after testing through a CVCT program.[30]

Zambia, a landlocked country in southern Africa with over 1 million PLHIV, has endorsed CVCT as a recommended testing strategy for couples for the past few decades. More than half of Zambian adults aged 15-49 have a spouse or cohabitating partner (DHS, 2018). One study showed that more than 20% of Zambian couples are either serodiscordant or seroconcordant positive.[30] Only one previous modeling study has illustrated the population effect of CVCT among serodiscordant couples in Zambia compared to TasP interventions, finding it to avert more than nine times more infections over five years. However, this study did not incorporate prevention benefits of CVCT or ART among seroconcordant positive couples and did not consider the improved clinical outcome benefit from CVCT.[30] There remains an opportunity to generate more comprehensive evidence on how well a nationally scaled-up CVCT program would perform at reducing population level HIV incidence relative to other testing and treatment interventions.

Zambia is one of the few ESA countries that has recently met the 90-90-90 UNAIDS targets, with 90% of PLHIV having been diagnosed, 95% of diagnosed PLHIV on treatment, and 90% of PLHIV on treatment with a suppressed viral load.[50] As the country enters the second phase of the fast-track response, a strong emphasis on the implementation of effective, scalable testing and

treatment approaches will be necessary for achieving 95-95-95 by 2030 with a focus on innovative testing and retention strategies.

In this study, we employ agent-based mathematical modeling to compare the long-term impact various testing, treatment, and retention interventions would have on the HIV epidemic among adults in Zambia.

Methods

Model Description

The Epidemiologic MODelling (EMOD) software platform was used to simulate the generalized HIV epidemic in Zambia for this study. The EMOD HIV model is a stochastic, agent-based simulator of heterosexual and vertical HIV transmission. The overall model structure has been described in detail in previous studies.[145-152] The EMOD HIV model framework allows for person-to-person disease transmission through contact networks; individuals form and break one or more partnerships that are remembered over time. The HIV model framework incorporates detailed data on mortality, age-specific fertility, and risk-varying sexual relationship formation types in order to demonstrate the movement of individuals through the various stages of the HIV care cascade which includes testing, linkage and retention in care, and ART treatment eligibility and retention.[152]

The model is comprised of four major structural components: 1) age-specific fertility and age- and sex-specific non-AIDS-related mortality rates, 2) relationships and contact networks, 3) intrahost

dynamics and HIV biology, and 4) a detailed HIV care cascade.[153] The model uses a feed-forward pair formation algorithm (PFA) to configure relationship formations and to track them over time, and numerous parameters to represent the type and duration of relationships. The PFA allows for the formation of sexual relationships with a specific joint age-mixing distribution and enables control over the rate of new relationships. Additionally, relationships are categorized into four different heterosexual relationship risk types (commercial, transitory, informal, and marital), which influence the partnership duration as well as the behavior of the individuals (e.g., coital frequency and probability of condom use) within a particular relationship.[146] This configuration allows the model to demonstrate population heterogeneity in terms of HIV acquisition risk as well as to target various interventions at specific risk groups.[152] The full mathematical description of the algorithm has been previously published.[154]

The EMOD HIV model also incorporates intrahost HIV biology to the heterosexual transmission of HIV in the person-to-person contact network. The model can be configured to produce HIV transmission rates, mortality rates, and biomarker progression (e.g., CD4 count) that are specific to treated or untreated HIV-infected individuals.[153] The model framework portrays untreated HIV infection in three different stages (acute, latent, and AIDS), the durations of which can be configured. HIV survival time is sampled from an age-dependent Weibull distribution since HIV prognosis is highly dependent on age at the time of infection.[153] The model structure representing intrahost HIV biology is coupled with an HIV care cascade component, which can be configured to provide a series of decisions, delays, and filters representing the process of delivering various health care interventions to individuals.[145]

In this study, we modelled a population illustrating the generalized HIV epidemic among Zambian adults aged 15-49 at the province-level since HIV epidemic, in terms of HIV prevalence and ART coverage, varies widely by the ten provinces within Zambia.

Sexual debut, sexual network, and sexual transmission of HIV

EMOD only allows individuals who have reached sexual debut to enter a relationship. Age at sexual debut is randomly drawn for each individual from a Weibull distribution, which is defined by three parameters: Weibull shape parameter, Weibull scale parameter, and the minimum age of sexual debut. These parameters are configured separately for males and females (Table 6-1). The model also summarizes age-specific transmission dynamics using self-reported patterns of age-specific sexual partners, which has been validated by phylogenetic and epidemiologic studies in South Africa.[152, 155] A number of parameters represent different aspects of infectivity and disease transmission. These parameters determine how infectious an individual is based on disease progression stage, the length of time for which they are infectious, and the impact of different interventions on an individual's base infectivity (Table 6-1).

HIV Interventions within EMOD

The EMOD HIV model can be configured to represent the HIV care cascade and to determine which individuals receive specific interventions. Interventions may include, for example, male circumcision, condom usage, HIV testing, and ART usage.

Male circumcision has been shown to decrease probability of HIV acquisition by 60%.[156] Traditional circumcision and voluntary medical male circumcision (VMMC) is accounted for by province, based on programmatic and DHS data. Condom usage rates are configured by relationship type; the rate is set at the beginning of the partnership, and probability of usage follows a sigmoidal curve, accounting for lower rate of usage in long-term relationships:

$$P(t) = {}^{h}\Big/\left[1 + e^{(-R(t-t_0))} + l\right]$$

Probability of condom usage at simulation time t, where h = maximum asymptote, l= minimum asymptote, t_0 = year of inflection point, R = rate proportional to the slope at the inflection point

There are numerous ways that individuals can receive an HIV testing intervention in the model; the three routine testing interventions used in this study are 1) individual voluntary HIV counseling and testing (iVCT), 2) symptomatic HIV testing (i.e., DCT), and 3) antenatal testing. Individuals are eligible for iVCT at or after sexual debut. The rate at which individual seek iVCT is based on reported rates of testing and proportion of adult population ever tested, according to national-level survey data. Once an individual receives routing iVCT testing, the agent returns for testing at an average rate of once every 18 months until there is a positive test result. Individuals with HIV can also get tested when they become symptomatic, which is based on CD4 count. Lastly, pregnant women can receive testing at 12-weeks gestation.

If an HIV test results in a positive diagnosis, the individual is linked to care by either initiating ART immediately, if eligible based on CD4 count, or by waiting to start treatment in a period of

time known as pre-ART. There is also a probability that the individual does not return for care and is thus considered lost to follow up (LTFU). Individuals in pre-ART are checked for treatment eligibility every six months. ART eligibility is based on WHO recommendations and follows the incremental treatment expansion as reflected in the Zambian national HIV treatment guidelines. ART retention is configured by an intervention based on ART delay to dropout, which is represented with an exponential distribution.

Description of CVCT within EMOD

For this study, we advanced EMOD by creating an HIV intervention featuring CVCT. This intervention provides a mechanism for health-seeking individuals to notify their sexual partner of their healthcare engagement.

The inclusion criteria for modeled CVCT eligibility were: 1) seeking HIV testing through iVCT, DCT, or ANC testing; 2) 18 years of age or older; 3) in a married or relationship (i.e., stable partnership). Married relationships within the model are the structure that defines basic relationship, pair formation, and concurrency parameters for marital relationships, while informal relationships are the structure that define these parameters for longer-term, non-marital relationships. When an individual meets these criteria, they broadcast a notification to their partner that they have received HIV testing. In the event of multiple partners, the partner from the longest relationship is selected. The broadcast notification triggers the partner to seek HIV testing immediately. The partner will broadcast a different notification that they received the CVCT intervention.

In order to demonstrate the preventive effects of CVCT through TasP and behavior modification, a few assumptions were made for all individuals who received the CVCT intervention (Figure 6-1). Regardless of serostatus, these individuals received a second intervention representing a reduced probability of HIV transmission by applying an increased probability of condom usage. Additionally, individuals who received the CVCT intervention and had a positive HIV diagnosis bypassed the pre-ART period and immediately initiated ART. We made the assumption that these individuals also were retained in the healthcare system and stayed on ART for the duration of the time horizons. The treatment assumptions were based on previous studies that have shown that couples who go through CVCT have better treatment outcomes, in terms of initiation and retention.[157] Condom usage assumptions were based on a previous study which showed that HIV incidence among seroconcordant negative couples decreased by 47% after going through couples counseling. In the present analysis, we assume this reduction is attributed to increased condom use.[158]

Model Calibration

An earlier version of EMOD (v0.8) was previously calibrated to simulate the Zambian HIV epidemic. For this analysis, we recalibrated an updated version of the model (v2.13) to incorporate more recent historical data. In order to simulate the Zambian HIV epidemic, the model was calibrated using Zambia-specific demographic data, including: 1) fertility by age, 2) mortality by age and sex, 3) age distribution by province, and 4) HIV prevalence and ART coverage by province and sex.

Calibration was performed using the parallel simultaneous perturbation optimization (PSPO) algorithm, which is an extension of the more commonly used simultaneous perturbation stochastic approximation (SPSA). This type of calibration technique is useful when optimizing with several unknown parameters. PSPO was used in this calibration to maximize the likelihood of fit of the model to historical data, in this case, data from the sources described below.[152] The specific details of this optimization extension have been described previously.[159, 160]

PSPO was run until the likelihood reached a plateau without any additional improvement. 250 model parameter sets were selected from a total set of 6300 simulations using roulette resampling in proportion to the likelihood. This calibration process generated a set of 44 fitted parameters (Appendix).

Data Sources

A number of data sources were used to ensure accuracy of historical HIV prevalence, HIV incidence, and ART coverage. For adult HIV prevalence, we included data from three population-level surveys, the 2001-2002 Zambia Demographic Health Survey, the 2007 Zambia Demographic Health Survey, the 2013-2014 Zambia Demographic Health Survey, as well as estimated data from the 2016 UNAIDS Spectrum model.[53, 84, 161-164] HIV prevalence was available at the provincial level and by sex for Zambian adults between the ages of 15-49. ART coverage data was derived from the 2016 Zambia Population-Based HIV Impact Assessment (ZAMPHIA) and from the UNAIDS Spectrum model for the years of 2014-2017.[27, 164] ZAMPHIA data was available by sex and 5-year

age bins for adults between 15 and 49 years old, while the UNAIDS Spectrum model provided province- and sex-level ART coverage estimates. HIV incidence data was provided by the available 2016 ZAMPHIA data, which was reported by sex and three age categories: 15-25, 25-35, and 35-49 (Appendix 2).[27, 164]

Modeling Scenarios

A baseline referent scenario and four counterfactual scenarios were modeled to understand the impact of various interventions on HIV incidence and prevalence in Zambian adults aged 15-49 years. Scenario 1 is the referent scenario, which projects the HIV epidemic in Zambia with no additional interventions added. For this scenario, testing and treatment rates are maintained from 2020 levels throughout the two time horizons. Scenarios 2-5 refer to four counterfactual scenarios, each of which incorporate different interventions beginning in 2020. Scenario 2 reflects a test-and-treat strategy in which any individual who receive a positive HIV diagnosis begins ART immediately after receipt of the positive test result. Scenario 3 reflects an increased ART retention program in which all individuals who begin ART starting in 2020 or later will stay on treatment for the remainder of the study period(s). Scenario 4 is an amalgamation of Scenario 2 and Scenario 3; individuals who initiate ART in 2020 or thereafter will be retained in the healthcare system and individuals who receive a positive HIV test results will immediately initiate ART. Scenario 5 represents a scaled-up national CVCT program in which individuals aged 18 and older who are in a married or informal (i.e., long-term, non-marital) relationship and receive an HIV test will bring their current partner to get tested as well. In the event that the individual has more than one partner at the time, the partner from the longest duration is brought for testing. Because

CVCT has a number of different components that could affect population HIV incidence, we also model each component separately in order to understand the biggest drivers of potential HIV incidence reduction.

Partners that are seroconcordant negative and test together are provided a preventive effect through a higher probability of condom use with all partners. Partners that are serodiscordant or seroconcordant positive will also have this preventive effect through increased condom use; however, partners who receive a positive HIV diagnosis initiate ART immediately and remain in care throughout the study period(s). Table 6-2 describes each scenario and corresponding assumptions in detail.

Each scenario was simulated over a 10-year timeframe, between 2020 and 2030, and a 30-year timeframe, between 2020 and 2050. Each scenario was run 250 times, and the results were summarized using the median values of all simulations as well as the 95% simulation intervals (SI).

Outcomes of Interest

We report changes in HIV incidence and prevalence over ten- and thirty-year time horizons (2030 and 2050, respectively), by province and sex, among Zambian adults aged 15-49. We compared the change in HIV incidence and prevalence between each counterfactual scenario in relation to baseline reference scenario. We also report on the number of people tested, number of HIV

infections averted (HIAs), and proportion of infections averted (PIAs) when comparing each counterfactual scenario relative to the baseline referent scenario in 2030 and 2050.

$$\boldsymbol{Incidence_{i,t}} = \frac{\#\ of\ new\ HIV\ diagnoses\ in\ year\ t}{\#\ of\ people\ living\ in\ year\ t - \#\ of\ people\ living\ with\ HIV\ in\ year\ t}\ x\ 1000$$

$$\boldsymbol{Prevalence_{i,t}} = \frac{\#\ of\ people\ living\ with\ HIV\ in\ year\ t}{\#\ of\ people\ alive\ in\ year\ t}$$

$$where\ i = Scenario\ (S1, S2, S3, S4, S5)$$

$$where\ t = Year\ (2030, 2050)$$

$$\boldsymbol{HIV\ infections\ averted_{j,b}} = \sum_{t=2020}^{n} HIV\ infections\ diagnosed_{bt} - \sum_{t=2020}^{n} HIV\ infections\ diagnosed_{jt}$$

$$\boldsymbol{Proportion\ of\ HIV\ infections\ averted_{j,b}} = \frac{\sum_{t=2020}^{n} HIV\ infections\ diagnosed_{tb} - \sum_{t=2020}^{n} HIV\ infections\ diagnosed_{tj}}{\sum_{t=2020}^{n} HIV\ infections\ diagnosed_{tb}}$$

$$where\ b = Scenario\ S1\ (baseline)$$

$$where\ j = Counterfactual\ Scenario\ (S2, S3, S4, S5)$$

$$where\ t = Year$$

$$where\ n = 2030, 2050$$

Results

We modeled HIV incidence among Zambian adults aged 15-49, stratified by gender across 250 parameter sets (Figure 6-3). Our fitted model reflects the precipitous increase in incidence during the 1980s and 1990s, followed by a dramatic decrease around 2003 after the introduction of antiretroviral therapy. Our baseline trajectory (Scenario 1) shows that HIV incidence in 2020 was 2.4 per 1000 people (95% SI: 1.82 – 3.10) among the adult population, 1.65 (95% SI: 1.20 – 2.18) among men, and 3.18 (95% SI: 2.25 – 4.16) among women. This scenario predicts that if the standard of care currently practiced in Zambia would stay constant, HIV incidence would decrease by an estimated 40% (95% CI: 37.1 – 43.7) by 2030 and 72% (95% CI: 67.4 – 76.8) by 2050. Similar reductions in incidence were seen in both men and women (Table 6-3).

Impact of Counterfactual Scenarios

We compared projected results from four different counterfactual scenarios with the baseline trajectory. Each counterfactual scenario illustrates the impact different HIV interventions beginning in 2020 and lasting for two time horizons: 10 years (2020 – 2030) and 30 years (2020 – 2050). Our first counterfactual scenario (Scenario 2) reflected a test-and-treat approach, in which anyone who received a positive HIV test diagnosis bypassed the traditional pre-ART period and immediately initiated therapy. This scenario had a significant impact on HIV incidence; overall 10-year incidence decreased by over 70% (72.1%, 95% SI: 69.99-74.86) to 0.67 cases per 1000 in 2030, and overall 30-year incidence decreased by over 90% (91.89%, 95% SI: 90.24-94.13) to 0.19 cases per 1000 in 2050.

Scenario 3 explored the counterfactual effects of an enhanced ART retention intervention. This scenario makes the assumption that individuals who initiate ART in 2020 or thereafter are never lost to follow up during the time periods of interest and stay in the health care system, a proxy for treatment adherence and subsequent viral suppression. Although this scenario does have an effect on incidence reduction, the change is not as remarkable as the universal test-and-treat counterfactual scenario, particularly on the 10-year time horizon. The enhanced retention intervention resulted in approximately 48% (48.05, 95% SI: 45.38-51.31) decrease in HIV incidence over 10 years and 84% (83.86, 95% SI: 79.94-87.63) over 30 years.

The next counterfactual scenario, Scenario 4, combines the effects of a test-and-treat strategy with an enhanced treatment enhancement approach - an amalgamation of the two previously described scenarios. The projected HIV incidence from this scenario was similar to, but slightly lower, than the effects of a universal test and treat program alone (Scenario 2). Incidence decreased by 76% in 10 years to 0.58 (95% SI: 0.39-0.78) per 1000 people and by 92.7% (95% SI: 0.09-0.29) in 30 years across the entire adult population. The similarity in the estimated 2030 and 2050 HIV incidence between test-and-treat plus an enhanced retention program (Scenario 4) and that of a test-and-treat counterfactual alone (Scenario 2) indicates that the test and treat component is driving the vast majority of the incidence reduction effect.

We modeled our final scenario to reflect the rapid scale-up of a national CVCT program, in which eligible individuals uptake counseling and testing services with their partner, after which both partners subsequently exhibit safer sexual practices (i.e., condom usage) and are started on

treatment upon receipt of an HIV diagnosis. The CVCT counterfactual showed considerable reductions in HIV incidence, as there was an incidence reduction of 64% (95% SI: 62.4 – 67.5) and 87% (95% SI: 83.3 – 90.3) after 10 years and 30 years, respectively among the 15-49 adult population. However, this magnitude of incidence reduction was not as remarkable as what was demonstrated in the test-and-treat scenarios.

Gender stratified results show that men experienced a somewhat larger 10-year incidence reduction compared to women in the test-and-treat scenarios; for example, in Scenario 4 (test-and-treat and enhanced retention), incidence reduction was 78.7% (95% SI: 75.97-81.59) among men and 74.5% (95% SI: 73.08-76.05) among women. Across all five scenarios, differences in 30-year percent incidence reduction between genders were negligible. Similar 10-year and 30-year trends were seen in HIV prevalence reduction (Table 6-4).

We also calculated HIV infections averted (HIA) and proportion of HIV infections averted (PIA) to understand the impact of each counterfactual scenario in relation to the standard of care projection (Scenario 1). As expected, test-and-treat plus enhanced healthcare retention averted the most infections: our model estimated that over 200,000 and 600,000 HIV infections would be averted over ten years and thirty years, respectively, under Scenario 4, This corresponds to almost half of all infections from the referent scenario averted (PIA - 49.2%, 95% SI: 45.08-52.9) by 2030, and almost 60% of infections averted (PIA - 59.1%, 95% SI: 55.51-62.33) by 2050. The enhanced retention counterfactual (Scenario 3) averted the least among of infection across the four counterfactual scenarios analyzed. Over 10 years, this scenario led to almost 5% of infections

averted (PIA: 4.87%, 95% SI: 1.46-10.81) and to approximately one-fifth of infections averted over 30 years (PIA: 19.36%, 95% SI: 12.61-25.41). We estimated that a scaled-up national CVCT program would lead to over 135,000 HIAs between 2020 and 2030 and over 400,000 HIAs between 2020 and 2050. This translates to over approximately a third of all infections averted in the 10-year period (PIA - 33.2%, 95% SI: 28.69-37.78) and almost 40% in the 30-year period (PIA - 39.5, 95% SI: 34.36-44.32).

Discussion

Zambia has had remarkable success in achieving the UNAIDS interim fast-track goals, having met or exceeded the 90-90-90 goals by 2020. However, it is unclear if and how the country will be able to end the epidemic by the global target of 2030. We explored the change in HIV incidence over 10-year and 30-year timeframes at the current rate of testing and treatment scale-up as well as four different counterfactual scenarios. Sustaining the current standard of care (baseline scenario), Zambia reaches a national adult HIV incidence of 1.43 cases per 1,000 people and an HIV prevalence of 6.36% in 2030. These results are consistent with other studies that have forecasted the HIV epidemic in Zambia.[61, 165]

The counterfactual scenarios modeled in this study are extremes of four possible testing and treatment strategies; we explored the effects of: 1) a true universal test and treat approach, in which all individuals who receive a positive HIV test result are automatically placed on treatment; 2) an enhanced healthcare retention approach, in which individuals who initiate ART are not LTFU and successfully achieve virologic suppression; 3) a combined approach of

universal test and treat and enhanced retention; and 4) a rapid national scale-up of couples counseling and testing approach, through which all eligible couples are tested for HIV simultaneously and are provided with prevention and treatment benefits through increased condom usage and immediate ART initiation for those who test positive. The scenario assumptions may seem implausible at first glance; however, Zambia has met or surpassed the 2nd 90 target (90% of people who know their positive status are on ART) in eight of its ten provinces and has already met the 2030 goal of at least 95% of people who know their status who are on ART in three provinces: Muchinga, Eastern, and Copperbelt.[6] Assuming that ART initiation and engagement will at least persist at current levels, it may be plausible for Zambia to implement a true test and treat or enhanced retention program, as illustrated by Scenario 2, Scenario 3, and Scenario 4.

Zambia has made excellent progress towards population level virologic suppression, as the country has reported that 90% of individuals who have initiated ART have also achieved virologic suppression. In our enhanced retention scenario, we assumed that individuals who initiated ART in or after 2020 would be adherent to treatment and would not be lost to follow up. Although the assumption that there would be no attrition among ART users is highly unlikely, our model provided valuable information on the impact of this optimistic scenario. Our results indicate that perfect ART adherence and healthcare retention only marginally decreases HIV incidence compared to the standard of care approach. This suggests that future efforts should be focused on testing and treatment initiation interventions.

Clinical trials have shown test-and-treat to be highly effective on a population scale, reducing HIV incidence by increasing overall ART coverage and reducing risk of forward HIV transmission by helping to suppress viral load.[46, 166] Our modeling results illustrate this effectiveness with the dramatic decrease in HIV incidence over ten and thirty years in the two scenarios with a test-and-treat approach. Research has shown that the time between HIV testing and ART initiation had decreased substantially in Zambia since the incorporation of the WHO's 2016 recommendation to start anyone with a positive diagnosis on treatment immediately. One study estimated that the time to ART initiation among a pediatric population fell from a median of 17 days (IQR: 1 – 161) in 2004 to a median of one day (IQR: 1-14) in 2017.[167] Another analysis from HPTN 071 (PopART) study showed that median time from referral to ART initiation decreased from 10 months to six months after the implementation of a "same day ART start".[168] Although Zambia has made large strides in ensuring treatment for an increasing number of PLHIV, it is still unclear whether or not the country has the infrastructure or capacity to deliver independently a sustainable test-and-treat approach.[166]

Although the benefits of expansive treatment are widely documented, long-term adverse health outcomes associated with test-and-treat programs should be considered. Successful implementation of test-and-treat programs is often challenged by suboptimal adherence, as recent studies have shown that LTFU has been higher under a universal test-and-treat policy, in which all PLHIV are diagnosed and treated, possibly because patients are in relatively good health at the time of therapy initiation and may not see a benefit to consistent healthcare engagement or medication adherence.[169, 170] As suboptimal adherence is associated with virologic

failure and resistance mutations, a poorly executed test-and-treat program could lead to severe health outcomes on a population-level.[171]

Eliminating CD4 thresholds for treatment eligibility and allowing all PLHIV access to treatment is a huge advancement that has been made in the last several years. However, ART eligibility does not always translate to immediate ART initiation. Barriers to treatment initiation persist on several levels despite ART eligibility, including inadequate counseling space and services, patient readiness to start treatment, and overburdened healthcare facilities. In order to be successful, test-and-treat programs must navigate several steps within a complex process from HIV diagnosis to HIV care system engagement.[123]

Even under the most controlled settings, such as in clinical trials demonstrating the effects of test-and-treat on local epidemics, HIV incidence level always remained above epidemic control levels (≤1 case per 1,000 person-years).[172] Thus, test-and-treat alone is not an answer to ending the epidemic; additional, innovative service delivery models and novel interventions for linkage to care are required to successfully engage with those who are driving the epidemic.[173]

Results from our study add to the existing evidence base that CVCT, a targeted intervention, has the potential to impact the HIV epidemic significantly in Zambia. Of all of the scenarios explored in this study, the CVCT intervention was the only approach that has an effect on each of the three pillars of the care cascade: 1) sexual partners are tested when they may not have been otherwise, increasing the number of PLHIV who know their status, since many couples do not have high

risk profiles; 2) testing with a regular partner has been shown to be a major factor associated with a higher likelihood of ART initiation; and 3) partners who have received CVCT are more likely adhere to ART due to partner support and encouragement.[158, 174, 175]

This study presents a few limitations. First, our model accounts only for the general heterosexual population in Zambia. Men having sex with other men, migrants, prisoners, transgender people, and people who inject drugs are all parts of the overall Zambian population that are often overlooked. More work needs to be done to gather quality data on these vulnerable groups who are less likely to be able to access healthcare and may be more susceptible to HIV acquisition. Second, our model did not include the impact of biomedical preventive interventions, or pre-exposure prophylaxis (PrEP). PrEP was incorporated into the Zambian national guidelines in 2018, and the Ministry of Health has begun operationalizing PrEP into the existing HIV prevention strategy.[176] However, it may be too early to understand the feasibility of a large national scale-up of a PrEP program in Zambia, especially since knowledge and awareness of PrEP is low.[177] Additionally, previous research has questioned the affordability of PrEP on a population-scale in resource-limited settings, despite its high clinical effectiveness.[178]

Lastly, we relied heavily on routinely collected data from country reports to inform our model. Analysis from routinely collected HIV data in Zambia has been shown to be inadequate oftentimes, a possible reflection on the lack of technical capacity and human resources.[179] Definitions of common indicators, such as number of people on treatment and LTFU rate, have

been shown to vary across different sources, which ultimately changes the estimated effects of an intervention.

Zambia has been a model country in meeting the 2020 90-90-90 targets and will continue to make strides in reducing HIV incidence if it is able to sustain the current scale up that has been achieved at this point. However, we provide evidence that additional interventions could lead to a greater impact, which can optimistically be translated to decision making and policy planning.

Table 6-1. Description of Select Parameters

Parameter Name	Description	Value
Acute Duration	Number of months since infection during which the Acute Stage Infectivity Multiplier is applied to coital acts	2.9
Acute Stage Infectivity Multiplier	Multiplier acting on the Base Infectivity parameter to determine the per-act transmission probability of an individual during acute stage	26
Base Infectivity	The probability of transmission when none of the transmission multipliers apply to a coital act	0.00233 (0.00231 - 0.00234)
AIDS Duration	Number of months prior to an AIDS-related death during which the AIDS Stage Infectivity Multiplier is applied to coital acts	9
AIDS Stage Infectivity Multiplier	Multiplier acting on the Base Infectivity parameter to determine the per-act transmission probability of an individual during AIDS stage	4.5
ART Dropout	Exponentially distributed mean number of days from ART initiation until ART dropout	7300
ART Linkage – Max	The right asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time	0.891 (0.671 - 1)
ART Linkage – Mid	The time of the inflection point in the sigmoid trend of probability of ART linkage (given eligibility) over time	2010.7 (2010.4 - 2010.9)
ART Linkage – Min	The left asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time	0
ART Linkage – Rate	The slope of the inflection point in the sigmoid trend of probability of ART linkage over time. (A Rate of 1 sets the slope to a 25% change in probability per year.)	1
ART Viral Suppression Multiplier	Multiplier acting on Base Infectivity parameter to determine the per-act transmission probability of an individual on ART. Less-than-perfect (<100%) reduction in risk is attributed to sub-optimal adherence, drug resistance, and delay in viral load suppression from ART initiation.	0.08

Parameter Name	Description	Value
CD4 at Death	Weibull distribution representing CD4 count at death	Shape – 0.7 Scale – 2.96
CD4 after post-Acute period	Weibull distribution representing CD4 count after the post-acute stage	Shape – 0.2756 Scale – 560.43
Male Circumcision – Acquisition Reduction	The reduction of susceptibility to HIV by voluntary male medical circumcision (VMMC)	0.6
Male to Female Relative Acquisition Multiplier (Old)	An array of scale factors governing the susceptibility of females relative to males, by age ≥ 25	2.844 (2.727 - 2.958)
Male to Female Relative Acquisition Multiplier (Young)	An array of scale factors governing the susceptibility of females relative to males, by age < 25	4.894 (4.747 - 5.041)
Low Risk Population	Proportion of the initial population that is low risk	0.85
Sexual Debut – Female	Weibull distribution representing sexual debut among females	Shape – 0.22 Scale – 15.09
Sexual Debut - Male	Weibull distribution representing sexual debut among males	Shape – 0.12 Scale – 15.58
Sexual Debut – Min Age	The minimum age at which individuals become eligible to form sexual relationships	13

Table 6-2. Scenario Descriptions

	Name	**Description**
Scenario 1 (Baseline)	Historical scale-up of ART (current standard of care)	Status quo scenario that aligns with the historical scale-up of ART coverage by sex and province; maintaining 2020 levels throughout the 10-year timeframe
Scenario 2	Immediate ART initiation after positive diagnostic test (universal test and treat)	All individuals who come in for HIV testing and receive a positive diagnostic test result are immediately initiated on ART (i.e., 100% immediate ART initiation post-HIV positive diagnosis)
Scenario 3	Enhanced retention in healthcare setting after ART initiation	All individuals who initiate on ART remain on treatment throughout the follow-up period (i.e., Treated individuals have no lapse in ART, no LTFU)
Scenario 4	Immediate ART initiation and enhanced ART retention	All individuals who come in for HIV testing and receive a positive diagnostic result are immediately initiated on ART and remain on treatment throughout the follow-up period (i.e., combination of 100% ART initiation and no lapse in ARTT)
Scenario 5	Couples Voluntary Testing and Counseling	All individuals over 18 years old in a stable relationship test for HIV together. Based on test results, the effects are as follows: Seroconcurrent negative: both partners increase condom usage with all partners Seroconcurrent positive: both partners increase condom usage with all partners, both partners initiate ART immediately and are not LTFU Serodiscordant: both partners increase condom usage with all partners, positive partner initiates ART immediately and is not LTFU

Table 6-3. Change in HIV Incidence over 10-year (2020 – 2030) and 30-year (2020 – 2050) Time Horizons By Gender, 5 scenarios

	2030				2050			
Scenario	**HIV Incidence (95% SI)**	**10-yr Percent Reduction (95% SI)**	**HIA compared to Baseline (95% SI)**	**PIA compared to Baseline (95% SI)**	**HIV Incidence (95% SI)**	**30-yr Percent Reduction (%, SI)**	**HIA compared to Baseline (95% SI)**	**PIA compared to Baseline (95% SI)**
Baseline – Historical Scale-up of ART (continuing current standard of care)								
All	1.43 (1.02-1.95)	40.36 (37.1-43.72)	Ref	Ref	0.68 (0.42-1.01)	71.84 (67.38-76.79)	Ref	Ref
Men	0.98 (0.65-1.33)	40.28 (38.84-45.81)	Ref	Ref	0.45 (0.25-0.71)	72.72 (67.5-79.1)	Ref	Ref
Women	1.89 (1.34-2.64)	40.57 (36.48-40.17)	Ref	Ref	0.9 (0.54-1.36)	71.64 (67.2-76.17)	Ref	Ref
Scenario 2 – Immediate ART initiation after positive diagnostic test (test and treat)								
All	0.67 (0.46-0.93)	72.1 (69.99-74.86)	185,406 (140,490-236,006)	45.29 (41.73-48.93)	0.19 (0.11-0.3)	91.89 (90.24-94.13)	553,750 (410,246-744,378)	54.47 (50.3-57.86)
Men	0.42 (0.25-0.59)	74.57 (72.94-79.11)	70,833 (51,941-91,146)	49.07 (44.97-53.34)	0.11 (0.04-0.2)	93.28 (91.01-96.47)	205,816 (150,967-276,340)	58.93 (54.57-62.41)
Women	0.92 (0.61-1.3)	70.94 (68.72-72.88)	114,574 (87,351-145,350)	43.23 (39.1-47.13)	0.28 (0.15-0.44)	91.28 (89.48-93.24)	347,934 (252,416-466,600)	52.13 (47.75-55.55)
Scenario 3 – Enhanced retention in healthcare setting after ART initiation (no LTFU after ART initiation)								
All	1.25 (0.9-1.71)	48.05 (45.38-51.31)	20,116 (6,004-47,150)	4.87 (1.46-10.81)	0.39 (0.23-0.63)	83.86 (79.94-87.63)	197,223 (116,619-286,577)	19.36 (12.61-25.41)
Men	0.85 (0.55-1.21)	48.54 (45.1-53.17)	7680 (3,042-17,762)	5.26 (2.34-12.31)	0.25 (0.13-0.43)	84.53 (80.38-88.98)	70,147 (36,366-108,129)	20.02 (11.79-26.78)
Women	1.66 (1.19-2.32)	47.96 (43.93-48.7)	12,436 (4,528-28,215)	4.64 (1.84-10.05)	0.52 (0.31-0.84)	83.68 (79.63-86.59)	127,076 (74,291-183,434)	19.0 (12.54-25.22)
Scenario 4 – Immediate ART initiation after positive diagnostic test and enhanced ART after treatment initiation (test and treat + enhanced retention)								
All	0.58 (0.39-0.78)	75.88 (74.99-78.84)	201,435 (150,161-258,901)	49.2 (45.08-52.9)	0.18 (0.09-0.29)	92.65 (90.86-95.07)	600,254 (440,660-804,108)	59.08 (55.51-62.33)
Men	0.35 (0.21-0.53)	78.72 (75.97-81.59)	76,489 (57,209-97,874)	52.98 (48.22-57.28)	0.1 (0.04-0.18)	93.7 (92.01-96.82)	220,253 (160,660-297,233)	63.1 (59.4-66.67)
Women	0.81 (0.56-1.12)	74.51 (73.08-76.05)	124,947 (94,402-160,864)	47.14 (43.06-50.7)	0.25 (0.13-0.42)	92.21 (89.88-94.46)	380,001 (279,280-510,953)	56.98 (53.05-60.27)
Scenario 5 – Couples' Voluntary Testing and Counseling (CVCT) for individuals over the age of 18 in a marital or long-term relationships								
All	0.87 (0.6-1.17)	63.95 (62.42-67.52)	135,846 (96,927-178,575)	33.16 (28.69-37.78)	0.32 (0.18-0.52)	86.78 (83.28-90.27)	402,195 (283,433-549,574)	39.54 (34.36-44.32)
Men	0.6 (0.38-0.87)	63.27 (59.99-68.16)	46,386 (31,647-61,623)	32.1 (26.2-37.97)	0.21 (0.11-0.37)	87.36 (83.08-91.09)	138,500 (93,943-190,549)	39.62 (33.42-45.39)
Women	1.13 (0.79-1.55)	64.48 (62.82-66.89)	89,461 (65,272-117,735)	33.73 (28.84-37.88)	0.43 (0.25-0.68)	86.64 (83.62-89.72)	263,695 (186,983-360,703)	39.5 (34.56-44.01)

Incidence – Infections per 1,000 people; HIA – HIV Infections Averted; PIA – Proportion of Infections Averted; SI – 95% Simulation Interval

Table 6-4. Change in HIV Prevalence over 10-year (2020 -2030) and 30-year (2020 – 2050) Time Horizons by Gender, 5 Scenarios

	2030		2050	
Scenario	**HIV Prevalence (%) (95% SI)**	**10-yr Percent Reduction (%) (95% SI)**	**HIV Prevalence (%, SI)**	**30-yr Percent Reduction (%, SI)**
Baseline – Historical Scale-up of ART (continuing current standard of care)				
All	6.36 (4.98-7.94)	37.98 (36.43-39.53)	2.3 (1.58-3.22)	77.61 (76.73-78.49)
Men	4.15 (3.17-5.29)	45.0 (43.9-46.1)	1.38 (0.94-1.97)	81.66 (81.11-82.21)
Women	8.54 (6.67-10.68)	33.96 (31.94-35.98)	3.2 (2.22-4.5)	75.29 (74.07-76.51)
Scenario 2 – Immediate ART initiation after positive diagnostic test (universal test and treat)				
All	5.82 (4.52-7.23)	43.24 (41.87-44.61)	1.19 (0.83-1.61)	88.38 (87.99-88.77)
Men	3.73 (2.83-4.73)	50.65 (49.69-51.61)	0.67 (0.46-0.9)	91.19 (90.95-91.43)
Women	7.88 (6.18-9.67)	39.09 (37.29-40.89)	1.71 (1.19-2.31)	86.8 (86.23-87.37)
Scenario 3 – Continued retention in healthcare setting after ART initiation (no LTFU after ART initiation)				
All	6.27 (4.84-7.83)	38.88 (37.37-40.39)	1.89 (1.28-2.66)	81.57 (80.86-82.28)
Men	4.08 (3.09-5.22)	45.94 (44.86-47.02)	1.14 (0.76-1.62)	84.92 (84.47-85.37)
Women	8.43 (6.54-10.46)	34.84 (32.88-36.8)	2.63 (1.78-3.66)	79.67 (78.69-80.65)
Scenario 4 – Immediate ART initiation after positive diagnostic test and continued ART after treatment initiation				
All	5.71 (4.44-7.09)	44.32 (42.99-45.65)	1.09 (0.77-1.49)	89.37 (89-89.74)
Men	3.66 (2.77-4.7)	51.54 (50.6-52.48)	0.62 (0.43-0.85)	91.85 (91.63-92.07)
Women	7.73 (6.05-9.58)	40.27 (38.53-42.01)	1.56 (1.08-2.13)	87.96 (87.41-88.51)
Scenario 5 – Couples' Voluntary Testing and Counseling (CVCT) for individuals aged 20-50 in a long-term relationship				
All	6.03 (4.67-7.46)	41.27 (39.84-42.7)	1.53 (1.07-2.11)	85.07 (84.52-85.62)
Men	4.04 (3.05-5.1)	46.52 (45.48-47.56)	0.97 (0.66-1.33)	87.21 (86.86-87.56)
Women	7.98 (6.23-9.86)	38.32 (36.5-40.14)	2.09 (1.45-2.89)	83.86 (83.12-84.6)

SI = simulation interval

Figure-6-1. Illustrative Schema of CVCT Intervention within EMOD

When a person eligible for CVCT presents for HIV testing, a notification is broadcast to the person's current partner of longest duration, which then triggers the partner to present for HIV testing immediately. If either partner tests negative, probability of future condom use increases to 60%, during subsequent coital acts. If either or both partners tests positive, the same preventive condom effect is applied and the partner(s) will initiate ART immediately.

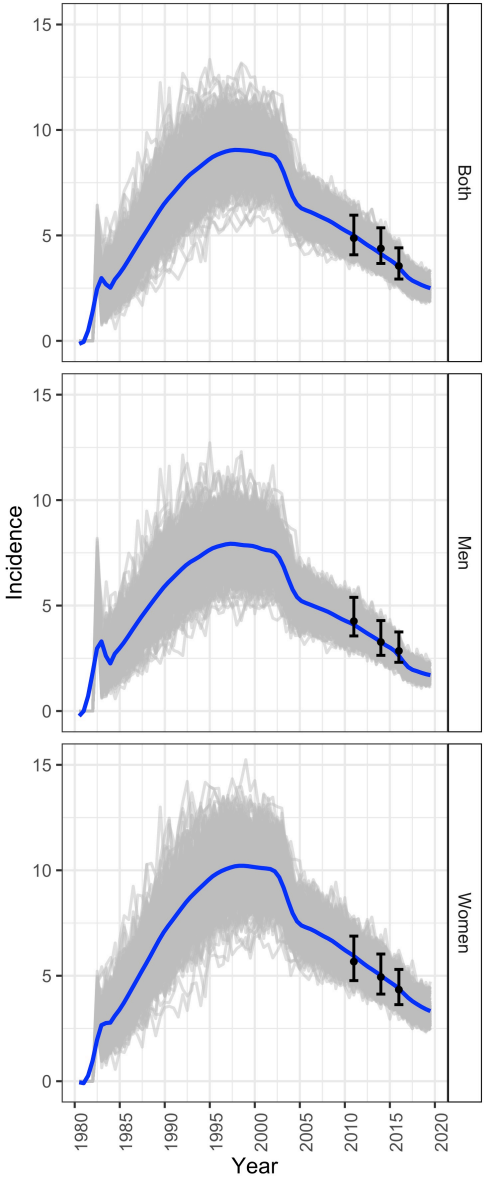


Figure-6-2. Best fitting HIV Incidence simulations, n=250

Grey lines represent individual simulations; Blue line represents the LOESS curve; Black data points and error bars are incidence point estimates extracted from UNAIDS. Incidence is defined as new cases per 1,000 people per year.

Figure 6-3. Estimated HIV Incidence Projections between 2020 – 2050 across 5 scenarios

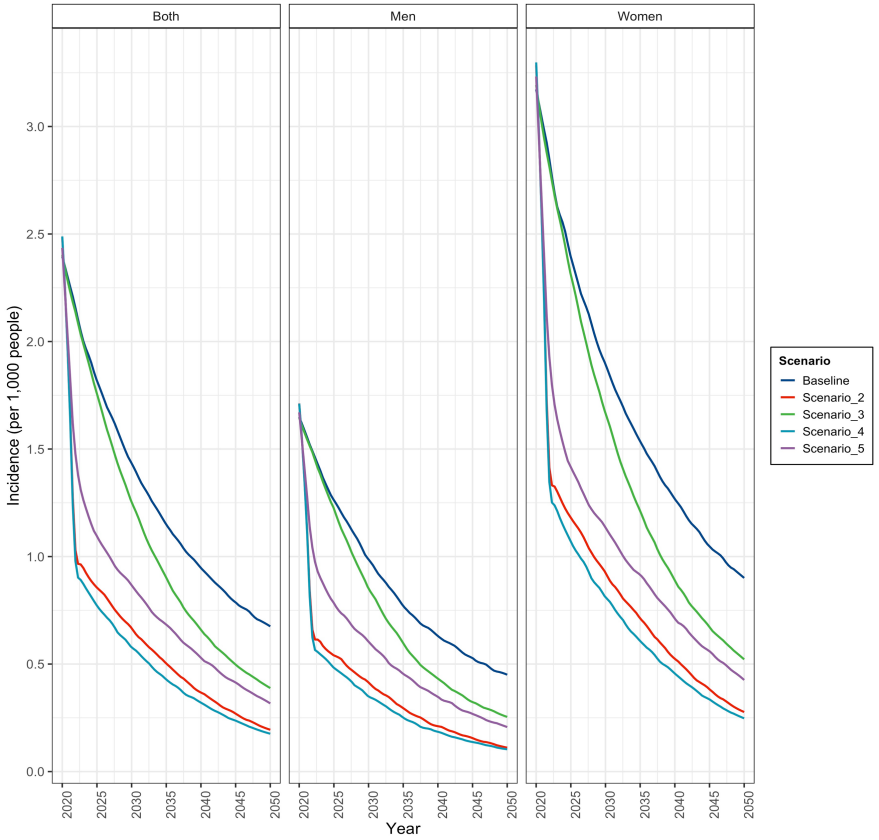


Table 6-5. Number of People Ever Tested for HIV in 2030 and 2050, by Gender

	2030		2050	
	Male	Female	Male	Female
Scenario #1 (Baseline)	3,322,070	4,020,861	6,137,995	6,880,164
Scenario #5 (CVCT)	4,104,865	4,120,890	7,389,836	7,259,812

Chapter 6 Appendix

Appendix Table 6-1. Fitted Parameters from Calibration

Parameter	Initial Value	Min Value	Max Value
Base Probability of HIV Infectivity	0.00065805	0.000463	0.000732
Circumcision – HIV Transmission Reduction	0.6	0.4	0.9
Age at Sexual Debut for Females:			
Weibull Scale Parameter	18.6061447	17.37209	20
Weibull Heterogeneity Parameter	0.22594081	0.097992	0.340693
Age at Sexual Debut for Males:			
Weibull Scale Parameter	16.5290633	15.21137	18.47653
Weibull Heterogeneity Parameter	0.16722784	0.047004	0.301883
Formation Rate, by Relationship Type:			
Transitory	0.00135027	0.000515	0.002148
Informal	3.27E-04	9.13E-05	0.00075
Marital	1.52E-04	8.35E-05	0.000221
Transmission Multipliers:			
Male to Young Female	2.02712074	1	3.521532
Male to Older Female	1.80702788	1	3
Max Probability of Condom Usage, by Relationship Type:			
Transitory	0.29476793	0.042467	0.497849
Informal	0.44293988	0.263329	0.6
Marital	0.2454659	0.139952	0.3
Max Probability of Condom Usage among Transitory Relationships, by Province:			
Central	0.68401047	0.50331	0.8
Copperbelt	0.42587585	0.197469	0.549003
Eastern	0.50862355	0.212995	0.8
Luapula	0.67562444	0.313664	0.8
Lusaka	0.18005021	0	0.662367
Muchinga	0.4844036	0.662367	0.8
Northern	0.60790849	0.354285	0.8
Northwestern	0.65442846	0.461396	0.8

Southern	0.73084427	0.488058	0.8
Western	0.64063048	0.404196	0.8
Max Probability of Condom Usage among Informal Relationships, by Province:			
Central	0.51102633	0.368304	0.6
Copperbelt	0.22692408	0	0.417629
Eastern	0.17035181	0.018981	0.40348
Luapula	0.53282653	0.406449	0.6
Lusaka	0.53119284	0	0.662367
Muchinga	0.20668922	0.038298	0.8
Northern	0.48763224	0.135008	0.580399
Northwestern	0.65442846	0.461396	0.6
Southern	0.52695616	0.344261	0.6
Western	0.08501451	0	0.311877
Max Probability of Condom Usage among Marital Relationships, by Province:			
Central	0.25420505	0.101208	0.351663
Copperbelt	0.33404161	0.232866	0.413877
Eastern	0.12594297	0.05	0.258156
Luapula	0.23366463	0.068375	0.424839
Lusaka	0.38068591	0.211397	0.5
Muchinga	0.09272307	0.05	0.233418
Northern	0.44898045	0.348732	0.5
Northwestern	0.29144055	0.091521	0.5
Southern	0.37411928	0.25608	0.5
Western	0.27806683	0.107138	0.4805

Appendix Table 6-2. HIV Prevalence, by Province and Gender

Province	Gender	Age Category	2002 Prevalence*	2007 Prevalence	2014 Prevalence	2016 Prevalence
Central	Female	[15:50)	0.17	0.22	0.15	0.16
Copperbelt	Female	[15:50)	0.22	0.22	0.20	0.17
Eastern	Female	[15:50)	0.16	0.11	0.12	0.10
Luapula	Female	[15:50)	0.13	0.12	0.19	0.11
Lusaka	Female	[15:50)	0.25	0.22	0.08	0.18
Muchinga	Female	[15:50)		0.07	0.15	0.08
Northern	Female	[15:50)	0.10	0.09	0.18	0.11
Northwestern	Female	[15:50)	0.09	0.08	0.10	0.08
Southern	Female	[15:50)	0.20	0.16	0.07	0.14
Western	Female	[15:50)	0.17	0.16	0.11	0.18
Central	Male	[15:50)	0.13	0.13	0.10	0.08
Copperbelt	Male	[15:50)	0.17	0.12	0.16	0.09
Eastern	Male	[15:50)	0.11	0.09	0.10	0.04
Luapula	Male	[15:50)	0.09	0.15	0.13	0.07
Lusaka	Male	[15:50)	0.19	0.19	0.06	0.11
Muchinga	Male	[15:50)		0.04	0.11	0.03
Northern	Male	[15:50)	0.06	0.05	0.13	0.08
Northwestern	Male	[15:50)	0.10	0.08	0.11	0.05
Southern	Male	[15:50)	0.15	0.13	0.06	0.11
Western	Male	[15:50)	0.08	0.14	0.08	0.12

*Muchinga officially became a province in 2011, thus 2002 data was not reported

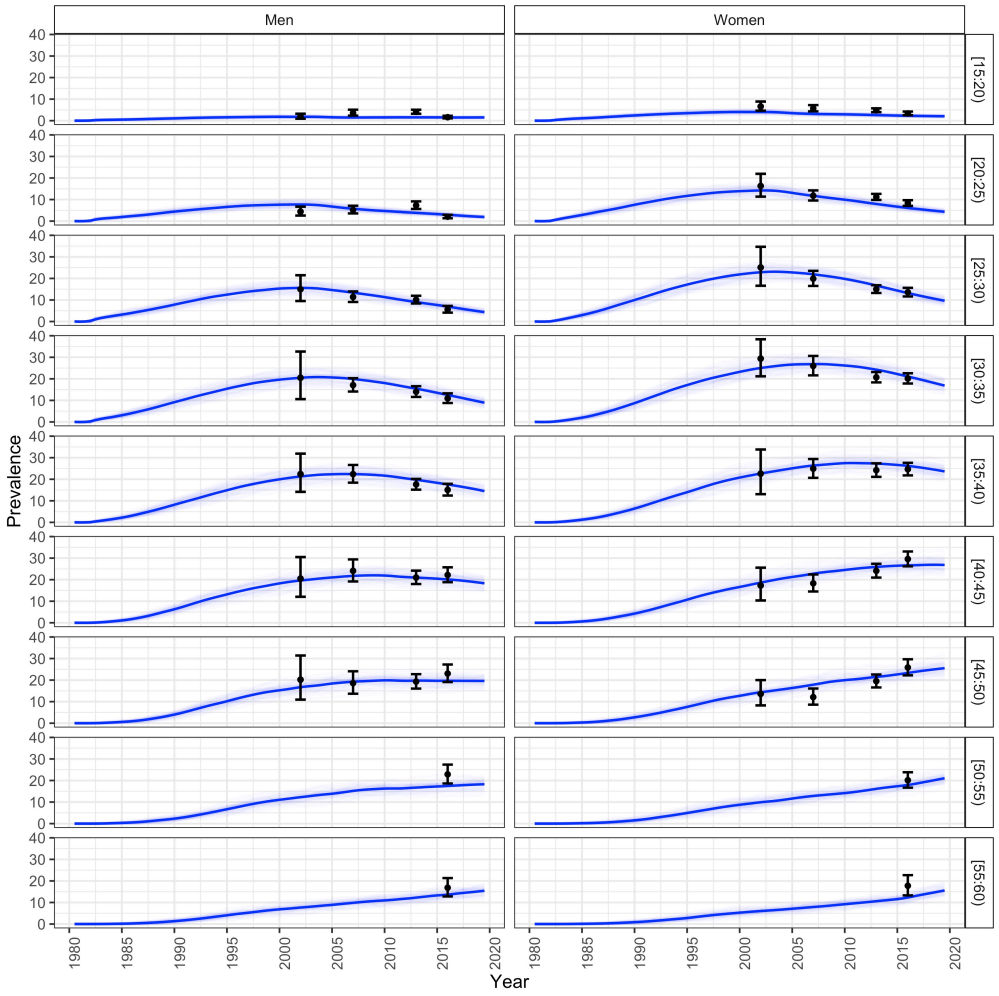
Appendix Table 6-3. Empiric Data on ART Coverage, by Gender

Year	Province	Gender	Age Category	ART Coverage
2016	All	Female	[15:20)	0.2653
2016	All	Female	[20:25)	0.3334
2016	All	Female	[25:30)	0.5448
2016	All	Female	[30:35)	0.5436
2016	All	Female	[35:40)	0.6466
2016	All	Female	[40:45)	0.7163
2016	All	Female	[45:50)	0.6633
2016	All	Male	[15:20)	0.3313
2016	All	Male	[20:25)	0.3731
2016	All	Male	[25:30)	0.2502
2016	All	Male	[30:35)	0.318
2016	All	Male	[35:40)	0.4849
2016	All	Male	[40:45)	0.6308
2016	All	Male	[45:50)	0.694

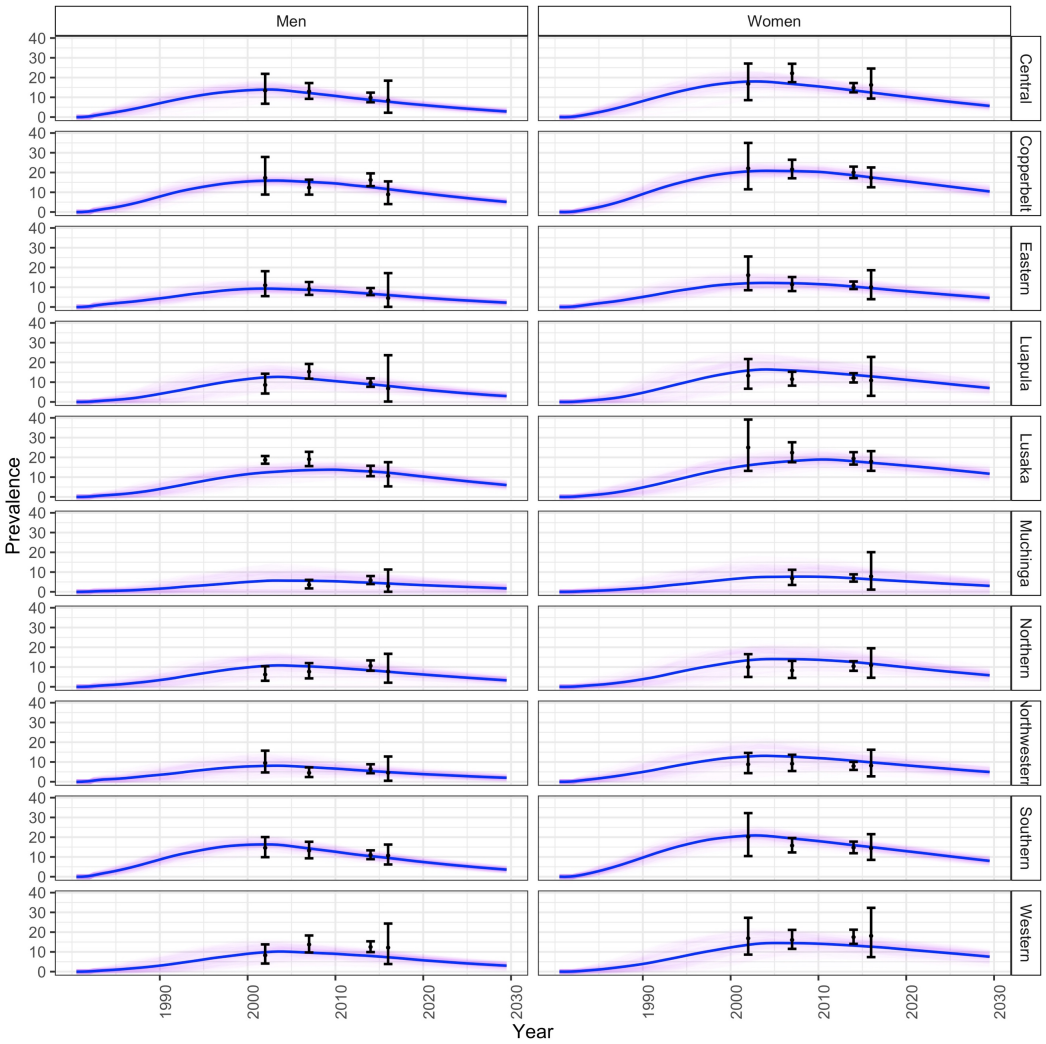
Appendix Table 6-4. Empiric Data on HIV Incidence, by Gender for Model Calibration

Year	Province	Gender	Age Category	HIV Incidence
2016	All	Female	[15:25)	0.0107
2016	All	Female	[25:35)	0.0116
2016	All	Female	[35:50)	0.0106
2016	All	Male	[15:25)	0.0008
2016	All	Male	[25:35)	0.0025
2016	All	Male	[35:50)	0.0087

Appendix Figure 6-1. Historical HIV Prevalence, by broad age categories



Appendix Figure 6-2. Historical HIV Prevalence, by Province



7 Aim 3

Couples Voluntary Testing and Counseling is Beneficial and Cost-Saving in the Context of HIV Testing and Treatment in Zambia: a simulation study

Introduction

The global HIV/AIDS response has made significant progress towards the UNAIDS goal of ending the epidemic by 2030. Substantial investments and resolute efforts in the past decade for both HIV prevention and care have resulted in a 38% reduction in new HIV infections and 49% reduction in AIDS-related mortality in sub-Saharan Africa (SSA), the region with the majority of global incidence and burden of HIV/AIDS.[50] By 2020, seven countries in SSA had already met the interim Fast-Track Targets otherwise known as 90-90-90: 90% of people living with HIV (PLHIV) diagnosed, 90% of those diagnosed treated with antiretroviral therapy (ART), and 90% of those treated achieving viral suppression.[50, 180] Despite these successes, the decline in HIV incidence has plateaued in recent years, and gaps in coverage of HIV services persist in the region.[178]

Additionally, there has been a recent decline in domestic and international funding for HIV which may widen these gaps and threaten the goal of ending the epidemic by 2030.[50] In 2019, total donor government funding for HIV declined by approximately $200 million compared to the year prior. This decline was driven mostly by the United States government, which has historically been the largest donor to global HIV programming.[80, 181] As of 2020, donor funding has declined to a level commensurate with that of a decade ago, despite a 25% increase in the number of people currently

living with HIV in low- and middle-income countries.[181] In response to these declines, countries with high HIV burden and incidence must attempt to make evidence-based decisions to select the most cost-effective strategies for HIV treatment and prevention.

Zambia, a country with an adult HIV prevalence of 12.1% as of 2019, made tremendous progress in achieving the interim Fast-Track Targets by 2020. Zambia is one of seven SSA countries to achieve 90-90-90, but must continue to accelerate this progress to reach UNAID's ambitious final Fast-Track Targets, i.e., 95-95-95 (95% of people living with HIV diagnosed, 95% of those diagnosed treated with antiretroviral therapy, and 95% of those treated achieving viral suppression), by 2030.[50]

Zambia's progress in expanding ART coverage is due in part to the country's 2016 adoption of the WHO guidelines recommending a universal test-and-treat strategy, in which all PLHIV should initiate and remain on ART, regardless of CD4 count.[182] The guidelines are based on both clinical benefits of early treatment initiation, which reduce AIDS-related complications and mortality, and population-level benefits known as treatment as prevention (TasP), known as treatment as prevention (TasP) or undetectable = untransmittable (U=U), in which PLHIV are unable to transmit the virus after achieving undetectable viral levels. However, there is no consensus in the existing literature regarding the extent to which test-and-treat programs significantly impact HIV incidence on a population level.[127, 132-134, 168, 183] Broad treatment expansion required for successful test-and-treat programs are associated with substantial financial,

infrastructure, and human resource requirements.[126, 127] More studies of the cost-effectiveness of test-and-treat at the population level are needed.

Another WHO recommended HIV prevention intervention is couples voluntary testing and counseling (CVCT) which has shown to be a high-impact, affordable approach to HIV prevention.[30, 184-186] CVCT encourages partners to test for HIV together, a strategy that raises awareness of partner serostatus, increases uptake of and adherence to treatment after diagnosis, and increases safe sex behaviors.[30, 74, 174, 187] A recently published study described the results from one CVCT program implemented in three provinces in Zambia (Copperbelt, Lusaka, and Southern) which served over 200,000 couples and averted an estimated 60% of incident infections compared to the standard of care and was shown to be cost-effective.[30] CVCT is an approach that is sensible for a country such as Zambia, where the vast majority of HIV transmission occurs between cohabitating partners, and is already a part of Zambia's HIV prevention toolkit as a recommended service in the national HIV strategy framework.[29] However, it is not yet broadly implemented, and its scale-up on a national level may facilitate achieving the Fast Track Targets at a lower cost.

Using data from the Zambian CVCTT study and coupling it with the most recently published UNAIDS data, we model the potential epidemiologic and economic impacts of the nationwide scale-up of two realistic scenarios in Zambia. This study compares the current standard of care for individual HIV testing and treatment among the adult Zambian population aged 15-49 with: 1) a nationally scaled-up test and treat program, in which all individuals who test positive for

HIV initiate ART and 2) a national test and treat program that incorporates CVCT, which adds upon the test-and-treat scenario by allowing eligible individuals to receive HIV testing with a partner.

Methods

To explore the impacts of large-scale testing programs in Zambia, we calibrated an infectious disease model to match the historical HIV epidemic in Zambia. Using this calibrated model, we projected health and cost outcomes among adults aged 15-49 of three scenarios, all described in detail below: the standard of care, with no additional interventions, a national test-and-treat program that guarantees treatment initiation for all individuals who receive a positive HIV test result, and a combined test-and-treat + CVCT program, which incorporates couples testing in addition to test-and-treat.

In developing this study, we followed the guidance and recommendations of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group on dynamic transmission modeling and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. [188, 189]

Model Framework

We used the Epidemiologic MODelling (EMOD) software platform, developed by the Bill & Melinda Gates Foundation's Institute for Disease Modelling (IDM), to simulate the HIV epidemic in Zambia.[146, 152, 153] EMOD is an agent-based, stochastic model that simulates disease transmission

using a sexual partnership network defined by linkage formation and dissolution patterns.[190] The model has been developed to support a variety of disease simulation types, including HIV. EMOD-HIV has been described in detail in previous studies. The model has the capacity to calibrate to different geographic regions, represent a sub-population-specific and time-variable HIV care continuum, and incorporate interventions targeted to specific population sub-groups.[149, 151, 153]

EMOD uses vital dynamics that are informed by fertility and mortality data provided as model input tables. Individuals become sexually active at a random age based on a specified Weibull distribution and a minimum age of 13, after which they may enter different types of relationships (marital, informal, transitory, and commercial), and may form concurrent relationships. The formation of relationships is based on the partner formation algorithm (PFA), which uses a relationship entry probability matrix based on male and female single-age categories. The age-mixing pattern is specified independently for each relationship type.[149, 151, 153]

Upon reaching sexual debut, individuals are able to receive standard HIV testing via three different routes: individual voluntary testing and counseling (iVCT), symptomatic testing, and antenatal care (ANC) testing. Additionally, infants may receive HIV testing if they are born to HIV-positive mothers. Rates of ANC and symptomatic testing are set to match the product of fertility rates, reported rates of ANC attendance among pregnant women, and reported HIV testing rates among ANC clients. Symptomatic testing and iVCT rates are set to match self-reported proportions ever tested and tested in the past year, as well as CD4 counts at initiation of

ART (to distinguish iVCT vs. symptomatic testing). After initial testing via iVCT, individuals return for routine testing at an average rate of 1.5 years until a positive test result. Additional details of the HIV care continuum in EMOD are available elsewhere [cite].

CVCT was simulated among individuals aged 18 and older who are in a sexual relationship categorized as marital or transitory and whose sexual partner has accessed HIV testing through voluntary testing, antenatal testing, or symptomatic-based testing modalities. If the individual has more than one concurrent partner, the partner from the longest relationship is provided with CVCT. If either or both partners receive diagnosis positive HIV test result, the partner(s) is immediately linked to treatment initiation, bypassing the pre-ART stage. All partners who receive CVCT, regardless of serostatus, reduce their future HIV transmission risk by XX-fold [cite], which reflects their future condom usage with all sexual partners and reduced concurrency.[14]

EMOD assumes three stages of HIV infection: acute, latent, and AIDS. The probability of disease transmission is calculated based on a per-act basis among serodifferent couples, and this probability varies based on the disease state of the partner with HIV. The per-act probability can is modified by factors including condom usage, male circumcision, and presence of an STI (assigned based upon concurrency propensity and participation in commercial sex)

Individuals enter the HIV care system once they receive a positive test result, after which they link to pre-ART or ART care. Prior to adoption of UTT, individuals who are not eligible to initiate ART at the time of testing undergo routine pre-ART monitoring visits every 6 months until

eligible for ART. Individuals can potentially experience loss to follow up at any point within the care cascade, including individuals on treatment.

In-depth details of the model structure and the cascade of care intervention are described elsewhere..[149, 151, 153]

Data Sources

We used several sources to inform our model of the HIV epidemic in Zambia. Historical HIV prevalence (disaggregated by 5-yr age categories, sex, and province) was extracted from the three most recent Zambia Demographic Health Surveys (2001-2002 ZDHS, 2007 ZDHS, 2013-2014 DHS) as well as from the UNAIDS Spectrum model.[53, 84, 161-164] Additionally, we incorporated HIV incidence and ART coverage data obtained from the 2016 Zambia Population-Based HIV Impact Assessment (ZAMPHIA) and from the UNAIDS Spectrum model for the years of 2014-2017.[27, 164] ZAMPHIA data were provided by sex and 5-year age categories for adults between 15 and 49 years old, while the UNAIDS Spectrum model provided province- and sex-level ART coverage estimates reported by the Zambian Ministry of Health.

Model Calibration

Model calibration was conducted using national- and provincial-level data specific to Zambia, including fertility by age, mortality by age and sex, age distribution by province, HIV prevalence and ART coverage by province and sex. The parallel simultaneous perturbation optimization (PSPO) algorithm was used for this calibration to maximize the likelihood of the model fitting to

historical data. 200 model parameter sets were selected from an overall 2100 simulations using roulette sampling in proportion to likelihood, which resulted in 74 fitted parameters.

Scenario Assumptions

We studied the impact of three scenarios over a ten-year period between 2020 and 2030. Characteristics of the three scenarios are delineated in Table 7-1. Key model parameters are listed in Table 7-2.

Basecase: Standard of Care

In this scenario, we use the calibrated model to project HIV infections, QALYs, and HIV-related deaths and extend it through the ten-year period without any changes to model interventions. Individuals enter the health care system through individual voluntary testing and counseling, symptomatic testing, and antenatal care testing. Upon receipt of a positive HIV test result, probability of initiating ART is based on a sigmoidal curve (Table 7-2).

Scenario #1: Test-and-treat Intervention

This scenario examined the impact of a national test-and-treat program. Individuals receive HIV testing in an identical manner as the basecase scenario described above. However, instead of basing probability of ART initiation on a sigmoidal curve, 100% of individuals who test positive initiate treatment beginning in 2020.

Scenario #2: Test-and-Treat Combined with Couples Voluntary Testing and Counseling

This scenario examines the additional impact of a nationally scaled-up CVCT program within the test-and-treat setting described in Scenario #2. Starting in 2020, individuals who seek testing through one of the three traditional testing modalities (VCT, symptomatic, ANC) are triggered to bring their partner in for testing if they are over the age of 18 and are married or in a long-term relationship. In the event that the individual seeking testing has more than one partner, the partner from the longest duration relationship is summoned for testing. After testing, we assume and set both partners' probability of condom usage at 60% for any future coital acts. Increased condom usage is based on previous study that demonstrated a 47% decrease in HIV incidence among seroconcordant negative partners. This decrease can likely be explained by behavioral changes, such as increased condom usage or decreased partner concurrency.[158] Additionally in this scenario, any individual with a positive HIV test result, regardless of testing modality, is initiated on ART.

Health Outcomes of Interest

We explored effectiveness of each scenario in terms of ten-year cumulative rates of three health outcomes: quality-adjusted life years (QALYs), HIV infections, and HIV-related deaths among the adult Zambian population aged 15-49.

Our model estimated QALYs by applying health utilities based on treatment status and CD4 levels. Health utilities were derived from the Centers for Disease Control and Prevention's Medical Monitoring Project (Table 7-3). [191]

We used to the following formula to calculate cumulative QALYs:

$$QALYS_j = \sum_{t=2020}^{2030} Pop_{HIV-} + (Pop_{ART} * UW_{ART}) + (Pop_{\text{high}} * UW_{high}) + (Pop_{\text{med}} * UW_{med}) + (Pop_{low} * UW_{low}) + (Pop_{\text{vlow}} * UW_{vlow})$$

$$where\ j = S1\ (Scenario\ 1), S2\ (Scenario\ 2), S3\ (Scenario\ 3)$$

$$t = Year$$

$$Pop_{HIV-} = Number\ of\ people\ who\ are\ uninfected$$

$$Pop_{ART} = Number\ of\ people\ on\ ART;\ UW_{ART} = Health\ utiility\ weight\ for\ people\ on\ ART$$

$$Pop_{\text{high}} = Number\ of\ untreated\ PLHIV\ with\ CD4\ count\ \geq 500;\ UW_{high} = Health\ utiliity\ weight\ for\ PLHIV\ with\ CD4\ count\ \geq 500$$

$$Pop_{\text{med}} = Number\ of\ untreated\ PLHIV\ with\ a\ CD4\ count\ \geq 350\ and\ < 500;$$

$$Pop_{\text{low}} = Number\ of\ untreated\ PLHIV\ with\ a\ CD4\ count\ \geq 200\ and\ < 350$$

$$Pop_{\text{vlow}} = Number\ of\ untreated\ PLHIV\ with\ a\ CD4\ count\ < 200$$

For each scenario, we calculated 10-year cumulative QALYs, cumulative HIV infections, and cumulated HIV-related deaths. To compare relative health outcomes across scenarios, we calculated QALYs gained, HIV infections averted (HIA), and HIV-related deaths averted (HDA) between each intervention scenario with the base-case as well as between the two intervention scenarios. A payer's perspective was considered for this analysis with a standard 3% annual discount rate applied when estimating health outcomes over the ten-year time horizon.[192]

Costs

We apply values from previously published studies that estimated unit costs for HIV testing inlcuding CVCT testing as well as annual healthcare costs for treated PLHIV and untreated PLHIV, by CD4 level (Table 5). One study described the costs associated with the 2010-2016 rollout of a five-year implementation of CVCT reaching 207,428 couples in three provinces in Zambia.[158] The majority of costs incurred during the CVCT program included training and support for CVCT counselors in government clinics, CVCT promotions and advocacy, and program coordinators and trainers. Appendix Table 7-1 describes the breakdown of each cost category. This CVCT implementation study calculated an estimated $25 cost per couple tested through CVCT during the maturation phase of the implementation program. For the current paper's main analysis, we applied 73% to the $25/couple estimate, resulting in an estimated $18/couple or $9/each partner who receiving HIV testing through CVCT.

Treatment and HIV care costs were derived from a study of a combined analysis of 12 mathematical models, four of which were calibrated in epidemic settings in Zambia.[193] The average of the four estimated Zambia-specific costs were applied to this current study.[193]

All costs were converted to 2020 USD. A payer's perspective was used, and a standard 3% annual discount rate was applied when estimating costs over the ten-year time horizon.[192]

Cost-Effectiveness

To analyze the cost-effectiveness of each intervention relative to the basecase, we estimated discounted 10-year health outcomes and costs across the adult Zambian population aged 15-49. We calculated the average cost-effectiveness ratio (ACER) of each scenario compared to the base case using the following formula:

$$ACER = \frac{\Delta\ in\ cost\ between\ scenario\ and\ base\ case}{\Delta\ in\ health\ outcome\ between\ scenario\ and\ base\ case}$$

Additionally, we calculated the incremental cost-effectiveness ratio (ICER), directly comparing the health outcomes and costs between test-and-treat and test-and-treat + CVCT scenarios:

$$ICER = \frac{\Delta\ in\ cost\ between\ intervention\ scenarios}{\Delta\ in\ health\ outcome\ between\ intervention\ scenarios}$$

There is no consensus on a standard cost-effectiveness threshold (CET) for Zambia. Historically, the WHO has recommended a CET based on 1-3 times a country's gross domestic product (GDP) per capita, an approach that has been used widely in cost-effectiveness studies.[194] For example, Zambia's 2019 GDP per capita is $1,305; interventions that yield an ICER between $1,305 and $3,915 per QALY gained would be deemed "cost-effective".[61] However, more recent research has argued that GDP-based thresholds are inadequate and limited.[195]

We based our CET on a study that calculated CETs from empirical estimates of opportunity costs from the English National Health Service, estimates of the relationship between country GDP per capita and the value of a statistical life, and a number of core assumptions regarding consumption value of health, the accuracy of healthcare spending in the UK, and the income elasticity of willingness to pay (WTP) for a QALY.[196] From this methodology, we used a CET range of $76 - $878 (2020 USD) per QALY gained in Zambia.

Uncertainty Analysis

We repeated each of the simulations for the base-case and two scenarios 250 times to check the robustness of our results to model parameter uncertainty and stochastic uncertainty. We reported the median value and 95% simulation intervals (95% SI) based on the 250 simulations. SI was defined as the values at the 2.5% percentile (lower bound) and 97.5% percentile (upper bound) across all simulations.

We also conducted one-way sensitivity analyses to understand the influence of certain key parameters on the cost-effectiveness results, including discount rate and CVCT costs.

Results

Cumulative Costs and Health Outcomes

Under the base case scenario, an estimated $2.23 billion is required to maintain the current rates of HIV testing and treatment over the next decade. In comparison, the test and treat program and

national combined test-and-treat + CVCT program cost $2.36 billion and $2.18 billion, respectively.

Both intervention scenarios yielded better health outcomes than the base-case, in terms of total QALYs, HIV infections, and HIV-related deaths. Furthermore, the combined intervention resulted in more desirable outcomes compared to the test-and-treat only scenario: 2.5 million more QALYs, > 82,000 fewer HIV infections, and > 66,000 fewer HIV-related deaths (Table 6).

Cost-Effectiveness Analysis

Compared to the base-case, a national CVCT intervention within a test-and-treat context would cost $134.61 (95% SI: $96.80 - $196.38) per QALY gained, $1,695.35 (95% SI: $941.96 - $2,762.97) per HIV infection averted, and $2,556.98 (95% SI: $1,701.73 – $3,313.33) per HIV-related death averted. A combined intervention would save $35 (95% SI: ($8.31 – $57.11) per QALY gained compared to the base-case, $1280 (95% SI: ($275.85 – $1944.83) per HIV infection averted, and $1,108 (95% SI: $243.20 – $1684.15) per HIV-related death averted (Table 7).

When determining the incremental cost-effectiveness between the two intervention scenarios, the combined test-and-treat + CVCT intervention performs better than the test-and-treat only intervention as it costs less and results in improved health outcomes. Although both interventions could be considered cost-effective compared to the basecase based on the Zambia-specific CET range, the combined test-and-treat + CVCT intervention is overwhelmingly cost-saving.

Sensitivity analyses showed that the cost-savings nature of a combined test-and-treat + CVCT approach persisted despite varying discount rates, increased CVCT costs, and lower treatment costs (Appendix Table 7-2).

Discussion

We compared the HIV-related costs, health outcomes, and cost-effectiveness of two intervention large-scale universal test and treat program scenarios to a standard of care base case among the adult population aged 15-49 in Zambia. We found that while a national program that focused solely on scaling up a test and treat strategy would be cost-effective, a strategy combining test and treat and couples counseling would be cost-saving over a 10-year time period.

Cost-effectiveness analyses of many real-world test-and-treat strategies are still underway; however, our results align with the preliminary cost data that has been published around test-and-treat and CVCT.[125, 158] Our study is the first, from our knowledge, to explore the synergistic impact of a large scale test-and-treat plus CVCT approach, which we have found to be cost-saving in Zambia. Our analyses showed that investments in training and promotion for CVCT within a test-and-treat setting is ultimately returned.

We based our CVCT assumptions on a recent study describing costs and health impacts of a five-year interventional program.[125, 158] This CVCT program was implemented in 73 government clinics in Zambia, and the analyses accounted for costs across all phases of the program, starting from program initiation. In our model, we assumed that the CVCT component of the test-and-

treat + CVCT intervention was in the maturation phase, the phase during which CVCT cost the least. In sensitivity analyses, model findings were robust to raising the cost per couples testing to that the initiation phase, when CVCT cost the most. These initiation costs are important to consider, especially for countries with no prior infrastructure for CVCT, including training of providers and demand creation.

In our model, we see that a test-and-treat strategy that incorporates CVCT on a national level over a ten-year period is able to make considerable gains in total QALYs and in averting HIV infections and HIV-related mortality. In our combined intervention scenario, we see that almost 900,000 additional people were ever tested for HIV by 2030 compared to our test-and-treat only intervention (Appendix 7-4). Our model specifically targeted couples in which one partner was already seeking HIV testing services, which is more realistic than targeting couples in which neither partner was engaged in testing services. Additionally, we made an assumption based on a previous study that people who received counseling as a couple were more likely to increase their condom usage with all partners. This study showed that HIV incidence decreased by 47% among seroconcordant negative couples after CVCT, compared to 63% lower among serodiscordant couples who were not on treatment and 79% lower among serodiscordant couples who were treated.[158] The mechanics of our model are reflected in what is seen in real-world settings. Previous studies have demonstrated that couples, after going through CVCT, increase condom usage and reduce concurrency of outside partners. For example, one study conducted in Rwanda, condom usage among serodiscordant couples increased from 4% to 57% after CVCT.[141]

Another study in Zambia showed that the proportion of cohabitating couples reporting condom use increased from 3% to over 80% one year after CVCT.[197]

Despite these known positive effects of CVCT, uptake of the intervention has remained low in Zambia. A significant difference between Zambia and Rwanda, where CVCT has been incorporated into standard of care for HIV testing services, is in CVCT access. Rwanda's success in CVCT can be attributed to the government's willingness to provide investment in training and overall funding for nationwide implementation.[187] Without upfront investment in adequate and specific training of health care workers and HIV counsellors, access to CVCT will continue to remain low.

Many studies have illustrated the high acceptance of CVCT in a number of settings across different groups, from men who have sex with men (MSM) in South Africa and the United States to individuals within heterosexual partnerships in Ghana and Zambia.[198-201] Previous studies in Zambia surveyed influential network leaders and couples who had previous tested together to understand the gap between willingness and actual uptake and found that promotional activities driven by leaders who have themselves been tested for HIV are more likely to resonate to couples through their personal experience.[202] Strategies such as recruiting leaders and community influencers who have received HIV testing with a partner to promote testing together are key to increasing overall CVCT awareness and uptake.

In our study, the intervention scenarios assume all PLWH who know their status immediately initiate ART, which in many countries, which may not be realistic. For example, a recent study in Zambia showed that among people eligible for ART at the time of enrollment, only 71.9% had initiated treatment within three months.[203] However, previous HIV modeling studies indicated that results were not sensitive to varying time to ART initiation.[152]

In the test-and-treat intervention, we assumed that testing rates did not differ from the basecase. However, universal test-and-treat (UTT) strategies incorporate community-based testing in order increase serostatus knowledge of PLHIV. The HPTN 071 (PopART) trial, which assessed the feasibility of UTT in Zambia and the Western Cape of South Africa, found that although testing coverage increased over time within the study communities, this progress slowed over time.[183] We focused only on facility-based testing, as both immediate ART initiation and CVCT are both strategies that have been incorporated into Zambia's Ministry of Health guidelines. These are both realistic interventions that already have approval from appropriate stakeholders.

Zambia has already put forth extraordinary efforts to achieve the 90-90-90 goals by the target year. However, as funding has plateaued, it will take innovative cost-savings strategies to help the country achieve the next targets, 95-95-95, and to ultimately end the AIDS epidemic.

Table 7-1. Modeling Scenarios

	Name	Description	Testing Types	ART Linkage	Additional Benefits
Scenario 1	Basecase	Standard of care scenario matching the historical scale-up of ART by age and sex and maintaining rates of HIV testing and ART linkage	iVCT Symptomatic testing Antenatal Care testing	Probability of linkage given eligibility based on sigmoidal curve	None
Scenario 2	National Test and Treat Program	Counterfactual scenario in which all individuals who receive a positive HIV diagnosis initiate ART	iVCT Symptomatic testing Antenatal Care testing	Initiate ART immediately after receipt of positive HIV diagnosis	None
Scenario 3	National Test and Treat Program with Couples Voluntary Counseling and Testing (CVCT)	Counterfactual scenario in which 100% of individuals who receive a positive HIV diagnosis initiate ART. Couples who test together engage in safer sex through increased condom use.	iVCT Symptomatic testing Antenatal Care testing CVCT for individuals 18+ yo and in a marital or long-term relationship	Initiate ART immediately after receipt of positive HIV diagnosis	Probability of future condom use per coital act increases to 70%

Table 7-2. Select Base-case Model Parameter Values

Parameter Name	Description	Value	Source
Base Infectivity	The probability of transmission per coital act (no transmission multiplier)	0.00233 (0.00231 - 0.00234)	[153]
Acute Phase Duration (months)	Number of months since infection during which the Acute Stage Infectivity Multiplier is applied to coital acts	2.9	[153]
Acute Stage Infectivity Multiplier	Multiplier acting on the Base Infectivity parameter to determine the per-act transmission probability of an individual during acute stage	26	[153]
Max Probability of ART Linkage	The right asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time	0.891 (0.671 - 1)	[153]
Inflection Point for ART Linkage	The time of the inflection point in the sigmoid trend of probability of ART linkage (given eligibility) over time	2010.7 (2010.4 - 2010.9)	[153]
Min Probability of ART Linkage	The left asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time	0	[153]
ART Linkage – Rate	The slope of the inflection point in the sigmoid trend of probability of ART linkage over time. (A rate of 1 sets the slope to a 25% change in probability per year.)	1	[153]
ART Viral Suppression Multiplier	Multiplier acting on Base Infectivity parameter to determine the per-act transmission probability of an individual on ART. Less-than-perfect (<100%) reduction in risk is attributed to sub-optimal adherence, drug resistance, and delay in viral load suppression from ART initiation.	0.08	[153]
CD4 after post-Acute period	Weibull distribution representing CD4 count after the post-acute stage	Shape – 0.2756 Scale – 560.43	[153]
ART Dropout	Exponentially distributed mean number of days from ART initiation until ART dropout	7300	[153]

AIDS Stage Infectivity Multiplier	Multiplier acting on Base_Infectivity parameter to determine the per-act transmission probability of an HIV+ individual during the AIDS stage.	4.5	[153]
AIDS Phase Duration (months)	Number of months prior to an AIDS-related death during which the AIDS Stage Infectivity Multiplier is applied to coital acts	9	[153]
Days between AIDS Symptom Onset and Death	The time between the onset of AIDS symptoms and death is sampled from a Weibull distribution	Shape – 0.5 Scale – 618.341625	[153]
HIV Adult Survival	Weibull distribution used to determine HIV survival time with untreated HIV infection	Intercept – 21.182 Slope – -0.2717 Shape – 2 Max Age – 50	[153]

Table 7-3. Health Status and Utility Weight Values

Health Status	**Utility Weight**	**Source**
HIV+ on ART	0.947	[204]
HIV+, not on ART, CD4 < 200	0.67	[191]
HIV+, not on ART, CD4 ≥ 200 and <350	0.70	[191]
HIV+, not on ART, CD4 ≥ 200 and <500	0.71	[191]
HIV+, not on ART, CD4 ≥ 500	0.73	[191]

Table 7-4. Cost Data

Parameter	**Value**	**Source**
COSTS	**2020 USD**	
HIV Testing (per individual, per test)	$4.62	[205]
HIV Identification (per individual, per positive test)	$80.17	[205]
Couples Testing (per couple, per visit)	$18	[30]
HIV+ not on ART (CD4 < 200) (annual)	$210.55	[206]
HIV+ not on ART (CD4 >= 200 and <350) (annual)	$158.20	[206]

HIV+ not on ART (CD4 >= 350) (annual)	$144.54	[206]
HIV+ on ART (annual)*	$407.45	[206]
End of Life care	$56.91	[206]

*includes drug and non-drug costs

Table 7-5. Cumulative 10-year (2020-2030) discounted costs and health effects of basecase and two intervention scenarios among Zambian adults aged 15-49

	Total Costs (2020 USD, in millions)	**Total QALYs** (in millions)	**Total HIV infections**	**Total HIV-related deaths**
Basecase	$2,281 ($1,841 - $2,706)	190.5 (183.6 - 196.6)	215,566 (172,451 – 270,308)	121,646 (96,946 – 144,939)
Test and Treat	$2,360 ($1,912.11 - $2,806.81)	191.1 (184.3 - 197.2)	168,309 (138,879 – 209,356)	90,765 (71,774 – 105,997)
Test and Treat + CVCT	$2,180 ($1,758 – $2,605)	193.6 (187.3 - 199.6)	85,665 (68,278 – 105,491)	24,653 (18,273 – 29,991)

Table 7-6. Cost-effectiveness of intervention scenarios

	QALYs		HIV Infections		HIV-related Deaths	
	ACER ($/QALY gained)	**ICER ($/QALY gained)**	**ACER ($/HIA)**	**ICER ($/HIA)**	**ACER ($/Death Averted)**	**ICER ($/Death Averted)**
Test and Treat	$134.61 ($96.80 – 196.38)	--	$1,695.35 ($941.96 - $2,762.97)	--	$2,556.98 ($1,701.73 – $3,313.33)	--
Test and Treat + CVCT	**Dominant** -$35.29 (-$8.31 – -$57.11)	**Dominant** -$77.29 (-$47.07 – -$111.80)	**Dominant** -$1282.18 (-$275.85 – -$1944.83)	**Dominant** -$2,162.25 (-$1,446.69 – -$2,855.86)	**Dominant** -$1,108.95 (-$243.20 – -$1684.15)	**Dominant** -$2828.64 (-$1740.18 – -$4122.41)

Chapter 7 Appendix

Appendix Table 7-1. Breakdown of cost data

Individual HIV Testing and HIV Identification (Mwenge et al.)

- Capital costs (building and storage, equipment, vehicles)
- Recurrent costs (personnel, test kits, supplies, supply chain, operation & maintenance, recurring training, waste management)

Couples Testing (Wall et al.)

- CVCT counsellors in government clinics
- Promotion, advocacy, communications
- Project coordinators and trainers
- Trainings
- Facilities and equipment
- Health commodities

PLHIV not on ART (Eaton et al.)

- Days in outpatient care
- Days in inpatient care

PLHIV on ART (Eaton et al.)

- First- and second-line ART regimens
- Laboratory tests
- Clinic visits

End-of-Life (Eaton et al.)

- Days in inpatient care

Appendix Table 7-2. ICER (cost per QALY gained) Results from Sensitivity Analyses

Parameter	**ICER comparing test-and-treat intervention with test-and-treat + CVCT**
Discount Rate	
1%	-$89.33 (-$54.30 – -$127.15)
5%	-$78.83 (-47.85 – -$118.62)
CVCT costs	
Per couple: $35	-$68.54 (-$39.36 – -$108.29)
Per couple: $75	-$39.76 (-$11.94 – -$78.20)
Annual ART Costs	
$100	-$60.47 (-$50.73 – -$78.58)

Appendix Table 7-3. Fitted Parameters from Calibration

Parameter	Initial Value	Min Value	Max Value
Base Probability of HIV Infectivity	0.00065805	0.000463	0.000732
Circumcision – HIV Transmission Reduction	0.6	0.4	0.9
Age at Sexual Debut for Females:			
Weibull Scale Parameter	18.6061447	17.37209	20
Weibull Heterogeneity Parameter	0.22594081	0.097992	0.340693
Age at Sexual Debut for Males:			
Weibull Scale Parameter	16.5290633	15.21137	18.47653
Weibull Heterogeneity Parameter	0.16722784	0.047004	0.301883
Formation Rate, by Relationship Type:			
Transitory	0.00135027	0.000515	0.002148
Informal	3.27E-04	9.13E-05	0.00075
Marital	1.52E-04	8.35E-05	0.000221
Transmission Multipliers:			
Male to Young Female	2.02712074	1	3.521532
Male to Older Female	1.80702788	1	3
Max Probability of Condom Usage, by Relationship Type:			
Transitory	0.29476793	0.042467	0.497849
Informal	0.44293988	0.263329	0.6
Marital	0.2454659	0.139952	0.3
Max Probability of Condom Usage among Transitory Relationships, by Province:			
Central	0.68401047	0.50331	0.8
Copperbelt	0.42587585	0.197469	0.549003
Eastern	0.50862355	0.212995	0.8
Luapula	0.67562444	0.313664	0.8
Lusaka	0.18005021	0	0.662367
Muchinga	0.4844036	0.662367	0.8
Northern	0.60790849	0.354285	0.8
Northwestern	0.65442846	0.461396	0.8
Southern	0.73084427	0.488058	0.8
Western	0.64063048	0.404196	0.8

Max Probability of Condom Usage among Informal Relationships, by Province:			
Central	0.51102633	0.368304	0.6
Copperbelt	0.22692408	0	0.417629
Eastern	0.17035181	0.018981	0.40348
Luapula	0.53282653	0.406449	0.6
Lusaka	0.53119284	0	0.662367
Muchinga	0.20668922	0.038298	0.8
Northern	0.48763224	0.135008	0.580399
Northwestern	0.65442846	0.461396	0.6
Southern	0.52695616	0.344261	0.6
Western	0.08501451	0	0.311877
Max Probability of Condom Usage among Marital Relationships, by Province:			
Central	0.25420505	0.101208	0.351663
Copperbelt	0.33404161	0.232866	0.413877
Eastern	0.12594297	0.05	0.258156
Luapula	0.23366463	0.068375	0.424839
Lusaka	0.38068591	0.211397	0.5
Muchinga	0.09272307	0.05	0.233418
Northern	0.44898045	0.348732	0.5
Northwestern	0.29144055	0.091521	0.5
Southern	0.37411928	0.25608	0.5
Western	0.27806683	0.107138	0.4805

Appendix Table 7-4. Number of People aged 15-49 in Zambia ever tested for HIV in 2030

Scenario	Number Ever Treated
Test-and-treat	7,342,909
Test-and-treat plus CVCT	8,225,668

8 Public Health Implications and Future Directions

The findings from this dissertation lends itself to a number of public health implications, both in terms of health policy and program implementation. In Aim 1, we used electronic health record data to estimate wait times experienced by PLHIV as they transitioned between HIV care enrollment and subsequently ART initiation. The study spanned an 11-year period, between 2004 and 2015, during which WHO eligibility for ART initiation changed three different times, with increasing CD4 thresholds. We observed that time to ART initiation decreased over time, allowing more PLHIV on treatment. Since the collection of Aim 1 data, WHO has changed its guidance once last time, now recommending that any individual who had tested positive for HIV is immediately eligible for treatment. As countries have begun to incorporate this guidance into their own national guidelines and strategy, the hope would be that PLHIV do not have to wait to begin treatment with early access to ART. However, recent studies have shown that delays in treatment persist despite immediate ART eligibility policies. One study found many reasons for deferring ART over 180 days after diagnosis and eligibility, most commonly that patients were not ready to take ART or that it did not feel urgent to them to start treatment, especially among patients with higher initial CD4 counts.[207] Another study showed that immediate ART initiation was associated with higher LTFU, perhaps because some patients were not ready for their HIV diagnosis and therefore not ready to engage in care.[208] Understanding these delays are even more important now that all PLHIV are eligible to start treatment and there is a risk of not retaining in care. Longitudinal analyses, such as the one conducted in Aim 1, can help identify the

demographic profiles of individuals who find HIV care challenging and can inform programs targeting these specific PLHIV.

In Aim 2, we simulated the adult Zambian population to illustrate what the HIV epidemic may look like in the few decades, under a number of different scenarios. We found that a test-and-treat strategy in which PLHIV engage in the healthcare system and stay on treatment, Zambia could experience a 44% and 89% reduction in HIV incidence, over 10-years and 30-years, respectively. This represents an ideal scenario, in which health-seeking individuals start ART immediately after diagnoses and are retained in care through life. We see that CVCT, an intervention that is targeted specifically at couples, can demonstrate similar reductions in HIV incidence. The benefits of CVCT have been known for many years, and our study provides more evidence that targeted interventions that help increase the overall number of people tested, encourage PLHIV to begin treatment, and stay in care, can impact the epidemic curve in countries, like Zambia, where HIV is most prevalence among heterosexual, cohabitating couples.

In the past few years, Zambia has done an incredible job in meeting, and exceeding, the 90-90-90 targets by 2020.[6] This was achieved due to efforts such as the Lusaka HIV Treatment Surge Project, which increased enrollment of PLHIV onto treatment.[209] However, with the emergence of COVID-19 in 2020, it is possible that the gains made in Zambia in meeting these global targets will be diminished. One modeling study showed that short interruptions in HIV care services could lead to substantial increases in HIV-related mortality in sub-Saharan Africa.[210] The long-term impact of the COVID-19 pandemic on PLHIV in Zambia is still unknown; however, targeted

interventions like CVCT may be one answer to ensure that the fast-track targets can continue to be met.

Additionally, as COVID continues to derail progress made in combating the HIV epidemic, funding for HIV may also be more threatened than before.[211] Funding for HIV was already plateauing prior to COVID-19, so it is even more important for governments to base policy decisions around cost-effective solutions. In Aim 3, we demonstrated that CVCT within a test-and-treat setting on a national scale in Zambia would be cost-savings compared to the current standard of care for HIV testing and care services and a test-and-treat approach. Although this would require an up-front investment in training and advocacy, the country could save over $100 million over ten years through a CVCT program.

This dissertation focuses exclusively on heterosexual individuals, and particularly, heterosexual cohabitating and married partners. Although it has been well-documented that the majority of PLHIV in Zambia fall into this subpopulation, it would be unfair to completely dismiss key populations, such as men who have sex with men, female sex workers, and people who inject drugs.[212] However, HIV-stigma and discrimination against these groups are pervasive, which makes it difficult to study their engagement with HIV care services.[118] Additionally, we chose not to include PrEP as an intervention in our modeling aims. The Zambia MoH incorporated PrEP into their national guidelines in 2016, but the number of people on PrEP continues to be minimal.[177] However, as PrEP becomes more available, it could easily be incorporated as part of CVCT counseling, which would be particularly beneficial for serodiscordant couples.[184]

As policymakers are faced with more restrictive budgets as HIV funding is declining and the number of people with HIV on the rise, we hope that the studies described in this dissertation are valuable for prioritization in HIV services and can help support the decision-making process for allocation purposes by the Ministry of Health in Zambia.[90]

9 References

1. Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. *Lancet*. Jul 19 2014;384(9939):258-71. doi:10.1016/S0140-6736(14)60164-1

2. Fettig J, Swaminathan M, Murrill CS, Kaplan JE. Global epidemiology of HIV. *Infect Dis Clin North Am*. Sep 2014;28(3):323-37. doi:10.1016/j.idc.2014.05.001

3. UNAIDS. Global HIV & AIDS statistics — 2019 fact sheet. https://www.unaids.org/en/resources/fact-sheet

4. Ambrosioni J, Calmy A, Hirschel B. HIV treatment for prevention. *J Int AIDS Soc*. May 25 2011;14:28. doi:10.1186/1758-2652-14-28

5. UNAIDS. *Miles to go: Closing gaps, breaking barriers, righting injustices*. 2018. *Global AIDS Update*. https://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf

6. UNAIDS. AIDSinfo: Trend of new HIV infections. http://aidsinfo.unaids.org

7. Ortblad KF, Lozano R, Murray CJL. The burden of HIV: insights from the Global Burden of Disease Study 2010. *AIDS (London, England)*. 2013;27(13):2003-2017.

8. Ghosn J, Taiwo B, Seedat S, Autran B, Katlama C. Hiv. *Lancet*. Aug 25 2018;392(10148):685-697. doi:10.1016/S0140-6736(18)31311-4

9. Chang CC, Crane M, Zhou J, et al. HIV and co-infections. *Immunol Rev*. Jul 2013;254(1):114-42. doi:10.1111/imr.12063

10. Collaborators GH. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. *Lancet HIV*. Aug 2016;3(8):e361-e387. doi:10.1016/S2352-3018(16)30087-X

11. Farahani M, Mulinder H, Farahani A, Marlink R. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. *Int J STD AIDS*. Jun 2017;28(7):636-650. doi:10.1177/0956462416632428

12. Poudel AN, Newlands D, Simkhada P. The economic burden of HIV/AIDS on individuals and households in Nepal: a quantitative study. *BMC Health Serv Res*. Jan 24 2017;17(1):76. doi:10.1186/s12913-017-1976-y

13. Australia Co. *The Potential Economic Impact of AIDS in Asia and the Pacific*. 2001. *HIV/AIDS and Development in Asia and the Pacific*.

14. UNAIDS. *Report on the global AIDS epidemic*. 2008.

15. Coovadia HM, Hadingham J. HIV/AIDS: global trends, global funds and delivery bottlenecks. *Global Health*. Aug 1 2005;1:13. doi:10.1186/1744-8603-1-13

16. Vermund SH. Global HIV epidemiology: A guide for strategies in prevention and care. *Curr HIV/AIDS Rep*. Jun 2014;11(2):93-8. doi:10.1007/s11904-014-0208-x

17. Organization WH. HIV/AIDS: Key Facts. https://www.who.int/news-room/fact-sheets/detail/hiv-aids

18. Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science*. Feb 22 2013;339(6122):966-71. doi:10.1126/science.1228160

19. Kharsany AB, Karim QA. HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. *Open AIDS J*. 2016;10:34-48. doi:10.2174/1874613601610010034

20. Bank TW. World Bank Open Data: Prevalence of HIV, total. https://data.worldbank.org/indicator/SH.DYN.AIDS.ZS?locations=ZG

21. UNAIDS. Country factsheets: Somalia. 2018

22. Chemaitelly H, Awad SF, Shelton JD, Abu-Raddad LJ. Sources of HIV incidence among stable couples in sub-Saharan Africa. *J Int AIDS Soc*. 2014;17:18765. doi:10.7448/IAS.17.1.18765

23. Sanders EJ, Okuku HS, Smith AD, et al. High HIV-1 incidence, correlates of HIV-1 acquisition, and high viral loads following seroconversion among MSM. *AIDS (London, England)*. 2013;27(3):437-446. doi:10.1097/QAD.0b013e32835b0f81

24. Baral S, Beyrer C, Muessig K, et al. Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis*. Jul 2012;12(7):538-49. doi:10.1016/s1473-3099(12)70066-x

25. Qiao S, Zhang Y, Li X, Menon JA. Facilitators and barriers for HIV-testing in Zambia: A systematic review of multi-level factors. *PLoS One*. 2018;13(2):e0192327. doi:10.1371/journal.pone.0192327

26. Ministry of Health Z. *National HIV/AIDS Strategic Framework 2017-2021*. 2016. https://www.nac.org.zm/sites/default/files/publications/NASF%202017%20-%202021.pdf

27. Ministry of Health Z. *Zambia Population-based HIV Impact Assessment (ZAMPHIA) 2016: Final Report.* 2019. Februrary 2019.

28. Central Statistical Office (CSO) MoHM, and ICF International. *2013-14 ZDHS Key Findings*. 2015. March 2015.

29. Dunkle KL, Stephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *Lancet (London, England)*. Jun 28 2008;371(9631):2183-91. doi:10.1016/s0140-6736(08)60953-8

30. Wall KM, Inambao M, Kilembe W, et al. HIV testing and counselling couples together for affordable HIV prevention in Africa. *International Journal of Epidemiology*. 2018/10/24 2018;48(1):217-227. doi:10.1093/ije/dyy203

31. Eyawo O, de Walque D, Ford N, Gakii G, Lester RT, Mills EJ. HIV status in discordant couples in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Infect Dis*. Nov 2010;10(11):770-7. doi:10.1016/s1473-3099(10)70189-4

32. Okawa S, Chirwa M, Ishikawa N, et al. Longitudinal adherence to antiretroviral drugs for preventing mother-to-child transmission of HIV in Zambia. *BMC pregnancy and childbirth*. 2015;15:258-258. doi:10.1186/s12884-015-0697-7

33. MacCarthy S, Hoffmann M, Ferguson L, et al. The HIV care cascade: models, measures and moving forward. *J Int AIDS Soc*. 2015;18:19395. doi:10.7448/ias.18.1.19395

34. Chung NC, Bolton-Moore C, Chilengi R, Kasaro MP, Stringer JS, Chi BH. Patient engagement in HIV care and treatment in Zambia, 2004-2014. *Trop Med Int Health*. Mar 2017;22(3):332-339. doi:10.1111/tmi.12832

35. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med*. Sep 01 2016;375(9):830-9. doi:10.1056/NEJMoa1600693

36. Rodger AJ, Cambiano V, Bruun T. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy (vol 316, pg 171, 2016). *Jama-Journal of the American Medical Association*. Nov 15 2016;316(19):2048-2048. doi:10.1001/jama.2016.16194

37. Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. *AIDS Res Ther*. 2016;13:35. doi:10.1186/s12981-016-0120-0

38. Ministry of Health Z. *Zambia National Guidelines for HIV Counselling and Testing*. 2006. https://aidsfree.usaid.gov/sites/default/files/hts_policy_zambia.pdf

39. Okeke NL, Ostermann J, Thielman NM. Enhancing linkage and retention in HIV care: a review of interventions for highly resourced and resource-poor settings. *Curr HIV/AIDS Rep*. Dec 2014;11(4):376-92. doi:10.1007/s11904-014-0233-9

40. Zambia P. *Country Operational Plan (COP) 2018 Strategic Direction Summary*. 2018. https://www.pepfar.gov/documents/organization/285848.pdf

41. Nyika H, Mugurungi O, Shambira G, et al. Factors associated with late presentation for HIV/AIDS care in Harare City, Zimbabwe, 2015. *BMC Public Health*. May 3 2016;16:369. doi:10.1186/s12889-016-3044-7

42. Hatcher AM, Turan JM, Leslie HH, et al. Predictors of linkage to care following community-based HIV counseling and testing in rural Kenya. *AIDS Behav*. Jul 2012;16(5):1295-307. doi:10.1007/s10461-011-0065-1

43. Organization WH. *Scaling up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2004. https://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf

44. Organization WH. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*. 2010. https://apps.who.int/iris/bitstream/handle/10665/44379/9789241599764_eng.pdf?sequence=1

45. Organization Wh. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. 2013. https://apps.who.int/iris/bitstream/handle/10665/85321/9789241505727_eng.pdf?sequence=1

46. Organization WH. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach - 2nd Edition*. 2016. https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

47. Lahuerta M, Ue F, Hoffman S, et al. The problem of late ART initiation in Sub-Saharan Africa: a transient aspect of scale-up or a long-term phenomenon? *J Health Care Poor Underserved*. Feb 2013;24(1):359-83. doi:10.1353/hpu.2013.0014

48. Geng EH, Nash D, Kambugu A, et al. Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions. *Curr HIV/AIDS Rep*. Nov 2010;7(4):234-44. doi:10.1007/s11904-010-0061-5

49. Organization WH. *Undetectable = Untransmittable: Public Health and HIV Viral Load Suppression*. 2018. https://www.unaids.org/sites/default/files/media_asset/undetectable-untransmittable_en.pdf

50. UNAIDS. UNAIDS Data 2020. https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf

51. Organization WH. Viral suppression for HIV treatment success and prevention of sexual transmission of HIV. https://www.who.int/hiv/mediacentre/news/viral-supression-hiv-transmission/en/

52. UNAIDS. *90-90-90: An ambitious treatment target to help end the AIDS epidemic*. 2014. https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf

53. UNAIDS. Global AIDS Update 2020: Seizing the Moment. https://www.unaids.org/sites/default/files/media_asset/2020_global-aids-report_en.pdf

54. UNAIDS. Accelerating towards 90–90–90. https://www.unaids.org/en/resources/presscentre/featurestories/2018/july/90-90-90-targets-workshop

55. Dehne KL, Dallabetta G, Wilson D, et al. HIV Prevention 2020: a framework for delivery and a call for action. *Lancet HIV*. Jul 2016;3(7):e323-32. doi:10.1016/s2352-3018(16)30035-2

56. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *Jama*. Oct 7 1998;280(13):1161-7. doi:10.1001/jama.280.13.1161

57. Metsch LR, Feaster DJ, Gooden L, et al. Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: the AWARE randomized clinical trial. *Jama*. Oct 23 2013;310(16):1701-10. doi:10.1001/jama.2013.280034

58. Farnham PG, Hutchinson AB, Sansom SL, Branson BM. Comparing the costs of HIV screening strategies and technologies in health-care settings. *Public Health Rep*. Nov-Dec 2008;123 Suppl 3:51-62. doi:10.1177/00333549081230s307

59. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev*. 2002;(1):Cd003255. doi:10.1002/14651858.Cd003255

60. Stover J, Rosen JE, Carvalho MN, et al. The case for investing in the male condom. *PLoS One*. 2017;12(5):e0177108. doi:10.1371/journal.pone.0177108

61. The World Bank. World Bank Open Data. Accessed December 12, 2016, 2016. http://data.worldbank.org/indicator/SH.DYN.AIDS.ZS

62. World Health Organization U. *A Framework for Voluntary Medical Male Circumcision*. 2016. https://apps.who.int/iris/bitstream/handle/10665/246234/WHO-HIV-2016.17-eng.pdf?sequence=1

63. World Health Organization DoHA. Voluntary Medical Male Cirumcision for HIV Prevention in 14 Priority Countries in Eastern and Southern Africa. https://apps.who.int/iris/bitstream/handle/10665/258691/WHO-HIV-2017.36-eng.pdf?sequence=1

64. Organization WH. *Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update*. 2012.

https://apps.who.int/iris/bitstream/handle/10665/70904/WHO_HIV_2012.12_eng.pdf?sequence=1

65. Kahn JG, Bollinger LA, Stover J, Marseille E. Improving the Efficiency of the HIV/AIDS Policy Response: A Guide to Resource Allocation Modeling. In: rd, Holmes KK, Bertozzi S, Bloom BR, Jha P, eds. *Major Infectious Diseases*. The International Bank for Reconstruction and Development / The World Bank
(c) 2017 International Bank for Reconstruction and Development / The World Bank.; 2017.

66. Forhan SE, Modi S, Houston JC, Broyles LN. Moving toward test and start: learning from the experience of universal antiretroviral therapy programs for HIV-infected pregnant/ breastfeeding women. *Aids*. Jun 19 2017;31(10):1489-1493. doi:10.1097/qad.0000000000001498

67. Phanuphak N, Seekaew P, Phanuphak P. Optimising treatment in the test-and-treat strategy: what are we waiting for? *The Lancet HIV*. 2019-10-01 2019;6(10):e715-e722. doi:10.1016/s2352-3018(19)30236-x

68. Hurst SA, Appelgren KE, Kourtis AP. Prevention of mother-to-child transmission of HIV type 1: the role of neonatal and infant prophylaxis. *Expert Rev Anti Infect Ther*. Feb 2015;13(2):169-81. doi:10.1586/14787210.2015.999667

69. Organization WH. *Prevention of Mother to Child Transmission of HIV (PMTCT) and Paediatric HIV Care Guidelines.* 2008. http://apps.who.int/medicinedocs/en/m/abstract/Js19270en/

70. Hamilton E, Bossiky B, Ditekemena J, et al. Using the PMTCT Cascade to Accelerate Achievement of the Global Plan Goals. *J Acquir Immune Defic Syndr*. May 1 2017;75 Suppl 1:S27-s35. doi:10.1097/qai.0000000000001325

71. Karnon J, Orji N. Option B+ for the prevention of mother-to-child transmission of HIV infection in developing countries: a review of published cost-effectiveness analyses. *Health Policy Plan*. Oct 2016;31(8):1133-41. doi:10.1093/heapol/czw025

72. Assembly UNG. *On the fast track to ending the AIDS epidemic*. 2016. http://sgreport.unaids.org/pdf/20160423_SGreport_HLM_en.pdf

73. Organization WH. *Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: recommendations for a public health approach.* 2012.

74. Inambao M, Kilembe W, Canary LA, et al. Transitioning couple's voluntary HIV counseling and testing (CVCT) from stand-alone weekend services into routine antenatal and VCT services in government clinics in Zambia's two largest cities. *PLoS One*. 2017;12(10):e0185142. doi:10.1371/journal.pone.0185142

75. Wall K, Allen S. Incentives to improve couples' HIV testing uptake and cost-effectiveness. *Lancet Glob Health*. Sep 2017;5(9):e847-e848. doi:10.1016/S2214-109X(17)30309-1

76. *Prevailing Against Pandemics by Putting People at the Centre*. 2020.

77. *Global AIDS Update 2019: Communities at the Centre*. 2019.

78. *Fast-Track Update on Investments Needed in the AIDS Response*. 2016.

79. Service CR. *Global Trends in HIV/AIDS*. 2018. https://fas.org/sgp/crs/row/IF11018.pdf

80. Foundation KF. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR). https://www.kff.org/global-health-policy/fact-sheet/the-u-s-presidents-emergency-plan-for/

81. Jen Kates AW. *Donor Government Funding for HIV in Low- and Middle-Income Countries in 2017*. 2018. http://files.kff.org/attachment/Report-Donor-Government-Funding-for-HIV-in-Low-and-Middle-Income-Countries-in-2017

82. PEPFAR. PEPFAR Panorama Spotlight. https://data.pepfar.gov/financial

83. Forsythe S, Stover J, Bollinger L. The past, present and future of HIV, AIDS and resource allocation. *BMC Public Health*. Nov 18 2009;9 Suppl 1:S4. doi:10.1186/1471-2458-9-S1-S4

84. *Goals Manual: A Model for Estimating the Effects of Interventions and Resource Allocation on HIV Infections and Deaths*. 2011. August 2011. https://www.avenirhealth.org/Download/Spectrum/Manuals/Goals_Manual_August_2011.pdf

85. Consortium THM. *Allocative Efficiency Tools & Methods to Support Country HIV Programme Budget Allocation*. 2015. http://www.hivmodelling.org/sites/default/files/publications/WP%2020_Allocative%20Efficiency%20Tools%20Wshop%20Meeting%20Report_Uploaded.pdf

86. Korenromp EL, Gobet B, Fazito E, Lara J, Bollinger L, Stover J. Impact and Cost of the HIV/AIDS National Strategic Plan for Mozambique, 2015-2019--Projections with the Spectrum/Goals Model. *PLoS One*. 2015;10(11):e0142908. doi:10.1371/journal.pone.0142908

87. Kerr CC, Stuart RM, Gray RT, et al. Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization. *J Acquir Immune Defic Syndr*. Jul 1 2015;69(3):365-76. doi:10.1097/qai.0000000000000605

88. Cassels S, Clark SJ, Morris M. Mathematical models for HIV transmission dynamics: tools for social and behavioral science research. *J Acquir Immune Defic Syndr*. Mar 1 2008;47 Suppl 1:S34-9. doi:10.1097/QAI.0b013e3181605da3

89. Lasry A, Richter A, Lutscher F. Recommendations for increasing the use of HIV/AIDS resource allocation models. *BMC Public Health*. Nov 18 2009;9 Suppl 1:S8. doi:10.1186/1471-2458-9-S1-S8

90. Jacobsen MM, Walensky RP. Modeling and Cost-Effectiveness in HIV Prevention. *Curr HIV/AIDS Rep*. Feb 2016;13(1):64-75. doi:10.1007/s11904-016-0303-2

91. Keeling MJ, Danon L. Mathematical modelling of infectious diseases. *Br Med Bull*. 2009;92:33-42. doi:10.1093/bmb/ldp038

92. Blackwood JC, Childs LM. An introduction to compartmental modeling for the budding infectious disease modeler. *Letters in Biomathematics*. 2018/12/14 2018;5(1):195-221. doi:10.1080/23737867.2018.1509026

93. Brauer F, Van den Driessche P, Wu J, Allen LJS. *Mathematical epidemiology*. Mathematical biosciences subseries. Springer; 2008:xviii, 408

94. Gallagher S. Comparing compartment and agent-based models. 2017

95. Chhatwal J, He T. Economic evaluations with agent-based modelling: an introduction. *Pharmacoeconomics*. May 2015;33(5):423-33. doi:10.1007/s40273-015-0254-2

96. Tracy M, Cerda M, Keyes KM. Agent-Based Modeling in Public Health: Current Applications and Future Directions. *Annu Rev Public Health*. Apr 1 2018;39:77-94. doi:10.1146/annurev-publhealth-040617-014317

97. Kowalska JD, Wojcik G, Rutkowski J, Ankiersztejn-Bartczak M, Siewaszewicz E. Modelling the cost-effectiveness of HIV care shows a clear benefit when transmission risk is considered in the calculations - A message for Central and Eastern Europe. *PLoS One*. 2017;12(11):e0186131. doi:10.1371/journal.pone.0186131

98. Vandewalle B, Llibre JM, Parienti JJ, et al. EPICE-HIV: An Epidemiologic Cost-Effectiveness Model for HIV Treatment. *PLoS One*. 2016;11(2):e0149007. doi:10.1371/journal.pone.0149007

99. Powers KA, Samoff E, Weaver MA, et al. Longitudinal HIV Care Trajectories in North Carolina. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2017-02-01 2017;74(2):S88-S95. doi:10.1097/qai.0000000000001234

100. Powers KA, Miller WC. Critical Review: Building on the HIV Cascade: A Complementary "HIV States and Transitions" Framework for Describing HIV Diagnosis, Care, and Treatment at the Population Level. *J Acquir Immune Defic Syndr*. Jul 1 2015;69(3):341-7. doi:10.1097/QAI.0000000000000611

101. Hogg RS. Understanding the HIV care continuum. *Lancet HIV*. Jun 2018;5(6):e269-e270. doi:10.1016/S2352-3018(18)30102-4

102. Haber N, Tanser F, Bor J, et al. From HIV infection to therapeutic response: a population-based longitudinal HIV cascade-of-care study in KwaZulu-Natal, South Africa. *Lancet HIV*. May 2017;4(5):e223-e230. doi:10.1016/s2352-3018(16)30224-7

103. Haber N, Pillay D, Porter K, Barnighausen T. Constructing the cascade of HIV care: methods for measurement. *Curr Opin HIV AIDS*. Jan 2016;11(1):102-8. doi:10.1097/COH.0000000000000212

104. Januraga PP, Reekie J, Mulyani T, et al. The cascade of HIV care among key populations in Indonesia: a prospective cohort study. *Lancet HIV*. Oct 2018;5(10):e560-e568. doi:10.1016/S2352-3018(18)30148-6

105. Jose S, Delpech V, Howarth A, et al. A continuum of HIV care describing mortality and loss to follow-up: a longitudinal cohort study. *Lancet HIV*. Jun 2018;5(6):e301-e308. doi:10.1016/s2352-3018(18)30048-1

106. Colombe S, Machemba R, Mtenga B, et al. Cascade of care for HIV-seroconverters in rural Tanzania: a longitudinal study. *AIDS Care*. Jul 10 2019:1-6. doi:10.1080/09540121.2019.1640842

107. Olney JJ, Braitstein P, Eaton JW, et al. Evaluating strategies to improve HIV care outcomes in Kenya: a modelling study. *Lancet HIV*. Dec 2016;3(12):e592-e600. doi:10.1016/S2352-3018(16)30120-5

108. Lee H, Hogan JW, Genberg BL, et al. A state transition framework for patient-level modeling of engagement and retention in HIV care using longitudinal cohort data. *Stat Med*. Jan 30 2018;37(2):302-319. doi:10.1002/sim.7502

109. Sikazwe I, Eshun-Wilson I, Sikombe K, et al. Retention and viral suppression in a cohort of HIV patients on antiretroviral therapy in Zambia: Regionally representative estimates using a multistage-sampling-based approach. *PLoS Med*. May 2019;16(5):e1002811. doi:10.1371/journal.pmed.1002811

110. Holmes CB, Sikazwe I, Sikombe K, et al. Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. *PLoS Med*. Jan 2018;15(1):e1002489. doi:10.1371/journal.pmed.1002489

111. Haber NA, Lesko CR, Fox MP, et al. Limitations of the UNAIDS 90-90-90 metrics: a simulation-based comparison of cross-sectional and longitudinal metrics for the HIV care continuum. *AIDS*. 06 2020;34(7):1047-1055. doi:10.1097/QAD.0000000000002502

112. UNAIDS. Fact Sheet - Global AIDS Update 2020. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

113. Teeraananchai S, Kerr S, Amin J, Ruxrungtham K, Law M. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. *HIV Medicine*. 2017-04-01 2017;18(4):256-266. doi:10.1111/hiv.12421

114. Lima VD, St-Jean M, Rozada I, et al. Progress towards the United Nations 90-90-90 and 95-95-95 targets: the experience in British Columbia, Canada. *Journal of the International AIDS Society*. 2017-11-01 2017;20(3):e25011. doi:10.1002/jia2.25011

115. Jones J, Sullivan PS, Curran JW. Progress in the HIV epidemic: Identifying goals and measuring success. *PLos Med*. 2019-01-18 2019;16(1):e1002729. doi:10.1371/journal.pmed.1002729

116. Marsh K, Eaton JW, Mahy M, et al. Global, regional and country-level 90–90–90 estimates for 2018. *AIDS*. 2019-12-01 2019;33:S213-S226. doi:10.1097/qad.0000000000002355

117. Ahmed S, Schwarz M, Flick RJ, et al. Lost opportunities to identify and treat HIV-positive patients: results from a baseline assessment of provider-initiated HIV testing and

counselling (PITC) in Malawi. *Trop Med Int Health*. 2016-04-01 2016;21(4):479-485. doi:10.1111/tmi.12671

118. Qiao S, Zhang Y, Li X, Menon JA. Facilitators and barriers for HIV-testing in Zambia: A systematic review of multi-level factors. *PloS one*. 2018;13(2):e0192327-e0192327. doi:10.1371/journal.pone.0192327

119. Johnson LF, Rehle TM, Jooste S, Bekker LG. Rates of HIV testing and diagnosis in South Africa: successes and challenges. *Aids*. Jul 17 2015;29(11):1401-9. doi:10.1097/qad.0000000000000721

120. Eaton JW, Terris-Prestholt F, Cambiano V, et al. Optimizing HIV testing services in sub-Saharan Africa: cost and performance of verification testing with HIV self-tests and tests for triage. *Journal of the International AIDS Society*. 2019;22(S1):e25237. doi:10.1002/jia2.25237

121. Silvestri DM, Modjarrad K, Blevins ML, Halale E, Vermund SH, McKinzie JP. A Comparison of HIV Detection Rates Using Routine Opt-out Provider-Initiated HIV Testing and Counseling Versus a Standard of Care Approach in a Rural African Setting. Article; Proceedings Paper. *Jaids*. Jan 2011;56(1):E9-E16. doi:10.1097/QAI.0b013e3181fdb629

122. Marwa R, Anaeli A. Perceived Barriers Toward Provider-Initiated HIV Testing and Counseling (PITC) in Pediatric Clinics: A Qualitative Study Involving Two Regional Hospitals in Dar-Es-Salaam, Tanzania . *HIV/AIDS - Research and Palliative Care*. 2020-03-01 2020;Volume 12:141-150. doi:10.2147/hiv.s235818

123. Herce ME, Chi BH, Liao RC, Hoffmann CJ. Re-thinking Linkage to Care in the Era of Universal Test and Treat: Insights from Implementation and Behavioral Science for Achieving the Second 90. *AIDS and behavior*. 2019-09-01 2019;23(S2):120-128. doi:10.1007/s10461-019-02541-5

124. Onoya D, Sineke T, Hendrickson C, et al. Impact of the test and treat policy on delays in antiretroviral therapy initiation among adult HIV positive patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study. *BMJ Open*. 2020-03-01 2020;10(3):e030228. doi:10.1136/bmjopen-2019-030228

125. Havlir D, Lockman S, Ayles H, et al. What do the Universal Test and Treat trials tell us about the path to HIV epidemic control? *Journal of the International AIDS Society*. 2020-02-01 2020;23(2)doi:10.1002/jia2.25455

126. Chihana ML, Huerga H, Van Cutsem G, et al. Impact of "test and treat" recommendations on eligibility for antiretroviral treatment: Cross sectional population survey data from three high HIV prevalence countries. *PLOS ONE*. 2018-11-26 2018;13(11):e0207656. doi:10.1371/journal.pone.0207656

127. Kerschberger B, Schomaker M, Jobanputra K, et al. HIV programmatic outcomes following implementation of the 'Treat-All' policy in a public sector setting in Eswatini: a prospective cohort study. *Journal of the International AIDS Society*. 2020-03-01 2020;23(3)doi:10.1002/jia2.25458

128. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *The Lancet*. 2019-06-01 2019;393(10189):2428-2438. doi:10.1016/s0140-6736(19)30418-0

129. Bavinton BR, Pinto AN, Phanuphak N, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. *The Lancet HIV*. 2018-08-01 2018;5(8):e438-e447. doi:10.1016/s2352-3018(18)30132-2

130. Baral S, Rao A, Sullivan P, et al. The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment. *The Lancet HIV*. 2019-09-01 2019;6(9):e632-e638. doi:10.1016/s2352-3018(19)30226-7

131. Nachega JB, Adetokunboh O, Uthman OA, et al. Community-Based Interventions to Improve and Sustain Antiretroviral Therapy Adherence, Retention in HIV Care and Clinical Outcomes in Low- and Middle-Income Countries for Achieving the UNAIDS 90-90-90 Targets. *Current HIV/AIDS reports*. 2016-10-01 2016;13(5):241-255. doi:10.1007/s11904-016-0325-9

132. Pascoe SJ, Fox MP, Huber AN, et al. Differentiated HIV care in South Africa: the effect of fast-track treatment initiation counselling on ART initiation and viral suppression as partial results of an impact evaluation on the impact of a package of services to improve HIV treatment adherence. *Journal of the International AIDS Society*. 2019-11-01 2019;22(11)doi:10.1002/jia2.25409

133. Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90–90–90 targets to end the AIDS epidemic by 2020 are not realistic: comment on "Can the UNAIDS 90–90–90 target be achieved? A systematic analysis of national HIV treatment cascades". *BMJ Global Health*. 2017-03-01 2017;2(2):e000227. doi:10.1136/bmjgh-2016-000227

134. Ndashimye E, Arts EJ. The urgent need for more potent antiretroviral therapy in low-income countries to achieve UNAIDS 90-90-90 and complete eradication of AIDS by 2030. *Infectious diseases of poverty*. 2019-12-01 2019;8(1)doi:10.1186/s40249-019-0573-1

135. Abuelezam NN, Mccormick AW, Surface ED, et al. Modelling the epidemiologic impact of achieving UNAIDS fast-track 90-90-90 and 95-95-95 targets in South Africa. *Epidemiology and Infection*. 2019-01-01 2019;147doi:10.1017/s0950268818003497

136. Nabukenya AM, Nambuusi A, Matovu JKB. Risk factors for HIV infection among married couples in Rakai, Uganda: a cross-sectional study. *BMC Infectious Diseases*. 2020-12-01 2020;20(1)doi:10.1186/s12879-020-4924-0

137. Kim HY, Harling G, Vandormael A, et al. HIV seroconcordance among heterosexual couples in rural KwaZulu-Natal, South Africa: a population-based analysis. *Journal of the International AIDS Society*. 2020-01-01 2020;23(1)doi:10.1002/jia2.25432

138. Joseph Davey DL, Wall KM, Kilembe W, et al. HIV Incidence and Predictors of HIV Acquisition From an Outside Partner in Serodiscordant Couples in Lusaka, Zambia. *Journal of acquired immune deficiency syndromes (1999)*. 2017;76(2):123-131. doi:10.1097/QAI.0000000000001494

139. Kaiser R, Bunnell R, Hightower A, et al. Factors Associated with HIV Infection in Married or Cohabitating Couples in Kenya: Results from a Nationally Representative Study. *PLoS ONE*. 2011-03-15 2011;6(3):e17842. doi:10.1371/journal.pone.0017842

140. Hailemariam TG, Nathan S, Seifu CN, Rawstorne P. Uptake of couples HIV testing and counselling among heterosexual couples in Sub-Saharan Africa: a systematic review and meta-analysis. *AIDS Care*. 2020-02-01 2020;32(2):137-147. doi:10.1080/09540121.2019.1619667

141. Allen S, Tice J, Van de Perre P, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. *Bmj*. Jun 20 1992;304(6842):1605-9. doi:10.1136/bmj.304.6842.1605

142. Group TVH-CaTES. Efficacy of voluntary HIV-1 counselling and testing in individuals and couples in Kenya, Tanzania, and Trinidad: a randomised trial. *The Lancet*. 2000-07-01 2000;356(9224):103-112. doi:10.1016/s0140-6736(00)02446-6

143. Farquhar C, Kiarie JN, Richardson BA, et al. Antenatal Couple Counseling Increases Uptake of Interventions to Prevent HIV-1 Transmission. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2004-12-01 2004;37(5):1620-1626. doi:10.1097/00126334-200412150-00016

144. Wall KM, Kilembe W, Nizam A, et al. Promotion of couples' voluntary HIV counselling and testing in Lusaka, Zambia by influence network leaders and agents. *BMJ Open*. 2012-01-01 2012;2(5):e001171. doi:10.1136/bmjopen-2012-001171

145. Bershteyn A, Mutai KK, Akullian AN, Klein DJ, Jewell BL, Mwalili SM. The influence of mobility among high-risk populations on HIV transmission in Western Kenya. *Infect Dis Model*. 2018;3:97-106. doi:10.1016/j.idm.2018.04.001

146. Bershteyn A, Gerardin J, Bridenbecker D, et al. Implementation and applications of EMOD, an individual-based multi-disease modeling platform. *Pathog Dis*. Jul 1 2018;76(5)doi:10.1093/femspd/fty059

147. Bershteyn A, Klein DJ, Eckhoff PA. Age-targeted HIV treatment and primary prevention as a 'ring fence' to efficiently interrupt the age patterns of transmission in generalized epidemic settings in South Africa. *Int Health*. Jul 2016;8(4):277-85. doi:10.1093/inthealth/ihw010

148. Bershteyn A, Klein DJ, Eckhoff PA. Age-dependent partnering and the HIV transmission chain: a microsimulation analysis. *Journal of the Royal Society, Interface*. Nov 6 2013;10(88):20130613. doi:10.1098/rsif.2013.0613

149. Bershteyn A, Klein DJ, Wenger E, Eckhoff PA. Description of the EMOD-HIV Model v0.7. *arXiv e-prints*. 2012. Accessed June 01, 2012. https://ui.adsabs.harvard.edu/abs/2012arXiv1206.3720B

150. Klein DJ, Eckhoff PA, Bershteyn A. Targeting HIV services to male migrant workers in southern Africa would not reverse generalized HIV epidemics in their home communities: a mathematical modeling analysis. *Int Health*. Mar 2015;7(2):107-13. doi:10.1093/inthealth/ihv011

151. Klein DJ, Bershteyn A, Eckhoff PA. Dropout and re-enrollment: implications for epidemiological projections of treatment programs. *Aids*. Jan 2014;28 Suppl 1:S47-59. doi:10.1097/qad.0000000000000081

152. Akullian A, Morrison M, Garnett GP, et al. The effect of 90-90-90 on HIV-1 incidence and mortality in eSwatini: a mathematical modelling study. *Lancet HIV*. May 2020;7(5):e348-e358. doi:10.1016/S2352-3018(19)30436-9

153. Intellectual Ventures Management LI. Welcome to EMOD HIV modeling. http://www.idmod.org/docs/hiv/index.html#

154. Klein DJ. Relationship formation and flow control algorithms for generating age-structured networks in HIV modeling. IEEE;

155. De Oliveira T, Kharsany ABM, Gräf T, et al. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. *The Lancet HIV*. 2017-01-01 2017;4(1):e41-e50. doi:10.1016/s2352-3018(16)30186-2

156. Prodger JL, Kaul R. The biology of how circumcision reduces HIV susceptibility: broader implications for the prevention field. *AIDS research and therapy*. 2017-12-01 2017;14(1)doi:10.1186/s12981-017-0167-6

157. Bui DD, Do NT, Pham LT, et al. Couples HIV testing and immediate antiretroviral therapy for serodiscordant HIV-positive partners: Translating evidence into programme in

Vietnam. *International Journal of STD & AIDS*. 2019-07-01 2019;30(8):739-747. doi:10.1177/0956462418825405

158. Wall KM, Inambao M, Kilembe W, et al. HIV testing and counselling couples together for affordable HIV prevention in Africa. *International Journal of Epidemiology*. 2019-02-01 2019;48(1):217-227. doi:10.1093/ije/dyy203

159. Alaeddini A, Klein DJ. Parallel Simultaneous Perturbation Optimization. *arXiv e-prints*. 2017. Accessed April 01, 2017. https://ui.adsabs.harvard.edu/abs/2017arXiv170400223A

160. Alaeddini A, Klein DJ. Application of a Second-order Stochastic Optimization Algorithm for Fitting Stochastic Epidemiological Models. *arXiv e-prints*. 2017. Accessed August 01, 2017. https://ui.adsabs.harvard.edu/abs/2017arXiv170800886A

161. Central Statistical Office/Zambia, Ministry of Health/Zambia, University of Zambia Teaching Hospital Virology Laboratory, University of Zambia Department of Population Studies, Tropical Diseases Research Centre/Zambia, ICF International. *Zambia Demographic and Health Survey 2013-14*. 2015. http://dhsprogram.com/pubs/pdf/FR304/FR304.pdf

162. Central Statistical Office/Zambia, Ministry of Health/Zambia, Tropical Disease Research Centre/Zambia, University of Zambia. *Zambia Demographic and Health Survey 2007*. 2009. http://dhsprogram.com/pubs/pdf/FR211/FR211.pdf

163. Central Statistical Office/Zambia, Central Board of Health/Zambia, ORC Macro. *Zambia Demographic and Health Survey 2001-2002*. 2003. http://dhsprogram.com/pubs/pdf/FR136/FR136.pdf

164. Spectrum. Avenir Health. https://avenirhealth.org/software-spectrum.php

165. Frank TD, Carter A, Jahagirdar D, et al. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2017, and forecasts to 2030, for 195 countries and territories: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. *The Lancet HIV*. 2019-12-01 2019;6(12):e831-e859. doi:10.1016/s2352-3018(19)30196-1

166. Topp SM, Chetty-Makkan CM, Smith HJ, et al. "It's Not Like Taking Chocolates": Factors Influencing the Feasibility and Sustainability of Universal Test and Treat in Correctional Health Systems in Zambia and South Africa. *Global Health: Science and Practice*. 2019;7(2):189-202. doi:10.9745/ghsp-d-19-00051

167. Munthali T, Michelo C, Mee P, et al. Impact of WHO guidelines on trends in HIV testing and ART initiation among children living with HIV in Zambia. *AIDS research and therapy*. 2020-12-01 2020;17(1)doi:10.1186/s12981-020-00277-0

168. Seeley J, Bond V, Yang B, et al. Understanding the Time Needed to Link to Care and Start ART in Seven HPTN 071 (PopART) Study Communities in Zambia and South Africa. *AIDS and Behavior*. 2019-04-01 2019;23(4):929-946. doi:10.1007/s10461-018-2335-7

169. Hirasen K, Fox MP, Hendrickson CJ, Sineke T, Onoya D. HIV Treatment Outcomes Among Patients Initiated on Antiretroviral Therapy Pre and Post-Universal Test and Treat Guidelines in South Africa . *Therapeutics and Clinical Risk Management*. 2020-03-01 2020;Volume 16:169-180. doi:10.2147/tcrm.s227290

170. Kabogo J, Muniu E, Wamunyokoli F, Musoke R, Songok E. Evidence of reduced treatment adherence among HIV infected paediatric and adolescent populations in Nairobi at the onset of the UNAIDS Universal Test and Treat Program. *BMC research notes*. 2018-12-01 2018;11(1)doi:10.1186/s13104-018-3205-0

171. Redd AD, Mukonda E, Hu N-C, et al. ART Adherence, Resistance, and Long-term HIV Viral Suppression in Postpartum Women. *Open Forum Infectious Diseases*. 2020-10-01 2020;7(10)doi:10.1093/ofid/ofaa346

172. Ortblad KF, Baeten JM, Cherutich P, Wamicwe JN, Wasserheit JN. The arc of HIV epidemics in sub-Saharan Africa: new challenges with concentrating epidemics in the era of 90-90-90. *Current opinion in HIV and AIDS*. Sep 2019;14(5):354-365. doi:10.1097/coh.0000000000000569

173. Bunda BA, Bassett IV. Reaching the second 90: the strategies for linkage to care and antiretroviral therapy initiation. *Current opinion in HIV and AIDS*. 2019;14(6):494-502. doi:10.1097/COH.0000000000000579

174. Chomba E, Allen S, Kanweka W, et al. Evolution of couples' voluntary counseling and testing for HIV in Lusaka, Zambia. *J Acquir Immune Defic Syndr*. Jan 1 2008;47(1):108-15. doi:10.1097/QAI.0b013e31815b2d67

175. Boyer S, Iwuji C, Gosset A, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. *AIDS Care*. 2016-06-02 2016;28(sup3):39-51. doi:10.1080/09540121.2016.1164808

176. Hendrickson C, Long L, van de Vijver D, et al. Novel metric for evaluating pre-exposure prophylaxis programme effectiveness in real-world settings. *The lancet HIV*. Apr 2020;7(4):e294-e300. doi:10.1016/s2352-3018(19)30344-3

177. Zimba C, Maman S, Rosenberg NE, et al. The landscape for HIV pre-exposure prophylaxis during pregnancy and breastfeeding in Malawi and Zambia: A qualitative study. *PLOS ONE*. 2019-10-04 2019;14(10):e0223487. doi:10.1371/journal.pone.0223487

178. Sarkar S, Corso P, Ebrahim-Zadeh S, Kim P, Charania S, Wall K. Cost-effectiveness of HIV Prevention Interventions in Sub-Saharan Africa: A Systematic Review. *EClinicalMedicine*. Apr 2019;10:10-31. doi:10.1016/j.eclinm.2019.04.006

179. Munthali T, Musonda P, Mee P, et al. Underutilisation of routinely collected data in the HIV programme in Zambia: a review of quantitatively analysed peer-reviewed articles. *Health research policy and systems*. 2017;15(1)doi:10.1186/s12961-017-0221-9

180. Nosyk B, Zang X, Krebs E, et al. Ending the HIV epidemic in the USA: an economic modelling study in six cities. *The Lancet HIV*. 2020-07-01 2020;7(7):e491-e503. doi:10.1016/s2352-3018(20)30033-3

181. Jen Kates AW. *Donor Government Funding for HIV in Low- and Middle-Income Countries in 2019*. 2020. http://files.kff.org/attachment/Donor-Government-Funding-for-HIV-in-Low-and-Middle-Income-Countries-in-2019.pdf

182. UNAIDS. UNAIDS Executive Director puts the spotlight on the HIV response in Lesotho, South Africa and Zambia during five-day visit. 2018.

183. Floyd S, Ayles H, Schaap A, et al. Towards 90-90: Findings after two years of the HPTN 071 (PopART) cluster-randomized trial of a universal testing-and-treatment intervention in Zambia. *PloS one*. 2018;13(8):e0197904. doi:10.1371/journal.pone.0197904

184. Wall KM, Inambao M, Kilembe W, et al. Cost-effectiveness of couples' voluntary HIV counselling and testing in six African countries: a modelling study guided by an HIV prevention cascade framework. *Journal of the International AIDS Society*. 2020-06-01 2020;23(S3)doi:10.1002/jia2.25522

185. Wall KM, Kilembe W, Inambao M, et al. Cost-effectiveness of integrated HIV prevention and family planning services for Zambian couples. *AIDS*. 09 2020;34(11):1633-1642. doi:10.1097/QAD.0000000000002584

186. *Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: recommendations for a public health approach.* 2012. https://apps.who.int/iris/handle/10665/44646

187. Karita E, Nsanzimana S, Ndagije F, et al. Implementation and Operational Research: Evolution of Couples' Voluntary Counseling and Testing for HIV in Rwanda: From Research to Public Health Practice. *Journal of acquired immune deficiency syndromes (1999)*. Nov 1 2016;73(3):e51-e58. doi:10.1097/qai.0000000000001138

188. Pitman R, Fisman D, Zaric GS, et al. Dynamic Transmission Modeling. *Medical Decision Making*. 2012-09-01 2012;32(5):712-721. doi:10.1177/0272989x12454578

189. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling Good Research Practices—Overview. *Medical Decision Making*. 2012-09-01 2012;32(5):667-677. doi:10.1177/0272989x12454577

190. Bershteyn A, Klein DJ, Eckhoff PA. Age-targeted HIV treatment and primary prevention as a 'ring fence' to efficiently interrupt the age patterns of transmission in generalized epidemic settings in South Africa. *International Health*. 2016;doi:10.1093/inthealth/ihw010

191. Whitham HK, Hutchinson AB, Shrestha RK, et al. Health Utility Estimates and Their Application to HIV Prevention in the United States: Implications for Cost-Effectiveness Modeling and Future Research Needs. *MDM Policy & Practice*. 2020-07-01 2020;5(2):238146832093621. doi:10.1177/2381468320936219

192. Nichols BE, Boucher CAB, van Dijk JH, et al. Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) in Preventing HIV-1 Infections in Rural Zambia: A Modeling Study. *PloS one*. 2013/03/18 2013;8(3):e59549. doi:10.1371/journal.pone.0059549

193. Eaton JW, Menzies NA, Stover J, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. *The Lancet Global health*. Jan 2014;2(1):e23-34. doi:10.1016/s2214-109x(13)70172-4

194. *WHO Commission on Macroeconomics and Health & World Health Organization*. 2001. https://apps.who.int/iris/handle/10665/42463

195. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bull World Health Organ*. Feb 2015;93(2):118-24. doi:10.2471/BLT.14.138206

196. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. *Value in Health*. 2016-12-01 2016;19(8):929-935. doi:10.1016/j.jval.2016.02.017

197. Allen S, Meinzen-Derr J, Kautzman M, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. *AIDS*. Mar 2003;17(5):733-40. doi:10.1097/00002030-200303280-00012

198. Stephenson R, Rentsch C, Sullivan P, et al. Attitudes Toward Couples-Based HIV Counseling and Testing Among MSM in Cape Town, South Africa. *AIDS and Behavior*. 2013-05-01 2013;17(S1):43-50. doi:10.1007/s10461-012-0293-z

199. Neme S, Goldenberg T, Stekler JD, Sullivan PS, Stephenson R. Attitudes towards couples HIV testing and counseling among Latino men who have sex with men in the Seattle area. *AIDS Care*. 2015-10-03 2015;27(10):1354-1359. doi:10.1080/09540121.2015.1058894

200. Baiden F, Remes P, Baiden R, et al. Voluntary counseling and HIV testing for pregnant women in the Kassena-Nankana district of northern Ghana: Is couple counseling the way forward? *AIDS Care*. 2005-07-01 2005;17(5):648-657. doi:10.1080/09540120412331319688

201. Reisner SL, Menino D, Leung K, Gamarel KE. "Unspoken Agreements": Perceived Acceptability of Couples HIV Testing and Counseling (CHTC) Among Cisgender Men with Transgender Women Partners. *AIDS and Behavior*. 2019-02-01 2019;23(2):366-374. doi:10.1007/s10461-018-2198-y

202. Kelley AL, Hagaman AK, Wall KM, et al. Promotion of couples' voluntary HIV counseling and testing: a comparison of influence networks in Rwanda and Zambia. *BMC Public Health*. 2016-12-01 2016;16(1)doi:10.1186/s12889-016-3424-z

203. Mody A, Glidden DV, Eshun-Wilson I, et al. Longitudinal Care Cascade Outcomes Among People Eligible for Antiretroviral Therapy Who Are Newly Linking to Care in Zambia: A Multistate Analysis. *Clinical Infectious Diseases*. 2020-12-17 2020;71(10):e561-e570. doi:10.1093/cid/ciaa268

204. Wang X, Guo G, Zheng J, Lu L. Cost-effectiveness of option B+ in prevention of mother-to-child transmission of HIV in Yunnan Province, China. *BMC Infectious Diseases*. 2019-12-01 2019;19(1)doi:10.1186/s12879-019-3976-5

205. Mwenge L, Sande L, Mangenah C, et al. Costs of facility-based HIV testing in Malawi, Zambia and Zimbabwe. *PLOS ONE*. 2017-10-16 2017;12(10):e0185740. doi:10.1371/journal.pone.0185740

206. Eaton JW, Menzies NA, Stover J, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. *The Lancet Global Health*. 2014-01-01 2014;2(1):e23-e34. doi:10.1016/s2214-109x(13)70172-4

207. Hoehn N, Gill MJ, Krentz HB. Understanding the delay in starting antiretroviral therapy despite recent guidelines for HIV patients retained in care. *AIDS Care*. 2017-05-04 2017;29(5):564-569. doi:10.1080/09540121.2016.1234678

208. Vu L, Burnett-Zieman B, Stoman L, et al. Effects of the implementation of the HIV Treat All guidelines on key ART treatment outcomes in Namibia. *PLOS ONE*. 2020-12-28 2020;15(12):e0243749. doi:10.1371/journal.pone.0243749

209. Boyd MA, Shah M, Barradas DT, et al. Increase in Antiretroviral Therapy Enrollment Among Persons with HIV Infection During the Lusaka HIV Treatment Surge - Lusaka Province, Zambia, January 2018-June 2019. *MMWR Morb Mortal Wkly Rep*. Aug 2020;69(31):1039-1043. doi:10.15585/mmwr.mm6931a4

210. Jewell BL, Mudimu E, Stover J, et al. Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple mathematical models. *The Lancet HIV*. 2020-09-01 2020;7(9):e629-e640. doi:10.1016/s2352-3018(20)30211-3

211. Are Funders Still Focusing On HIV/AIDS? *Health Affairs*. 2020-09-01 2020;39(9):1647-1648. doi:10.1377/hlthaff.2020.01392

212. Pilgrim N, Musheke M, Raymond HF, et al. Quality of care and HIV service utilization among key populations in Zambia: a qualitative comparative analysis among female sex

workers, men who have sex with men and people who use drugs. *AIDS Care*. Apr 2019;31(4):460-464. doi:10.1080/09540121.2018.1524119