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Mathematical Models to Evaluate the Clinical and Economic Impact of  
Biomedical HIV Prevention Strategies in the United States

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**Abstract**

Mathematical Models to Evaluate the Clinical and Economic Impact of  
Biomedical HIV Prevention Strategies in the United States

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As the marginal clinical impact returns on innovations to treat and prevent HIV diminish, strategic investments are required for timely and efficient HIV eradication. The overall goal of this dissertation research is to evaluate the potential cost-effectiveness of several pharmacotherapy-related interventions included in the National HIV/AIDS Strategy for the United States in order to inform decision-making and policy design. Rising HIV program costs along with poor results in patient access and service utilization make determining the value of new HIV interventions very important for the vulnerable populations bearing the disease burden. Today, pre-exposure prophylaxis (PrEP) drugs are a short-term solution. Quite soon, programs offering financial incentives for viral suppression are expected to expand. Over the long term, many view the development of a safe and effective HIV vaccine as the only hope to completely eradicate AIDS. I develop a series of mathematical models to examine the clinical and

economic impact of financial incentives, PrEP, and HIV vaccines using local and national surveillance data drawing on the results of large clinical trials. Importantly, I examine the potential interaction and competition between PrEP and HIV vaccines which needs to be understood to achieve optimal benefit from the combined use of the two in the coming decades. Lastly, I make policy and R&D investment recommendations aimed to support efficient progress towards the national strategic goals.



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# DEDICATION

For Penelope and Daphne



Ouch!!!

by Blythe Adamson  
cover by Penelope  
Hand written and drawn Adamson ~~and drawn~~

# Chapter 1

## Introduction

## 1.1 BACKGROUND

### 1.1.1 HIV Burden in the United States

Currently, in the United States, an estimated 1.2 million people live with HIV, including 14% with undiagnosed infections [1]. HIV remains a tremendous problem in the US, especially among young Black and Latino men who have sex with men (MSM) [2–4]. MSM comprise 62% of the approximately 40,000 new HIV infections in the US each year [5]. Antiretroviral therapy (ART) lengthens lives, yet infected individuals face challenges from stigma, adherence to daily medication, increased comorbidities, and higher health care expenses. It is estimated that less than 30% of all HIV infections are virally suppressed [1,6,7]. The high and rising cost of HIV medicines is receiving increasing attention in the US, and federal funding for domestic HIV care is correspondingly increasing [8]. Rising HIV program costs along with poor results in access make the assessing the value of new HIV interventions very important.

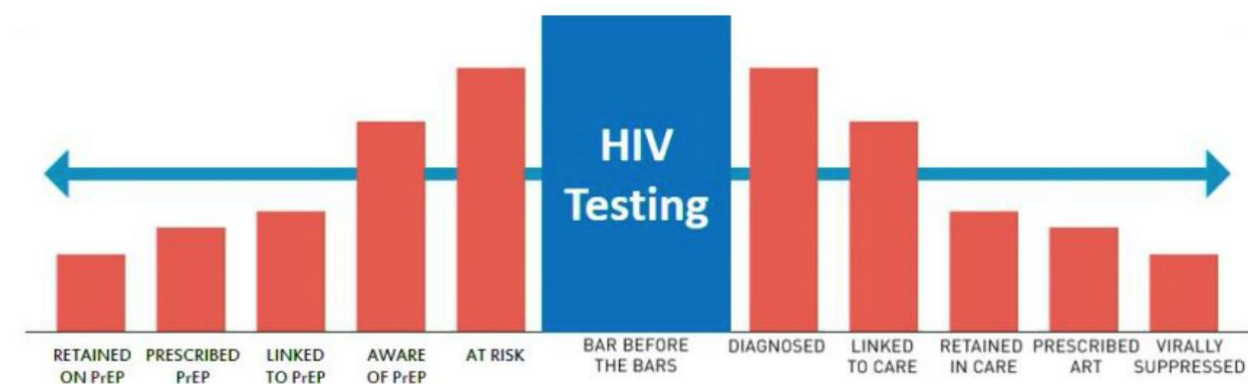


Figure 1.1. The neutral care continuum for HIV prevention and treatment.

Source: Scott H, CROI 2018 [10].

If the current trend continues, 50% of black MSMs will become HIV infected in their lifetime [5].

There are many related social determinants of health. People living in places with a high HIV burden are less likely to have health insurance, more likely to live in poverty, less likely to have a high school education, and more likely to live in an area with severe income inequality (Figure 1.2) [9]. Other important issues are structural racism, stigma, and medical mistrust. The HIV care cascade now works in both directions of a “status neutral” continuum that demands HIV viral load testing for both HIV positive and negative people (Figure 1.1). The Ryan White Foundation has presented evidence that continuous access to care helped to improve continuous viral suppression from 69.5% VS in 2010 to 84.9% in 2016. Interventions targeting segments of the cascade, especially those that increase the proportion virally suppressed, show promise to improve health and slow transmission.

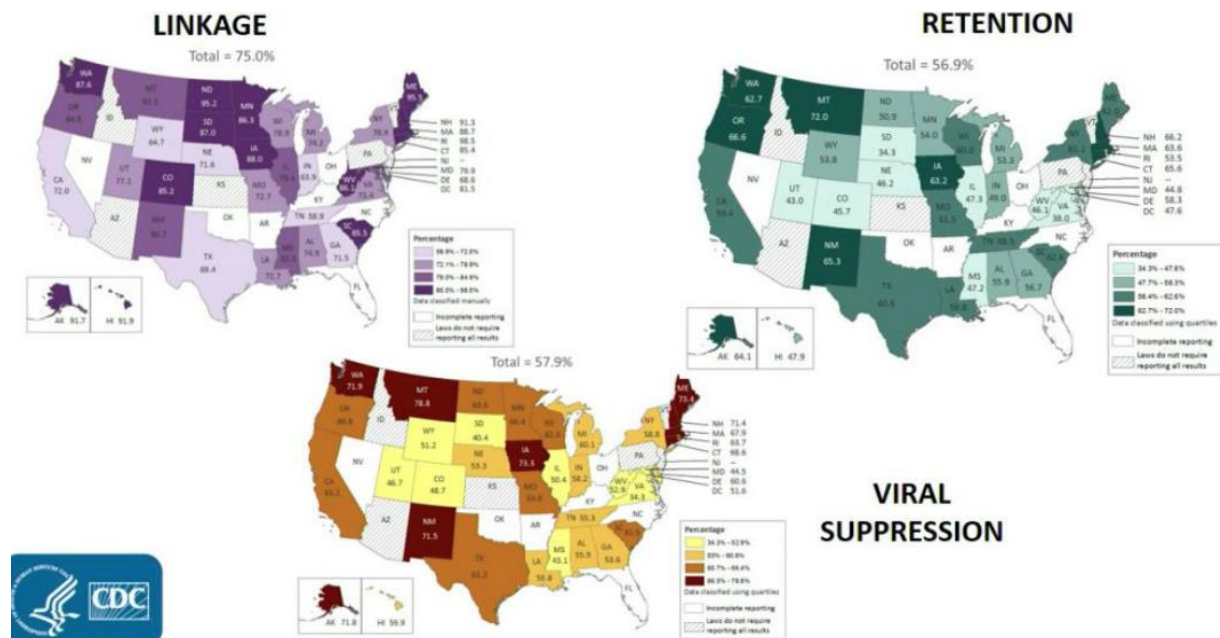


Figure 1.2. Regional variation in linkage to care, retention and viral suppression

Source: US Centers for Disease Control

An important concern is the inadequate growth in the number of HIV care providers. The CDC estimates the need to take care of an additional 100,000 patients by 2019. HIV care provider workforce supply and demand projections from 2010 to 2015 revealed a shortage of 133 FTE HIV clinicians in 2010 (representing roughly 7 percent of actual supply), growing to a shortage of 502 FTE HIV clinicians in 2015 (representing nearly 30 percent of actual supply) [11].

### 1.1.2 National Strategic Plan

The “National HIV/AIDS Strategy for the United States: Updated to 2020” defines strategic goals to (1) reduce HIV infections, (2) improve health care access and HIV-related health outcomes, (3) reduce HIV-related disparities, and (4) achieve a more coordinated national response to the HIV epidemic [6]. To achieve these goals, currently available interventions include risk reduction counseling, HIV testing, strengthening the care continuum, syringe exchanges, pre-exposure prophylaxis (PrEP), and more. Specifically, the update calls for “economic evaluations of HIV prevention strategies, including cost-effectiveness analyses of single and combination HIV prevention interventions. . . to provide stakeholders with tools to set priorities and measure impact for high-risk populations.” A very recent critique of The Strategy suggests a lack of evidence-based guidance for implementing, prioritizing, and paying for its recommendations [12]. Achieving all Strategy indicators may have a large impact on the US health care expenditures and domestic federal funding for HIV.

The nation’s first HIV/AIDS Strategy was released in 2010 resulting from a large initiative by the Division of HIV/AIDS Prevention at the Centers for Disease Control (CDC) [13]. The recent update to 2020 defines goals to (1) reduce new HIV infections, (2) increase access to care and improve health outcomes for people living with HIV, (3) reduce HIV-related disparities and health in equities, and (4) achieve a more coordinated national response to the HIV epidemic [6]. The Strategy aims to achieve the following vision:

The United States will become a place where new HIV infections are rare, and when they do occur, every person, regardless of age, gender, race/ethnicity, sexual orientation, gender identity, or socio-economic circumstance, will have unfettered access to high quality, life-extending care, free from stigma and discrimination.

*– Vision Statement from the National HIV/AIDS Strategy for the United States: Updated to 2020 [6]*

The Strategy emphasizes reaching marginalized populations and encouraging pre-exposure prophylaxis (PrEP), and it highlights advances in HIV vaccine development [6]. Washington State was cited for the collaborative work “Get Insured, Get PrEP, Get Tested, Get Treatment” by End AIDS Washington through the Washington Health Plan Finder, for its mission to reduce the rate of new HIV infections in Washington by 50% by 2020 [14]. A key indicator defined to measure development and progress is an increase the percentage of persons with diagnosed HIV infection who are virally suppressed to at least 80%, from the baseline of 43.4%.

An independent analysis of the strengths, weaknesses, opportunities, and threats (SWOT) of the Strategic Plan identified some key omissions regarding (1) population size and burden of unmet need, (2) implementation strategies and payment for PrEP expansion, and (3) concrete recommendations to address the cascade of care [12]. Economic analyses that can help to facilitate implementation of the National HIV/AIDS Strategy objectives are needed.

### **1.1.3 Impact of ACA and Medicaid Expansion**

Medicaid is the single largest source of healthcare coverage for people living with HIV in the United States, covering approximately half of people with HIV [15]. Passage of the Patient Protection and

Affordable Care Act (ACA) in 2010 led to a substantial increase in the number of Medicaid enrollees because of expanded eligibility in participating states to most adults with incomes at or below 138% of the federal poverty level. The previous policy was considered a “catch-22” because many low-income people with HIV were not eligible for Medicaid coverage until they were disabled with sickness that could have been avoided with proper HIV care and treatment. The impact of the ACA and Medicaid expansion on HIV and progress towards national strategic goals and 90:90:90 goals remain uncertain.

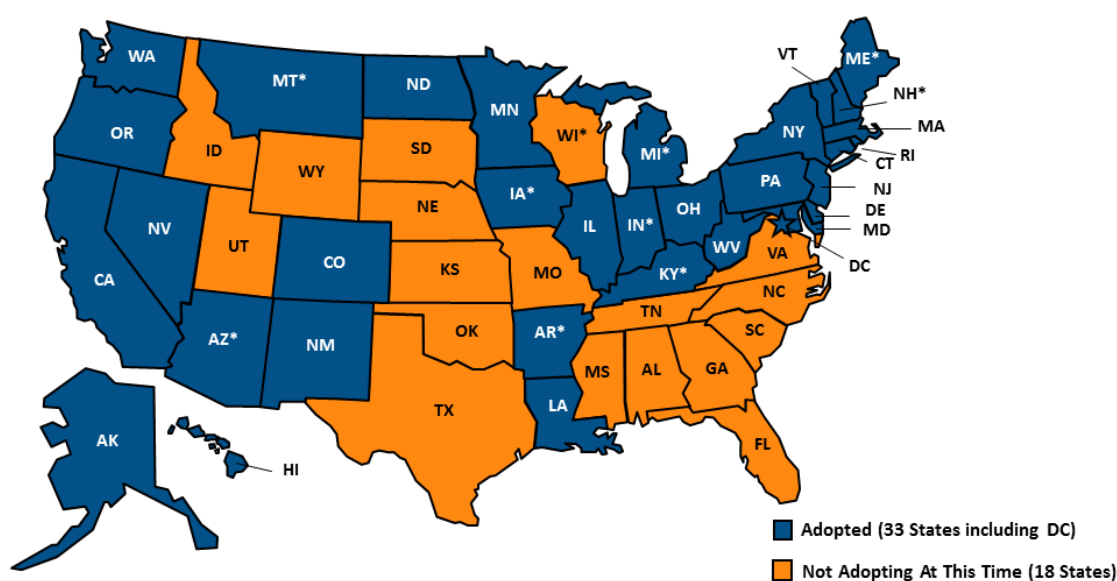


Figure 1.3. Current status of state Medicaid expansion decisions

NOTES: Current status for each state is based on KFF tracking and analysis of state executive activity. \*AR, AZ, IA, IN, KY, MI, MT, and NH have approved Section 1115 expansion waivers. KY initially adopted expansion through a state plan amendment but received CMS approval for the Kentucky HEALTH expansion waiver on January 12, 2018; implementation will start in April 2018 with full implementation by July 2018. ME adopted the Medicaid expansion through a ballot initiative in November 2017; the ballot measure requires submission of a state plan amendment within 90 days and implementation of expansion within 180 days of the measure’s effective date. WI covers adults up to 100% FPL in Medicaid, but did not adopt the ACA expansion.

Source: “Status of State Action on the Medicaid Expansion Decision,” KFF State Health Facts, updated January 16, 2018. <http://kff.org/health-reform/state-indicator/state-activity-around-expanding-medicaid-under-the-affordable-care-act/> [16]

To date, 18 states have not yet expanded Medicaid (Figure 1.3) and 40% of new diagnoses were in four of these states alone (Table 1.1). A difference-in-differences analysis comparing pre- versus post-expansion, capturing the effect of the private Marketplace and Medicaid, used an instrumental variable approach to

estimate the treatment effect, based on the assumption that the instrument (state expansion) affects outcomes only through the predictor of interest (insurance coverage) [17]. By 2016, they found significant changes for outcomes related to coverage, access, affordability, and prevention ( $p < 0:05$ ) and quality ( $p < 0:10$ ), but not for utilization or self-reported health. The authors found a 41-percentage point increase in having a usual source of care among those gaining coverage. While the probability of having a usual source of care increased (41-percentage-points) on-average for people gaining insurance, there was not a significant improvement for adults with chronic conditions. Of 18 states that have not expanded Medicaid, most of those states are in the south. Of the 2.4 million people who have not benefitted from Medicaid expansion, 89% live in the south. In 2016, 40% of the new HIV diagnoses occurred in four states that did not expand Medicaid (Table 1.1)

Table 1.1. Four non-expanded southern states representing 40% of new US diagnoses

State	New HIV Diagnoses in 2016	Rate (per 100,000)
Florida	4,957	24.0
Texas	4,472	16.1
Georgia	2,716	26.3
North Carolina	1,414	13.9

Source: del Rio, C. CROI 2018 [18]

Lipira and colleagues suggested the potential for the ACA and Medicaid to shift the burden of HIV care costs from one public payer source to another public payer, and the potential for people living with HIV to experience increasing out-of-pocket payments for their healthcare as a result [19]. The Ryan White HIV/AIDS Program (RWHAP) provides uninsured and underinsured people living with HIV access to supplemental services, such as housing, transportation, and nutritional support. People living with HIV who gained insurance under the ACA may not have necessarily increased access to health care if it meant losing some benefits from the RWHAP. RWHAP Part B funds state-administered AIDS Drug Assistance Programs (ADAP) that can be used by states to either pay directly for ART or purchase qualifying health insurance, so it is unclear whether the ACA increased access to ART for people living with HIV.

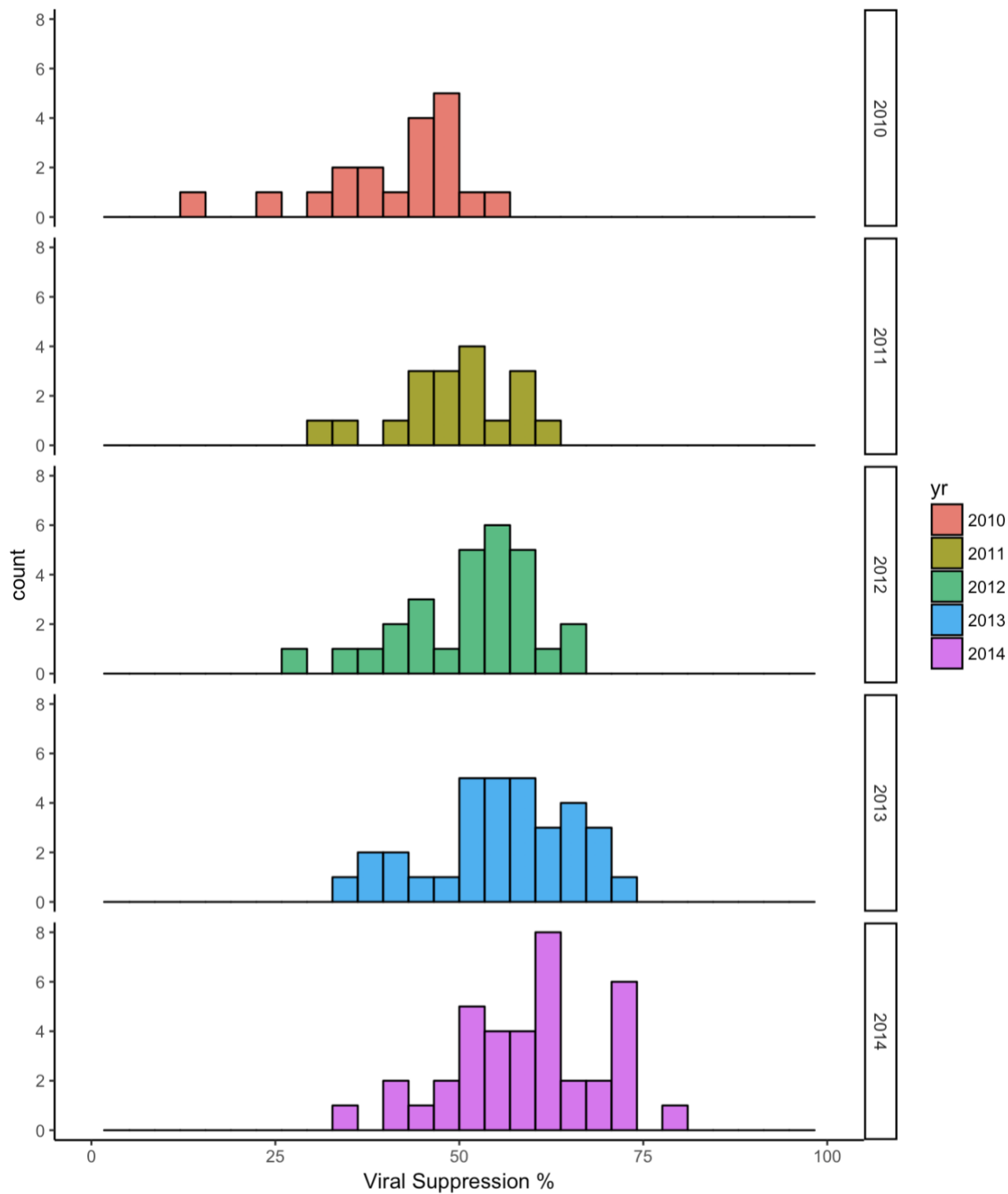


Figure 1.4. Shifting trend in distribution of viral suppression (%) among all US states

*Data Source: CDC Atlas Plus [20]*

People belong to multiple groups (i.e., with non-random sexual mixing patterns and varying risks of HIV transmission and acquisition). Individual risks are also dependent on stage in the HIV care continuum. This heterogeneity is relevant for evaluation ACA and Medicaid expansion policy-making because the policies can impact groups differently. HIV incidence and transmission goals for 2020 and 2025 depend on improvements in the care case [21]. The implication of Medicaid coverage of more than 250,000 people living with HIV is that the availability and uptake of HIV treatment and prevention interventions can have substantial budget impact for Centers for Medicare and Medicaid (CMS).

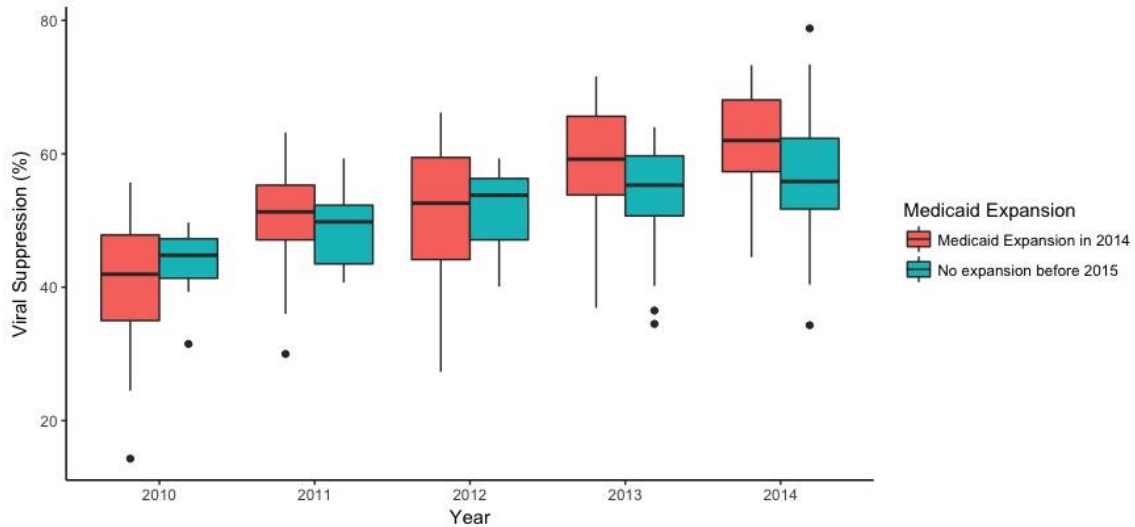


Figure 1.5. States with Medicaid expansion are making progress in viral suppression (%) faster than states without Medicaid expansion before 2015.

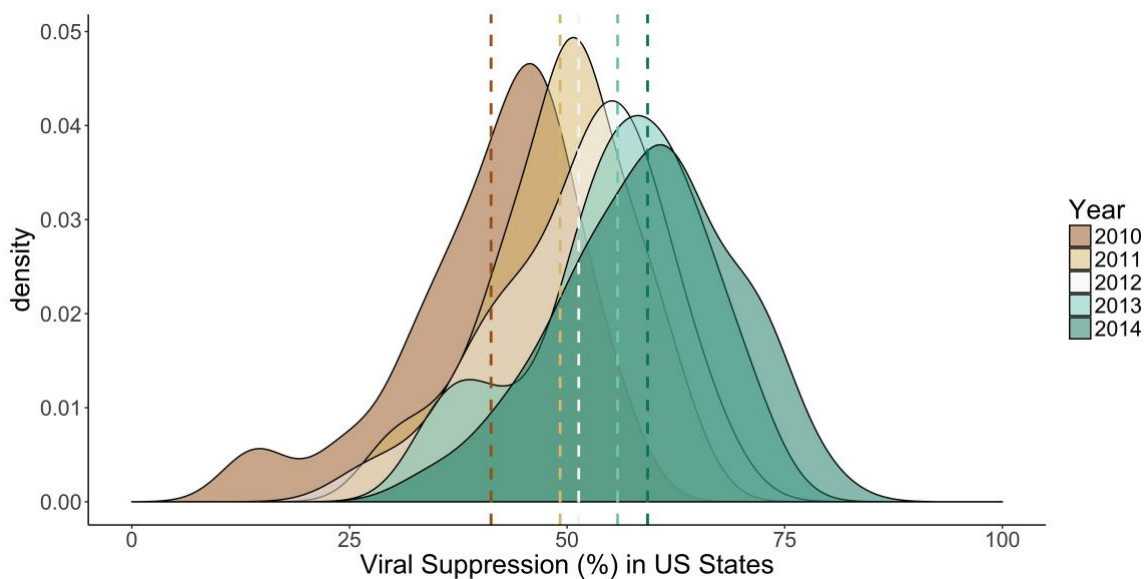


Figure 1.6. Shifting trend in density of viral suppression among states with and without Medicaid expansion before 2015

NOTE: The dataset used to generate this figure developed using CDC Atlas Plus, CDC Surveillance Supplemental Reports (2010-2015), and Medicaid expansion dates reported by the Kaiser Family Foundation. Dashed lines represent the mean viral suppression (%) among diagnosed people living with HIV across US states.

Table 1.2. Impact of the ACA and Medicaid expansion on the HIV care cascade

Target	Evidence of Impact	References
HIV Diagnoses	Insurance effect of 64.7-percentage-point-increase in likelihood of checkup in past year	Sommers et al. 2017 [17]
Linkage to Care	Insurance effect of 40.9-percentage-point-increase in likelihood of having a personal doctor for adults with chronic conditions	Sommers et al. 2017 [17]
Engagement in Care	Greater decline in “fair/poor quality of care” with Medicaid expansion compared to not expanding  Insurance effect of 55.9-percentage point-increase in regular care for adults with chronic conditions	Sommers et al. 2017 [17]
Viral Suppression	Insurance effect of 50.8-percentage-point reduction in skipping medication because of cost for adults with chronic conditions	Sommers et al. 2017 [17]

Abbreviations: ACA, Affordable Care Act

## 1.2 INNOVATIONS IN HIV PREVENTION

This research explores three biopharmaceutical-related intervention approaches to prevent and control sexual transmission of HIV in the US: PrEP, HIV vaccines, and financial incentives for viral suppression. ART and PrEP have been shown to be significantly effective at reducing HIV transmissions (Figure 1.7).

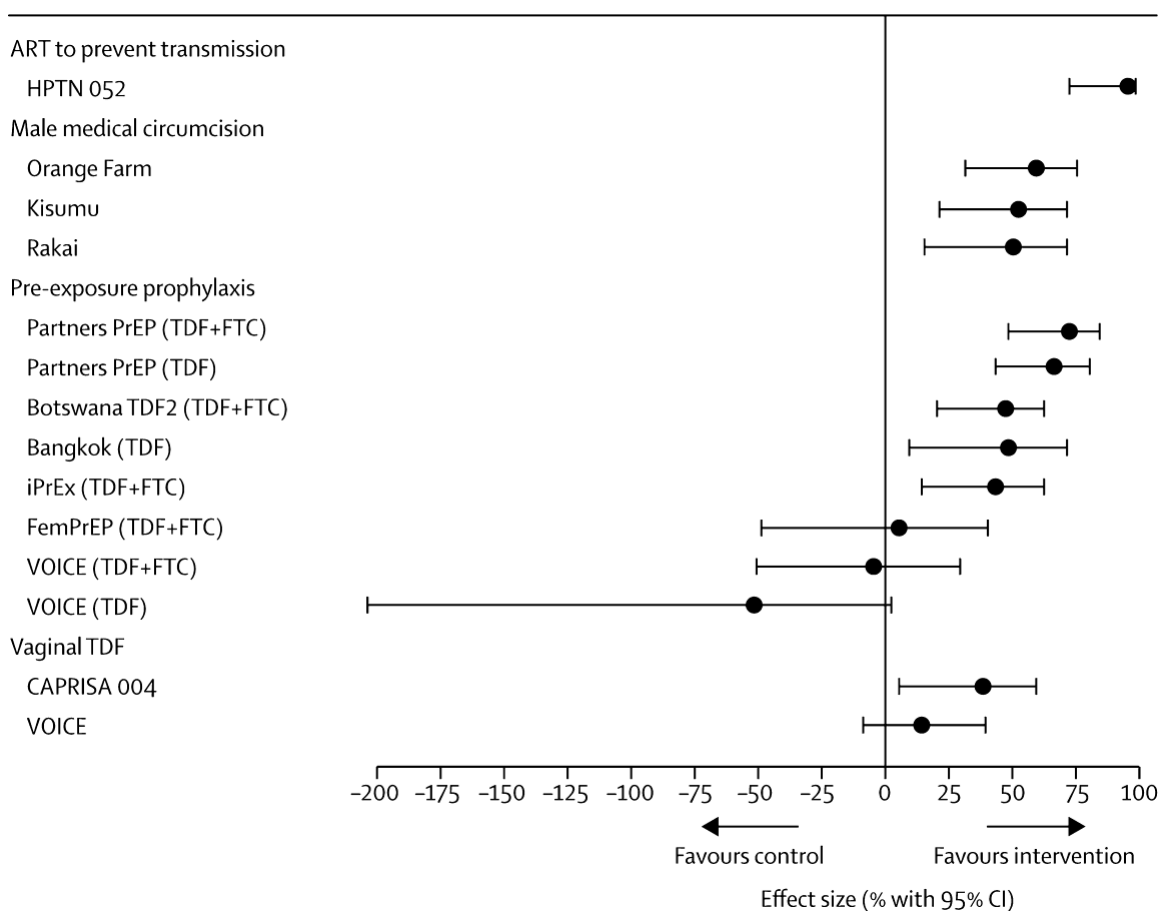


Figure 1.7. Clinical trials of interventions to prevent sexual transmission of HIV-1

TDF=tenofovir. FTC=emtricitabine.

Source: Maartens et al. 2014 [22]

### 1.2.1 Pre-Exposure Prophylaxis

In 2012, the FDA approved the daily oral medication TRUVADA<sup>®</sup> for PrEP to reduce the risk of HIV infection. Almost 200,000 people in the United States were using PrEP in 2016 (Figure 1.8), following

studies reporting a large range of protection levels depending on adherence [23–25]. A key challenge is adherence to daily medication by healthy people.

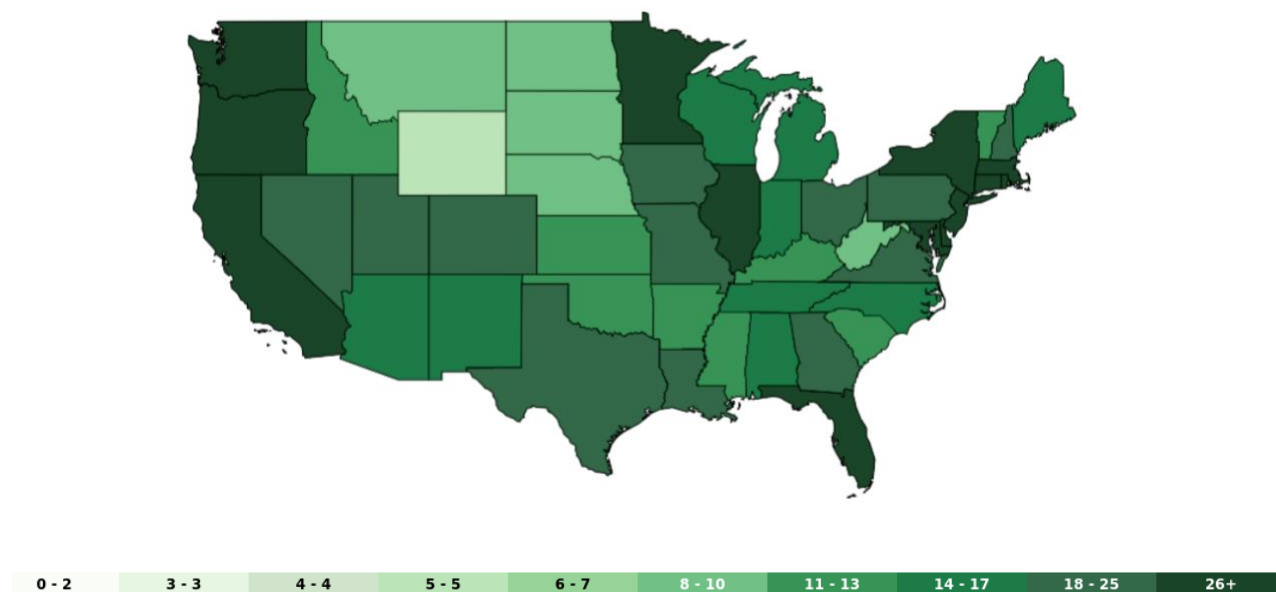


Figure 1.8. Rate of persons using PrEP, 2016

Source: AIDSvu [9]

### 1.2.2 HIV Vaccine Development

Seven efficacy trials have been conducted to evaluate HIV vaccine candidates (see Table 1.3). A groundbreaking 2009 Phase III trial in Thailand tested an HIV vaccine trial candidate and observed significant vaccine efficacy averaging 31% over three years [26]. A confirmatory trial is ongoing in South Africa, with modifications to improve the Thai regimen and hypothesized HIV vaccine efficacy of 50% [27]. Research evaluating new HIV vaccine candidates continues.

Table 1.3. HIV-1 vaccine efficacy trials

Study	Vaccines	Phase	Location	Result
Vax004	AIDSVAX B/B gp 120 in alum	3	USA and Europe	No efficacy [28]
Vax003	AIDSVAX B/E gp 120 in alum	3	Thailand	No efficacy [29]
HVTN 502 Step Trial	MRKAd5 HIV-1 gag/pol/nef B	2b	USA	No efficacy; transient increased infection rate in vaccines [30,31]
RV144	ALVAC-HIV vCP15121 and AIDSVAX B/E rgp120 in alum	3	Thailand	31.2% efficacy at 42 months, 60% at 12 months against HIV acquisition. No effect on plasma viral load and CD4 count [32,33]
HVTN 503	MRKAd5 HIV-1 gag/pol/nef B	2b	South Africa	No efficacy; increased HIV infection rate in vaccines [34,35]
HVTN 505	DNA and rAd5 (A,B, and C)	2b	USA	Stopped for futility; no efficacy on HIV acquisition, plasma viral load and CD4 count [36]
HVTN 702	ALVAC vCP2438 with clade C HIV insert and bivalent protein boost gp120 with MF59 adjuvant	2b/3	Southern Africa	Ongoing [37]

*Adapted from Excler and Michael 2016 [38]*

The Pox-Protein Public Private Partnership (P5) program, composed of the Bill & Melinda Gates Foundation, the National Institutes of Health, Sanofi Pasteur, GlaxoSmithKline (GSK), the South African Medical Research Council, the HIV Vaccine Trials Network (HVTN), and the US Military HIV Research Program, developed a base-case “Target Product Profile” (TPP) for an HIV vaccine (Figure 1.9) [37].

<b>Base case TPP</b>	
<b>Indication</b>	» Prevention of HIV infection
<b>Target population</b>	» Seronegative adults at high risk for acquiring HIV infection
<b>Vaccine efficacy</b>	» $\geq 50\%$ reduction in HIV infection at 24 months after first administration
<b>Safety</b>	» Well tolerated, AE profile comparable to standard adult vaccines
<b>Duration of protection</b>	» 24 months from first administration (may require periodic boosting)
<b>Doses</b>	» 5 doses administered over 12 months

Figure 1.9. Base-case Target Product Profile designed by the Pox-Protein Public-Private Partnership

Source: Russell and Marovich 2016 [37]

### 1.2.3 Financial Incentives

Financial incentives for viral suppression also offer promise as a cost-effective approach to treat and prevent HIV. The randomized trial HPTN 065 aligns with the National Strategic goals by evaluating the effectiveness of financial incentives for viral suppression in HIV patients. From 2010-2013, a \$2.8 million-dollar study of 39 HIV clinics in Bronx, NY and Washington, D.C. randomized sites to provide \$70 Visa gift cards to patients at quarterly clinic visits with viral suppression or provide the standard of care. Financial incentives continued for two years and led to a significant 3.7% percentage-point improvement in viral suppression compared to the control clinics. Initial findings from HPTN 065 were highly publicized and reported in The New York Times [39]. Walensky and colleagues found some HIV treatment and prevention strategies to be cost-effectiveness based on an HPTN study [40]. The research in Chapter 4 is the first cost-effectiveness analysis estimating the lifetime clinical and economic impact of financial incentives as offered in HPTN 065.

### 1.3 DECISION-MAKING AND POLICY OPTIONS

Eliminating HIV burden requires a combination of prevention programs strategically implemented and guided by policy. Some evidence-based prevention interventions are available now while others are in the research and development pipeline. Ideally, decisions made today would consider the landscape of other biomedical products that are on the horizon of availability, and the optimal design of future policies considers the risks that may mitigate the potential benefit from new products. Strategic investments in biomedical innovation should concurrently plan for efficient spending today and for the potential combination of new and old products for the future. Timely clinical and economic mathematical modeling facilitates planning and development of approaches to mitigate many risks. Making optimal investments in technologies available today and developing of technologies for tomorrow depends on a thorough understanding of the tradeoffs.

### 1.4 SPECIFIC AIMS

The overall goal of this dissertation research is to inform decision-making and policy design by evaluating the clinical and economic impact of a mix of pharmacotherapy-related interventions mentioned in the Strategic Plan for HIV/AIDS in the United States [6]. The Specific Aims of this dissertation are to:

1. ***Specific Aim 1:*** Construct and utilize an economic model, based on clinical trial data, to evaluate the cost-effectiveness of financial incentives for viral suppression in HIV patients compared to standard HIV care in Bronx, NY, and Washington, D.C.
2. ***Specific Aim 2:*** Evaluate, using a dynamic transmission model of HIV, the cost-effectiveness of combined use of HIV vaccines and PrEP compared to a standard for prevention with PrEP alone as potential components of the National HIV/AIDS Strategy for the United States.

- ***Specific Aim 2 Part A:*** Adapt the structure and equations of an existing HIV compartmental model by adding HIV vaccines, costs, and patient health state utilities, and then parameterize and calibrate the model for King County MSM to evaluate the cost-effectiveness of PrEP.
- ***Specific Aim 2 Part B:*** Estimate, using the dynamic transmission model from Part A, the potential cost-effectiveness at a population-level of the combined use of an HIV vaccine with PrEP compared to PrEP as the standard of care, and identify thresholds for characteristics of a clinically and economically viable HIV vaccine for the United States.

Economically viable implementation strategies are needed to fulfill goals of The National HIV/AIDS Strategy. This doctoral dissertation research responds to the National Strategy's call for cost-effectiveness analyses of single and combination HIV prevention interventions to help stakeholders establish priorities for funding allocation and maximize benefits. CDC surveillance allows monitoring of progress toward national goals for HIV prevention and care [41]. The application of local and national-level CDC surveillance data is a theme running through the chapters of this dissertation. Surveillance data was used as an important input for analyses in Chapter 3 on the potential competition between PrEP and HIV vaccines in Seattle and Chapter 4 on the financial incentives in the Bronx, NY and Washington, DC.

## 1.5 SIGNIFICANCE

According to economic models, a person infected with HIV at age 35 should expect to lose, on average, 5 to 7 fewer discounted, lifetime quality-adjusted life years (QALYs) and to accumulate \$229,800 more in lifetime medical costs (2012 USD) compared to a person who avoids HIV infection [42–44]. Medicaid covers half of all HIV patients and spent more per-member per-year on HIV treatment in 2015 than on

any other specialty drug [8]. In 2015, HIV drug costs (per 30-day supply) and utilization increased in the US by 12% and 4.6%, respectively [8]. The government responded by increasing the requested budget for domestic HIV care by only 5.6% for 2017. Among HIV drugs, TRUVADA<sup>®</sup> had the largest market share (17%) [8]. Compared to all drugs, spending on TRUVADA<sup>®</sup> by Medicaid (\$24.64 per-member per-year) was second only to Harvoni<sup>®</sup>, a cure for hepatitis C. The 2017 US federal budget requested \$27.5 billion for domestic HIV efforts, representing a 3.1% increase over FY 2016 [45]. Domestic HIV prevention accounted for only 2.6% of the total federal funding for HIV requested for 2017.

Table 1.4. Federal funding for HIV/AIDS by category, fiscal year (FY) 2011 – FY 2017 request (US\$ Billions)

Category	FY 2011	FY 2012	FY 2013 <sup>a</sup>	FY 2014	FY 2015	FY 2016	FY 2017
Domestic	\$21.8	\$22.0	\$22.5	\$23.9	\$25.5	\$26.4	\$27.5
Care	\$15.3	\$15.5	\$16.1	\$17.4	\$18.9	\$19.7	\$20.8
Cash/Housing	\$2.7	\$2.8	\$2.9	\$3.0	\$3.0	\$3.0	\$3.1
Prevention	\$0.9	\$1.0	\$0.9	\$0.9	\$0.9	\$0.9	\$0.9
Research	\$2.8	\$2.8	\$2.7	\$2.7	\$2.7	\$2.7	\$2.7
Global	\$6.5	\$6.4	\$6.3	\$6.6	\$6.6	\$6.6	\$6.6
<b>TOTAL</b>	<b>\$28.3</b>	<b>\$28.5</b>	<b>\$28.8</b>	<b>\$30.5</b>	<b>\$32.1</b>	<b>\$33.0</b>	<b>\$34.0</b>

<sup>a</sup>Includes the effects of sequestration

Source: Kaiser Family Foundation [45]

The overall goal of this dissertation research is to evaluate the potential cost-effectiveness of several pharmacotherapy-related interventions recommended in the National HIV/AIDS Strategy Updated to 2020 and prioritize investments in further innovation and in implementation of these HIV prevention strategies.

### Human Subjects Approval

Aim 1 conducts a cost-effectiveness analysis of the HPTN 065 study. HPTN 065 involved minimal risk and outcomes were reported using only quarterly site-aggregated surveillance data (no additional

individual data were collected from sites); thus a waiver of patient informed consent was granted under 45 CFR 46.116 (c) and (d) by each site's affiliated Institutional Review Board (IRB). The proposed analysis in Aim 2 was found to be eligible for exemption from consent. The dynamic model in Aim 2 uses publically available de-identified data from clinical trials, local and national HIV surveillance, and published studies.

# Chapter 2

## The Potential Cost-Effectiveness of HIV Vaccines: A Systematic Review

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## ABSTRACT

**Objective:** The aim of this paper was to review and compare HIV vaccine cost-effectiveness analyses and describe the effects of uncertainty in model, methodology, and parameterization.

**Methods:** We systematically searched MEDLINE (1985 through May 2016), EMBASE, the Tufts CEA Registry, and reference lists of articles following Cochrane guidelines and PRISMA reporting. Eligibility criteria included peer-reviewed manuscripts with economic models estimating cost-effectiveness of preventative HIV vaccines. Two reviewers independently assessed study quality and extracted data on model assumptions, characteristics, input parameters, and outcomes.

**Results:** The search yielded 71 studies, of which 11 met criteria for inclusion. Populations included low-income (n=7), middle-income (n=4), and high-income countries (n=2). Model structure varied including decision tree (n=1), Markov (n=5), compartmental (n=4), and microsimulation (n=1). Most measured outcomes in quality adjusted life-years (QALYs) gained (n=6) while others used unadjusted (n=3) or disability adjusted life-years (n=2). HIV vaccine cost ranged from \$1.54 -\$75 USD in low-income countries, \$55-\$100 in middle-income countries, and \$500-\$1,000 in the United States. Base case ICERs ranged from dominant (cost-offsetting) to \$91,000 per QALY gained.

**Conclusion:** Most models predicted HIV vaccines would be cost-effective. Model assumptions about vaccine price, HIV treatment costs, epidemic context, and willingness to pay influenced results more consistently than assumptions on HIV transmission dynamics.

## **KEY POINTS**

- Most economic models predict HIV vaccines will be cost-effective.
- Static and dynamic HIV transmission modeling methods found similar results.
- HIV vaccine cost-effectiveness will likely depend on HIV prevalence, the durability of vaccine protection, and the price per series and boost.

## 2.1 BACKGROUND

The search for an HIV vaccine began over three decades ago with a breakthrough in 2009 [46]. A Phase III HIV vaccine trial in Thailand (RV144) found HIV vaccine efficacy of 31.2% over three years [26,47]. Though the durability of protection was low, vaccine boosting 4-5 years later restored the immune response to HIV [48]. An efficacy trial in South Africa (HVTN 702) is ongoing to confirm the canarypox-based vaccine ALVAC-HIV and a bivalent gp120 protein subunit boost with funding from NIAID and other members of the P5 Pox-Protein Public Private Partnership. The vaccine product was modified to match the predominant HIV strain in Africa and includes the potentially more immunogenic adjuvant MF59. With an added vaccine dose at 12 months totaling 5 injections, the regimen is expected to increase the magnitude and duration of vaccine-elicited immune responses [49]. Previously, Walensky et al. defined several characteristics of a “good enough” therapeutic vaccine for HIV infected individuals to replace ART in the United States [50], but the characteristics of a clinically and economically viable HIV vaccine have not been defined. When licensed, HIV vaccines may complement or compete with other HIV prevention interventions such as voluntary male circumcision, treatment as prevention, and now pre-exposure prophylaxis (PrEP). Decision makers now balance investment in the continued development of HIV vaccines and confirmatory trials in Southern Africa with other opportunities to incrementally improve combination HIV prevention effectiveness [27]. Over the long-term, many view the development of a safe and effective HIV vaccine as the only hope to completely eradicate AIDS [51,52]. This review aims to review existing studies of HIV vaccine cost-effectiveness to identify characteristics of HIV vaccines that may be essential the value and viability of vaccination.

### 2.1.1 Rationale

Cost-effectiveness research guides efficient spending of limited healthcare resources and also contributes to R&D decision-making and prioritization of early phase products through a clinical trial pipeline. Multifaceted decision making and value assessment of vaccines in development often draw upon

economic modeling predictions [53]. Many complex mathematical models have simulated the potential impact of HIV vaccines on transmission of the virus, but few have included costs or measured health outcomes comparable for comparison to other health care investments. Unlike models of chronic diseases, sexually transmitted infections often require the addition of transmission dynamics to capture the indirect effect, or positive externality, of herd immunity. Brisson and Edmunds previously showed the impacts of modeling, methodological, and parameter uncertainty on economic analyses of varicella vaccination, and emphasized how choices in model development can lead to disparate results [54]. Because few cost-effectiveness studies exist in this area, we aimed to assess methodological differences between studies that may influence implications of value from a vaccine. Comparing detailed characteristics of the small number of existing studies allows us to identify key methods or population characteristics that strongly influence results. As vaccine development progresses, it will be of key importance to assess both clinical and economic feasibility of widespread vaccination campaigns. In this review we aimed to identify key methodological drivers of, and variability in, potential cost-effectiveness of an HIV vaccine. Our aim for this work is to help facilitate an informed and successful roll out of a future vaccine. While the cost-effectiveness of PrEP for HIV prevention has been systematically reviewed previously, this is the first review of HIV vaccine cost-effectiveness [55,56].

### 2.1.2 Objectives

The main objective of this review was to identify and summarize HIV vaccine cost-utility analyses to understand conditions where vaccination has potential to be cost-effective or cost-saving. Based on the economic models identified through a systematic review, the secondary objective was to evaluate and compare modeling, methodological, and parameter uncertainty based on guidelines and best practices for dynamic transmission modeling. The range in approaches to address uncertainty provided a case study for methodological comparison of economic modeling in infectious diseases. This paper was targeted at

clinical trial scientists and funders to guide identification of characteristics of an HIV vaccine that would be most critical to the economic viability of the vaccine.

## **2.2 METHODS**

We conducted a systematic review following methods from the Cochrane Collaboration and the Agency for Healthcare Research and Quality (AHRQ) guides for systematic reviews [57,58]. Content aligns with the PRISMA Statement for transparent reporting of systematic reviews [59].

### **2.2.1 Eligibility Criteria**

Eligible articles were published in peer-reviewed journal articles from 1985 to May 2016 in the English language and included an analysis that predicted the economic impact of an HIV vaccine. Eligibility was limited to studies estimating incremental costs and health outcomes measured in units comparable across diseases, including: quality-adjusted life years (QALYs) gained, disability adjusted life years (DALYs) averted, or life years (LYs). For ease of comparability, the review was limited to preventative vaccines of uninfected individuals and excluded therapeutic vaccines for existing HIV patients. Budget impact analyses, HIV vaccine acceptability, and willingness to participate studies were excluded, as were editorial commentaries, conference abstracts, and book chapters.

### **2.2.2 Search Methods and Sources**

Two reviewers independently searched databases using a pre-specified protocol. The PubMed and MEDLINE search included: (("cost benefit analysis"[MeSH Terms] OR "cost effectiveness"[All Fields]) AND ("aids vaccines"[MeSH Terms] OR "hiv vaccine"[All Fields])). EMBASE was searched for key words 'cost effectiveness analysis' AND ('aids vaccine' OR 'hiv vaccine'). The Tufts CVER CEA Registry

was searched for “HIV vaccine” and “AIDS vaccine.” Authors screened reference lists of relevant articles for additional studies not identified in the database searches.

### **2.2.3 Study Selection**

Records identified through database and registry searches were merged into the reference manager Mendeley and duplicates were removed. Two reviewers (author BA and acknowledged contributor NV) independently searched and screened the titles and abstracts of all identified records, excluded those not meeting the defined criteria, and then assessed the full text of all remaining articles for eligibility. Disagreements or uncertainty in eligibility were discussed and resolved with input from a third reviewer (BD).

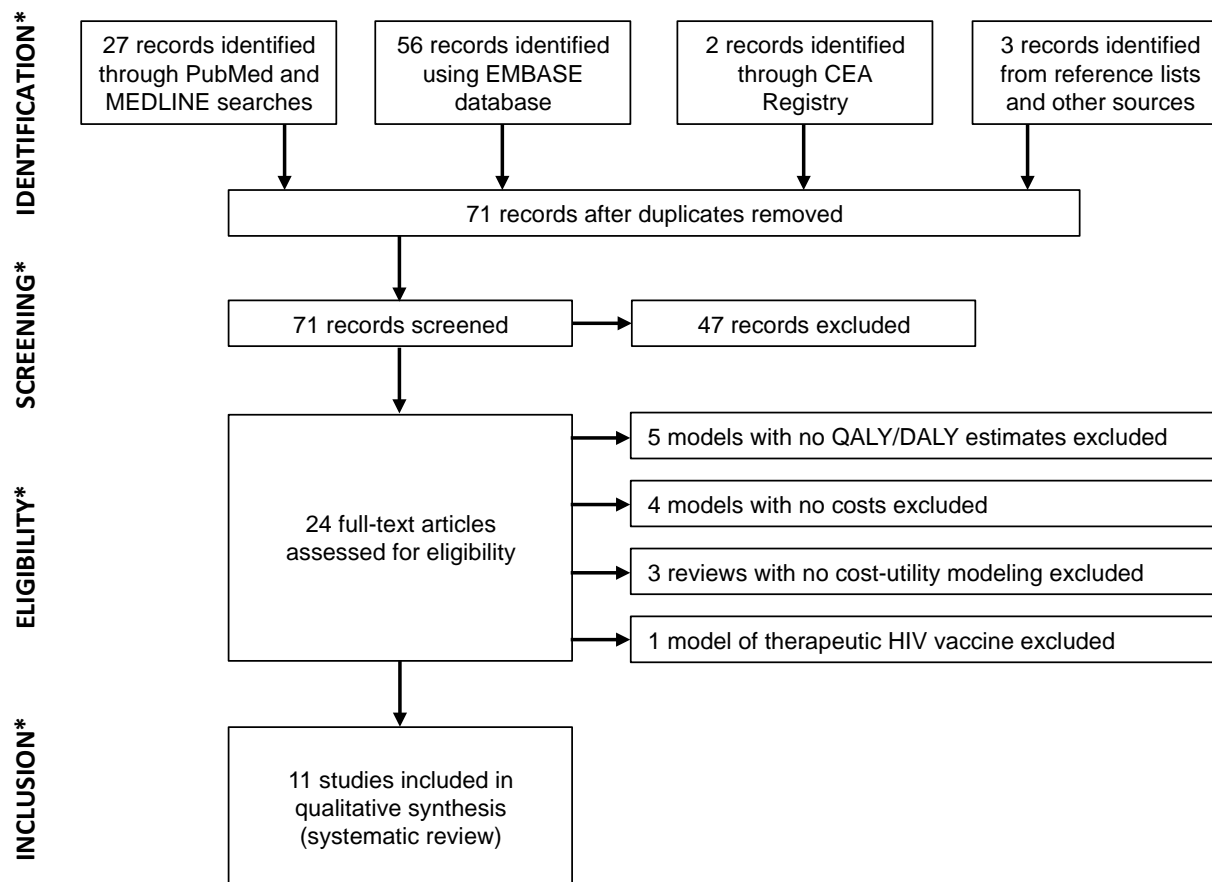


Figure 2.1. Flow of information through different phases of HIV vaccine cost-effectiveness model systematic review process

#### 2.2.4 Data Extraction

Two reviewers (authors BA and DD) extracted model characteristics, methods, parameter values, and results from identified manuscripts by populating a standardized table. The following data elements were sought from each manuscript and its supplemental materials: population studied (region, demographics, local HIV prevalence and incidence), HIV vaccine characteristics (regimen, efficacy, durability, and price), model features (name, structure, outcome measure, perspective, discount rates, time-horizon, years modeled, transmission dynamics, and assumptions), and results (incremental cost-effectiveness ratio (ICER), willingness-to-pay (WTP) or cost-effectiveness threshold, interpretation of cost-effectiveness

results, sensitivity analysis methods, and findings of sensitivity analyses). Incremental cost-effectiveness ratio (ICER) was defined as the marginal cost per marginal health gained with the equation:

$$ICER = \frac{Cost_{intervention} - Cost_{standardcare}}{QALYs_{intervention} - QALYs_{standardcare}}$$

To compare the magnitude of cost-effectiveness in relation to the corresponding country GDP and compare results across studies, we present raw study-reported ICERs and “standardized” cost-effectiveness. Standardized cost-effectiveness was defined as the ratio of ICER to the study-defined WTP threshold, where standardized ICER/WTP values less than one are consistent with the reviewed study author’s interpretation as “cost-effective,” values greater than one are “unlikely cost-effective,” and negative values are likely cost-saving for the case of vaccines.

### 2.2.5 Critical Appraisal

Quality of model reporting was evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist [60]. Recommendations from the US Panel on Cost-Effectiveness in Health and Medicine, the WHO Guide to Cost-Effectiveness, and Briggs et al. guided comparisons of model uncertainty and results [61–63]. Reviewers assessed the frequency of utilizing best practices recommended by the ISPOR-SMDM Modeling Good Research Practices Task Force on dynamic transmission modeling [64]. The terms “cost-effectiveness” and “cost-utility” are used interchangeably through this review aligning with language from the selected articles while recognizing that cost-utility is a sub-type of cost-effectiveness where the outcome is in units such as QALYs or DALYs.

Though types of model structures are not mutually exclusive, for simplicity the studies were categorized into general types. Decision trees include a series of chance nodes with the probability each outcome will

occur using a series of branches. Markov and semi-Markov describe transitions through health states of a cohort of patients over time. Compartmental models use a system of differential equations to describe a fluctuating population in health states over time. Finally, the microsimulation model structure describes individual agents with defined characteristics as part of a whole fluctuating population over time. Technical strengths and limitations of dynamic transmission assumptions were interpreted with infectious disease mathematical modeling texts by Keeling and Rohani, and Vynnycky and White [65,66].

## **2.3 RESULTS**

### **2.3.1 Selection of Studies**

Of the 71 unique records identified from searches, the reviewers assessed 24 full-text articles for eligibility, and excluded 13 articles during full-text assessment (Figure 1). Table 2.1 summarizes the 11 economic modeling studies meeting the eligibility criteria for inclusion in this review [67–77].

Table 2.1. Summary of 11 economic models reviewed

Year	2001	2006	2006	2009	2011	2011	2011	2014	2016	2016a	2016b
<b>Article</b>											
First Author	<b>Bos</b>	<b>Amirfar</b>	<b>Ono</b>	<b>Long 1</b>	<b>Long 2</b>	<b>Hontelez</b>	<b>Leelahavarong</b>	<b>Stover</b>	<b>Harmon</b>	<b>Moodley 1</b>	<b>Moodley 2</b>
Journal, Ref	Pharmacoecon.	JAIDS	Jpn J Infectious Dis	Vaccine	Vaccine	Vaccine	BMC Public Health	PLOS one	PLOS one	Medicine	BMC Public Health
<b>Study Population</b>											
Region	Sub-Saharan Africa	South Africa	Thailand	United States	United States	Hlabisa sub-district in South Africa	Thailand	24 low and middle income countries	24 low and middle income countries	South Africa	South Africa
Targeted group	Infants	15-year old females	10-year old children	ages 15-49 years, gen. pop., MSM and IDU	ages 15-64 years, gen. pop., MSM and IDU	ages 15-49 years	ages 18-30 years, gen. pop., FSW, MSM, IDU and military	ages 15-49 years, gen. pop., FSW, MSM and IDU	15-49 years	9-year old children	10-year old children
HIV Epidemiology	35% lifetime chance of infection	8% HIV prevalence, 2.5-15% HIV incidence	1.5% HIV prevalence, Gender-specific Thai HIV incidence, not presented	HIV prevalence 0.14%-0.29% gen. pop, 11-19% MSM, 14-17% IDU	HIV prevalence 0.1%-0.22% gen. pop, 12.6-18.8% MSM, 12.9-17.3% IDU	HIV prevalence 30%	HIV incidence 0.1% gen. pop, 2.2% FSW, 5.55 MSM, 3.4% IDU	Prevalence 0.1 - 18.8, country specific	Prevalence 0.1 - 18.8, country specific	HIV prevalence 9.9% men, 14.4% women- HIV incidence 1.21% men, 2.28% women-	Age specific HIV prevalence
<b>Vaccine</b>											
Vaccine Efficacy	60%	10-50%	30%	75%	31% over 3 years	31% over 3 years	50%	60-80%	70%	50%	50%
Durability of Protection	Lifetime	Waning	Lifetime	Lifetime	Waning, booster every 3-5 years	Waning, booster every 3-5 years	Lifetime or booster every 5-10 years	Booster every 3-10 years	Booster every 5 years	10 years, annual boosters	10 years, annual boosters
Price per series	\$5	\$20	\$1.54	\$1,000	\$500	\$75	\$100	\$20, \$55	\$20, \$55	\$60	\$60
<b>Model Structure</b>											
Structure	Decision tree	Markov	Markov	Compartmental	Compartmental	Micro-simulation	Semi-Markov	Compartmental	Compartmental	Semi-Markov	Semi-Markov
Outcome	DALY	LY	LY and DALY	QALY	QALY	LY - DALY	QALY	QALY	QALY	QALY	YPG
Perspective	Societal	Payer*	Medical service decision makers	Societal*	Societal	Societal*	Government Perspective	Health System*	Health System*	Health care service provider	Health care service provider
Discounting, 3%	Costs & Outcomes	Costs only	Costs & Outcomes	Costs & Outcomes	Costs & Outcomes	Costs & Outcomes	Costs & Outcomes	Costs only	Costs only	Costs & Outcomes	Costs & Outcomes
Time Horizon	55 years	10 years	Lifetime	20 years	10 years	10 years	99 years	25 years	43 years	Lifetime	Lifetime
Transmission	Static	Static	Static	Dynamic	Dynamic	Dynamic	Static	Dynamic	Dynamic	Static	Static
<b>Results</b>											
ICER	\$3.4/DALY	Dominant, cost-offsets	\$99/DALY	\$15,000/QALY	\$91,000 per QALY	Dominant, cost-saving	\$9,5000 per QALY	\$1,160 - \$11,000 per QALY	\$1,000 - \$10,000/QALY	\$43 per QALY	\$5/LYG
Threshold for Cost-Effectiveness	\$100/DALY	not defined	\$21,000/DALY	\$50,000/QALY	\$50,000/QALY	\$30,420/DALY	\$6,000/QALY	not defined	\$4,671, \$28,400/QALY	\$7,508/QALY	\$7,508/QALY
Interpretation of Cost-Effectiveness	Cost-Effective	Cost-Saving	Cost-Effective	Cost-Effective, Cost-saving if target high-risk	Not cost-effective, Cost-saving if target high-risk	Cost-effective if price <\$100	Not cost-effective, Cost-Effective if 70% efficacy	No interpretation	Highly cost-effective	Highly cost-effective	Highly cost-effective

Notes: The parameters and ICERs represent the base case or average values in each analysis and do not reflect ranges evaluated in sensitivity analyses. \*These studies did not explicitly state their economic perspective, and the perspective listed here was deduced by review authors based on context. Two values are listed for several Harmon parameters to reflect the separate low-income country (LIC) and middle-income country (MIC) analyses. Blue shading: 2011 study is an update to the 2009 model by same author. Pale grey shading: Stover and Harmon studies both used the Goals model with Spectrum software, so parameters are similar. Dark grey shading: two models in one calendar year by same first author with similar parameters.

### 2.3.2 Characteristics of Studies

Methods, population studied, vaccine assumptions, and results are presented in Table 2 and Supplementary Figure S1. The regions of interest included low-income (n = 7), middle-income (n = 4), and high-income countries (n = 2). Two studies using the Goals model (SPECTRUM software package, Avenir Health) included 26 countries in Africa, Asia, Latin America, and Eastern Europe [74,78]. All models reported parameterization using local epidemiological data on HIV. Economic perspectives included the payer (n = 1), government (n = 1), health system (n = 5), and societal or limited societal (n = 4). All studies included a reference group scenario following regional HIV prevention practices and the standard of care in HIV treatment. Stover et al. additionally compared vaccines to scale-up of treatment as prevention (TasP) and explored combining vaccines with TasP and PrEP [78]. The number of studies

following each ISPOR-SMDM dynamic transmission task-force best practice recommendation is provided in Supplementary Table S1. Though a best practice suggests varying the time horizon in dynamic transmission models, none of the studies varied the time horizon in sensitivity analyses.

The most frequent measure of intervention impact was incremental QALYs gained ( $n = 6$ ). Two studies estimated DALYs averted, and the remaining three compared differences in total life-years. The study by Bos et al. incorporated the cost of counseling for an infant's mother with the vaccination series that may parallel the future of VISIP counseling. No studies included a transient or long-term disutility associated with vaccination.

Table 2.2. Target population, modeling methods, vaccine characteristics, and cost-effectiveness results of the 11 studies reviewed

Attribute	N	%	Attribute	N	%
<b>POPULATION &amp; PERSPECTIVE</b>			<b>HIV VACCINE CHARACTERISTICS</b>		
Region*			Age at Vaccination		
South Africa	7	64%	Infant	1	9%
Thailand	4	36%	9-15 years	4	36%
United States	2	18%	>15 years	6	55%
Other	2	18%	HIV Vaccine Efficacy, average		
Population Scope			<50%	7	64%
District	1	9%	>50%	4	36%
Single Country	7	64%	Vaccine Durability		
Several Countries	3	27%	Lifetime Protection	3	27%
Perspective			Waning Protection	8	73%
Payer	1	9%	Vaccine Boosting	7	64%
Government	1	9%	Price per series*		
Health System	5	45%	<=5	2	18%
Limited Societal	4	36%	\$20	3	27%
Defined Willingness To Pay	9	82%	\$50-100	6	55%
Discounted Costs, 3%	11	100%	>\$500	2	18%
Discounted Outcomes, 3%	8	73%	Risk Compensation		
			5	45%	
<b>MODELING METHODS</b>			<b>RESULTS &amp; CONCLUSIONS</b>		
Model Type			ICERs (per QALY, DALY, or LY)		
Decision Tree	1	9%	Dominant, Cost-Saving	2	18%
Markov or Semi-Markov	5	45%	\$3 - \$100	4	36%
Compartmental, ODE	4	36%	>\$1,000	5	45%
Agent-Based	1	9%	Cost-Effectiveness Interpretation		
Dynamic HIV Transmission	5	45%	Cost-Effective	8	73%
Outcome Measurement			Unlikely Cost-Effective	2	18%
LYs	4	36%	No interpretation	1	9%
DALYs	2	18%			
QALYs	6	55%			
Time Horizon					
10 year horizon	3	27%			
20-43 year horizon	3	27%			
Lifetime horizon	5	45%			

\*The Goals model includes 24 countries and assumed a price of \$20 for low-income countries and \$55 for middle-income countries.

Abbreviations: ODE, ordinary differential equations; LYs, Life Years; DALYs, disability adjusted life years; QALYs, quality adjusted life years.

### 2.3.3 Model Structure

The earliest study in 2001 evaluated HIV vaccination with a simple decision tree. Five years later two Markov models were published and then followed by the first dynamic transmission cost-effectiveness model in 2009. Since 2009, half of the HIV vaccine economic models used differential equations to simulate HIV transmission (4 of 8) (Table 2). The Markov, compartmental, and micro-simulation based models stratified the risk of HIV infection by age, gender, and/or risk group.

In contrast to the closed cohort populations in the decision tree and Markov models, the compartmental and microsimulation models allowed for fluctuating populations with susceptible individuals entering the population at their sexual debut. Models by Leelahavarong [73] and Moodley [76,77] tried to overcome the memoryless nature inherent in Markov models by using tunnel states. Alternatively, a microsimulation [79] explicitly modeled sexual partnerships while accounting for heterogeneity between people. This structure makes it easier to model preferential/targeted vaccination and revaccination and was designed to reflect individual preferences for participation in health care and prevention programs.

Studies modeled HIV transmission as static ( $n = 6$ ) or dynamic ( $n = 5$ ). In the static models, including the decision-tree and Markov models, the probability of HIV transmission each time step remained constant over time. In the dynamic models, including ordinary differential equation and agent-based microsimulation models, infections depend on the number of infected and uninfected individuals at each time point as well as on the sexually mixing between different groups. As a result, dynamic models captured not only the direct effects of the intervention on the susceptibility of the vaccinated individuals but also the indirect effects on the HIV transmission by accounting for the decreasing exposure to HIV over time (herd immunity). The static models did not address sexual mixing. The hypothesis of risk compensation, assuming that individuals exhibit riskier sexual behavior when perceiving that they are

protected from HIV, was explored in four of the models [71,72,74,78]. Hontelez [80] concluded this potential change in risk following vaccination could nullify the epidemic impact in South Africa.

#### 2.3.4 Vaccine Effectiveness

The average of 3-year HIV vaccine efficacy values across all studies was 51.3% (Figure 2). Sensitivity analyses included a range of efficacy from 10-90%. Though uncertainty in HIV vaccine efficacy decreased following the Thai trial results in 2009, the average of estimates from models before 2009 (VE = 49%, n = 4) did not greatly differ from the average of the estimates after 2009 (VE = 52%, n = 7). A majority of the studies (8 of 11) assumed that vaccine efficacy protection remained constant over time, while three studies modeled efficacy declining over time since immunization. All studies published after 2009 included boosts from re-vaccination to ensure continuity of protection, following the results from the Thai trial [26]. Two studies from a 2011 theme issue of Vaccine (Hontelez and Long 2) modeled vaccine efficacy decaying over time with a functional form of  $VE=0.78 \times \exp^{-0.06t}$ , where  $t$  = time since vaccination in months [71,79].

#### 2.3.5 Costs

All studies discounted total costs by 3% annually and most described ranging this rate in the sensitivity analysis. Health outcomes were discounted 3% in eight (73%) of analyses [69–73,76,77,81]. In the year of this review, HIV vaccines are not licensed and the market price has not been set. Modelers assumed the average cost of a vaccine series was \$1.54 - \$75 USD in low-income countries, \$55 - \$100 in middle-income countries, and \$500 - \$1,000 in the United States (Figure 2.2). There was no observable trend in pricing assumptions by efficacy across studies (Figure 2.4.c). The cost of HIV care and treatment varied widely between studies according to local health care costs, and contributed greatly to differences in cost-

effectiveness results. No studies included future research and development costs for the HIV vaccine leading to licensure.

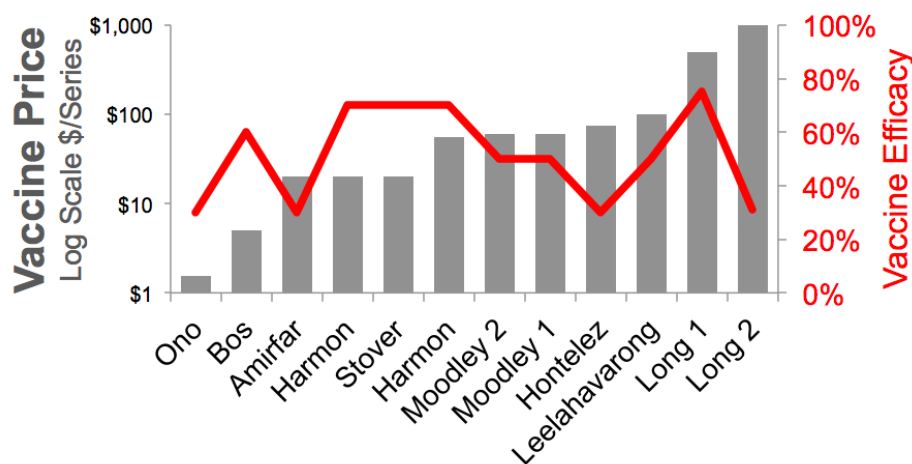


Figure 2.2. Assumed HIV vaccine efficacy and price per series (log scale) across the 11 studies reviewed.

### 2.3.6 Cost-Effectiveness

Base case ICERs ranged from dominant (cost-offsets) to \$91,000 per QALY gained (Table 2.1 and Figure 2.3.a). Two studies used the Goals model (SPECTRUM software package, Avenir Health) and found similar ICER estimates ranging from approximately \$1,000 - \$11,000 per QALY across 24 low and middle-income countries [74,78]. Nine of 11 studies pre-specified a local willingness-to-pay or cost-effectiveness threshold to interpret results. Base case vaccination scenarios were not cost-effective in 3 of 11 models, including one low, one middle, and one high income country (Figure 2.3.b). Stover et al. [82] did not explicitly interpret the cost-effectiveness of their results, so we have inferred the cost-effectiveness threshold from the supporting information from Harmon et al. From the rest of the studies, three projected that vaccinations in their base case scenarios were cost-effective, three were highly cost-effective, and two were cost-saving. Several models used sensitivity analyses to identify target populations for cost-saving vaccination. All modelers agreed targeting groups with highest HIV incidence improves cost-effectiveness. As expected, WTP standardized ICERs increased as price increased (Figure

2.4.a). There was no clear trend in association between vaccine efficacy and cost-effectiveness across studies (Figure 2.4.b).

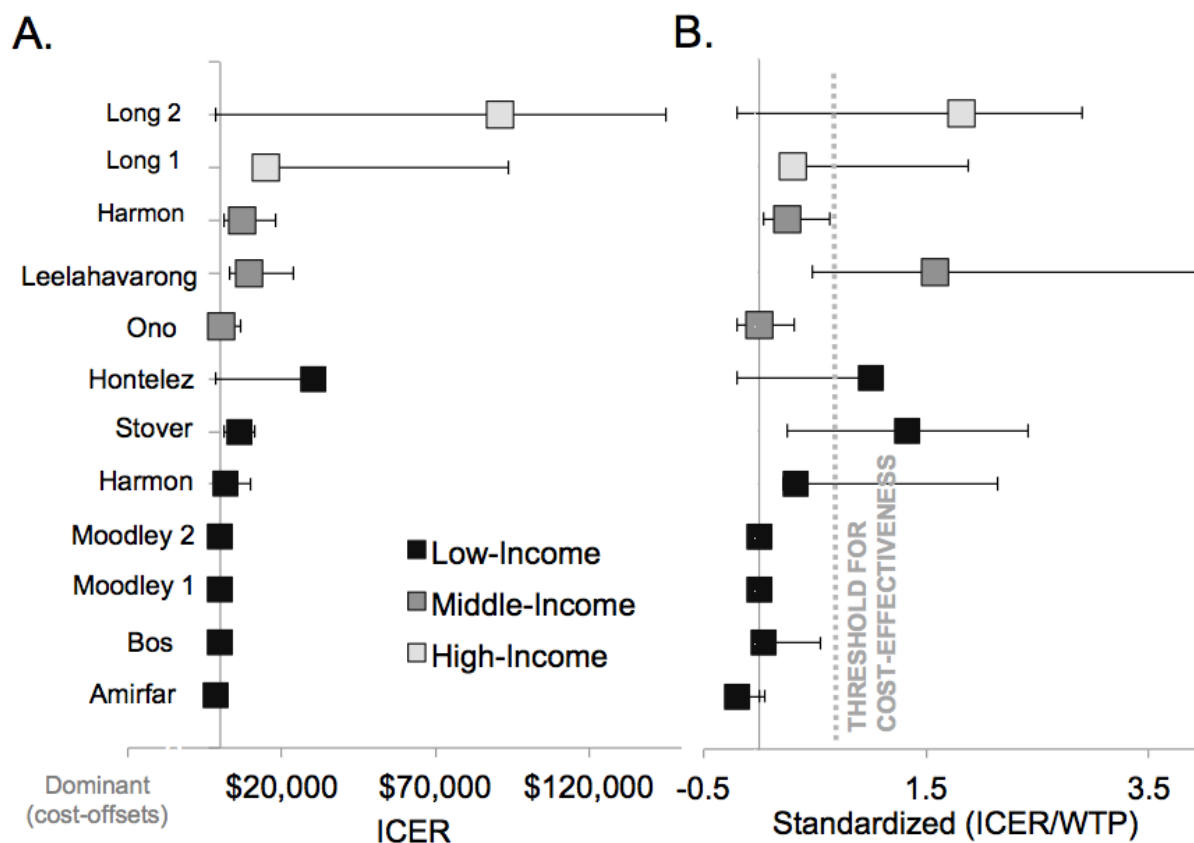


Figure 2.3. Cost-effectiveness studies of HIV vaccines.

A) Incremental cost-effectiveness ratio results from the base case of each study reviewed with error bars representing lower and upper ranges from the sensitivity analysis; B) same as Panel A with ICER standardized to willingness-to-pay threshold specified by study (see Table 1). Footnotes: The ICER uncertainty from Hontelez et al. is reported in one direction as a result of the threshold analysis method to set the vaccine price, resulting in an ICER equal to the country-specific willingness-to-pay. Three authors are included twice to reflect different results from multiple publications (Long and Moodley) while another presented results for two populations within one publication (Harmon). Amirfar and Stover did not explicitly state cost-effectiveness thresholds. The threshold from Harmon et al. was applied to the Stover study as both model the same 26 countries. Standardized ICER = ICER/WTP. ICER, Incremental Cost-Effectiveness Ratio. WTP, willingness to pay per health unit gained.

All studies evaluated parameter uncertainty based on one-way sensitivity analyses. Five used scenario analyses to understand uncertainty by changing several parameters at one time to observe the change on cost-effectiveness. Both models by Moodley [76,77] in 2016 performed multivariate sensitivity analysis using 1,000 Monte Carlo simulations based on random draws from each variable distribution to evaluate

the combined effect of parameter uncertainty on the study results. Appropriate to the differing structural form, Hontelez [80] correspondingly characterized combined uncertainty with simulation of 1,000 individuals and scenarios. A minority of studies (3 of 11) reported model validation of epidemic predictions using historical HIV surveillance data. Scenario analyses focused on men who have sex with men and injection drug users were found to be more cost-effective than vaccination of the general population. Several studies discussed how a targeted immunization strategy for high-risk sub-populations could result in cost savings for a health system. The microsimulation structure captured patient heterogeneity and sexual mixing more specifically and intentionally than the other economic models and reached very similar conclusions.

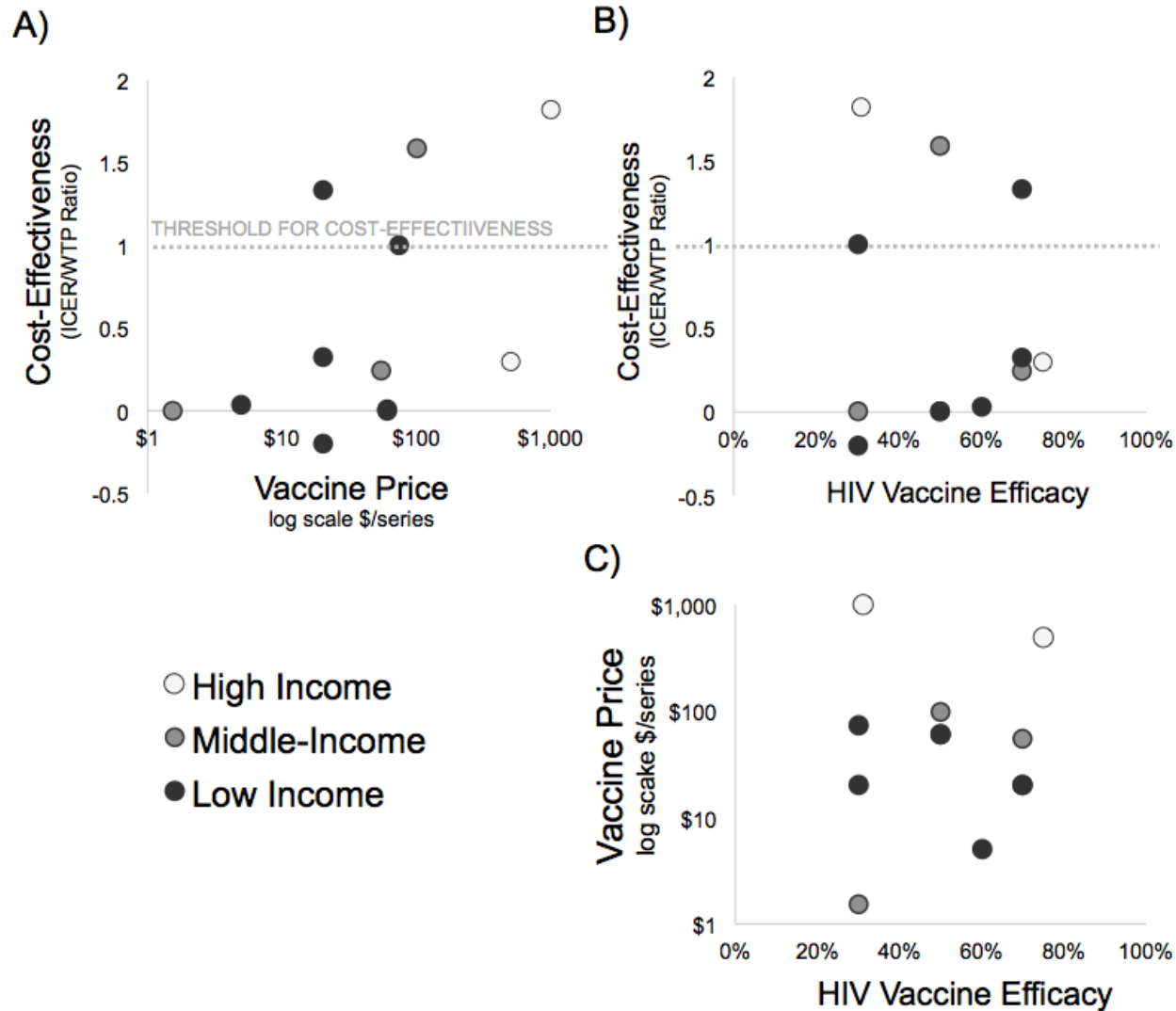


Figure 2.4. Vaccine price and efficacy relationship with standardized cost-effectiveness (ICER/WTP) stratified by country income level.

Notes: The ICER uncertainty from Hontelez et al is reported in one direction as a result of the threshold analysis method to set the vaccine price, resulting in an ICER equal to the country-specific willingness-to-pay. Three authors are included twice to reflect different results from multiple publications (Long and Moodley) while another presented results for two populations within one publication (Harmon). Amirfar and Stover did not explicitly state cost-effectiveness thresholds. The threshold from Harmon et al was applied to the Stover study as both model the same 26 countries. Standardized ICER = ICER/WTP. ICER, Incremental Cost-Effectiveness Ratio; WTP, willingness to pay per health unit gained.

## 2.4 DISCUSSION

This systematic review aimed to identify HIV vaccine characteristics and vaccination conditions that may be critical for an HIV vaccine to be cost-effective and valuable. The comparison of the published modeling studies suggested HIV vaccines with average 50% efficacy waning over three years and supplemented by boosting every few years may be a realistic profile for a “good enough” vaccine to make a large impact on the HIV epidemic. As shown in this collection of economic models, a moderately effective vaccine could be cost-effective in developed and developing countries. The potential cost-effectiveness of vaccination was strongly linked to the HIV burden in each population, but due to the heterogeneity in the studies, a formal meta-analysis was not conducted. In two studies [71,73] where HIV vaccines were predicted to be unlikely cost-effective, they had in common a lower-incidence general population as the target for vaccination. Vaccines targeted to individuals at greater risk of HIV infection will improve cost-effectiveness within the health system and models did not predict that sexual mixing patterns would dilute the effects of targeted vaccination.

The potential cost-effectiveness of HIV vaccines depended on price and average efficacy. As the price of an HIV vaccine series increased in sensitivity analyses, there reached a point where vaccination would no longer be longer cost-effective. This threshold for vaccine price depended on each country’s GDP per capita. Several studies explored the components contributing towards average efficacy, such as the rate of decay in immunogenicity, the corresponding durability of protection, the proportion of people who response, and the frequency of boosting. Our qualitative review indicated a moderately effective vaccine profile with poor durability and frequent boosting could have greater impact on the HIV epidemic than a single vaccination series with improved durability. This suggests future studies in non-human primates and humans should carefully evaluate the change in breadth and depth of immunological response following repeated boosting every 2-5 years.

While we did not find any infectious disease modeling method reviewed to be more valid than others, the structure and assumptions should be carefully selected based on the question of interest and data available. As HIV prevention and treatment guidelines change dramatically over time, future economic models in HIV prevention should clearly define the reference standard of care and consider including pre-exposure prophylaxis as a component in the reference for comparison. This need for standardized components, methods, and perspectives to enhance comparability among studies is further supported by a new report from the Second Panel on Cost-Effectiveness in Health and Medicine [83,84].

The 11 studies published between 2001 and 2016 exemplified a diverse range of model structure choices, economic methods, and population-specific parameter values. Almost half ( $n=5$ ) of the studies did not clearly state or define an economic perspective. Impact measured in unadjusted life years gained did not consider quality of life and may have underestimated the total benefit from vaccination [77,85,86].

Fundamental to the epidemiology of infectious diseases, one expects the average age at diagnosis to increase as HIV prevalence decreases and exposure to infection is delayed. For example, two infected lives ending at 60 years from death unrelated to HIV have the same value in LYs if HIV infection occurred at 30 or 55 years of age. Alternatively, studies estimating QALYs or DALYs capture a difference in total health based on the preference for more healthy years lived before HIV infection. A surprising majority of studies measured impact in QALYs when considering a perception that DALYs are used more often than QALYs for developing countries. We assume the interpretation of QALYs gained versus DALYs averted is the same, though the potential for differences has been discussed elsewhere [87,88].

If most of the health gains from a vaccine were accumulated late in the time horizon, then models discounting costs-only [78,85,89] would be more likely to produce results that are cost-effective compared to studies that discount both costs and QALYs. Reports including plots of cumulative health

outcomes, changes in HIV incidence over time, and sensitivity analyses with undiscounted costs and outcomes most effectively communicated the timing of initial vaccine investment, accrual of HIV care cost-savings, and the time to capture significant population health gains.

Despite professional society best practice recommendations for dynamic transmission modeling [64], no studies presented results using more than one time horizon. Most studies justified their choice of model structure and conducted some sensitivity analyses of structural assumptions. A minimal modeling movement advocates development of models as simplistic as possible to answer one question of interest [90]. The articles reviewed highlight that a benefit of simple models is the ease of interpretation. Evaluating and balancing the importance of clinical and epidemiological assumptions is vital for readers to assess face validity of economic models. Each modeling choice has trade-offs, and while a behavioral HIV prevention intervention may require model complexity of heterogeneous sexual networks with concordancy and preferential mixing, researchers of different intervention not affecting these dynamics may value the benefits of simplicity more than potential incremental validity gained.

We identified a diverse variety of modeling structures and assumptions applied to this infectious disease. Decision trees and Markov models are often developed to evaluate the cost-effectiveness of pharmaceuticals, though in this case only the compartmental and microsimulation models captured the indirect effects of vaccination. Fundamental features for HIV vaccines included local HIV incidence data, a clearly defined population, assumption of efficacy and its waning, the local willingness to pay for health gains, and importantly the vaccine price. Like the results Brisson and Edmunds, our qualitative review highlights that choices in 1) the model type and structure, 2) economic methods, and 3) parameter values all introduced uncertainty for decision makers [54,91,92].

This qualitative review had several limitations. The uncertainty in future HIV vaccine characteristics and small number of studies available posed a challenge in drawing definitive conclusions based on this review. As the epidemic context and economic conditions varied greatly between study populations, a meta-analysis was not possible. Over years 2001-2016 when the 11 studies were published, the technology, access, and standards for HIV testing and treatment changed over time and by country. However, all the studies published after 2009 modeled similar regimens of multi-dose vaccination with waning efficacy over time that correspond to the vaccine candidates currently tested in clinical studies. Reference groups for comparison are different and limit the ability to compare across studies. We assumed methodological differences measuring health outcomes in units of QALYs, DALYs, and LYs did not change overall findings or ICER interpretation. There was potential for incomplete retrieval of published research manuscripts, and publication bias may have prevented analyses with inconclusive findings from being submitted to or acceptance in journals. Well-crafted economic models of HIV vaccines presented in book chapters, conference presentations, or languages other than English were potentially missed.

#### **2.4.1 Conclusion**

Eleven published studies found HIV vaccines cost-effective under certain conditions. HIV vaccine cost-effectiveness depended most on efficacy, price, and HIV incidence in the target population. Country-specific cost inputs and willingness to pay thresholds may explain differences in cost-effectiveness. The studies provided evidence that immunization with a modestly effective HIV vaccine is likely an efficient use of resources in the United States, Thailand, and several sub-Saharan African countries, though decision makers must balance the studies findings with acknowledgement of great uncertainty. The review suggests regional HIV epidemiology and assumed willingness to pay thresholds were more influential on study findings than differences from a methodological choice of static or dynamic HIV transmission. The broad disciplinary range among authors affirms the need for interdisciplinary

collaboration between health economists, epidemiologists, clinicians, infectious disease mathematical modelers, biostatisticians, and clinical trial scientists to develop valid and meaningful results.

**Data Availability Statement**

The studies systematically reviewed are available from National Library of Medicine on PubMed.

**Author Contributions**

Blythe Adamson designed the review, searched for studies, extracted data, analyzed findings, and drafted the manuscript. Dobromir Dimitrov extracted data from selected studies and wrote sections of the manuscript. Beth Devine helped design the review, interpret results, and edit the manuscript. Ruanne Barnabas interpreted the extracted data and wrote sections of the manuscript.

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**Compliance with Ethical Standards**

Blythe Adamson, Dobromir Dimitrov, Beth Devine, and Ruanne Barnabas declare no competing interests. This review was supported in part by a fellowship to BA from grant number T32HS013853 from the Agency for Healthcare Research and Quality and in part by a 2015 Trainee Support Grant from the University of Washington Center for AIDS Research (CFAR), an NIH funded program under award number P30AI027757. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality or the National Institutes of Health.

# Chapter 3

## Potential Competition between Biomedical HIV

### Prevention Strategies in Seattle, Washington

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## ABSTRACT

**Background:** Promising HIV vaccine candidates are steadily progressing through the clinical trial pipeline. HIV vaccines may be a complement or possibly a competitor with other biomedical prevention strategies such as pre-exposure prophylaxis (PrEP). Accordingly, the value of HIV vaccines and the policies for rollout may depend on the rate of this substitution and the cost of PrEP. In this economic modeling analysis, we estimate the cost-effectiveness of HIV vaccines when considering the potential interaction with PrEP interventions.

**Methods:** We developed a dynamic transmission model of HIV that included potential interactions between PrEP and HIV vaccines. The study population included men who have sex with men (MSM) in Seattle, WA, between the ages of 15-64 years. We used a time horizon of 2025-2045 and an annual discount rate of 3% for costs and quality-adjusted life years (QALYs). Costs were adjusted to a common currency of 2017 USD. Benchmarking on the price of an HPV vaccine, we assume that HIV vaccines launch with a price of \$1,267 per dose, totaling \$8,121 for a 5-dose series. The primary economic endpoint is the incremental cost-effectiveness ratio (ICER).

**Results:** Vaccine access achieving 90% coverage of high-risk men and 60% coverage of others is projected to reduce HIV prevalence in Seattle by 1.4% and avoid 37.9% of new HIV infections between 2025-2045 compared to continuing current practice without a vaccine. Assuming PrEP users will be vaccinated during a preventative clinic visit and then have an average shorter duration using PrEP, we would expect 63% fewer MSM to be using PrEP in 2045 compared to projection of 2045 without vaccine. The model projects that vaccines would increase discounted total healthcare costs by \$224 million, with some PrEP costs shifted to HIV vaccines. HIV vaccines are estimated to have an ICER of \$110,622/QALY, which would be cost-effective at threshold of \$150,000/ QALY.

**Conclusion:** Access to an HIV vaccine is desirable as it could increase the overall effectiveness of combination HIV prevention efforts and improve population health. Planning for the rollout and scale-up of HIV vaccines should carefully consider the design of policies that guide interactions between vaccine and PrEP utilization.

### 3.1 INTRODUCTION

Combinations of evidence-based HIV treatment and prevention interventions will be necessary to eradicate HIV. Investment and policy decisions consider not only effectiveness, but also aspects of access, acceptability, behavior change, and costs. This is an important question because current prevention interventions are imperfect. Decision-makers weigh population-level trade-offs for opportunities that offer small benefits to a large number of individuals or large benefits to a small number of individuals. The spillover benefit of herd immunity makes the comparison of these opportunities very sensitive to the potential rate of uptake and target coverage size.

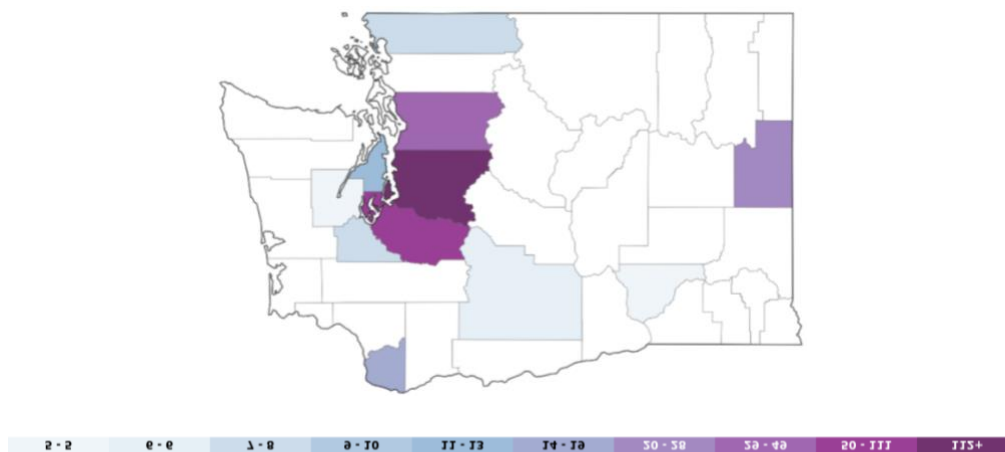


Figure 3.1. Number of persons newly diagnosed with HIV in Washington state, 2015

Source: AIDSvu [9]

In the United States, Seattle is an urban leader and early adopter of evidence-based HIV strategies. Seattle-King County Public Health surveillance rigorously monitors epidemic indicators and care cascade milestones, and it was the first US urban city to reach the “90-90-90” goal set by WHO. In King County, health officials estimate 6,980 residents lived with diagnosed HIV infection in 2014, totaling more than half of all HIV cases in the state (Figure 3.1 and Figure 3.3) [93]. With 12.6% of all men who have sex with men (MSM) in King County HIV infected, more than two-thirds of all new infections are in MSM.

In 2014, 281 people were newly diagnosed with HIV in King County, with local data suggesting rectal gonorrhea or early syphilis as one of the strongest risk factors [94].

Seattle has combated new infections with pre-exposure prophylaxis (PrEP), a once-daily oral prescription medicine that can help reduce the risk of getting HIV. TRUVADA® (Gilead Sciences, Inc.) is a combination product of 200 mg emtricitabine (FTC) and 300 mg tenofovir disoproxil fumarate (TDF) that is used for PrEP. In March 2018, the Federal Supply Schedule (FSS) price of TRUVADA® was \$1,050 for a 30-day supply [95]. As a complement to national guidelines for prescribing and monitoring PrEP [96], Public Health Seattle & King County with the Washington State Department of Health offer local guidance in Figure 3.2 for medical providers to recommend and discuss PrEP with priority populations [97]. PrEP are recommended to get tested every three months for HIV and other STIs. The contribution of PrEP use to the prevalence of detectable drug resistance has been greater than anticipated [98], considering high levels of TDF/FTC resistance (6%) have been identified among genotypic sequences of people living with HIV in King County, WA [99].

<b>Recommend PrEP for MSM who...</b>	<b>Discuss PrEP<sup>c</sup> with MSM who...</b>
<ul style="list-style-type: none"> <li>• Report use of meth or poppers<sup>a</sup>,</li> <li>• Have been diagnosed with rectal gonorrhea or syphilis<sup>a,b</sup>,</li> <li>• Provided sex in exchange for money or drugs<sup>a</sup>, OR</li> <li>• Are in ongoing sexual partnership(s) with HIV-positive partner(s) who are not on ART, started ART ≤6 months ago, or are not virally suppressed</li> </ul>	<ul style="list-style-type: none"> <li>• Report condomless anal sex (CAS) with a non-main/primary partner or with a partner of unknown or positive HIV status<sup>a,d</sup>,</li> <li>• Have been diagnosed with urethral gonorrhea or rectal chlamydia<sup>a</sup>,</li> <li>• Report use of non-prescription injection drugs<sup>a</sup>, OR</li> <li>• Are in ongoing sexual partnership(s) with HIV+ partner(s) who have been on ART &gt;6 months and are virally suppressed</li> </ul>
<p><sup>a</sup>In the past 12 months; <sup>b</sup>The guidelines refer to a diagnosis of early syphilis. In this analysis, we consider any diagnosis of syphilis as an indication for PrEP. <sup>c</sup>Other indications for discussing PrEP not measured in the survey include being in a relationship with an HIV+ female partner trying to become pregnant, completing a course of non-occupational post-exposure prophylaxis, and seeking a prescription for PrEP. <sup>d</sup>Proxy measure for CAS outside of a long-term, mutually monogamous relationship with a man who is HIV-negative.</p>	

Figure 3.2. Washington state PrEP implementation guidelines for MSM

Source: Rao CROI 2018 [100]

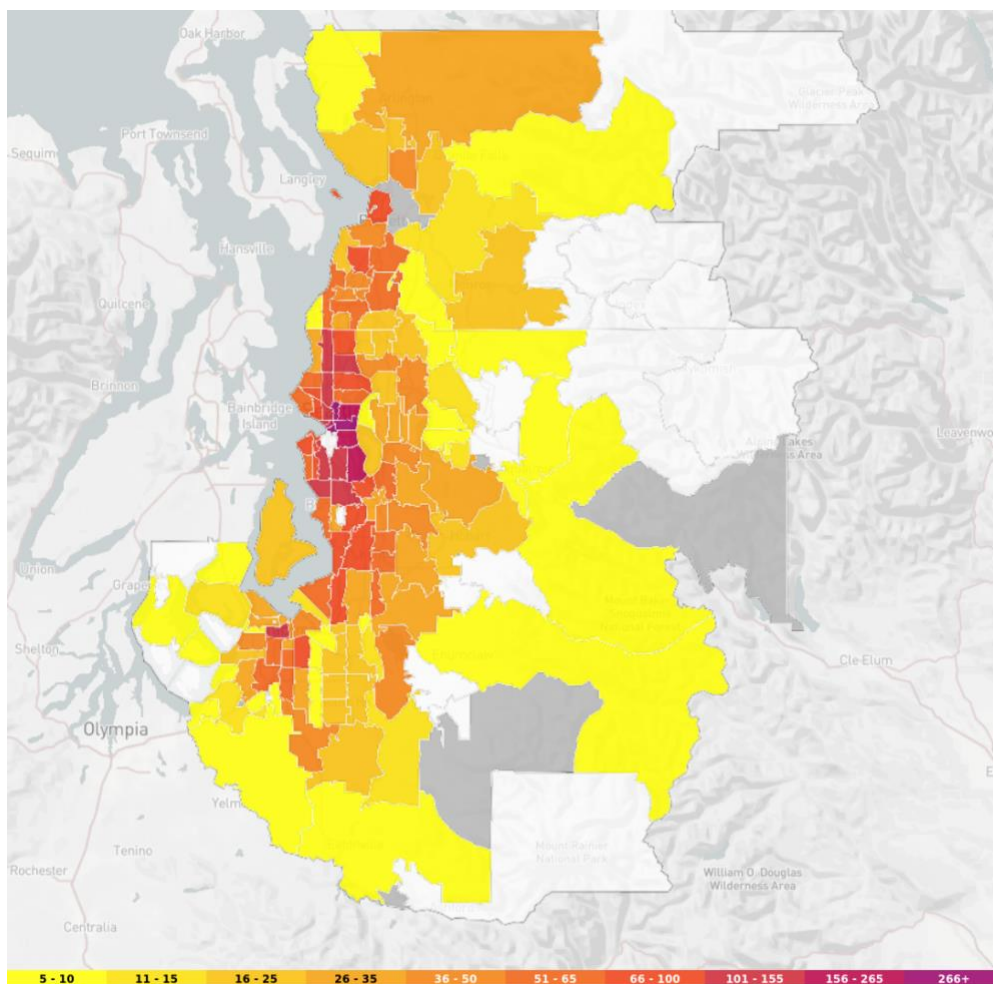


Figure 3.3. Number of males living with diagnosed HIV in Seattle, WA, 2015

Source: AIDSvu [9]

Recent progress in HIV vaccine development means another biomedical product for prevention is approaching the horizon of availability [101]. A summary of HIV vaccine efficacy trials to date is provided in Table 1.3. A breakthrough 2009 Phase 3 trial in Thailand found significant HIV vaccine efficacy averaging 31% fewer infections over three years [26]. Confirmatory trials are ongoing in South Africa, with modifications to improve the Thai regimen – powered to detect HIV vaccine efficacy of 50% [27]. Based on prospectively defined immunogenicity thresholds, criteria were met for the Pox-Protein Public Private Partnership (P5) to support the launch of a Phase 2b/3 study in Africa: HIV Vaccine Trials Network 702 Study [37].

Real trade-offs have to be made when offering imperfect prevention products. This is an important question because all available biomedical products for HIV prevention are imperfect, and the evidence of PrEP cost-effectiveness is mixed [56,103–105]. One framework for optimal resource allocation for investments is a static optimization model to evaluate potential combination HIV prevention strategies [102]. A systematic review identified 11 published cost-effectiveness analyses of HIV vaccines. Previous modeling studies have separately examined the cost-effectiveness of PrEP [56,105,106] and the potential cost-effectiveness of HIV vaccines [67–77]. Two models evaluating the potential combined effect of protection using both a vaccine and PrEP together found lower costs and improved health outcomes compared to using PrEP alone [74,107]. This is the first modeling study to examine the economic impact of potential competition between HIV vaccine and PrEP products. In this economic modeling analysis, we estimate the cost-effectiveness of HIV vaccines when considering the potential interaction with PrEP.

## 3.2 METHODS

### 3.2.1 Study Population

The study population includes men who have sex with men ages 15-64 in Seattle, WA over the time horizon of 2025-2045. Over time MSM enter the population at age of sexual debut and exit the population at age 64. Public Health Seattle-King County and the Washington State Department of Health estimate this population size as 5.4% of males [93]. Within this population, 80% self-identify as gay and half had 5 or more male sex partners in the last 12 months.

### 3.2.2 Model Overview

We developed a compartmental mathematical model (see Figure 3.4) to simulate the HIV epidemic among MSM in Seattle and evaluate the clinical and economic impact of an HIV vaccine with PrEP. The model consists of a system of differential equations describing HIV transmission and disease progression through a series of health states. We consider the MSM population of Seattle first stratified into two groups by HIV infection status: the susceptible population and the infected population. Individuals are divided into risk groups ( $i$ : low risk <5 partners or high risk 5+ partners in past 12 months), age groups ( $k$ : young 15-24 years, middle 25-44 years, or older 45-64 years), and sexual role ( $j$ : insertive, receptive, or versatile position). The susceptible population  $S_q$  is grouped by current use HIV prevention, where  $q \in \{1$  (no protection), 2 (PrEP), 3 (vaccine), 4 (PrEP and vaccine)} represents coverage from a single or combination of products offering partial protection from infection.

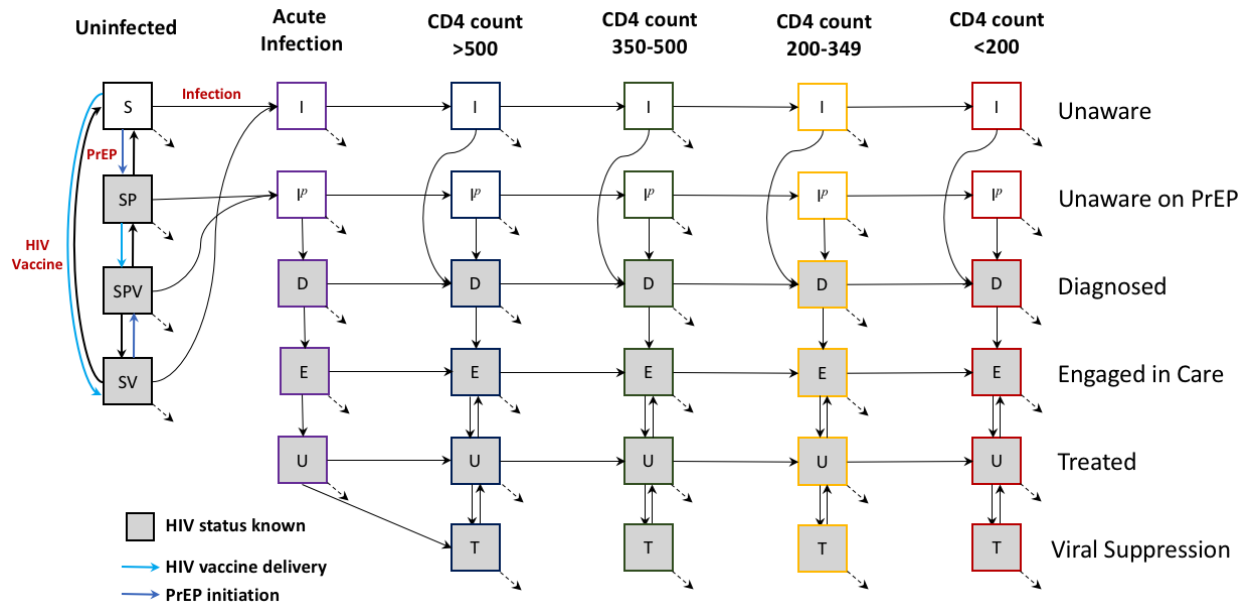


Figure 3.4. Schematic model diagram

This schematic represents the deterministic dynamic compartmental model. The boxes represent disease-stage compartments of men who have sex with men and the arrows represent transitions between compartments. Individuals enter into the unvaccinated population and may die or exit the population at various disease stages. Not represented in the diagram is stratification by age group (15-24, 24-44, and 45-64 years), risk group (low and high), and sexual role (anal insertive, receptive, or versatile).

The infected individuals are stratified by disease progression and where they fit into the HIV care cascade. Those who are infected but are unaware of their HIV status are in group  $I_\phi$ , where  $\phi \in \{1$  (acute), 2 (CD4>500), 3 (CD4 350-500), 4 (CD4 200-349), 5 (CD4<200)} represents the disease stage of the individual stratified by CD4 count. Infected individuals are also assigned in compartments by treatment status as undiagnosed, diagnosed but not yet on ART, using ART but not virally unsuppressed, and virally suppressed while using ART. Those who are infected, diagnosed, but not engaged in care are in group  $D_\phi$ . Those who are engaged in care, but not on ART are in group  $E_\phi$ . Those who are on ART, but not virally suppressed due to lack of adherence or drug resistance are in group  $U_\phi$ . Finally, those who are virally suppressed from ART are in group  $T_\phi$ . We assume that PrEP and vaccination do not affect the course of infection. The rate of mixing between populations depends on the current distribution of risk, role, and age groups. We ensure the overall number of partnerships between groups remains balanced by continually updating the fraction of partners someone with a particular risk, role and age group has with the rest of the population.

We assume that it takes longer than three months to go through the care cascade and become virally suppressed. This means that newly suppressed people move from  $U_1$  into  $T_2$ . We assume that those who are suppressed stay in their respective CD4 categories (so that if they stop treatment they return to their original unsuppressed state) but have the same behavior, infectivity, and utility across the CD4 dimension ( $T_2 - T_5$ ). Individuals on ART may interrupt treatment and reinitiate it again. Susceptible MSM who become sexually active join the community at constant rate, corresponding to estimated population growth among the MSM population in Seattle [108]. The rates at which individuals acquire HIV infection depends on the annual number of partners per susceptible person, the number of sex acts per partnership,

the fraction of sex acts protected by condoms, and the HIV acquisition risk per receptive and insertive anal intercourse with HIV infected partner.

The model is used to simulate HIV epidemics without an HIV vaccine to provide a reference scenario for the evaluation of the vaccine impact. The effectiveness of the intervention over the 2025-2045 period is evaluated by comparison of the intervention to the reference scenario assuming no changes in the current CDC guidelines for HIV prevention and treatment [96]. The following metrics of effectiveness are evaluated for each scenario over 20 years of intervention: cumulative number and fraction of HIV infections prevented, reduction in HIV incidence and HIV prevalence due to the vaccine program. All metrics are compared across intervention coverage levels for 100 simulations using the preselected sets of epidemic parameters identified in the calibration procedure.

### 3.2.3 Model Equations

#### 3.2.3.1 Parameters

In general:

- Risk status  $i \in \{1 \text{ (low risk)}, 2 \text{ (high risk)}\}$
- Role status  $j \in \{1 \text{ (insertive)}, 2 \text{ (receptive)}, 3 \text{ (versatile)}\}$
- Age status  $k \in \{1 \text{ (young)}, 2 \text{ (middle)}, 3 \text{ (old)}\}$
- Prevention status  $q \in \{O \text{ (no biomedical prevention coverage)}, P \text{ (PrEP)}, V \text{ (vaccine)}, PV \text{ (PrEP and vaccine)}\}$
- Disease stage  $\phi \in \{1 \text{ (acute)}, 2 \text{ (CD4 > 500)}, 3 \text{ (CD4 350-500)}, 4 \text{ (CD4 200-350)}, 5 \text{ (CD4 < 200)}\}$
- Awareness status  $A \in \{I \text{ (Infected)}, P \text{ (Infected on PrEP)}, D \text{ (Diagnosed)}, E \text{ (Engaged in care)}, U \text{ (On ART, Unsuppressed)}, T \text{ (On ART, Suppressed)}\}$

$\nu^i$ : Fraction of new PrEP from susceptibles OFF PrEP with risk status  $i$  and prevention status  $q$

$\upsilon_q^i$ : Fraction of new vaccinations from susceptibles with risk status  $i$  and prevention status  $q$

$\omega_q^i$ : Fraction of discontinuing PrEP from susceptibles ON PrEP with risk status  $i$  and prevention status  $q$

$\varpi_q^i$ : Fraction of losing vaccine coverage from vaccinated susceptibles with risk status  $i$  and prevention status  $q$

$d_k$ : Death rate (non-HIV related) for age  $k$

$\mu_\phi$ : HIV-related death rate for disease stage  $\phi$

$a_k$ : Aging rate from age  $k$  to age  $k+1$

$\rho_{i,k}$ : Fraction of population with risk status  $i$  and in age group  $k$

$r_j$ : Fraction of population with role status  $j$

$b$ : Population birth (aging into population) rate

$\sigma_{A,\phi}$ : Forward awareness transfer rate based on disease stage  $\phi$  and awareness status  $A$  (vertical flows)

$\tau_{A,\phi}$ : Drop rate from awareness status  $A$  (losing suppression, dropping ART or leaving care) into disease stage  $\phi$

$\delta_{A,\phi}$ : Disease progression rate based on disease stage  $\phi$  (horizontal flows) and awareness/treatment status  $A$  (vertical flows)

$\lambda^{i,j,k}$ : Force of infection for newly infected population entering  $I_1^{i,j,k}$

$\lambda_P^{i,j,k}$ : Force of infection for newly infected population using PrEP entering  $I_{P,1}^{i,j,k}$

$\lambda_V^{i,j,k}$ : Force of infection for newly infected vaccinated population entering  $I_1^{i,j,k}$

$\lambda_{PV}^{i,j,k}$ : Force of infection for newly infected vaccinated population using PrEP entering  $I_{P,1}^{i,j,k}$

$S_q^{i,j,k}$ : Susceptible population with prevention status  $q$ , risk status  $i$ , role group  $j$  and age group  $k$

$I_{\phi}^{i,j,k}$  : Infected population OFF PrEP with risk status  $i$ , role group  $j$  and age group  $k$  who are in disease stage  $\phi$

$I_{P,\phi}^{i,j,k}$  : Infected population ON PrEP with risk status  $i$ , role group  $j$  and age group  $k$  who are in disease stage  $\phi$

$D_{\phi}^{i,j,k}$  : Diagnosed infected population with risk status  $i$ , role group  $j$  and age group  $k$  who are in disease stage  $\phi$

$E_{\phi}^{i,j,k}$  : Infected population who are engaged in care but not on ART with risk status  $i$ , role group  $j$  and age group  $k$  who are in disease stage  $\phi$

$U_{\phi}^{i,j,k}$  : Infected population who on ART but unsuppressed with risk status  $i$ , role group  $j$  and age group  $k$  who are in disease stage  $\phi$

$T_{\phi}^{i,j,k}$  : Infected population who on ART and suppressed with risk status  $i$ , role group  $j$  and age group  $k$  who are in disease stage  $\phi$

$I$  : Infected population size  $I = \sum_{i,j,k,\phi} \left( I_{\phi}^{i,j,k} + I_{P,\phi}^{i,j,k} + D_{\phi}^{i,j,k} + E_{\phi}^{i,j,k} + U_{\phi}^{i,j,k} + T_{\phi}^{i,j,k} \right)$ . Here  $T_1^{x,y,z} = 0$ .

$S$  : Susceptible population size  $S = \sum_{i,j,k} \left( S^{i,j,k} + S_P^{i,j,k} + S_V^{i,j,k} + S_P^{i,j,k} \right)$

$N$  : Total population size  $N = S + I$

$\delta_{i,j}$  : Kronecker delta function

### 3.2.3.2 Equations

For simplicity, all variables corresponding to age group  $k = 0$  have a value 0.

$$\frac{dS^{i,j,k}}{dt} = b\delta_{1,i}r_j\rho_{i,k}N + \omega S_P^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l S^{l,j,k-1} - (d_k + v^i + a_k) S^{i,j,k} - \lambda^{i,j,k} S^{i,j,k},$$

$$\frac{dS_P^{i,j,k}}{dt} = v^i S^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l S_P^{l,j,k-1} - (d_k + v_P^i + a_k) S_P^{i,j,k} - \lambda_P^{i,j,k} S_P^{i,j,k},$$

$$\frac{dS_V^{i,j,k}}{dt} = \omega_{PV} S_{PV}^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l S_V^{l,j,k-1} - (d_k + a_k) S_V^{i,j,k} - \lambda_V^{i,j,k} S_V^{i,j,k},$$

$$\frac{dS_{PV}^{i,j,k}}{dt} = v_V^j S_V^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l S_{PV}^{l,j,k-1} - (d_k + \omega_{PV}^i + a_k) S_{PV}^{i,j,k} - \lambda_{PV}^{i,j,k} S_{PV}^{i,j,k},$$

$$\frac{dI_1^{i,j,k}}{dt} = \lambda^{i,j,k} S^{i,j,k} + \lambda_V^{i,j,k} S_V^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l I_1^{l,j,k-1} - (d_k + \dot{\partial}_{l,1} + a_k) I_1^{i,j,k},$$

$$\frac{dI_\phi^{i,j,k}}{dt} = \dot{\partial}_{l,\phi-1} I_{\phi-1}^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l I_\phi^{l,j,k-1} - (\mu_\phi + d_k + \dot{\partial}_{l,\phi} + \sigma_{l,\phi} + a_k) I_\phi^{i,j,k},$$

$$\phi = 2, \dots, 5$$

$$\frac{dI_{P,1}^{i,j,k}}{dt} = \lambda_P^{i,j,k} S_P^{i,j,k} + \lambda_{PV}^{i,j,k} S_{PV}^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l I_{P,1}^{l,j,k-1} - (d_k + \dot{\partial}_{P,1} + \sigma_{P,1} + a_k) I_{P,1}^{i,j,k},$$

$$\frac{dI_{P,\phi}^{i,j,k}}{dt} = \dot{\partial}_{P,\phi-1} I_{P,\phi-1}^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l I_{P,\phi}^{l,j,k-1} - (\mu_\phi + d_k + \dot{\partial}_{P,\phi} + \sigma_{P,\phi} + a_k) I_{P,\phi}^{i,j,k},$$

$$\phi = 2, \dots, 5$$

$$\frac{dD_1^{i,j,k}}{dt} = \sigma_{P,1} I_{P,1}^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l D_1^{l,j,k-1} - (d_k + \dot{\partial}_{D,1} + \sigma_{D,1} + a_k) D_1^{i,j,k},$$

$$\frac{dD_\phi^{i,j,k}}{dt} = \dot{\partial}_{D,\phi-1} D_{\phi-1}^{i,j,k} + \sigma_{P,\phi} I_{P,\phi}^{i,j,k} + \sigma_{I,\phi} I_\phi^{i,j,k} + \tau_{E,\phi} E_\phi^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l D_\phi^{l,j,k-1}$$

$$- (\mu_\phi + d_k + \dot{\partial}_{D,\phi} + \sigma_{D,\phi} + a_k) D_\phi^{i,j,k},$$

$$\phi = 2, \dots, 5$$

$$\frac{dE_1^{i,j,k}}{dt} = \sigma_{D,1} D_1^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l E_1^{l,j,k-1} - (d_k + \dot{\partial}_{E,1} + \sigma_{E,1} + a_k) E_1^{i,j,k},$$

$$\begin{aligned} \frac{dE_\phi^{i,j,k}}{dt} = & \dot{\sigma}_{E,\phi-1} E_{\phi-1}^{i,j,k} + \sigma_{D,\phi} D_\phi^{i,j,k} + \tau_{U,\phi} U^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l E_\phi^{l,j,k-1} \\ & - (\mu_\phi + d_k + \tau_{E,\phi} + \dot{\sigma}_{E,\phi} + \sigma_{E,\phi} + a_k) E_\phi^{i,j,k}, \\ & \phi = 2, \dots, 5 \end{aligned}$$

$$\frac{dU_1^{i,j,k}}{dt} = \sigma_{E,1} E_1^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l U_1^{l,j,k-1} - (d_k + \dot{\sigma}_{U,1} + \sigma_{U,1} + a_k) U_1^{i,j,k},$$

$$\begin{aligned} \frac{dU_\phi^{i,j,k}}{dt} = & \dot{\sigma}_{U,\phi-1} U_{\phi-1}^{i,j,k} + \sigma_{E,\phi} E_\phi^{i,j,k} + \tau_{T,\phi} T_\phi^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l U_\phi^{l,j,k-1} \\ & - (\mu_\phi + d_k + \tau_{U,\phi} + \dot{\sigma}_{U,\phi} + \sigma_{U,\phi} + a_k) U_\phi^{i,j,k}, \\ & \phi = 2, \dots, 5 \end{aligned}$$

$$\frac{dT_2^{i,j,k}}{dt} = \sigma_{U,1} U_1^{i,j,k} + \sigma_{U,2} U_2^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l T_2^{l,j,k-1} - (d_k + \tau_{T,\phi} + a_k) T_2^{i,j,k},$$

$$\frac{dT_\phi^{i,j,k}}{dt} = \sigma_{U,\phi} U_\phi^{i,j,k} + a_{k-1} \frac{\rho_{i,k}}{\sum_l \rho_{l,k}} \sum_l T_\phi^{l,j,k-1} - (d_k + \tau_{T,\phi} + a_k) T_\phi^{i,j,k}, \quad \phi = 3, 4, 5$$

### 3.2.3.3 Force of Infection

$\eta^{i,k}$  : number of partners for individuals in risk group  $i$  and age group  $k$ ,

$n^{i,k,x,z}$  : number of acts per year in partnership between risk group  $i$ , age group  $k$  and risk group  $x$ , age group  $z$ ,

$\theta_\phi$  : relative number of acts per year in partnership by disease stage  $\phi$  as a multiplier for reduced sexual activity by disease stage with CD4 >500 as the reference,

$m_\rho^{i,k,x,z}$  : risk mixing probability between people with risk group  $i$ , age group  $k$  and risk group  $x$ , age group  $z$ ,

$m_r^{j,y}$  : role mixing probability between people with role  $j$  and role  $y$ ,

$\alpha_c$  : condom efficacy in reducing susceptibility per act,

$c^{i,k,x,z}$  : rate of condom use in partnership between people with risk group  $i$ , age group  $k$  and risk group  $x$ , age group  $z$ ,

$\theta_\phi$  : relative HIV acquisition risk by disease stage  $\phi$ , using asymptomatic stage (CD4 >500) as a reference

$\beta$  : HIV-transmission risk per unprotected insertive anal act from untreated infected MSM in asymptomatic stage (CD4>500) to uninfected MSM not using PrEP or vaccine,

$\psi^{j,y}$  : fraction of acts which are receptive in partnership between role groups  $j$  and  $y$ ,

$\theta_R$  : relative HIV acquisition risk per receptive act compared to insertive acts,

$\alpha_{U,art}$  : ART efficacy in reducing infectiousness per act when virally unsuppressed,

$\alpha_p$  : PrEP efficacy in reducing susceptibility per act,

$\alpha_v$  : Vaccine efficacy in reducing susceptibility per act,

$N^{x,y,z}$  : Population size with risk status  $x$ , role group  $y$ . and age group  $z$

$$N^{x,y,z} = S^{x,y,z} + S_P^{x,y,z} + \sum_{\phi} \left( I_{\phi}^{x,y,z} + I_{P,\phi}^{x,y,z} + D_{\phi}^{x,y,z} + E_{\phi}^{x,y,z} + F_{\phi}^{x,y,z} + T_{\phi}^{x,y,z} \right). \text{ Here } T_1^{x,y,z} = 0.$$

The force of infection on a susceptible individual that is not protected by PrEP or an HIV vaccine is:

$$\begin{aligned} \lambda^{i,j,k} = & \eta^{i,k} \sum_{x,y,z} m_r^{i,k,x,z} m_\rho^{j,y} \left( \sum_{\phi} \left( 1 - (1 - (1 - \alpha_c) \theta_\phi \beta)^{(1-\psi^{j,y})} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z} \right) \cdot (1 - \theta_\phi \beta)^{(1-\psi^{j,y})} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z} \right) \cdot \\ & (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta)^{\psi^{j,y} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot (1 - \theta_R \theta_\phi \beta)^{\psi^{j,y} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \left( \frac{I_\phi^{x,y,z} + I_{P,\phi}^{x,y,z} + D_\phi^{x,y,z} + E_\phi^{x,y,z}}{N^{x,y,z}} \right) + \\ & \sum_{\phi} \left( 1 - (1 - (1 - \alpha_c) \theta_\phi \beta (1 - \alpha_{U,art})) \right)^{(1-\psi^{j,y})} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z} \cdot (1 - \theta_\phi \beta (1 - \alpha_{U,art}))^{(1-\psi^{j,y})} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z} \cdot \\ & (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta (1 - \alpha_{U,art}))^{\psi^{j,y} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot (1 - \theta_R \theta_\phi \beta (1 - \alpha_{U,art}))^{\psi^{j,y} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \left( \frac{U_\phi^{x,y,z}}{N^{x,y,z}} \right). \end{aligned}$$

The force of infection for an average PrEP user not vaccinated is:

$$\begin{aligned} \lambda_p^{i,j,k} = & \eta^{i,k} \sum_{x,y,z} m_r^{i,k,x,z} m_\rho^{j,y} \left( \sum_{\phi} \left( 1 - (1 - (1 - \alpha_c) \theta_\phi \beta (1 - \alpha_p)) \right)^{(1-\psi^{j,y})} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z} \right) \cdot \\ & (1 - \theta_\phi \beta (1 - \alpha_p))^{(1-\psi^{j,y})} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z} \cdot (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta (1 - \alpha_p))^{\psi^{j,y} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot \\ & (1 - \theta_R \theta_\phi \beta (1 - \alpha_p))^{\psi^{j,y} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \left( \frac{I_\phi^{x,y,z} + I_{P,\phi}^{x,y,z} + D_\phi^{x,y,z} + E_\phi^{x,y,z}}{N^{x,y,z}} \right) + \\ & \sum_{\phi} \left( 1 - (1 - (1 - \alpha_c) \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_{U,art})) \right)^{(1-\psi^{j,y})} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z} \cdot \\ & (1 - \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_{U,art}))^{(1-\psi^{j,y})} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z} \cdot \\ & (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_{U,art}))^{\psi^{j,y} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot \\ & (1 - \theta_R \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_{U,art}))^{\psi^{j,y} (1 - c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \left( \frac{U_\phi^{x,y,z}}{N^{x,y,z}} \right). \end{aligned}$$

The force of infection on a susceptible individual who is partially protected by an HIV vaccine without PrEP is:

$$\begin{aligned}
\lambda_V^{i,j,k} &= \eta^{i,k} \sum_{x,y,z} m_r^{i,k,x,z} m_\rho^{j,y} \left( \sum_{\phi} \left( 1 - (1 - (1 - \alpha_c) \theta_\phi \beta (1 - \alpha_v)) \right)^{(1-\psi^{j,y}) c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \right. \\
& (1 - \theta_\phi \beta (1 - \alpha_v))^{(1-\psi^{j,y})(1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \cdot (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta (1 - \alpha_v))^{(\psi^{j,y} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z})} \\
& \left. (1 - \theta_R \theta_\phi \beta (1 - \alpha_v))^{(\psi^{j,y} (1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z})} \frac{(I_\phi^{x,y,z} + I_{P,\phi}^{x,y,z} + D_\phi^{x,y,z} + E_\phi^{x,y,z})}{N^{x,y,z}} + \right. \\
& \sum_{\phi} \left( 1 - (1 - \alpha_c) \theta_\phi \beta (1 - \alpha_v) (1 - \alpha_{U,art}) \right)^{(1-\psi^{j,y}) c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \\
& \quad (1 - \theta_\phi \beta (1 - \alpha_v) (1 - \alpha_{U,art}))^{(1-\psi^{j,y})(1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \\
& \quad (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta (1 - \alpha_v) (1 - \alpha_{U,art}))^{(\psi^{j,y} c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z})} \\
& \left. (1 - \theta_R \theta_\phi \beta (1 - \alpha_v) (1 - \alpha_{U,art}))^{(\psi^{j,y} (1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z})} \frac{U_\phi^{x,y,z}}{N^{x,y,z}} \right).
\end{aligned}$$

The force of infection on an individual who is partially protected with a combination of PrEP and an HIV vaccine is:

$$\begin{aligned}
\lambda_{PV}^{i,j,k} = & \eta^{i,k} \sum_{x,y,z} m_r^{i,k,x,z} m_\rho^{j,y} \left( \sum_{\phi} \left( 1 - (1 - (1 - \alpha_c) \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v)) \right)^{(1-\psi^{j,y}) c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot \right. \\
& (1 - \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v))^{(1-\psi^{j,y})(1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \cdot (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v))^{(\psi^{j,y}) c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot \\
& (1 - \theta_R \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v))^{(\psi^{j,y})(1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \left. \frac{\left( I_\phi^{x,y,z} + I_{P,\phi}^{x,y,z} + D_\phi^{x,y,z} + E_\phi^{x,y,z} \right)}{N^{x,y,z}} + \right. \\
& \sum_{\phi} \left( 1 - (1 - \alpha_c) \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v) (1 - \alpha_{U,art}) \right)^{(1-\psi^{j,y}) c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot \\
& (1 - \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v) (1 - \alpha_{U,art}))^{(1-\psi^{j,y})(1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \cdot \\
& (1 - (1 - \alpha_c) \theta_R \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v) (1 - \alpha_{U,art}))^{(\psi^{j,y}) c^{i,k,x,z} \theta_{n,\phi} n^{i,k,x,z}} \cdot \\
& \left. (1 - \theta_R \theta_\phi \beta (1 - \alpha_p) (1 - \alpha_v) (1 - \alpha_{U,art}))^{(\psi^{j,y})(1-c^{i,k,x,z}) \theta_{n,\phi} n^{i,k,x,z}} \right) \frac{U_\phi^{x,y,z}}{N^{x,y,z}}.
\end{aligned}$$

### 3.2.4 Data Sources and Parameterization

The model is parameterized with epidemiological data representative of the HIV epidemic among MSM in Seattle. Demographic and sexual behavior characteristics including average number of partners per year, frequency of sex acts, proportion of acts protected by condoms, and lifetime duration of sexual activity are estimated from published data (see The high-risk group was defined as MSM having five or more partners in the past 12 months, as a surrogate for the many risk factors identified in Seattle's clinical guidelines for PrEP use [96]).

Table 3.1). The inputs for mixing between age and risk sub-groups was imputed from a meta-analysis of sexual behavior patterns among men who have sex with men that included a sample of men from Seattle [109]. King County HIV prevalence was calibrated to estimates from the 2015 HIV/AIDS Epidemiology Report from the Public Health Seattle-King County and Washington State Department of Health [93]. This report with findings from the CDC-sponsored 2014 Seattle area National HIV Behavioral Survey of Men Who Have Sex with Men Sexual (NHBS-MSM4) informed values for sexual risk behaviors, HIV testing, and PrEP use [110]. The high-risk group was defined as MSM having five or more partners in the past 12 months, as a surrogate for the many risk factors identified in Seattle's clinical guidelines for PrEP use [96].

Table 3.1. Dynamic transmission model inputs

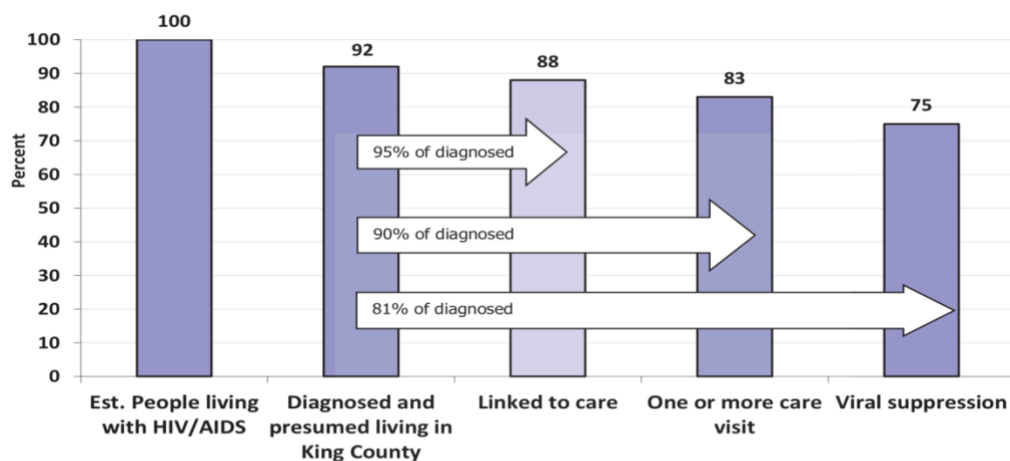
Parameter	Value	Source
Population size, men who have sex with men, ages 15-64 years, King County, 2004	75000	US Census [111]
Fraction young, 15-24 years	0.168	US Census Reporter [112]
Fraction middle-aged, 25-44 years	0.463	US Census Reporter [112]
Male maturation rate, rate of aging into the population	0.015	US Census Reporter [112]
Initial fraction of population who are uninfected, 2004	0.9457	Seattle HIV/AIDS Epi Report 2005 [113]
Risk Levels, fraction of population at high risk of HIV infection (>6 partners in the last 12 months)		
Young adults at high risk	0.31	Seattle HIV/AIDS Epi Report [114]
Middle-aged at high risk		
Older adults at higher risk		
Initial fraction of population who are diagnosed	0.92	Seattle HIV/AIDS Epi Report [114]
Initial fraction of screened infected population who are engaged in care	0.90	Seattle HIV/AIDS Epi Report [114]
Initial fraction of infected population who are on ART and suppressed	0.83	Seattle HIV/AIDS Epi Report [114]
<b>HIV Prevention Effectiveness</b>		
Condom efficacy	0.9	
Condom use, fraction of acts protected by a condom		
Susceptible individuals	0.63	
PrEP users	0.125	Montano 2017 [115]
Vaccinated, low-risk	0.125	Assumed similar to PrEP users
Vaccinated, high-risk	0.63	Assumed similar to susceptible low-risk men
PrEP efficacy, reduction in susceptibility per act	0.80	
Insertive anal sex role, fraction of population with the role group "insertive"	0.325	Table 7, CDC 2016 [116]
Versatile anal sex role, fraction of population with the role group "versatile"	0.268	Table 7, CDC 2016 [116]
Number of sexual partners in the past 12 months		
High-risk with young adults	6	
High-risk with middle-aged	17	
High-risk with older adults	16	
Low-risk with young adults	1.5	Wall 2015 [117]
Low-risk with middle-aged	1.5	Wall 2015 [117]
Low-risk with older adults	1	Wall 2015 [117]
Death rate, non-AIDS, probability of dying between age x [midpoint of age category] and x+1		
Ages 15-24 years	0.001319	Life tables, Arias 2016 [118]
Ages 25-44 years	0.001574	Life tables, Arias 2016 [118]
Ages 45-64 years	0.008438	Life tables, Arias 2016 [118]
PrEP efficacy, per sex act	0.80	
HIV vaccine efficacy	0.50	Expert opinion
HIV vaccine durability, years	5	Expert opinion
<b>Utilities</b>		
Acute infection	0.69	Whitham 2016 [119]
CD4 count >500	0.73	Whitham 2016 [119]
CD4 count 350-500	0.71	Whitham 2016 [119]
CD4 count 200-349	0.69	Whitham 2016 [119]
CD4 count <200	0.69	Whitham 2016 [119]
<b>Costs, USD 2017</b>		
Clinic visit for HIV prevention services, at each dose of HIV vaccine and/or each quarter of PrEP use		
Preventive medicine counseling, 30 min office visit	51	National Physician Fee Schedule Relative Value File [120], HCPCS code 99402 (0.98 RVUs)
Laboratory tests, total	164	NASTAD PrEP Billing Code Guide [121] and CMS 2017 Clinical Diagnostic Laboratory Fee Schedule, mid-point [122]
HIV, 4th generation test	44	CPT® code 87389

Chlamydia test	22	CPT® code 86631
Gonorrhea test	37	CPT® code 87590
Syphilis test	25	CPT® code 86780
Hepatitis B test	19	CPT® code 87340
Measurement of blood urea and nitrogen serum creatinine levels	17	CPT® codes 84520 and 82565
PrEP medication, 30-day supply	1,050	Federal Supply Schedule price, US Veterans Affairs [95]
HIV vaccine, price per dose in 5-dose series	1,267	Assumes 30% increasing benchmark compared to FSS price of GARDASIL-9® HPV vaccine [95]
HIV care costs, quarterly		
CD4 count >500	5,872	Gebo 2010 [123], Farnham 2013 [43]
CD4 count 350-500	5,959	Gebo 2010 [123], Farnham 2013 [43]
CD4 count 200-349	6,915	Gebo 2010 [123], Farnham 2013 [43]
CD4 count <200	14,378	Gebo 2010 [123], Farnham 2013 [43]

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Costs have been adjusted to a common currency of 2017 USD.

Abbreviations: CMS, Centers for Medicare and Medicaid Services; FSS, Federal Supply Schedule; PrEP, pre-exposure prophylaxis; HPV, human papilloma virus; RVUs, relative value units; SKCPH & DOH Seattle & King County Public Health & Washington State Department of Health



	Estimated people living with HIV/AIDS <sup>a</sup>	Diagnosed and presumed living in King County <sup>b</sup>	Linked to care in 2015 <sup>c</sup>	One or more care visit <sup>d</sup>	Viral suppression <sup>e</sup>
Number of people	7400	6808	228/239	6157	5524

Figure 3.5. King County HIV Care Continuum in 2015

Source: Seattle Public Health King County, (data reported through of June 30, 2016)

<sup>a</sup> Percent undiagnosed was calculated as 6% among MSM for King County; prior estimate of 15% was used for non-MSM (based on CDC and Washington State estimates) resulting in an estimate of 7.3% overall, rounded up to 8% for a slightly more conservative estimate (this may be the most uncertain bar in the continuum). Estimated people living with HIV/AIDS is calculated by dividing “diagnosed and presumed living in King County” residents by 0.92.

<sup>b</sup> Diagnosed cases are those presumed living in King County during 2015. Individuals with no contact for ten or more years were presumed to have relocated or died (N=249). Others with unconfirmed deaths or relocations (identified, for example by online Internet database searches, but not confirmed by the new jurisdiction or another secondary source) and no laboratory results reported for >18 months were also excluded (N=161).

<sup>c</sup> Linked to care in 2015 is not a subset of earlier data (hence different color in the graph) and is based on the percent diagnosed in 2015 with a CD4 or viral load test within 3 months of diagnosis. The percent linked in the figure, 88%, is the percent of diagnosed cases in 2015 who linked (95.4%) times 92.0% to account for undiagnosed cases.

<sup>d</sup> One or more care visit was based on one or more reported laboratory result (CD4, viral load, genotype).

<sup>e</sup> Viral suppression is defined as the most recent viral load test result in 2015 less than 200 copies.

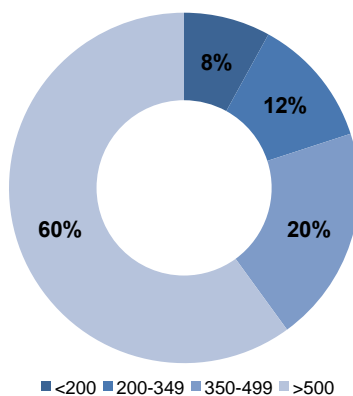


Figure 3.6. Distribution of CD4+ T-cell counts among people living with diagnosed HIV in King County, WA

NOTES: Based on lab values of 6,507 people included in the Seattle-King County Public Health Department Epidemiology Report 2015 [93].

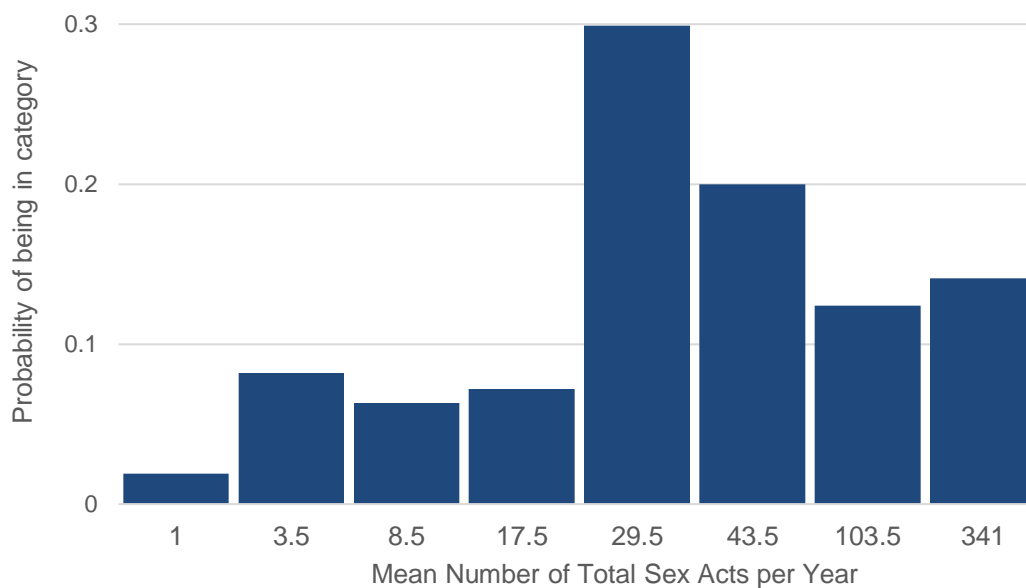


Figure 3.7. Distribution of sex act frequency

NOTES: Figure based on data reported from Wall and colleagues based on a population of men who have sex with men in the United States; bins are based on ordered categories [117].

### 3.2.5 Model Calibration

The model begins in 2004 and we calibrated to targets in 2014 to select a parameter set that best captures the epidemic trends and clinical disease progression observed in King County, WA [110,113]. In order to calibrate the model, we fit outcomes to the HIV prevalence and the treatment cascade among MSM in King County, WA using a calibration procedure and goodness of fit criteria [93] described in the Appendix [65,124]. Monte Carlo filtering was used to select 100 parameter sets closely matching the calibration targets. The distribution of a sample of PLWH in King County ( $n = 6,507$ ) among CD4 T-cell counts categories in 2014 will be used as a calibration target for the HIV care cascade (Figure 3.6) [93].

### 3.2.6 Interventions

#### 3.2.6.1 Pre-exposure prophylaxis

The number of people using PrEP is increasing over time and experts speculate PrEP coverage will soon reach a point of saturation in Seattle. We assume that by 2025 that PrEP will be used 80% of high-risk, some low-risk, and an average of 20% of all MSM; each year about 7% initiate and 20% discontinue (dashed blue line in Figure 3.8). Evidence from the iPrex, Partners, Ipergay, and PROUD studies show that PrEP efficacy varies by adherence [24,125–132]. We assume PrEP reduces the chance of HIV infection by 80% per act and does not reduce infectivity once infected. Recent evidence shows that condom use decreases when people using PrEP. On average, 63% of MSM sex acts are protected by a condom; while using PrEP, only 12.5% of MSM sex acts are protected by condoms on average [115]. We do not include a disutility to account for PrEP adverse events, assuming that individuals with intolerable side effects would discontinue its use.

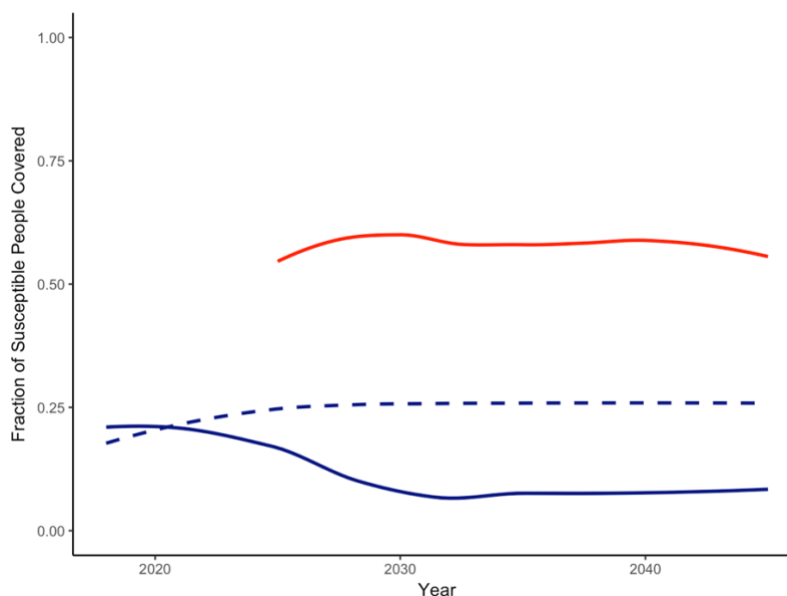


Figure 3.8. Interactions in the utilization of PrEP with HIV vaccines

NOTES: Projected utilization of PrEP (blue dashed line) among all MSM in the absence of vaccine, compared to a potential decline in utilization of PrEP (blue solid line) corresponding to the entry of HIV vaccines (solid red line). The majority of PrEP use is among high-risk men while HIV vaccines are used by low- and high-risk men.

### 3.2.6.2 HIV vaccine

The intervention is implementation of a partially effective HIV vaccine in 2025 recommended for all MSM. The model simulates a 5-dose regimen of a canarypox-based vaccine ALVAC-HIV vCP2438 DNA prime (Sanofi Pasteur) and bivalent gp120 protein subunit boost with MF59<sup>®</sup> adjuvant (GSK) [37]. The vaccine components, regimen, intellectual property owners, and trial funders for the Thai and South African studies are provided in Table 3.2. Following a complete series of HIV vaccine doses, protection from infection wanes over time [133,134], and we assume an average efficacy of 50% reduction in risk of infection lasting 5 years in duration [48,135]. We implement vaccination in campaigns every 5 years at targeted coverage of 90% for those on PrEP and 60% for those who are not on PrEP (resulting in the coverage seen in Figure 3.8). Condom replacement, also known as risk compensation or behavioral disinhibition, is a decrease in condom that may occur among vaccinated people as has been observed with PrEP [130]. We assume that some condom replacement among high-risk MSM that are vaccinated but not

for low-risk men. We assume the vaccine has no disutility and that future technologies in HIV testing will overcome any previously reported social risks from vaccine-induced sero-positivity [136,137].

Table 3.2. HIV vaccine candidate components, owners of intellectual property, and funders for the RV144 study in Thailand and HVTN 702 study in South Africa.

Vaccine Component	RV144 Thai Trial			HVTN 702 South Africa Trial		
	DNA Prime	Protein Boost	Adjuvant	DNA Prime	Protein Boost	Adjuvant
<b>Description</b>	ALVAC-HIV recombinant canarypox vaccine, subtype B and E	AIDSVAX® B/E bivalent HIV gp120 envelope glycoprotein vaccine, subtypes B and E	600 µg of alum adjuvant	Canarypox-based vaccine ALVAC-HIV subtype C	bivalent gp120 protein subunit vaccine, subtype C	MF59
<b>Owner</b>	Developed by Virogenetics Corporation (Troy, NY) and manufactured by Sanofi Pasteur (Marcy-l'Étoile, France)	Originally manufactured by Genentech, Inc., and further developed by VaxGen, Inc. (later acquired by Global Solutions for Infectious Diseases (San Francisco, CA))	VaxGen, Inc, no IP	Sanofi Pasteur	GSK	GSK
<b>Funder</b>	Supported in part by an Interagency Agreement (Y1-AI-2642-12) between the U.S. Army Medical Research and Materiel Command and the National Institute of Allergy and Infectious Diseases and by a cooperative agreement (W81XWH-07-2-0067) between the Henry M. Jackson Foundation for the Advancement of Military Medicine and the U.S. Department of Defense. Sanofi Pasteur provided the ALVAC-HIV vaccine, and Global Solutions for Infectious Diseases (VaxGen) provided the reagents for the immunogenicity assays.			P5 members are NIAID, the Bill & Melinda Gates Foundation (BMGF), the South African Medical Research Council (SAMRC), HVTN, Sanofi Pasteur, GSK and the U.S. Military HIV Research Program. NIAID, BMGF and SAMRC fund the P5. The National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring and funding HVTN 702. Sanofi Pasteur and GSK are providing the investigational vaccines for the trial.		

### 3.2.6.3 Interactions between PrEP and vaccine

The model explores potential interactions between HIV vaccines, PrEP, and condoms that risk mitigating the clinical and economic impact. We assume the cumulative protection from combination of PrEP with an HIV is multiplicative, as  $1 - (1-0.80)*(1-0.50) = 0.90$  efficacy of protection. The demand for condoms may decrease as the supply of PrEP increases and the demand for PrEP may decrease as the supply of HIV vaccine increases. We make the following assumptions about future utilization of PrEP and HIV vaccine delivery: vaccine licensure in 2025; PrEP users being 3 times more likely to receive an HIV vaccine; HIV immunization campaign coverage of 60% coverage of MSM every 5 years beginning in

2025 (red line in Figure 3.8); low-risk PrEP users switch to vaccine; PrEP users are vaccinated and continue PrEP for an additional year, then continue with vaccine only. PrEP utilization decreases as a function of vaccine implementation (solid blue line in Figure 3.8). While PrEP is targeted to high-risk MSM, the vaccine is targeted to all MSM.

### 3.2.7 Approach to Health Outcomes

Health impact will be measured in HIV infections averted and total QALYs gained, both discounted 3% annually [91,92]. The solved solution for compartment size mid-point moments each quarter represent units of one-quarter person-year time. This “life year” matrix integrates with a function to adjust for health-state specific utility weights and discount 3% annually. The sum of the resulting “QALY matrix” from 2025-2045 represents the total population-level discounted QALYs for a simulation. To calculate average QALYs per person in a model with fluctuating population size, we sum the number of people alive in each year of the model and divide by the time horizon length to find the average population size for the simulation. In summary, person-time in each health state multiplied by the corresponding preference-based utility weights will be summed and discounted 3% annually to estimate total QALYs [138–142].

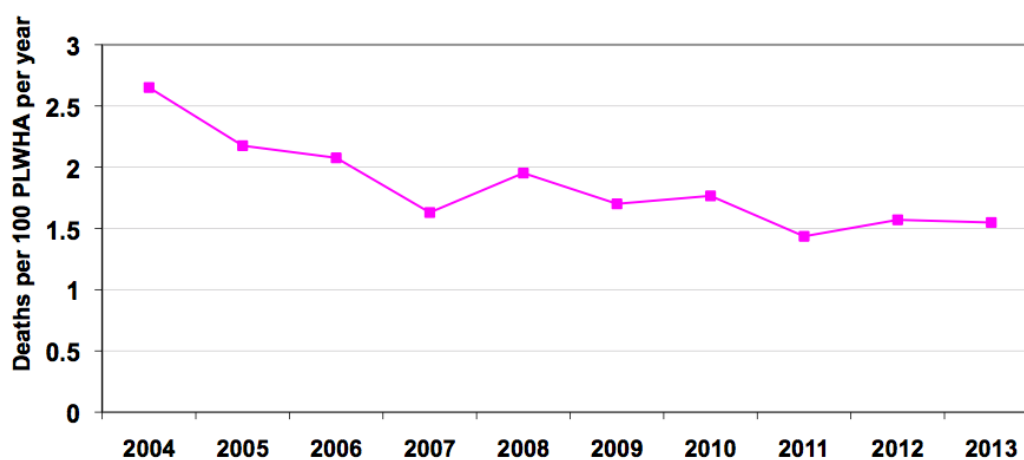


Figure 3.9. Adjusted death rates per 100 people living with HIV/AIDS in Washington State, 2004- 2013

*Source:* 2015 HIV/AIDS Epidemiology Report: Washington State and King County [93]

### 3.2.8 Approach to Costing

Costing of HIV prevention services follows a unit costing approach, also known as ingredients-based, while the cost of HIV treatment relies on published studies based on aggregate healthcare costs. The cost of a clinic visit for HIV prevention services with risk reduction counseling is based on CMS reimbursement rates for the corresponding relative value units in the Physician Fee Schedule January 2018 release [143]. Medication costs reflect the National Acquisition Center (CCST) Federal Supply Schedule prices from March 2018. Laboratory

#### 3.2.8.1 PrEP Costs

PrEP costs include medication, quarterly clinic visits, testing for HIV and STIs, other routine laboratory tests for monitoring (Table 3.1). The Federal Supply Schedule (FSS) price of TRUVADA<sup>®</sup> was \$1,050 for a 30-day supply in March 2018 [95]. We explore the potential impact of generic manufacturers on the average cost of PrEP in the sensitivity analysis.

#### 3.2.8.2 HIV Vaccine Costs

The launch price of an HIV vaccine is unknown. Experts suggest benchmarking on the price of a recombinant human papillomavirus (HPV) vaccine because they similarly prevent transmission of a sexually transmitted virus. The FSS price for a dose of GARDASIL-9 (Merck & Co., Inc.), was \$1,623.72 in March 2018 [95]. While the HPV vaccine is delivered to adults in a 3-dose series, ongoing Phase IIB clinical trials of HIV vaccines are testing a 5-dose series of vaccinations. To benchmark an estimate of HIV price per dose, we assume a 30% higher cost per dose for HIV vaccines compared to the 2018 FFS

price of an HPV vaccine. Assuming this launch price of \$2,111 per dose, the total cost is \$10,555 for a completed five-dose series.

### 3.2.8.3 HIV Care Costs

Cost data from a study in Birmingham of annual health care expenditures among HIV patients will inform the cost parameters for CD4+ count categories on ART in Figure. Costs will be discounted 3% annually. The greatest uncertainty among variables is in vaccine price. Vaccine regimen cost and potential range will be informed by reference to U.S. prices for vaccines to prevent other sexually transmitted diseases like HPV and expert opinion [144,145]. In the base case, an initial series of HIV vaccination costs \$1,000 and ranges from \$200 to \$10,000 in the sensitivity analysis. Boosts with co-administration of the DNA and protein cost 1/5 the total cost of the initial series. Alternatively, a strategy boosting with only DNA and no protein will cost substantially less.

### 3.2.9 Estimating Cost-Effectiveness

We evaluate ICERs using a cost-effectiveness threshold ranging from 1-3x the GDP per capita, or approximately \$50,000 - \$150,000 per QALY gained using the equation

$$ICER = \frac{Cost_{intervention} - Cost_{standardcare}}{QALYs_{intervention} - QALYs_{standardcare}}.$$

We follow a value-assessment framework developed by the Institute for Clinical and Economic Review, an independent not-for-profit research organization helping stakeholders interpret evidence, improve patient outcomes, and control costs [146]. The value of broader public health impact will be simplified by assuming it is the difference between the ICER from this dynamic transmission model and the ICER from a static cohort Markov model of the same population and HIV vaccine intervention.

### 3.2.10 Threshold Analyses within Scenarios

Characteristics of a clinically and economically viable HIV vaccine will be based on a threshold analysis of efficacy, durability, boosting potential, and price. For example, a vaccine may be clinically viable with moderate levels of each characteristic or alternatively viable with low efficacy and boosting potential, moderate price, but high durability. The criteria for clinical viability will include the pre-specified minimum vaccine efficacy used to power a significant difference in HVTN 702 and a maximum number needed to vaccinate to prevent one HIV infection that will be set by expert opinion. Criteria for economic viability will include a range of willingness to pay thresholds between 1-3 times GDP per capita.

### 3.2.11 Sensitivity Analysis

Parameter uncertainty and structural uncertainty was evaluated in a sensitivity analysis [54,60,64,92]. One-way sensitivity analyses will evaluate the effect of uncertainty from individual parameters. Scenario analysis will evaluate multi-way parameter uncertainty. To understand how robust the estimates of outcomes were to the choice of calibration parameters, we performed an uncertainty analysis using 100 calibration sets of inputs within a plausible range varying with respect to one another. To understand the combined uncertainty in model input values I will estimate results using 100 sample Monte Carlo parameter sets from the initial calibration. Following ISPOR-SMDM best practices for dynamic transmission modeling, sensitivity analyses will include results with a range of time horizons and discount rates [64]. Structural uncertainty will be evaluated by comparing results from scenarios modifying key structural assumptions.

The model was developed in C++ and analyzed using R version 3.4.2.

### 3.3 RESULTS

#### 3.3.1 Epidemiological projections with existing HIV prevention products

With a starting population size of 45,000 MSM in 2004, the model projects growth to 62,388 men by 2045. In the absence of an HIV vaccine, while maintaining the current trends of PrEP use, rates of diagnoses, linkage to care, treatment, and viral suppression, our analysis estimates that 4,503 new HIV infections will occur in Seattle by 2045, with 2,935 expected between 2025-2045. We project a prevalence of 7.7% of all MSM will living with HIV in Seattle in 2045. Assuming a saturation in the PrEP market of 80% high-risk MSM and 20% low-risk MSM as prevalent users (dashed blue line in Figure 3.8), we expect 1,993 fewer prevalent HIV cases than 2018 (dashed black line in Figure 3.10). On the path to this decline in prevalence, the model projects almost 15,000 HIV-uninfected men using PrEP in 2045, double the number in 2018, resulting in the partial protection 29.9% of MSM.

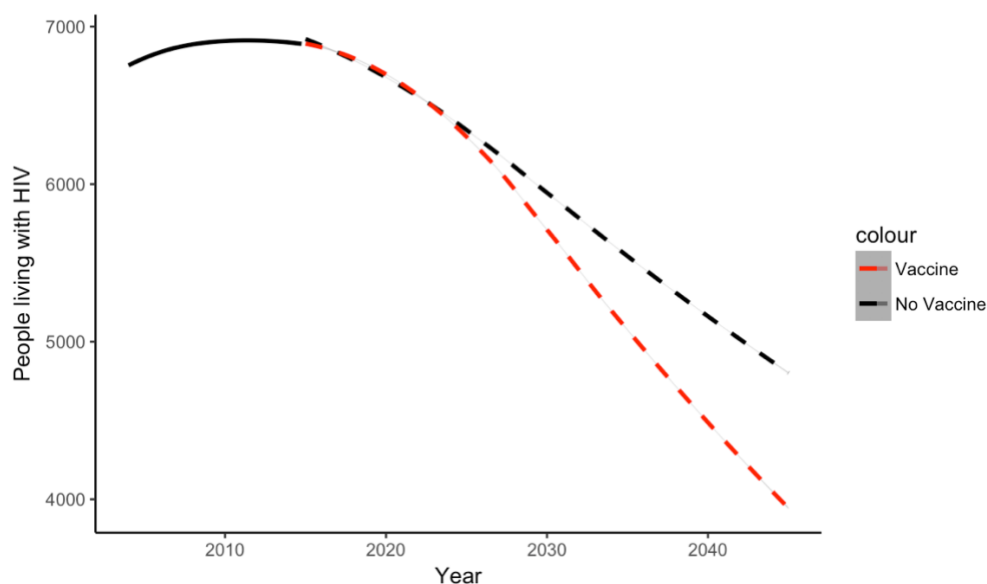


Figure 3.10. Projected prevalence of HIV among MSM in Seattle

The solid black line shows the model estimate of people living with HIV from 2004-2015, based on calibrated fit to available Seattle-King County surveillance data. The dashed black line shows model projects for the number of people living with HIV as a reference for existing HIV treatment and prevention with PrEP. The dashed red line assumes HIV vaccine availability in 2025.

### 3.3.2 Population health impact of introducing HIV vaccines

Results showing the impact of launching an HIV vaccine in 2025 are presented in Table 3.3. A total of 638,307 HIV vaccine doses would need to be delivered in Seattle over 20 years for a majority of susceptible MSM to be partially protected by vaccine (Figure 3.8). Vaccine access is projected to reduce the reduce HIV prevalence in the city by 1.4% and avoid 37.9% of new HIV infections by 2045 compared to continuing current practice without a vaccine. Assuming PrEP users will be vaccinated during a preventative clinic visit and then have an average shorter duration using PrEP, we would expect 63% fewer MSM to be using PrEP in 2045 compared to the projected number in 2045 with no vaccine. In total, considering the imperfect protection of both PrEP and a vaccine, the model projects that a 46% increase in the number of MSM partially protected would result in 1,164 new HIV infections avoided and 0.04 QALYs gained per capita.

Table 3.3. Model results

<b>Outcome</b>	<b>Current Practice</b>	<b>HIV Vaccine</b>	<b>Incremental Difference</b>	<b>Relative Difference (%)*</b>
<b>HIV Burden</b>				
New HIV infections, 2025-2045	3,074	1,910	-1,164	-37.9
New HIV diagnoses 2025-2045	2,935	2,121	-814	-27.7%
People living with HIV in 2045	4,806	3,949	-857	-17.8%
HIV prevalence (%) in 2045	7.7%	6.3%	-1.4%	-18.2%*
<b>Utilization of Biomedical Prevention</b>				
Protected by PrEP in 2025	11,233	11,233	0	0
Total protected by PrEP or vaccine in 2045	14,905	36,680	21,775	46.1%
PrEP alone (% of susceptible)	14,905	5,494	-9412	-63.1%
HIV vaccine alone (% of susceptible)	0	31,158	31,158	-
PrEP + HIV vaccine (% of susceptible)	0	29	29	-
<b>Health Outcomes</b>				
Total LYs**	1,147,838	1,148,735	897	0.1%
per capita***	22.24	22.26	0.02	-
Total QALYs	684,711	686,733	2,021	0.3%
per capita	13.27	13.31	0.04	-
<b>Costs</b>				
Total cost (millions \$)	1,346.2	1,569.8	223.6	16.6%
PrEP costs (millions \$)	549.2	137.0	-366.3	-48.6%
per capita susceptible (\$)	12,133	3,027	-8,093	-48.6%
HIV vaccine costs (millions \$)	0	619.5	619.5	-
per capita susceptible (\$)	0	13,688	13,688	-
HIV care costs (millions \$)	797.1	767.4	-29.7	-3.7%
ICER (\$ per QALY)	-	-	\$110,622	-

Costs are presented in a common currency of 2017 USD. Cost-effectiveness analysis uses time horizon of 2025-4045. Per capita and per capita susceptible calculations are based on the common population size of MSM projected in 2025.

\*The relative difference in HIV prevalence is slightly different from the relative difference in number of people living with HIV 2045 because in more MSM are alive in 2045 with the vaccine and this factors into the denominator of HIV prevalence but does not factor into the number of cases living with HIV.

\*\*LY and QALYs summed among MSM ages 15-64 years between the years 2025-2045

\*\*\*Per capita calculations are made using the estimated population size of all MSM in 2025 (n = 51,606) or size of susceptible uninfected MSM in 2025 (n = 45,261)

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALYs, quality-adjusted life years;

### 3.3.3 Cost Projections

In the absence of HIV vaccines, the model projects that HIV-related healthcare costs from 2025-2045 would be a discounted total cost of \$1,345 million (Table 3.3). The cost of PrEP accounted for 40.8% of the total costs in this reference case, averaging \$12,133 per man susceptible in 2025. HIV vaccine availability could substantially affect healthcare costs. In the period of 2025-2045, HIV vaccines could increase discounted total HIV-related healthcare costs by \$224 million, assuming a price of \$1,267 per dose. Projected total costs change for the following three reasons: (1) added cost of vaccines, (2) reduced spending on PrEP, and (3) reduced spending on HIV treatment. Disaggregated total costs show spending on HIV vaccines costs \$620 million when including HIV and STI testing and risk-reduction counseling with each dose. As the assumed competition between PrEP and vaccine reduces the utilization of PrEP, the share of spending on PrEP decreases from 41% to 9% of total costs. HIV treatment costs are reduced by \$30 million.

### 3.3.4 Cost-Effectiveness

A policy recommending HIV vaccines for all MSM in 2025 is projected to have an ICER of \$110,622 per QALY gained. This policy would be cost-effective using a threshold of 3x GDP per capita (approximately \$150,000/QALY) but not cost-effective using a threshold of 1x GDP per capita.

### 3.3.5 Sensitivity Analysis

The cost-effectiveness of the vaccine was highly dependent on the launch price for a vaccine and the future costs of PrEP drugs. If competition from the entry of generic PrEP products reduces the medication cost to half by 2025, then the addition of an HIV vaccine would cost \$246,161 per QALY gained compared to no vaccine. Further reduced to 20% of the FSS price, or \$253 for a 30-day supply, would increase the ICER to \$266,615. A threshold analysis (see Figure 3.11) shows the maximum HIV vaccine

series price that would be cost-effective using a \$50,000/QALY (dotted gold line) and \$150,000/QALY (solid gold line) cost-effectiveness threshold, across a range of PrEP costs. The magnitude of health benefit from a vaccine was sensitive to the degree of condom replacement assumed when partially protected by PrEP and/or vaccine.

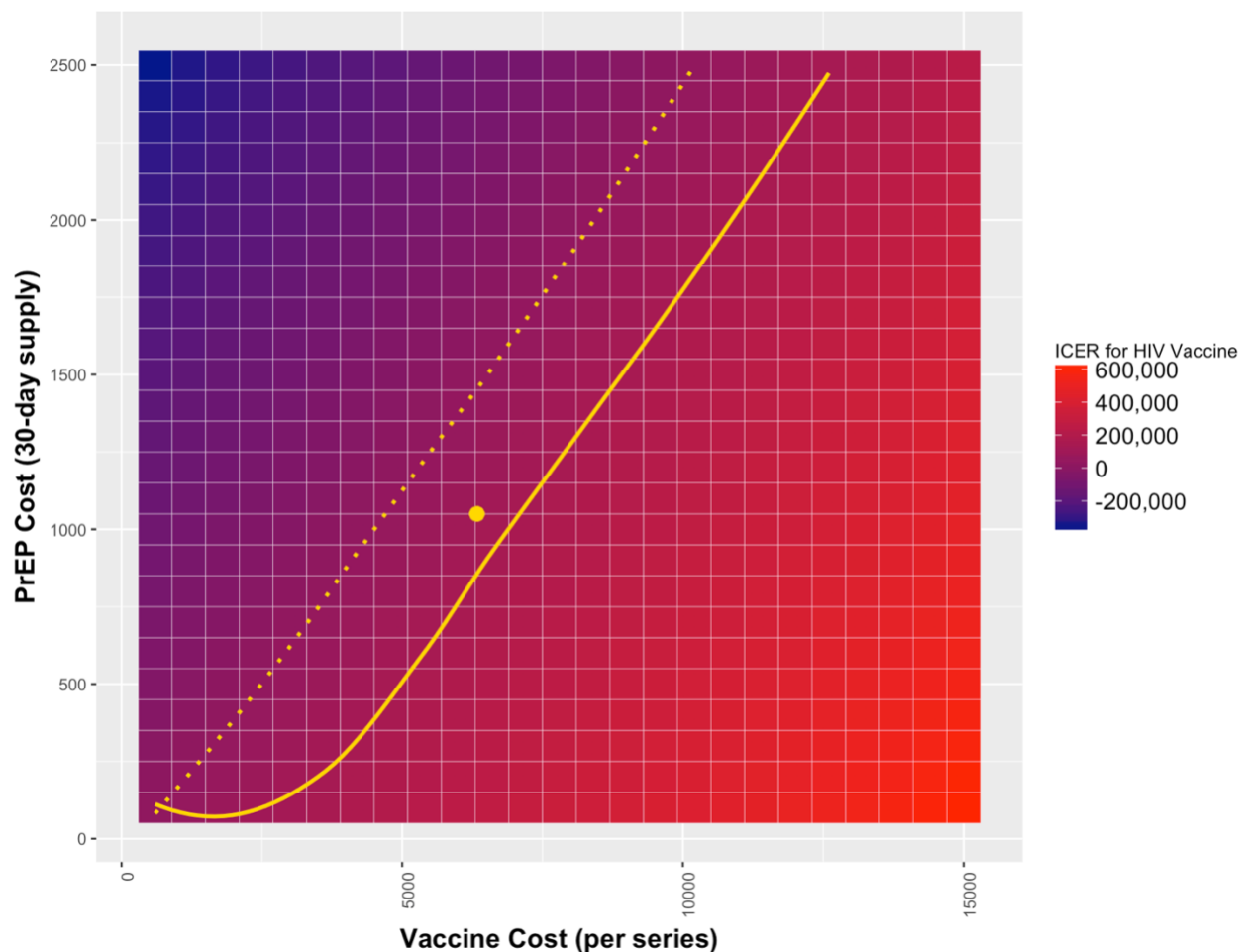


Figure 3.11. Sensitivity analysis of ICER varying the cost of PrEP and HIV vaccines

Darker regions represent combinations of PrEP and vaccine prices that produce lower ICERs for implementation of an HIV vaccine compared to current practice with no vaccine. The gold dot shows input values used in the main analysis. A threshold analysis shows the maximum HIV vaccine series price that would still be cost-effective using a \$50,000/QALY (dotted gold line) and \$150,000/QALY (solid gold line) cost-effectiveness threshold, dependent upon the cost of a 30-day supply of PrEP drugs. Costs are 2017 US\$. Abbreviations: ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis.

### 3.4 DISCUSSION

This study used a dynamic transmission model to evaluate the cost-effectiveness of an HIV vaccine launch in 2025, assuming the vaccine would complement and substitute some PrEP use. The tradeoffs from competition between two imperfect biomedical HIV prevention products include (a) the opportunity to vaccinate a larger fraction of the population than with PrEP alone and (b) the downside from potential substitution with a less effective prevention product. Assuming that 80% of high-risk MSM and 20% of low-risk MSM in Seattle are using PrEP in 2025, and that about 60% of all MSM are soon covered by an HIV vaccine, and that PrEP use declines with increasing vaccine uptake, we found that HIV vaccines costing \$8,120 per 5-dose series would generate an ICER of \$110,622 per QALY gained compared to current practice with PrEP and no vaccine. In this case, HIV vaccines would be cost-effective using a \$150,000/QALY threshold but not cost-effective using a \$50,000/QALY threshold. Though HIV vaccines could add \$620 million to healthcare costs, more than one-half of the costs are offset by reduction in treatments and prevention drugs needed. We estimate the introduction of HIV vaccines could increase total HIV-related health care costs by 16%.

Key uncertainties in the analysis affect the results under different scenarios. As expected, scenarios with greater vaccine efficacy were more likely to find vaccines cost-effective and led to a higher maximum threshold price where the vaccine would remain cost-effective. Results were also sensitive to assumptions about the rate of switching from PrEP to vaccines. If PrEP users who become vaccinated continued to use PrEP for the same length of time as non-vaccinated PrEP users, the vaccine has a higher ICER and is therefore less likely to be cost-effective. If all high-risk men using PrEP switched immediately to a vaccine, the vaccine has a lower ICER and would be more likely to be cost-effective, but the total population-level health benefit is slightly smaller. A scenario with no change in condom use among people using PrEP or vaccines led to a higher ICER, meaning the vaccine would be less likely to be cost-effective. Lastly, scenarios assuming generic PrEP prices in the future led to the vaccine being less likely

cost-effective, while alternative scenarios simulating the launch of newer, branded, long-acting, injectable products for PrEP at higher prices affected the results by lowering the ICER for HIV vaccine introduction, meaning vaccines would be more likely to be cost-effective.

This modeling analysis yields two important lessons: (1) the cost-effectiveness of HIV vaccines will depend on the utilization and cost of PrEP at the time of launch and (2) condom substitution with vaccines, or behavioral disinhibition, could diminish the potential benefit of vaccines for the population and lower its value. Even if, however, vaccines induce some condom displacement and decline in PrEP use, we project overall population health benefits. Policies guiding the interactions between these interventions could have substantial impact on the value of each product alone and in combination. The findings from this study will affect public and commercial healthcare payers and people living with HIV. There may be a substantial budget impact to the Centers for Medicare and Medicaid (CMS) as life-extending ART shifts the age distribution of HIV patients and an increasing number of people with HIV have dual eligibility for Medicaid and Medicare each year. As several rigorous economic models have highlighted [147–149], more frequent HIV testing of MSM in the US is extremely valuable, and both PrEP and vaccine protocols increase the frequency of standard HIV testing compared to standard care.

We compared the results of this model with two other published studies evaluating the cost-effectiveness of HIV vaccines in the United States, and our conclusions were consistent when assuming the same vaccine price. A dynamic transmission model of HIV vaccines conducted in the pre-PrEP era estimated an ICER of \$91,000/QALY for universal HIV vaccination and net cost-savings from targeting MSM when assuming a cost of \$500 per vaccine series [71]. A more recent static HIV model comparing PrEP offered with HIV vaccines to PrEP alone, assuming vaccines cost \$2,500 per series, also estimated a net

cost-savings for MSM [107]. In our sensitivity analysis varying HIV vaccine costs, we similarly found vaccines costing \$500 or \$2,500 per series would have a net cost-savings for MSM.

There are several limitations to this study that deserve mention. A key uncertainty in the model is HIV vaccine efficacy and effectiveness. The economic model does not account for the societal impact of development of drug-resistant HIV strains, though this is a concern for PrEP users with poor adherence or the diminished end of a candidate PrEP injection's long-acting durability. Alternative modeling structures, such as network- or agent-based models, could be developed to strengthen the assumption of structural validity. Bernard and colleagues suggest, however, that varying model structures—when applied to this HIV vaccine question—do not substantially change the cost-effectiveness results [150]. Also, the generalizability of HIV vaccine these findings should be limited to MSM in the US. Not only is the future cost of PrEP uncertain, the products that will be used for PrEP in the future are also uncertain. With no additional approvals of for new drugs or indications, we would expect generic TDF/FTC products to become available at lower cost. If the TAF/FTC product recently approved for HIV treatment receives an additional indication for PrEP and offers the benefit of fewer side effects, this would effectively extend the patent period and prices are unlikely to decline. Another limitation is that tested model interactions between vaccine and PrEP utilization are limited and rely on plausible scenarios and assumptions described by expert opinion. We do not account for the contribution of PrEP use to the increasing prevalence of detectable drug resistance to TDF/FTC or its downstream impacts. Adverse events from PrEP and HIV vaccines are not well defined and estimating any related disutility is difficult. Finally, the analysis does not consider vaccine manufacturing costs or commercial viability.

The findings from this study point to several policy considerations. First, further public investment in US HIV vaccine clinical trials is warranted to reduce the uncertainty in expected vaccine efficacy. Second, more research on and education to prevent a decrease in condom use associated with HIV immunization

is needed to optimize the potential effectiveness and prevent further outbreak of other sexually transmitted infections such as syphilis and gonorrhea. Third, value-based pricing of the vaccine at launch should consider both the risk level of the indicated population and the current cost of PrEP. Risk to public investment in immunization campaigns could be mitigated with outcomes-based risk-sharing agreements between government payers and the manufacturer with support from existing CDC surveillance systems.

Access to an HIV vaccine is desirable as it could increase the overall effectiveness of combination HIV prevention efforts and improve population health. HIV vaccines have the potential to reach subpopulations that PrEP has been unable to reach. Though more than one-half of patients with new HIV diagnoses in the US are African-American and less than a quarter are white, 75% of patients starting PrEP from 2012-2015 were white [151]. The barriers to implementation of and access to vaccines could be lower with provision at clinic visits compared to prescription drugs that require high adherence to be effective. Planning for the rollout and scale-up of HIV vaccines should carefully consider the design of policies that guide interactions between vaccines and PrEP utilization and educate community members on the risks of condom displacement.

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**Conflicts of Interest**

The authors declare no competing interests.

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# Chapter 4

## The Cost-Effectiveness of Financial Incentives for Viral Suppression: HPTN 065 Study

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## **ABSTRACT**

Evidence on the effect and durability of financial incentives in low-income settings is generally encouraging, yet little evidence exists in its application to healthcare in the US. To fill this gap, the HPTN 065 Study randomized 39 clinics in New York, NY and Washington, DC, to offer quarterly financial incentives (\$70) for viral suppression. Over two years, the intervention significantly improved viral suppression compared to patients randomized to standard care. Based on a mathematical model of disease progression and HIV transmission, we estimate these financial incentives reduce total costs, improve patient health, and reduce new HIV infections by 9%. We identify economies of scale related to clinic and population heterogeneity. By improving adherence to HIV drugs, we suggest that financial incentives are likely to be dominant or cost-effective compared to standard care in the US, depending on the perspective. Finally, we generate new evidence to show the durability of effect on health outcomes after discontinuation of financial incentives.

## KEY POINTS

- Financial incentives (FIs) offer a promising option for enhancing the benefits of medication. The randomized HPTN 065 Study showed FIs (valued \$70) improved adherence to treatment and viral suppression (VS) among people living with HIV. The FIs had a statistically significant overall effect on VS with a 3.8 percentage-point (95% CI, 0.7% -6.8%; P=0.01) increase in the proportion of patients with VS compared to standard care clinics, after adjusting for the baseline clinic proportion virally suppressed.
- This economic evaluation estimates that two years of FIs improved the quality and length of life for patients, prevented HIV transmissions to partners, and saved lifetime costs from a societal perspective when compared to standard HIV care. We find these findings hold even if the benefits of partner transmissions, productivity gains, and assumed durability are ignored.
- FIs, as used in the HPTN 065 study, could be a cost-effective and potentially cost-saving tool yielding individual and societal benefits. This provides an opportunity to strengthen the HIV care cascade and an efficient approach to achieve goals outlined in the US National Strategic Plan for HIV. These findings may not be transferrable to other epidemic settings where key inputs such as staff salary, the cost of HIV drugs, and willingness to pay for health gains may differ substantially.

## 4.1 INTRODUCTION

Barriers to daily oral medication adherence are common and complex for patients with chronic disease [152]. For people living with HIV, adherence to antiretroviral therapy (ART) reduces the risk of opportunistic infections, improves quality of life, and extends survival [142,153–155]. Several studies support the role of ART in reducing the likelihood of HIV transmission to others by decreasing viral load levels [156–162]. Yet, only 58% of persons living with HIV in the United States achieve viral suppression (VS) [41]. There is little evidence of effective interventions to improve VS, despite this being a critical step in the HIV care continuum as described in the National HIV/AIDS Strategy for the United States [6,12,163,164].

Promising evidence shows financial incentives (FIs) can improve adherence to treatment and VS among people living with HIV [165–170]. The largest of these studies, the HIV Prevention Trials Network (HPTN) 065 Study assessed the effectiveness of FIs on VS among patients on ART at 39 HIV care sites in the Bronx, NY and Washington, DC [171]. The study design has been described in detail previously [172]. Clinics were randomized to provide either standard of care (SOC) with support for adherence or SOC plus provision of an FI gift card (equivalent of \$70 in 2011) to eligible patients at quarterly clinic visits with VS (HIV RNA viral load <400 copies/mL). The FIs had a statistically significant overall effect on VS with a 3.8 percentage-point (95% CI, 0.7%–6.8%; P=0.01) increase in the proportion of patients with VS compared to SOC clinics, after adjusting for the baseline clinic proportion virally suppressed [171].

Mathematic models have helped in estimating the effectiveness of HIV prevention [173–176] and assessing the value of an intervention from an economic perspective by projecting long-term outcomes beyond the trial period and estimating the incremental benefits and costs [71,104,107,177,178]. With VS as a surrogate outcome, mathematical modeling is a helpful tool to estimate the impact on important

outcomes that accrue longer-term, such as morbidity, mortality, and HIV transmission [84,179,180]. To inform decisions about efficient public investment in HIV treatment and prevention programs offered at clinics in the United States, we developed and utilized an economic model, based on HPTN 065 clinical trial data, to evaluate the clinical and preventive benefits, costs, and cost-utility of FI for VS compared to current practice.

## 4.2 METHODS

### 4.2.1 Analytic Overview

We conducted a model-based economic evaluation of the two-year HPTN 065 FI intervention in order to project the lifetime costs and health outcomes for patients and their sexual partners. A conceptual model enumerated how costs and benefits could accrue longer-term (Figure 4.1). The impact of the FIs compared to SOC was estimated by development and utilization of a mathematical model of disease progression and ongoing transmission (Appendix Figure 2). Our analytic methods and reporting follow guidelines from the Second Panel on Cost-Effectiveness in Health and Medicine [84,179], the International Society for Pharmacoeconomics and Outcomes Research - Society for Medical Decision Making Task Force on Good Research Practices for Randomized Clinical Trials Cost-Effectiveness Analysis [181], and the Consolidated Health Economic Evaluation Reporting Standards statement (see checklist in Appendix) [60].

As recently recommended by the Second Panel, our analysis considers both a societal and a healthcare sector perspective and is accompanied by an Impact Inventory (Appendix Table 1). The model estimates clinical outcomes (per-patient quality-adjusted life years), primary transmission outcomes, and lifetime costs (intervention, healthcare, and other societal costs). Factors that are not accounted for are explained in the Impact Inventory. We simulated 6 months of baseline care, a 2-year intervention period, and then projected the expected outcomes over a lifetime horizon (i.e., until every member of the simulated index

cohort died) and assumed VS differences diminish to pre-trial levels 6 months after FIs discontinue. We analyzed trial data in Stata IC version 13.1 and coded the model using both VBA in Microsoft Excel version 14.7.2 and R version 3.3.1.

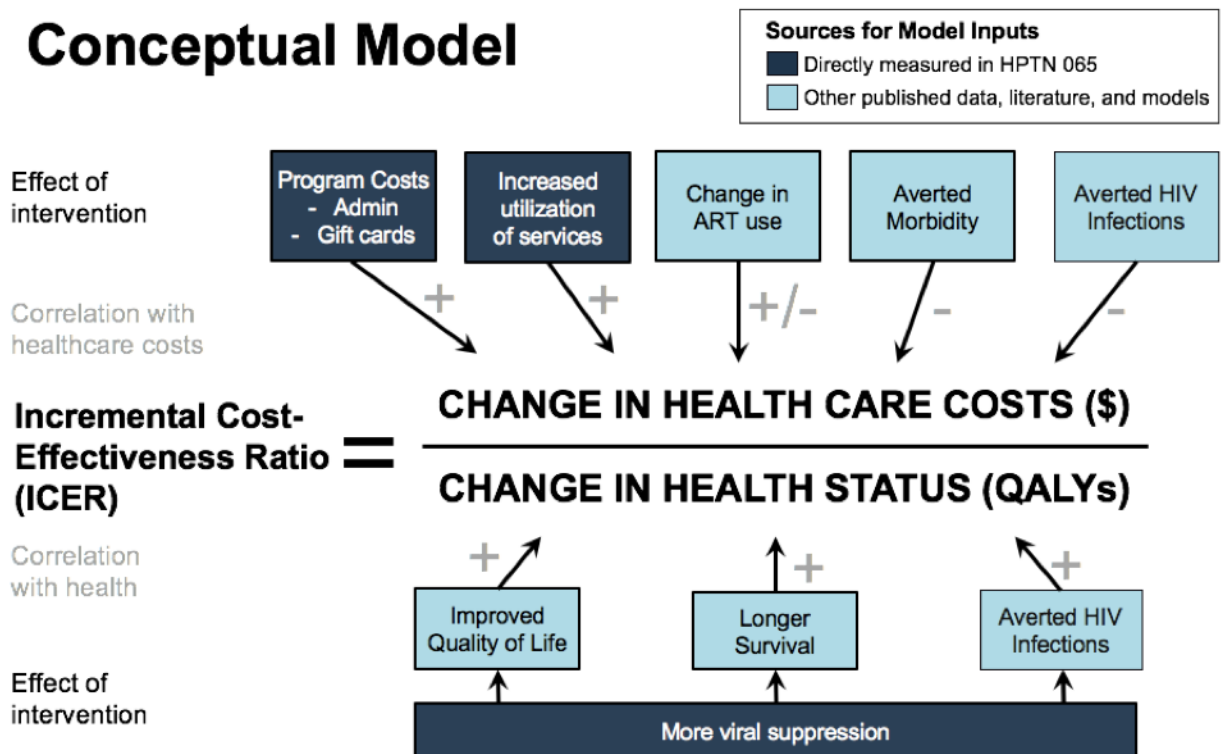


Figure 4.1. Conceptual Model

The conceptual model describes the accruing long-term costs and benefits from financial incentives for viral suppression, based on a framework from Kahn et al. 2011 [182].

#### 4.2.2 Data Sources

The primary data source for our model was the HPTN 065 study (baseline n=16,208 patients in care), with key model inputs, ranges, and sources summarized in Table 4.1. Unit costs were calculated using HPTN 065 study budgets, FI utilization reports, and staff interviews. The number, frequency, and characteristics of sexual partnerships were self-reported by a sub-set (n=948) of participants [172]. Additional input values were obtained from the Medical Monitoring Project [183], Centers for Disease

Control (CDC) HIV Surveillance reports [184,185], US Census Current Population Survey [186] and Life Tables [187], the US Bureau of Labor Statistics [188], and published literature.

Table 4.1. Key model inputs

Parameter	Value (Range)	Source
HIV-positive patients in care, mean number per site (SD)	347 (478)	Trial [171,172]
Age at baseline, mean years	47 (35 - 55)	Trial [171,172]
Fraction of patients in risk category*, %		
Men who have sex with men	32.6	Trial [171,172]
Heterosexual men	32.3	Trial [171,172]
Women	35.1	Trial [171,172]
Proportion VS* at baseline, median % patients in care	61.9 (22.5 - 80.1)	Trial [171,172]
FI distributed per clinic quarter, mean No.	286 (21-1331)	Trial [171,172]
Discount rate for costs and outcomes, %	3 (0-5)	Neumann 2016 [84]
<b>Costs, median (range), 2017 US\$</b>		
Financial Incentives Coordinator, per clinic per year	49 997 (39 998, 59 996)	Trial [171], Inflated to US\$ 2017
Equipment: laptop and printer in year 1, per clinic	1 600 (1280-1920)	Trial [171], Inflated to US\$ 2017
Office supplies, per clinic per year	160 (130-192)	Trial [171], Inflated to US\$ 2017
Financial incentive gift card value, each	74.66 (20 – 500)	Trial [171], Inflated to US\$ 2017
HIV-related healthcare costs, quarterly †		
ART costs, by CD4 stratum	3983 - 4359 (3752-4500)	Gebo 2010 [123], calculated
Outpatient costs, by CD4 stratum	162 - 224 (155-240)	Gebo 2010 [123], calculated
Labs and other health care costs, by CD4 stratum	1360 - 4328 (1092-4459)	Gebo 2010 [123], calculated
AIDS death	4328 (2229-6426)	Gebo 2010 [123], calculated
Earnings from productivity, annual age-specific	37,344-53,392	US Census Current Population Survey [186]
Consumption costs outside of health care, annual age-specific <sup>d</sup>	38,123 – 69,753	US Census Consumer Expenditures Survey [188]
<b>Clinical Inputs</b>		
Efficacy‡, mean percentage points increase from baseline proportion VS at clinic	3.8 (0.7 – 6.8)	Trial [171,172]
Increase in outpatient visits with incentives, %	8.7 (4.2-13.2)	Trial [171,172]
Hazard ratio of death from all causes if CD4<500	1.77 (1.17-2.55)	Roger 2013 [155]
Baseline probability of death from all causes, given age	Appendix	US Life Tables[189]
<b>Utilities</b>		
General population, age-specific	0.782 – 0.928	Hanmer 2006 [190]
HIV patients in care		
CD4+ T-cells >500	0.73 (0.63-0.83)	Evidence synthesis by Whitham 2016 [119]
CD4+ T-cells 350-500	0.71 (0.59-0.82)	Whitham 2016 [119]
CD4+ T-cells <350	0.69 (0.58-0.80)	Whitham 2016 [119]
<b>HIV Transmission, age-specific</b>		
Average No. sexual partners per year	1.7 (0.5 – 11)	Trial [171,172]
Probability of partner HIV infection from outside cohort, ages 45-54, quarterly	3.9E-05 (3.3E-5 – 4.6E-5)	CDC Surveillance Report Vol. 27 [185]
Probability of partner HIV infection from outside cohort, ages >=55, quarterly	8.2E-06 (6.3E-6 – 1.0E-5)	CDC Surveillance Report Vol. 27 [185]

Transmission probability per unsuppressed and unprotected insertive vaginal act of female participant with male partner	0.004 (0.003 – 0.005)	Boily, Lancet Infect Dis 2009 [191]
Transmission probability per unsuppressed and unprotected insertive anal act with male or female study participant as recipient of partner being insertive	0.006 (0.005 – 0.007)	Jin, AIDS 2010 [192]
Transmission probability per unsuppressed and unsuppressed and unprotected vaginal receptive act of infected participant transmitting to female partner	0.003 (0.002 – 0.004)	Boily, Lancet Infect Dis 2009 [191]
Transmission probability per unsuppressed and unprotected anal receptive act	0.014 (0.011 – 0.017)	Baggaley, International Journal of Epidemiology 2010 [193]
Risk reduction of transmission probability for virally suppressed HIV-infected patient	1.00 (0.80 – 1.00)	
Condom efficacy per vaginal act	0.94 (0.87 – 0.97)	Pinkerton, Soc. Sci. Med., 1997 [194]
Condom efficacy per anal act	0.7 (0.58 – 0.79)	Smith, JAIDS 2015 [195]

Abbreviations: FI, financial incentives; VS, viral suppression

\*Viral suppression defined as viral load < 400 copies/mL

†Mean costs and SD of HIV-related healthcare categories are summarized across strata. The expanded table of disaggregated costs is provided in Appendix Table 6

‡Overall efficacy across all clinics. Efficacy for eight clinic subgroups is provided in Appendix Table 7.

### 4.2.3 Study Population

We defined patients in the cohort as people living with HIV who were engaged in care, and using ART at study clinics in the Bronx, NY, and Washington, DC (Appendix Table 2 and Appendix Figure 1). At study enrollment, these patients were, on average, 47 years of age, 63% male, and infected with HIV for 16 years. Clinics had a mean number of 374 HIV patients in care with 62% virally suppressed. The cohort also included all hypothetical sexual partners of patients during the intervention.

### 4.2.4 Disease Model Description

Building on existing HIV prevention frameworks and HIV care continuum models, we developed a Markov model of disease progression and related HIV transmission equations (see conceptual diagram Appendix Figure 2) [7,140,141,177,182]. Simulations begin six months prior to the intervention, corresponding to the baseline study observation period, and continue until the last member of the cohort has died (lifetime horizon). VS and CD4+ cell count-defined health states were initialized using laboratory data from the study (Appendix Figures 3 and 4). Quarterly transition probabilities between

states with different CD4+ cell counts and VS are described in the Supplementary Appendix. As VS increases, the probability of transition into an improved health state (higher CD4+ cell count) correspondingly increases. We calculate quality-adjusted life years (QALYs) as the product of the utility value and quarterly person-time in each health state discounted 3% annually and summed over a lifetime horizon.

#### **4.2.5 HIV Transmission**

A set of HIV transmission risk equations (see Supplemental Appendix) for men who have sex with men (MSM), heterosexual men, and women include adjustment for patient age, VS, condom use, type of sexual activity (vaginal or anal sex), number of partners per patient, number of sex acts per partnership and the prevalence of HIV among partners (Appendix Table 3). HIV-uninfected partners were also susceptible to infection from sexual contact outside the patient cohort based on age-dependent probabilities of HIV infection (Appendix Table 3).

#### **4.2.6 Effectiveness of Financial Incentives**

The statistical methods used to estimate the intervention efficacy have been described previously [171,172]. Consistent with the trial design, the model simulates a 9-month ramp-up period for the scale-up of FIs and behavior change followed by a 15-month period of full implementation with efficacy of 3.8 (95% CI: 0.7-6.8) percentage-point improvement in VS. This implies, for example, that for a clinic randomized to the FI arm, 62% of its patients were virally suppressed at baseline and 65.8% of its patients were virally suppressed at the end of the two-year intervention. We assumed this effect diminishes to zero over the six months after the FIs were discontinued and performed sensitivity analyses on this assumption. HPTN 065 also observed an 8.7% increase in the number of clinic visits in the financial

incentive group, and the model infers a corresponding increase in outpatient utilization and ART costs during the intervention period [171,196].

#### 4.2.7 **Costs**

All costs are reported using a 3% annual discount rate and common currency of 2017 USD [197,198].

##### 4.2.7.1 *Administration Costs*

We retrospectively performed clinic-level micro-costing of FIs using an “ingredients-based” approach. The study team defined an implementation process for one quarter, enumerated the resources used as inputs, identified prices for the inputs, and summed the quantity multiplied by the price across inputs [84,199]. Total clinic cost divided by the average number of HIV patients in care produced the administration cost per patient. Due to the randomization of heterogeneous clinics, facility-level calculations provided the possibility to estimate potential economies of scale using sub-groups.

##### 4.2.7.2 *Healthcare and Other Societal Costs*

The trial did not collect data on healthcare costs. We incorporated published quarterly healthcare expenditures for people living with HIV [123]. The societal perspective, as described by the Second Panel [84,179], additionally included individuals’ productivity and consumption. Persons with CD4+ >200 cells/ML earned the national average for their age [186], and all consumed the national average for their age based on non-healthcare-related expenditures [188].

#### 4.2.8 **Sensitivity and Scenario Analyses**

We conducted univariate, scenario and probabilistic sensitivity analyses to characterize the impact of important model assumptions and uncertainties. In the univariate sensitivity analysis, parameters were set to the lowest and highest values for reasonable ranges (see Table 1) in order to observe the impact on

model outputs and to identify drivers of uncertainty in cost-effectiveness results. A multi-way sensitivity analysis evaluated pre-specified clinic sub-groups based on: study community (Bronx vs Washington, DC), smaller vs larger sites ( $\leq$ / $>$  median number of patients), hospital vs community-based sites, and lower vs higher percent with VS at baseline ( $\leq$ / $>$  median percent), where FI effectiveness varied by sub-group according to the trial results (Appendix Table 6). A threshold analysis was conducted to determine the minimal level of effectiveness and the maximum FI value, holding all other variables constant, for FIs to be considered cost-effective in this population.

A probabilistic sensitivity analysis evaluated the impact of stochastic uncertainty in the model inputs on the cost-effectiveness results. We selected and fit parameter distributions using 95% confidence intervals from published studies or a reasonable input range. Probabilistic draws used the beta distribution for utility values and probabilities, gamma distribution for costs, and log-normal distribution for relative risks. We sampled parameter sets for 10,000 Monte Carlo simulations and estimated the outcomes for each scenario.

## 4.3 RESULTS

### 4.3.1 Health Outcomes

Based on the HPTN 065 study results, the model projected that patients offered two years of FIs for VS survive 1 month longer than SOC patients (18.46 vs 18.38 life years, respectively). Adjusting for quality of life, FI patients had slightly better health outcomes compared to SOC patients (9.35 vs 9.31 lifetime discounted QALYs respectively) and a gained 0.04 QALYs per patient. FI patients had 9.5% fewer HIV transmissions to their sexual partners. We estimate 1 HIV infection was prevented per 200 patients offered FIs for VS (Table 4.2). This spillover benefit to partners gained an additional 0.02 QALYs per patient. This produced an impact total of 0.06 QALYs gained per patient by combining benefits to

patients and partners. Over the lifetime horizon, 94% of the health gains occurred during the trial period. Partner benefit accounted for 36% of total QALYs gained.

#### 4.3.2 Costs

The total discounted lifetime societal cost was \$4,210 lower for FI patients compared to the SOC patients (\$268,255 vs \$272,464 per patient respectively). From a health sector perspective, excluding productivity and non-healthcare expenditures, FIs for VS cost \$3,033 more per patient compared to the SOC cost (\$487,993 vs. \$484,961). Disaggregated costs in Appendix Tables 6 and 7 show how spending changed with a 2% increase in ART drugs, 0.5% decrease in visits and laboratory tests, and 0.3% increase in earnings.

At the facility-level, intervention supplies and FI coordinator salary cost \$167,714 per clinic. Distributed incentives averaged \$169 per patient each FI year. FI program implementation for two years cost, on average, \$706 per patient, varying between clinics and ranging \$558 - \$1,546 per patient at large and small clinics due to the economies of scale for a full-time FI coordinator. By preventing some HIV infections, partners of FI patients had substantially lower health care costs. From a societal perspective, a majority of FI cost savings were attributable to lifetime productivity gains of \$10,686 per patient. Limited to a healthcare sector perspective, the greatest change among cost categories was the \$3,685 per patient increase in lifetime ART drug costs for FI compared to SOC.

Table 4.2. Cost-Effectiveness Results

Perspective	Comparator	HIV Transmissions per 100 Patients*	Total Lifetime Costs per Patient† (2015 USD)	Total QALYs per Patient†	ICER (\$/QALY)
Societal	Standard of Care	7.94	\$272,464	38.51	
	Financial Incentives	7.19	\$268,255	38.57	
	<i>Incremental</i>	-0.76	-\$4,210	0.06	Dominant
Healthcare Sector	Standard of Care	7.94	\$484,961	38.51	
	Financial Incentives	7.19	\$487,993	38.57	
	<i>Incremental</i>	-0.76	\$3,033	0.06	\$49,877

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

\*Average cumulative number of HIV infections in the partner cohort per 100 patients, including transmissions from partners outside the study population.

†Lifetime horizon and 3% annual discount rate.

### 4.3.3 Cost-Effectiveness

From a societal perspective, FIs for VS gained 0.06 QALYs per patient and avoided \$4,210 per patient compared to the SOC (Table 4.2). FIs “dominated” the SOC because patients and partners had better health outcomes for a lower cost. Restricted to a healthcare sector perspective, excluding non-healthcare costs and productivity, FIs for VS were cost-effective with an incremental cost-effectiveness ratio (ICER) of \$49,877 per QALY gained compared to the SOC (Appendix Figures 5-7). The incremental cost of preventing one HIV infection was \$401,541. In sub-group scenarios, ICERs ranged from cost-saving to \$53,818 per QALY using a societal perspective and ranged from cost-saving to \$182,801 per QALY using a healthcare sector perspective. Of eight sub-groups, DC sites and the sites with a low proportion of patients virally suppressed at baseline achieved the greatest value from FIs for VS compared to similar SOC sites (Appendix Table 7). FI were cost-effective in New York from a societal perspective but not from a healthcare sector perspective, given a \$150,000 per QALY cost-effectiveness threshold; FI were cost-saving in DC.

#### 4.3.4 Sensitivity Analyses

Intervention effectiveness was the main driver of ICER variability in the univariate sensitivity analysis because of the large efficacy uncertainty interval from the trial (Figure 4.2). When assuming that no infections are prevented, the finding of cost-effectiveness associated with FIs as used in this study remains. In the threshold analysis, varying efficacy while keeping other variables constant, FIs that achieve at least a 0.73% percentage-point improvement in VS within 2 years would be cost-effective compared to SOC. Other than efficacy, FIs for VS were cost-effective over entire parameter ranges in the univariate analysis (Figure 4.2). The increase in utilization of clinic services was an important driver of cost-effectiveness. Results were also sensitive to the inclusion of partners in the cohort, depending on the threshold and perspective. Excluding partners from the analysis and limiting it to a healthcare sector perspective, the ICER increased to \$139,256/QALY – remaining cost-effective given a \$150,000/QALY threshold.

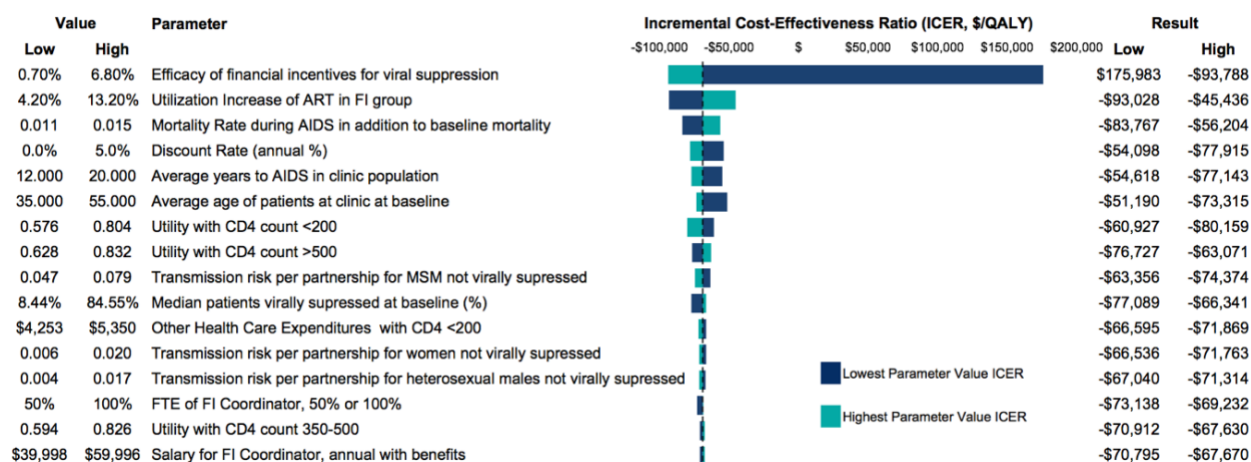


Figure 4.2. One-way sensitivity analysis

Univariate sensitivity analysis examining parameter uncertainty impact on the incremental cost-effectiveness ratio

Stochastic simulations revealed great uncertainty in the cost-effectiveness estimate with a median ICER \$34,252/QALY and 95% Credible Range from cost-saving to \$501,610/QALY (Figure 4.3 and Appendix

Table 8). The cost-effectiveness acceptability curve (Appendix Figure 8) shows 73% of simulations are cost-effective and 38% highly cost-effective or cost-saving.

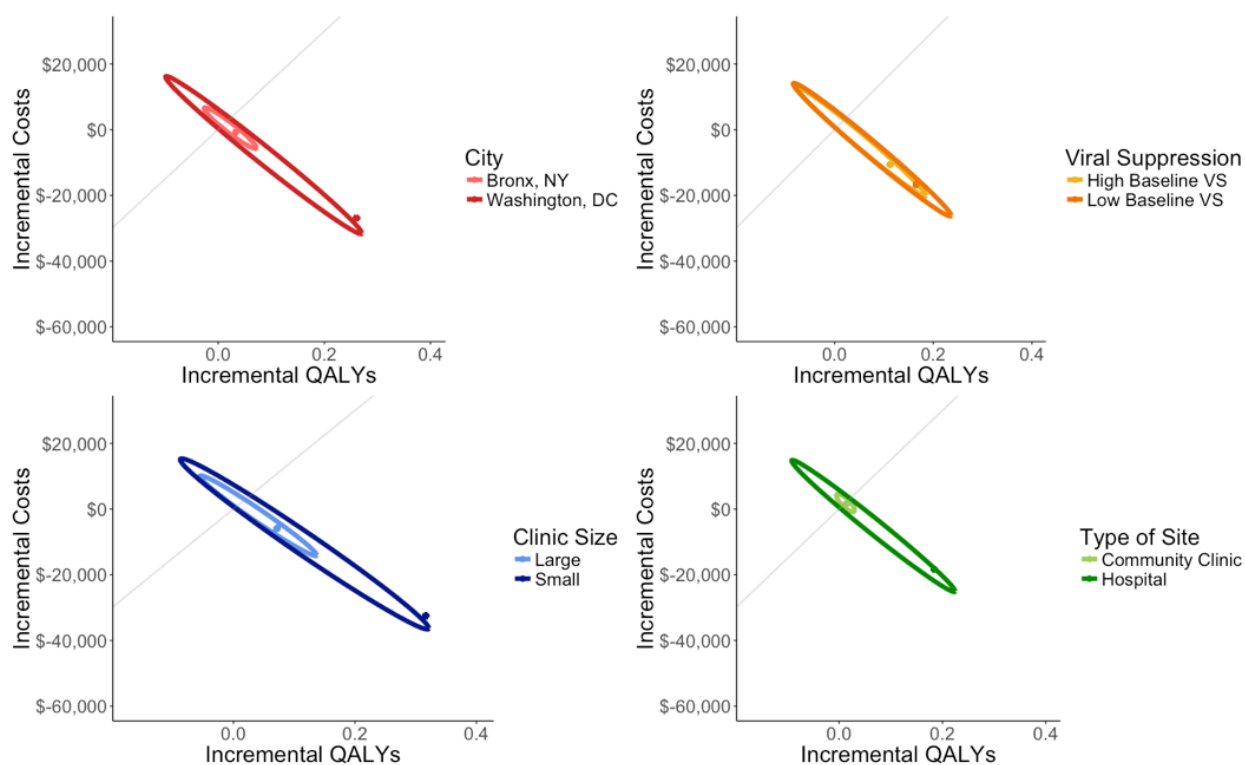


Figure 4.3. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis of sub-groups plotted on the cost-effectiveness plane. Ellipses represent 95% credible range from 10,000 Monte Carlo simulations of each sub-group; the grey line represents a \$150,000/QALY cost-effectiveness threshold.

## 4.4 DISCUSSION

We conducted a cost-effectiveness analysis of the use of FI for VS in the HPTN 065 study. Our findings provide evidence that FIs can be cost-effective and potentially cost-saving in the US. Modeled outcomes from FIs yielded better health and quality of life as well as 9% fewer HIV transmissions to sexual partners. Though the absolute changes in health and costs were relatively small, each unit of health gained came at a very small cost. Without a generally agreed-upon willingness to pay for healthcare in the US, we followed value assessment guidelines from the Second Panel [84] and Institute for Clinical and

Economic Review [200] by assuming a cost-effectiveness threshold range from \$50,000 - \$150,000 per QALY gained based on 1-3 times the US GDP per capita.

There are two main implications of this study. First, FIs can be cost-effective and potentially cost-saving in the United States. Notably, the \$70 gift card value of FI used in this study was a relatively small contributor to the cost, considering a threshold analysis found FIs less than \$1,000 would be cost-effective from a healthcare sector perspective using a \$150,000/QALY threshold and the same efficacy. This can inform public health resource allocation decision-makers by showing how an investment in FI programs can reap long-term health gains and cost-offsets. Second, these findings held even if the benefits of partner transmissions, productivity gains, and assumed durability are ignored. The main cost-effectiveness drivers were the magnitude of the FI efficacy, the cost of ART drugs, and the lifetime earnings of individuals. Effective FIs may affect the lifetime spending on ART for the following three reasons: 1) increased ART adherence requires patients to refill prescriptions more often, 2) patients who live longer use ART for longer durations, and 3) the demand for ART is reduced with HIV transmissions prevented. Another economic evaluation reached similar conclusions: an 18-month study using electronic medication monitors to improve viral load was also found to be cost-effective with a per-person QALY gain only 15% different than the lifetime estimate in this analysis [201].

The study has several strengths and limitations. The strengths include the large study size, the availability of patient-level laboratory data and the use of two reference cases (societal and healthcare sector). The economic model we used has some limitations. The key driver of uncertainty in health impact that may alter policy decisions is the efficacy of the intervention, in this case in enhancement of VS. In the HPTN 065 study, the 95% confidence interval for effectiveness of the FIs for achieving VS ranged from 0.7% to 6.8%. If the true effectiveness is close to the lower bound, then the use of FI for VS would not be cost-effective. This creates some risk that implementation would not be the optimal decision: an alternative

intervention may be a better investment. Findings from another FI program may provide further data to inform cost-effectiveness analyses [202]. It is important to note that the model does not capture the potential emotional benefit from the FIs effect on quality of life, or the potential health benefits from the diagnosis and treatment of other diseases with more frequent visits, and thus may underestimate QALYs gained. Qualitative interviews demonstrated that the main value FI participants perceived was feeling emotionally cared for and rewarded [203]. In addition, HIV transmission is limited to a cohort of partners and does not capture the dynamics of the full sexual network or mother-to-child transmissions. As a result, the model likely under-estimates the reduction in HIV transmission by not taking into account the indirect effects of the intervention by preventing future infections, and, therefore, our analysis provides a conservative estimate of the value of FIs. There remains model structural uncertainty given that only one model was developed [150]. Lastly, generalizability of the study results may be limited to urban settings in the US, consistent with where this study was conducted. These findings may not be transferrable to other epidemic settings where key inputs such as staff salary, the cost of HIV drugs, and willingness to pay for health gains may differ substantially.

Findings from this study demonstrated that FIs, as used in the HPTN 065 study, could be a cost-effective and potentially cost-saving tool yielding individual and societal benefits. Investment in an FI intervention, which incentivizes adherence and VS, could be an efficient application of healthcare resources when striving to reach the goals set out in the US National Strategic Plan for HIV.

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# Chapter 5

## Conclusion

Efficient stewardship of federal resources and practical implementation of HIV prevention efforts requires prioritization of goals. The results, sensitivity analyses, and discussions included in this dissertation aim to provide evidence for decision makers in their efforts to design and pursue efficient healthcare policies that could make a substantial impact on the HIV epidemic. In closing, the research presented in this dissertation will hopefully help to address the need for economic evaluations of HIV prevention strategies that has been called for in the US:

Investments must be prioritized for maximum impact. Economic evaluations of HIV prevention strategies, including cost-effectiveness analyses of single and combination HIV prevention interventions, are needed to provide stakeholders with tools to set priorities and measure impact for high-risk populations. Resource allocation models are necessary to identify optimal prevention funding allocation among populations and programs to maximize the impact of HIV care and prevention at the national and local levels.

- *The National HIV/AIDS Strategy for the United States: Updated to 2020* [6]

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# APPENDIX A: SUPPLEMENTARY MATERIAL FOR THE HPTN 065 MODEL

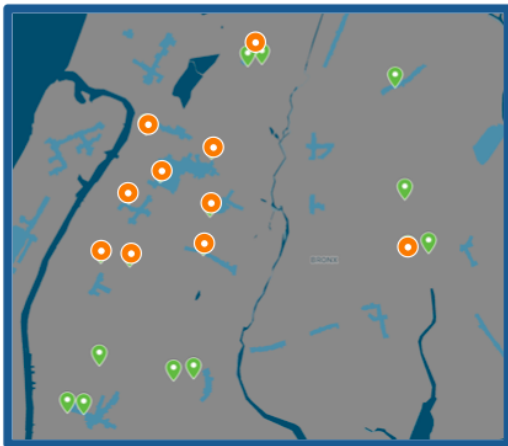
**Appendix Table 1.** Impact Inventory

<b>IMPACT INVENTORY</b>				
Sector	Type of Impact	Included in This Reference Case Analysis From ... Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
<b>Formal Health Care Sector</b>				
	<b>Health Outcomes (effects)</b>			
	Longevity effects of patient	Yes	Yes	Modeled
	Health-related quality of life	Yes	Yes	Evidence synthesis by Whitham 2016 [119]
	Primary HIV Transmissions	Yes	Yes	Calculated. We did not include mother to child transmission because this is rare in the United States and would be even more rare for people engaged in care
	Partner QALYs	Yes	Yes	Modeled, the number of total partners was estimated from behavioral surveys
	<b>Intervention Costs</b>			
	Staff time of FI Coordinator	Yes	Yes	Study budgets and interviews. All intervention sites had a full time FI coordinator no matter the size of the clinic
Health	Startup cost of laptop and printer	Yes	Yes	Study budgets
	Office supplies used for program each year	Yes	Yes	Study budget
	Visa gift cards for incentive, \$70 each	Yes	Yes	Based on study budgets and study results with the number of cards dispensed each quarter at each clinic
	<b>Direct Medical Costs</b>			
	Paid for by third-party payers	Yes	Yes	Gebo 2010 [123], calculated
	Paid for by patients out-of-pocket	Yes	Yes	Gebo 2010 [123], calculated
	Future related medical costs (payers and patients)	Yes	Yes	Gebo 2010 [123], modeled. This included the cost from increased utilization of services but did not include prevention of other diseases with detection from increased visits
	Future unrelated medical costs (payers and patients)	Yes	Yes	Gebo 2010 [123], modeled
<b>Informal Health Care Sector</b>				
	Transportation costs	NA	No	Insufficient evidence available to include
Health	Patient-time costs	NA	No	Insufficient data available to include
	Unpaid caregiver-time costs	NA	No	Insufficient evidence available to include
<b>Non-Health Care Sectors</b>				

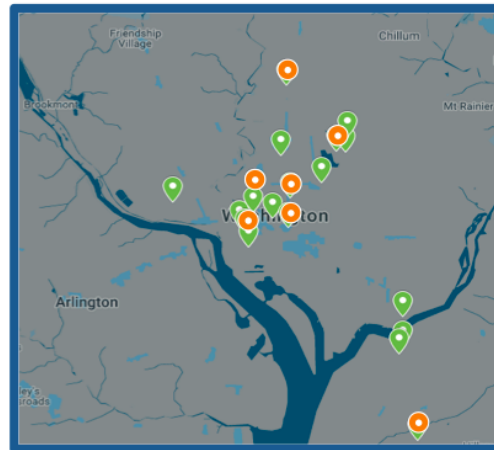
Productivity	Labor market earnings lost	NA	Yes	US Census Current Population Survey [186], specific for age categories
	Cost of unpaid lost productivity due to illness	NA	Yes	Patients assumed able to earn unless in AIDS stage or dead
Consumption	Future consumption unrelated to health	NA	Yes	US Census Consumer Expenditures Survey [188], specific to age categories

\*Administration costs include FI Coordinator Salary, office supplies, and startup cost of laptop and printer. All costs and QALYs are over the lifetime horizon and discounted 3% annually to reflect present value. QALYs, quality-adjusted life years

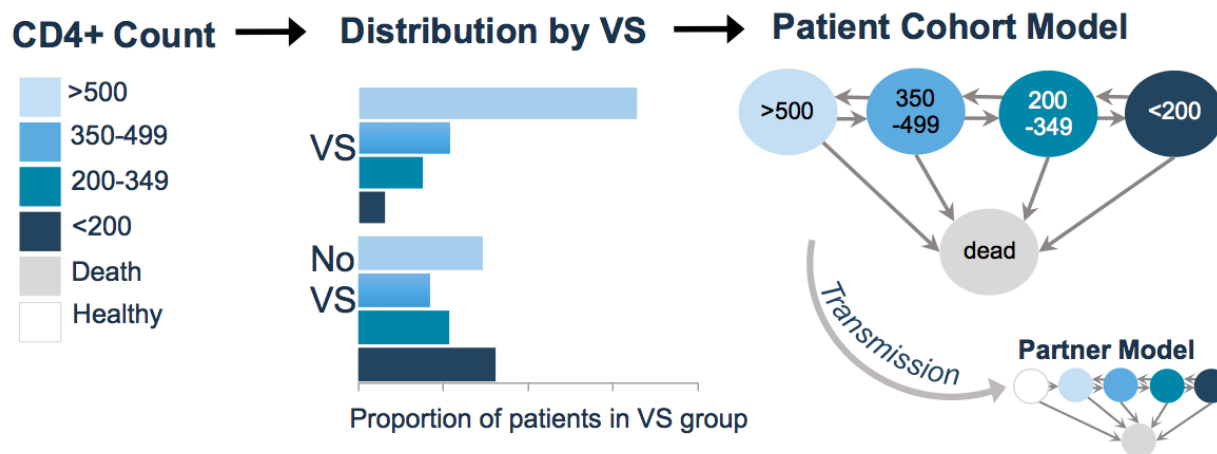
## The Bronx, New York



## Washington, D.C.



**Appendix Figure 1.** Locations of HPTN 065 HIV care sites in the Bronx, NY (left) and Washington, DC (right) randomized to deliver financial incentives for viral suppression (orange) or standard HIV care (green).



**Appendix Figure 2.** Conceptual diagram of Markov model health states and the relationship between viral suppression status and distribution of CD4+ T-cell counts.

Health states are defined by CD4 count (>500, 350-499, 200-349, and <200) and viral load are subject to age-specific mortality and HIV-related death.[189] Disease progression is modeled using quarterly transition probabilities between health states given the time since HIV sero-conversion. Based on recent evidence, persons with CD4 <500 experience 1.77 (1.17-2.55) times the hazard of non-AIDS death from all causes compared to persons uninfected.[155] As VS improves, the probability of transition into an improved CD4-count health state correspondingly increases (see Supplementary Appendix). Health states are initialized by the distribution of each CD4-count group by VS based on laboratory data from a subset of patients participating in HPTN 065 (Appendix Figure 3).[154] We calculate quality-adjusted life years (QALYs) as the product of the utility value and quarterly person-time in each health state summed over a lifetime horizon and discounted 3% annually. The quality of life of HIV uninfected partners was adjusted using age-stratified utility values elicited from a general US population.[190] An HIV transmission module connected patient and partner cohorts to estimate primary HIV transmissions. Partners are followed from the start of the study until their death. The average age of partners was assumed to be the same as the average age of the patients' cohort.

**Appendix Table 2.** Demographics of HIV patients in care at clinical sites participating in HPTN 065

Number in Care	Overall		Bronx		DC	
	N	%	N	%	N	%
	24704	100%	13874	100%	10830	100%
Year of Diagnosis						
<=1990	1906	8%	1195	9%	711	7%
1991-1995	3467	14%	2396	17%	1071	10%
1996-2000	5380	22%	3467	25%	1913	18%
2001-2005	6516	26%	3710	27%	2806	26%
2006-2010	5784	23%	2394	17%	3390	31%
2011-2012	1651	7%	712	5%	939	9%
Age						
13-24	1327	5%	759	5%	568	5%
25-34	3078	12%	1505	11%	1573	15%
35-44	5371	22%	2842	20%	2529	23%
45-54	8987	36%	5192	37%	3795	35%
55+	5941	24%	3576	26%	2365	22%
Male (%)	16041	65%	8041	58%	8000	74%
Race						
Black/African American	14250	58%	6534	47%	7716	71%
Hispanic/Latino	7331	30%	6632	48%	699	6%
White	2599	11%	459	3%	2140	20%
Multiple Races/Other	524	2%	249	2%	275	3%
Foreign Born						
Yes	3310	13%	2644	19%	666	6%
No	17555	71%	7868	57%	9687	89%
Unknown	3839	16%	3362	24%	477	4%
Risk Group <sup>a</sup>						
Male to male sexual	7314	30%	2346	17%	4968	46%
Male injection drug use	2580	10%	1875	14%	705	7%
MSM and IDU	746	3%	413	3%	333	3%
Male heterosexual	1707	7%	897	6%	810	7%
Male other	3694	15%	2510	18%	1184	11%
Female injection drug use	1668	7%	1117	8%	551	5%
Female heterosexual	3404	14%	2061	15%	1343	12%
Female other	3590	15%	2655	19%	935	9%
Risk Category						
MSM		33%		20%		49%
Heterosexual Men		32%		38%		25%
Women		35%		42%		26%
		100%		100%		100%

<sup>a</sup> Category reported at time of initial diagnosis by clinician to CDC Surveillance system as suspected route of HIV transmission

### **Transition Probabilities**

The mathematical model is a set of difference equations solved at quarterly time steps. The probability of being in compartment  $i$  at time  $t$  is a function of the probability of being in compartment  $i$  at time  $t-1$ , the rate of HIV disease progression while on ART, baseline mortality [189], viral load, time since HIV infection, and CD4-count category-dependent increased risk of death from all causes [155].

The model is subject to the Markovian assumption that transitions are memoryless, as the probability of moving into one health state does not depend on the path through previous health states. We accommodate this limitation when necessary using time dependent variables. As all members of the cohort begin with an average age, and continue to increase in age at the same rate, many of the time dependent variables are coded so the value at time  $t$  is dependent on the average cohort age at time  $t$  (i.e., mortality, HIV incidence).

Age-specific baseline mortality was based on Life Tables published by the US Census Bureau (US Census 2015).

### ***Converting Rates to Probabilities***

When data sources reported rates, such as the annual hazard [counted number of events per unit of time], we converted the rate to the quarterly probability of an event, infection, transition to another state, and death using the equation

$$p = 1 - e^{(-rate*t)}$$

where  $t$  is ratio of the unit of the time for the rate to the corresponding number of quarterly time steps (i.e., for an annual hazard  $t = .25$ )

### ***Improvement in CD4 from Intervention Effect on Viral Suppression***

“Backward transitions” correspond to improvement in health status that result from the intervention effect on viral suppression. During intervention periods, the probability of quarterly transition into one health state improved

$$p_{Improve|i,t,n} = 1 - \exp\left(-\left(p_{i|vs=1} * (p_{vs=1|n} + effect_n) + (p_{i|vs=0} * (1 - p_{vs=1|n} - effect_n))\right) * \frac{1}{c}\right)$$

where

$i$  = health state compartment [CD4 $\geq$ 500, 350 $\leq$ CD4 $<$ 500, 200 $<$ CD4 $<$ 350, CD4 $\leq$ 200]

$vs$  = viral suppression status indicator variable [1 = virally suppressed; 0 = not suppressed]

$p_{i|vs}$  = proportion of clinic patients with CD4-count category  $i$  when viral load status is  $vs$

$n$  = clinic sub-group [all, NY, DC, low VS, high VS, hospital, community, small, large]

$effect$  = the percentage point increase in the proportion of clinic patients with viral suppression (assuming no effect in the first [baseline] quarter, half of the effect in the ramp up period Q2-Q4, full effect in period Q5-9, and half the effect in Q10-11, and no effect after Q12)

$c$  = time cycles of FI intervention duration, with two quarters of observation before the financial incentive intervention begins

We assume the intervention effect diminishes over six months after incentives end, and approximate this by decreasing the probability of improvement by half and applying it for two quarters after incentives end. After the trial period (2 quarters observation + 8 quarters incentives + 2 quarters effect decay = 3 years), there is a zero probability of transitioning into an improved health state.

Initialize the population size in the compartments at  $t=0$ . This is based on the distribution of CD4 counts for patients who are virally suppressed and those who are not virally suppressed that is weighted to the baseline proportion of virally suppressed patients.

$$p_{i|t=0} = p_{i|vs=1} * p_{vs=1|n,t} * n + p_{i|vs=0} * (1 - p_{vs=1|n,t}) * n_i$$

where

$n$  = the average number of patients in clinic subgroup  $i$

### ***Difference Equations for Disease Progression***

The probability of being in any cohort at time  $t$  is solved by the set of equations

$$p_{>500|t} = p_{>500|t-1} - p_{500|t-1} * mr_{age|t-1}$$

$$+ p_{improve|i,t,n,FI_t=1} * p_{350-500|t-1} * d_t$$

$$p_{>500|t-1} * p_{progress\ to\ 350-500}$$

$$p_{350-500|t} = p_{350-500|t-1} - (p_{350-500|t-1} * mr_{age|t-1} * hrHIV)$$

$$+ p_{improve|i,t,n,FI_t=1} * p_{200-350|t-1} * d_t$$

$$- p_{improve|i,t,n,FI_t=1} * p_{350-500|t-1} * d_t$$

$$p_{350-500|t-1} * p_{progress\ to\ 200-350}$$

$$+ p_{>500|t-1} * p_{progress\ to\ 350-500}$$

$$p_{200-350|t} = p_{200-350|t-1} - p_{200-350|t-1} * mr_{age|t-1} * hrHIV$$

$$+ p_{improve|i,t,n,FI_t=1} * p_{200-350|t-1} * d_t$$

$$- p_{improve|i,t,n,FI_t=1} * p_{200-350|t-1} * d_t$$

$$p_{200-350|t-1} * p_{progress\ to\ <200}$$

$$+ p_{350-500|t-1} * p_{progress\ to\ 200-350}$$

$$p_{<200|t} = p_{<200|t-1} - p_{<200|t-1} * mr_{age|t-1} * hrHIV - p_{<200|t-1} * mrAIDS$$

$$- p_{improve|i,t,n,FI_t=1} * p_{<200|t-1} * d_t$$

$$+ p_{200-350|t-1} * p_{progress\ to\ <200}$$

$$p_{dead|t} = p_{dead|t-1} + p_{500|t-1} * mr_{age|t-1}$$

$$+ p_{350-500|t-1} * mr_{age|t-1} * hrHIV$$

$$+ p_{200-350|t-1} * mr_{age|t-1} * hrHIV$$

$$+ p_{<200|t-1} * mr_{age|t-1} * hrHIV + p_{<200|t-1} * mrAIDS$$

given that

$mr$  = probability of death in previous quarter given age, based on US lifetables

$hrHIV$  = increased hazard of non-AIDS death (i.e., cardiac arrest or cancer) among HIV patients with CD4 <500

$mrAIDS$  = quarterly probability of AIDS death

$FI_t$  = financial incentives distributed at time  $t$  [1 = Yes; 0 = No]

$t_d$  = time at which the intervention effect wanes to zero

$d$  = percentage reduction in the probability of health state improvement during the two quarters after incentives end [50% for 2 quarters after FI end; 1 otherwise]

and the probability of being in a health state cannot be less than zero.



**Appendix Table 3.** Complete list of parameter values, ranges, and data sources

<b>Parameter</b>	<b>Value (Range)</b>	<b>Source</b>
Clinic size, median No. patients per quarter	347 (43-2262)	HPTN 065
Patient age, mean years	47 (35-55)	HPTN 065
Baseline clinic VS <sup>a</sup> , median % patients in care	61.9 (22.5-80.1)	HPTN 065
FI distributed in ramp up quarters per clinic, mean No.	254 (7 – 1117)	HPTN 065
FI distributed in intervention quarters per clinic, mean No.	286 (21-1331)	HPTN 065
<b>Costs (2017 US\$)</b>		
Financial Incentives Coordinator, per clinic per year	49 997 (39 998, 59 996)	HPTN 065, inflated to 2017
Equipment: laptop and printer in year 1, per clinic	1 500 (1280-1920)	HPTN 065, inflated to 2017
Office supplies, per clinic per year	160 (130-192)	HPTN 065, inflated to 2017
Financial incentive gift card value, each	74.66 (20 – 500)	HPTN 065, inflated to 2017
<b>ART costs, quarterly</b>		
CD4 >500	4359 (4217 - 4501)	Gebo 2010, calculated
CD4 350-499	3939 (3752 - 4126)	Gebo 2010, calculated
CD4 200-349	4116 (3970 - 4363)	Gebo 2010, calculated
CD4 <200	4182 (3939 - 4425)	Gebo 2010, calculated
<b>Outpatient costs, quarterly</b>		
CD4 >500	162 (156 -169)	Gebo 2010, calculated
CD4 350-499	174 (166 - 183)	Gebo 2010, calculated
CD4 200-349	195 (185 - 204)	Gebo 2010, calculated
CD4 <200	224 (208 - 241)	Gebo 2010, calculated
<b>Labs and other health care costs, quarterly</b>		
CD4 >500	1360 (1310 - 1411)	Gebo 2010, calculated
CD4 350-499	1855 (1675 - 2036)	Gebo 2010, calculated
CD4 200-349	2565 (2385 - 2745)	Gebo 2010, calculated
CD4 <200	4802 (4253 - 5350)	Gebo 2010, calculated
AIDS death	5192 (2674 - 7710)	Gebo 2010, calculated
<b>Outcomes</b>		

<sup>b</sup> Efficacy, mean percentage points increase from baseline proportion VS at clinic	3.7 (0.5 – 6.9)	HPTN 065
Increase in outpatient visits with incentives, %	8.7 (4.2-13.2)	HPTN 065
Hazard ratio of death from all causes if CD4<500	1.77 (1.17-2.55)	Roger 2013
<b>HIV Utility Values</b>		
Utility, CD4 >500	0.73 (0.63-0.83)	Whitham 2016
Utility, CD4 350-500	0.71 (0.59-0.82)	Whitham 2016
Utility, CD4 <350	0.69 (0.58-0.80)	Whitham 2016
Discount rate for costs and outcomes, %	3 (0-5)	Neumann 2016
<b>Healthy Utility Values</b>		
Ages 20-29	0.928 (0.922-0.942)	Hamner 2006
Ages 30-39	0.918 (0.912 – 0.925)	Hamner 2006
Ages 40-49	0.887 (0.880 – 0.894)	Hamner 2006
Ages 50-59	0.861 (0.853 – 0.870)	Hamner 2006
Ages 60-69	0.840 (0.827 – 0.852)	Hamner 2006
Ages 70-79	0.802 (0.788 – 0.816)	Hamner 2006
Ages >80	0.782 (0.757 – 0.807)	Hamner 2006
<b>HIV Transmission</b>		
Average No. sexual partners per year	1.7 (0.5 – 11)	HPTN 065
Probability of partner HIV infection from outside cohort, ages 45-54, quarterly	3.9E-05 (3.3E-5 – 4.6E-5)	CDC Surveillance Report
Probability of partner HIV infection from outside cohort, ages >=55, quarterly	8.2E-06 (6.3E-6 – 1.0E-5)	CDC Surveillance Report
Transmission probability per unsuppressed and unprotected insertive vaginal act of female participant with male partner	0.004 (0.003 – 0.005)	Boily, Lancet Infect Dis 2009
Transmission probability per unsuppressed and unprotected insertive anal act with male or female study participant as recipient of partner being insertive	0.006 (0.005 – 0.007)	Jin, AIDS 2010

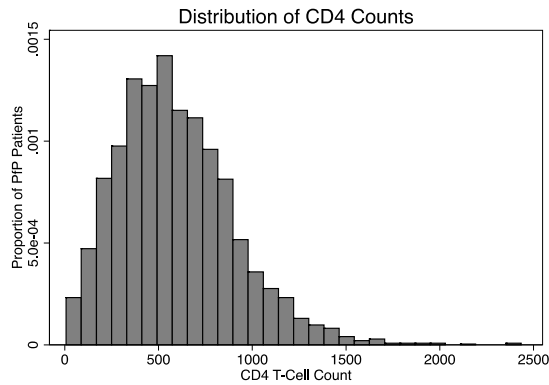
Transmission probability per unsuppressed and unsuppressed and unprotected vaginal receptive act of infected participant transmitting to female partner	0.003 (0.002 – 0.004)	Boily, Lancet Infect Dis 2009
Transmission probability per unsuppressed and unprotected anal receptive act	0.014 (0.011 – 0.017)	Baggaley. International Journal of Epidemiology 2010
Risk reduction of transmission probability for virally suppressed HIV-infected patient	1.00 (0.80 – 1.00)	
Condom efficacy per vaginal act	0.94 (0.87 – 0.97)	Pinkerton, Soc. Sci. Med., 1997
Condom efficacy per anal act	0.7 (0.58 – 0.79)	Smith, JAIDS 2015
Fraction of patients in risk category*, %		
Men who have sex with men	32.6	HPTN 065
Heterosexual men	32.3	HPTN 065
Women	35.1	HPTN 065

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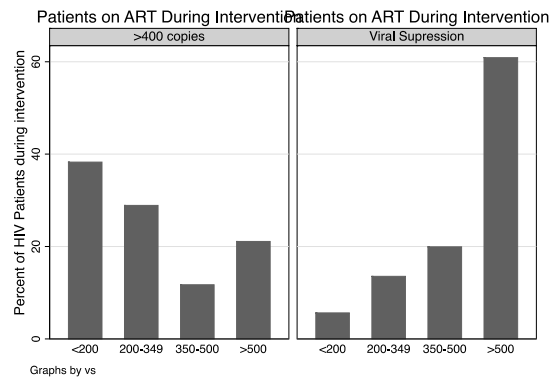
\* Varied in sub-group analysis

The number, frequency, and characteristics of sexual partnerships were self-reported by a sub-set of HPTN 065 patients in care in the CARE+ survey (n=948) from the Positives for Prevention component of HPTN 065 which was conducted at some of the study sites and which informed the transmission risk equations of the mathematical model. Salary and benefits for one full-time staff member per clinic were provided for a financial incentives coordinator. Fixed startup costs included one laptop and printer per clinic, and office supplies were a recurring annual cost. The number of distributed gift cards varied quarterly according to the number of eligible patients. For ramp-up and intervention periods, separately, we multiplied the unit cost per incentive by the quarterly number of incentives distributed and defined the mean and distribution of quarterly incentive expenditures across all clinics.

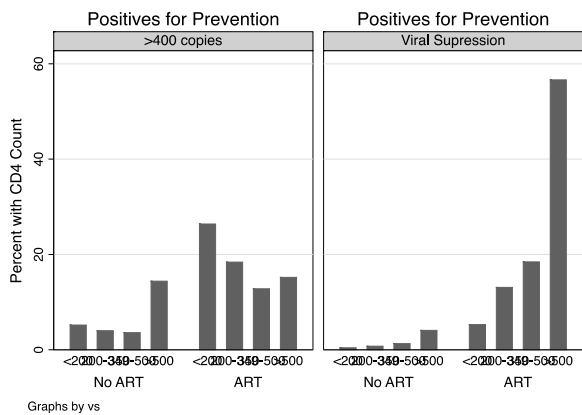
A.



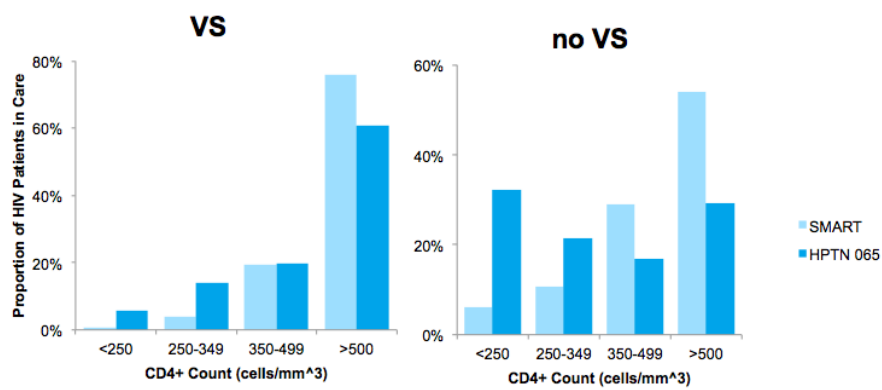
B.



C.



**Appendix Figure 3.** Distribution of CD4 T-cell counts A) in HPTN 065 Positives for Prevention patients, B) by CD4-count category stratified by viral suppression status, and C) stratified by CD4-count category, viral suppression status, and reported ART use. Viral suppression defined as <400 RNA copies/ml and not suppressed as  $\geq$ 400 copies/ml.



**Appendix Figure 4.** Comparison of CD4 T-cell count category distributions in sub-set of HPTN 065 participants and reported SMART study participants (SMART 2006).

**Appendix Table 4.** Distribution across CD4-count categories by intervention group

	<b>&gt;500</b>	<b>350-500</b>	<b>200-350</b>	<b>&lt;200</b>
Percent of all HIV	0.48733199	0.187372739	0.167534658	0.157760613
Percent of HIV >200 CD4	0.578614581	0.222469694	0.198915725	
Ramp Up:	0.48983599	0.187607139	0.166931458	0.155625413
FI: Percent of all HIV	0.49233999	0.187841539	0.166328258	0.153490213
FI: Percent >200	0.581611693	0.221901202	0.196487106	

## HIV Transmission Risk Equations

We estimate the HIV transmission risk per partnership from virally unsuppressed patients (women, heterosexual men, and MSM) over 2-year period given by:

$$p_w = (1 - \pi_w) \left[ 1 - \left[ (1 - \beta_{vi})^{(1-c_w)n_{wv}} (1 - (1 - \varepsilon_v)\beta_{vi})^{c_w n_{wv}} \right. \right. \\ \left. \left. (1 - \beta_{ai})^{(1-c_w)n_{wa}} (1 - (1 - \varepsilon_a)\beta_{ai})^{c_w n_{wa}} \right] \right]$$

$$p_m = (1 - \pi_m) \left[ 1 - (1 - \beta_{vr})^{(1-c_m)n_{mv}} (1 - (1 - \varepsilon_v)\beta_{vr})^{c_m n_{mv}} \right. \\ \left. (1 - \beta_{ar})^{(1-c_m)n_{ma}} (1 - (1 - \varepsilon_a)\beta_{ar})^{c_m n_{ma}} \right]$$

$$p_{msm} = (1 - \pi_{msm}) \left[ 1 - (1 - \beta_{ar})^{\frac{(1-c_{msm})n_{msm}}{2}} (1 - (1 - \varepsilon_a)\beta_{vi})^{\frac{c_{msm}n_{msm}}{2}} \right. \\ \left. (1 - \beta_{ai})^{\frac{(1-c_{msm})n_{msm}}{2}} (1 - (1 - \varepsilon_a)\beta_{ai})^{\frac{c_{msm}n_{msm}}{2}} \right]$$

Here:

- $\pi_w$ ,  $\pi_m$  and  $\pi_{msm}$  represent the HIV prevalence among partners of women, heterosexual men and MSM
- $n_{wv}$  and  $n_{wa}$  are the numbers of vaginal and anal acts that female patients have per partnership
- $n_{mv}$  and  $n_{ma}$  are the numbers of vaginal and anal acts that heterosexual male patients have per partnership
- $n_{msm}$  is the number of anal acts that MSM patients have per partnership (assumed half insertive and half receptive)
- $c_w$ ,  $c_m$  and  $c_{msm}$  are the fractions of protected acts which women, heterosexual men and MSM have
- $\varepsilon_v$  and  $\varepsilon_a$  is the condom efficacy per vaginal and anal act
- $\beta_{vi}$  ( $\beta_{ai}$ ) and  $\beta_{vr}$  ( $\beta_{ar}$ ) are the transmission probability per unprotected insertive and receptive vaginal (anal) act

The total number of infections is estimated as:

$$(N_w * p_w * f_w + N_m * p_m * f_m + N_{msm} * p_{msm} * f_{msm}) * \rho_u * P$$

- $N_w$ ,  $N_m$  and  $N_{msm}$  are the number of partners women, heterosexual men and MSM have
- $f_w$ ,  $f_m$  and  $f_{msm}$  are the fractions of the patients who are women, heterosexual men and MSM
- $\rho_u$  is the fraction of the virally suppressed patients
- $P$  is the total number of patients

## Validation

Internal validity was evaluated in the one-way sensitivity analysis for verification each model component behaved as intended. The correlations were in the expected direction and the number of projected infections was reasonable. Projected life expectancies for HIV patients and their sexual partners were compared to the health-adjusted life expectancies observed in a recent retrospective study of HIV-infected and HIV-uninfected persons in Canada [204]. The total remaining discounted lifetime cost of HIV-related

healthcare projected was compared to modeled lifetime cost of HIV estimates considering, adjusting for time since HIV infection [43,44].

**Appendix Table 5.** Estimated health outcomes compared to model results for face validity.

CD4 Count at Diagnosis/ entry to care	Lifetime Discounted QALYs Lost	Additional Life Expectancy (yrs)	Onset of AIDS (yr)	Lifetime Transmissions
<200	7.95	30.73	9.42	1.40
201-350	5.15	36.57	16.30	1.19
351-500	4.52	37.94	19.20	0.99
>500	4.45	38.08	19.50	0.72
Average	5.52	35.83	16.11	1.08

Source: Farnham JAIDS 2013

**Appendix Table 6.** Disaggregated costs

Patients and Partners	Control	Intervention	Incremental	% Change
ART	\$189,475	\$192,535	\$3,060	1.615%
Labs	\$177,797	\$177,184	-\$612	-0.344%
Visits	\$31,691	\$31,324	-\$367	-1.158%
AIDS death	\$1,946	\$1,932	-\$14	-0.738%
FI Program	\$0	\$706	\$706	-
Expenditures	\$2,427,919	\$2,430,969	\$3,049	0.126%
Productivity	-\$2,638,830	-\$2,648,142	-\$9,312	0.353%
Total	\$189,998	\$186,508	-\$3,490	-1.837%

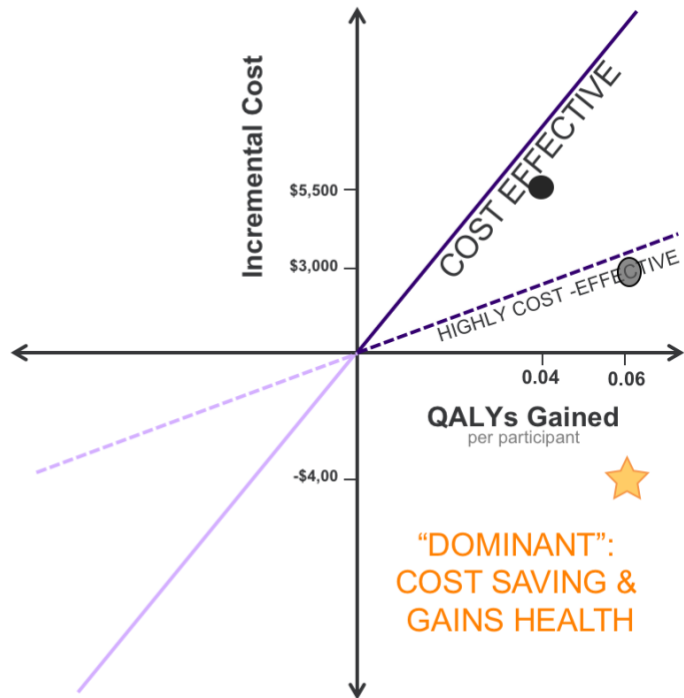
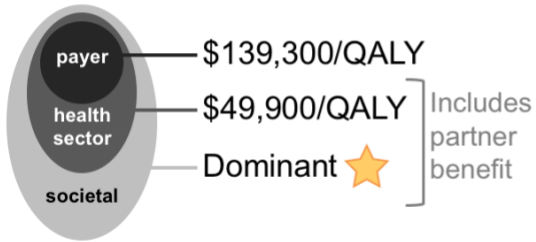
<b>Patients Only</b>	Control	Intervention	Incremental	% Change
ART	\$188,392	\$191,475	\$3,083	1.636%
Other HIV Costs	\$159,269	\$159,026	-\$243	-0.153%
Visits	\$9,131	\$9,250	\$119	1.301%
AIDS death	\$1,749	\$1,738	-\$11	-0.606%
Intervention	\$0	\$706	\$706	-
Consumption	\$702,344	\$704,849	\$2,505	0.357%
Productivity	-\$402,562	-\$410,062	-\$7,500	1.863%

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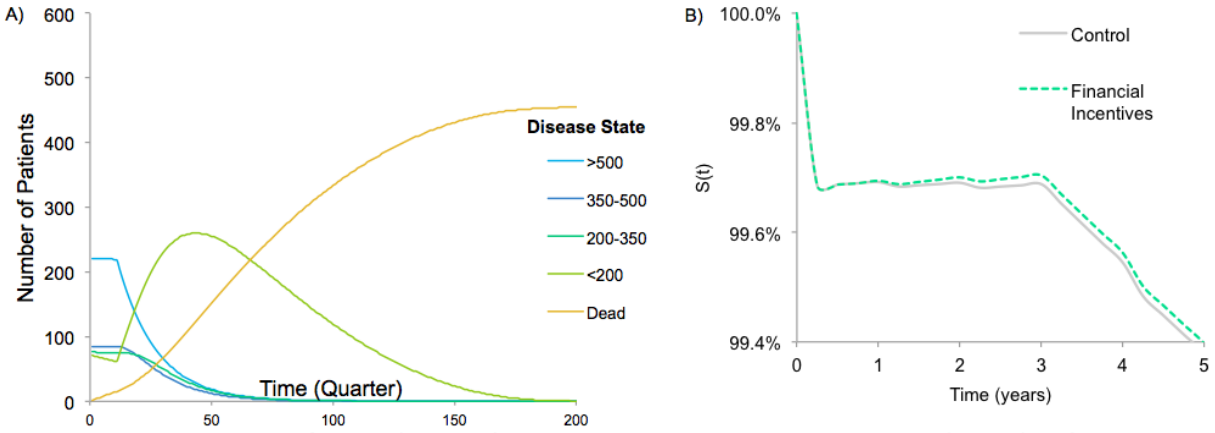
The cross validity of long-term health outcomes from our Markov model of disease progression was assessed by comparing our model simulated health outcomes to real-world outcomes. We compared the lifetime patient and partner QALYs lost from HIV, additional life expectancy, time to onset of AIDS, and lifetime HIV transmissions estimated in our model to results from Farnham et al., 2013. Considering the average HIV patients participating in HPTN 065 seroconverted an average 11.9 years prior to study participation, we compared the additional life expectancy of patients to the Farnham estimate of life expectancy minus 11.9 years. Face validity of the model, assumptions, and application was supported by expert co-authorship and poster presentation feedback.

## **Additional Results**

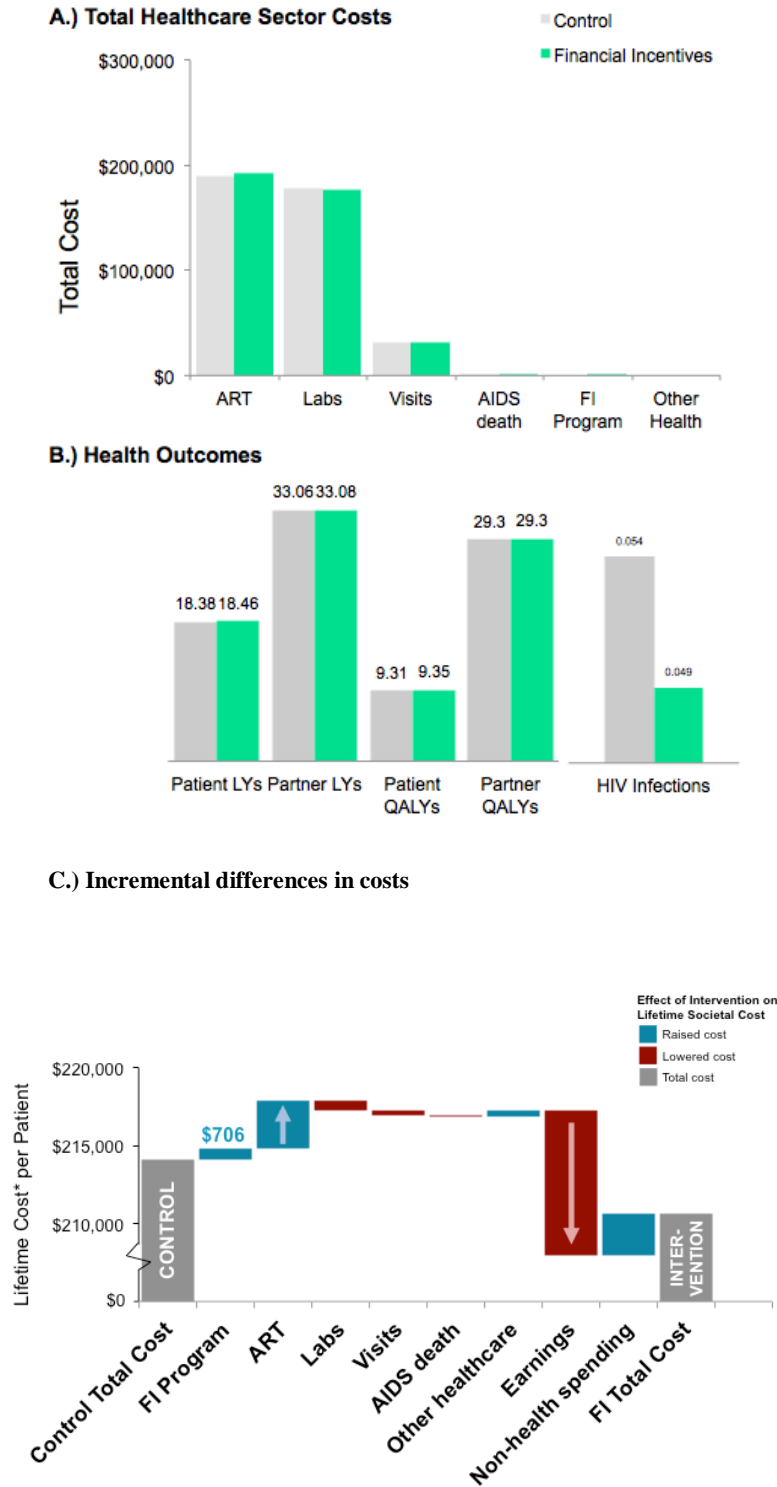
**ICER, given perspective**



**Appendix Figure 5.** ICERs from several economic perspectives.



**Appendix Figure 6.** Disease Progression and Survival. A) Number of patients in each health state over time in control group (solid line) and financial incentives group (dashed line) over a lifetime horizon; B) quarterly probability of survival in the control group (grey) and financial incentives group (green).



**Appendix Figure 7.** Disaggregated A) total healthcare sector costs; B) health outcomes for patients and partners, standardized per patient for control (grey) and financial incentives group (green); C) Incremental differences in disaggregated costs leading to the total cost-savings using a societal perspective.

**Appendix Table 7.** Efficacy, mean percentage points increase from baseline proportion VS at clinic

<b>Parameter</b>	<b>Efficacy (95% CI)</b>	<b>Source</b>
Overall	3.7 (0.5 – 6.9)*	HPTN 065
City: New York	1.6 (-1.3-4.5)	HPTN 065
City: DC	6.6 (2.0-11.2)*	HPTN 065
Size: Small	4.9 (1.3-8.6)*	HPTN 065
Size: Large	0.6 (-3.0-4.2)	HPTN 065
Baseline VS: Low	11.5 (-1.6-24.6)	HPTN 065
Baseline VS: High	2.8 (-0.8-6.4)	HPTN 065
Type: Hospital	4.8 (-1.6-11.1)	HPTN 065
Type: Community	3.7 (0.1-7.3)*	HPTN 065

**Additional Sensitivity Analyses**

\*Statistically significant

**Appendix Table 8.** Probabilistic sensitivity analysis results for 10,000 Monte Carlo simulations per sub-group.

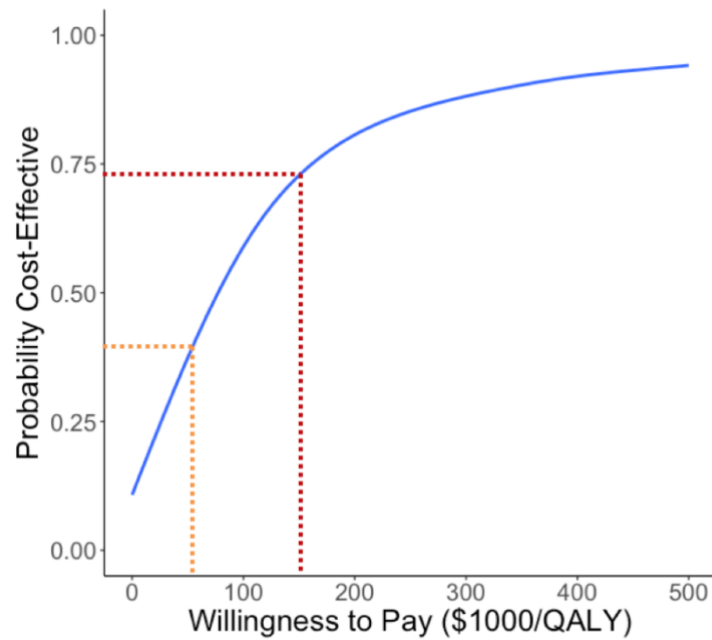
<b>Sub-Group <sup>a</sup></b>	<b>Baseline VS</b>	<b>Effectiveness (95% CI)</b>	<b>Mean ICER (95% Credible Range) <sup>b</sup></b>
OVERALL CLINICS	61.9%	3.8% (.7% - 6.8%)	\$34,245 (-\$433,120 - \$501,610)
City: New York	62.0%	1.6% (-.6% - 3.9%)	\$170,876 (-\$687,750 - \$1,029,501)
City: DC	61.8%	6.6% (1.9% - 11.3%)	<b>\$40,830</b> (-\$481,345 - \$399,685)
Size: Small	54.9%	11.8% (-.1% - 23.7%)	<b>\$72,388</b> (-\$265,826 - \$121,051)
Size: Large	69.4%	2.7% (-.3% - 5.7%)	\$52,354 (-\$621,368 - \$726,076)
Baseline VS: Low	52.6%	5.6% (.% - 11.3%)	<b>\$31,184</b> (-\$408,073 - \$345,705)
Baseline VS: High	73.0%	3.6% (.3% - 7.%)	\$16,579 (-\$609,492 - \$642,649)
Type: Hospital	59.2%	4.9% (1.4% - 7.%)	\$2,251 (-\$817,031 - \$821,532)
Type: Community	63.6%	1.2% (-2.% - 4.3%)	\$244,893 (-\$313,127 - \$802,913)

<sup>a</sup> Varies number of average of patients in care per quarter, baseline proportion of patients with viral suppression, intervention effectiveness, patient demographics, number of incentives distributed by clinic each quarter

<sup>b</sup> Societal perspective, lifetime horizon, patient and partner population

Abbreviations: VS, viral suppression; ICER, incremental cost-effectiveness ratio; CI, confidence interval

We used a cost-effectiveness acceptability curve (Appendix Figure 8) to present the probability that financial incentives for VS are cost-effective compared to the standard of care considering a continuous range of willingness-to-pay thresholds.



**Appendix Figure 8.** Cost-effectiveness acceptability curve, based on 10,000 Monte Carlo simulations, showing the probability financial incentives for viral suppression are cost-effective given a range of willingness-to-pay thresholds. Dashed lines indicate 1xGDP threshold (orange) and 3xGDP threshold (red).

## APPENDIX B: PUBLISHED PAPERS

This dissertation research has resulted in the following published papers to date:

1. Adamson B, Dimitrov D, Devine D, Barnabas R. The Potential Cost-Effectiveness of HIV Vaccines: A Systematic Review. *Pharmacoeconom Open*. 2017 Mar;1(1):1-12. doi: 10.1007/s41669-016-0009-9. Epub 2017 Jan 30.
  - a. *Highlight*: Several types of models predict HIV vaccines cost effective. *PharmacoEcon Outcomes News* (2017) 771: 29. doi:10.1007/s40274-017-3740-2
2. Adamson B, Carlson J, Kublin J, Garrison L. The Potential Cost-Effectiveness of Pre-exposure Prophylaxis Combined with HIV Vaccines in the United States. *Vaccines* 2017, 5(2), 13; doi:10.3390/vaccines5020013
3. de Montigny S\*, Adamson B\*, Masse B, Garrison L, Kublin J, Gilbert P, Dimitrov D. Improved effectiveness and added value of campaign HIV vaccination in South Africa: A modeling study. 2017. *Nature Scientific Reports*. *In Press*, 2018. \*Authors contributed equally to this study



## The Potential Cost-Effectiveness of HIV Vaccines: A Systematic Review

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### Abstract

**Objective** The aim of this paper was to review and compare HIV vaccine cost-effectiveness analyses and describe the effects of uncertainty in model, methodology, and parameterization.

**Methods** We systematically searched MEDLINE (1985 through May 2016), EMBASE, the Tufts Cost-Effectiveness Analysis (CEA) Registry, and the reference lists of articles following Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eligibility criteria included peer-reviewed manuscripts with economic models estimating the cost-effectiveness of preventive HIV vaccines. Two reviewers independently assessed study quality and extracted data on model assumptions, characteristics, input parameters, and outcomes.

**Results** The search yielded 71 studies, 11 of which met the inclusion criteria. Populations included low-income ( $n = 7$ ), middle-income ( $n = 4$ ), and high-income countries ( $n = 2$ ). Model structure varied, including decision

tree ( $n = 1$ ), Markov ( $n = 5$ ), compartmental ( $n = 4$ ), and microsimulation ( $n = 1$ ). Most studies measured outcomes in quality-adjusted life-years (QALYs) gained ( $n = 6$ ), whereas others used unadjusted ( $n = 3$ ) or disability-adjusted life-years ( $n = 2$ ). The range of HIV vaccine costs were \$US1.54–75 in low-income countries, \$US55–100 in middle-income countries, and \$US500–1000 in the USA. Base-case incremental cost-effectiveness ratios (ICERs) ranged from dominant (cost offsetting) to \$US91,000 per QALY gained.

**Conclusion** Most models predicted HIV vaccines would be cost-effective. Model assumptions about vaccine price, HIV treatment costs, epidemic context, and willingness to pay influenced results more consistently than did assumptions on HIV transmission dynamics.

### Key Points for Decision Makers

Most economic models predict HIV vaccines will be cost-effective.

Static and dynamic HIV transmission modeling methods found similar results.

Vaccine cost-effectiveness will likely depend on HIV prevalence, durability of protection, and price of regimen and boosts.

**Electronic supplementary material** The online version of this article (doi:10.1007/s41669-016-0009-9) contains supplementary material, which is available to authorized users.

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### 1 Introduction

The search for an HIV vaccine began over 3 decades ago and had a breakthrough in 2009 [1]. A phase III HIV vaccine trial in Thailand (RV144) found HIV vaccine

## Several types of models predict HIV vaccines cost effective

Several types of models predict that HIV vaccination would be cost effective, according to findings of a review published in *PharmacoEconomics - Open*.

MEDLINE, EMBASE, the Tufts Cost-Effectiveness Analysis (CEA) Registry, and reference lists of articles following Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, were searched from 1985 to May 2016 for peer-reviewed cost-utility analyses using models to estimate the cost effectiveness of vaccines for the prevention of HIV infections.

The 11 studies which met the selection criteria used Markov (5 studies), compartmental (4), decision tree (1) or microsimulation (1) models to evaluate the cost effectiveness of HIV vaccines in low-, middle- or high-income countries, from a healthcare system (5), societal (4), government (1) or payer (1) perspective over time horizons ranging from 10 years (3) to lifetime (5). Outcomes measured were QALYs (6 studies), unadjusted life-years (LYs; 3) or disability-adjusted life-years (DALYs; 2).

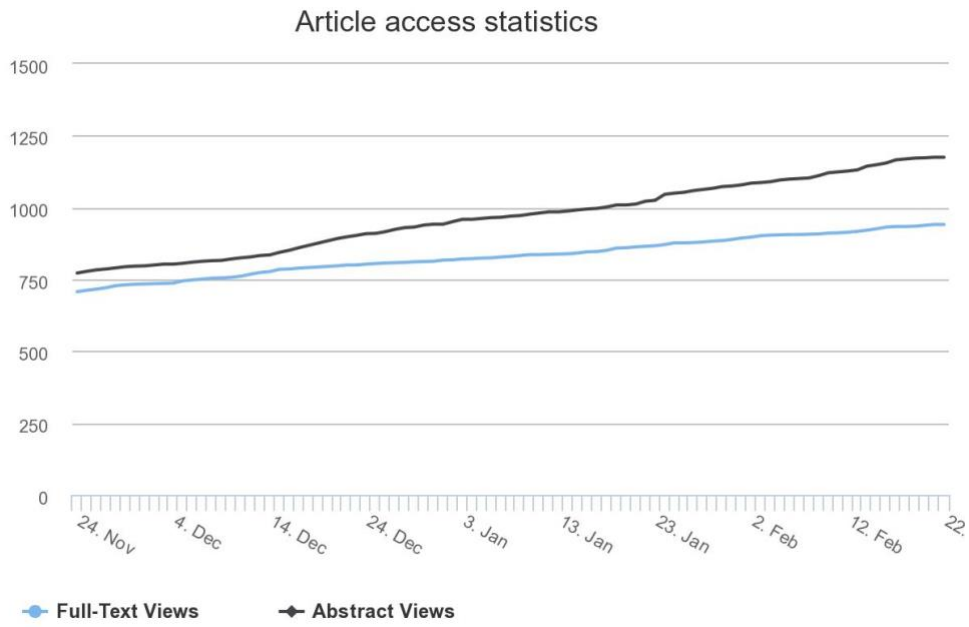
HIV vaccines cost \$1.54–\$75\* in low-income countries, \$55–\$100 in middle-income countries, and \$500–\$1000 in USA. HIV vaccines were found to be dominant (more effective and less costly) in two studies. Base-case incremental cost-effectiveness ratios (ICERs) of HIV vaccine compared with no vaccine in the other studies ranged from \$3 to \$100 per QALY, LY or DALY gained in four studies and from \$1000 to to \$91 000 per QALY, LY or DALY gained in five studies.

"Most models predicted HIV vaccines would be cost-effective. Model assumptions about vaccine price, HIV treatment costs, epidemic context, and willingness to pay influenced results more consistently than did assumptions on HIV transmission dynamics," concluded the authors. "The studies provided evidence that immunization with a modestly effective HIV vaccine is likely an efficient use of resources in the USA, Thailand, and several sub-Saharan African countries," they said.

\* US dollars

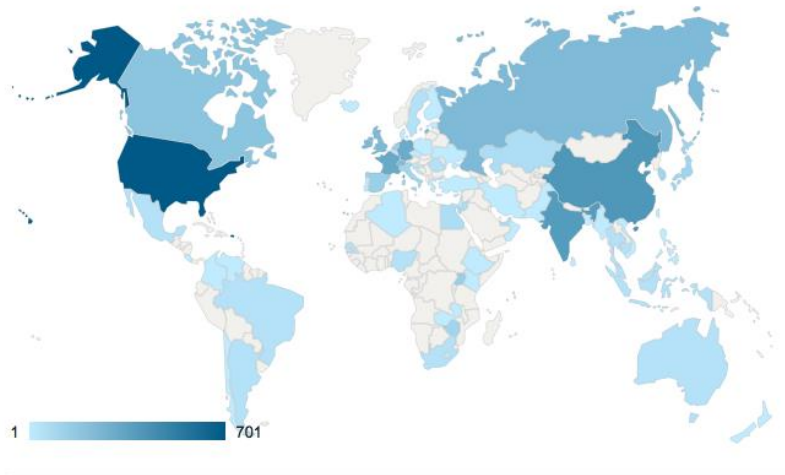
Adamson B, et al. The Potential Cost-Effectiveness of HIV Vaccines: A Systematic Review. *PharmacoEconomics-Open* : 30 Jan 2017. Available from: URL: <http://dx.doi.org/10.1007/s41669-016-0009-9> 803222541

The systematic review of HIV vaccine cost-effectiveness analyses has had broad readership around the world, as summarized by the article access statistics below.



### Article Access Statistics

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Article

# The Potential Cost-Effectiveness of Pre-Exposure Prophylaxis Combined with HIV Vaccines in the United States

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**Abstract:** This economic evaluation aims to support policy-making on the combined use of pre-exposure prophylaxis (PrEP) with HIV vaccines in development by evaluating the potential cost-effectiveness of implementation that would support the design of clinical trials for the assessment of combined product safety and efficacy. The target study population is a cohort of men who have sex with men (MSM) in the United States. Policy strategies considered include standard HIV prevention, daily oral PrEP, HIV vaccine, and their combination. We constructed a Markov model based on clinical trial data and the published literature. We used a payer perspective, monthly cycle length, a lifetime horizon, and a 3% discount rate. We assumed a price of \$500 per HIV vaccine series in the base case. HIV vaccines dominated standard care and PrEP. At current prices, PrEP was not cost-effective alone or in combination. A combination strategy had the greatest health benefit but was not cost-effective (ICER = \$463,448/QALY) as compared to vaccination alone. Sensitivity analyses suggest a combination may be valuable for higher-risk men with good adherence. Vaccine durability and PrEP drug prices were key drivers of cost-effectiveness. The results suggest that boosting potential may be key to HIV vaccine value.

**Keywords:** economic evaluation; mathematical modeling; HIV vaccines; pre-exposure prophylaxis; cost-effectiveness

## 1. Introduction

HIV treatment and prevention in the United States (USA) requires substantial societal resources and the treatment of HIV-infected patients is generally cost-effective. Based on economic models, if treated, a person infected with HIV at age 35 in the U.S. will, on average, suffer from lower quality and length of life and accumulate \$247,500 (2015 USD) more in lifetime medical costs compared to people who are not HIV infected [1–3]. Federal funds in 2016 allocated \$20 billion for domestic HIV care and \$1 billion for domestic HIV prevention [4]. To date, only one drug has a Food and Drug Administration (FDA)-approved indication for prevention. Truvada<sup>®</sup> is a single-pill fixed-dose antiretroviral combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) launched in 2004 to treat HIV (Gilead Sciences, Inc., Foster City, CA, USA). The FDA approval expanded Truvada's<sup>®</sup> indication in 2012 as a safe and effective daily oral medication to reduce the risk of sexually acquired HIV infection, a form of pre-exposure prophylaxis (PrEP). PrEP studies including Pre-exposure Prophylaxis Initiative (iPrEX), Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD), France Recherche Nord et Sud Sida- HIV et Hépatites (ANRS), Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY), and Kaiser Permanente studies

# Projected effectiveness and added value of campaign HIV vaccination in South Africa: A modeling study

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## ABSTRACT

Promising multi-dose HIV vaccine regimens are being tested in trials in South Africa. We estimate the potential epidemiological and economic impact of HIV vaccine campaigns compared to continuous vaccination, assuming that vaccine efficacy is transient and dependent on immune response. We used a dynamic economic mathematical model of HIV transmission calibrated to 2012 epidemiological data to simulate vaccination with anticipated antiretroviral treatment scale-up in South Africa.

We estimate that biennial vaccination with a 70% efficacious vaccine reaching 20% of the sexually active population could prevent 0.48-0.65 million HIV infections (13.8% -15.3% of all infections) over 10 years. Assuming a launch price of \$15 per dose, vaccination was found to be cost-effective with an incremental cost-effectiveness ratio of \$13,746 per quality-adjusted life-years compared to no vaccination. Increasing vaccination coverage to 50% will prevent more infections but is less likely to achieve cost-effectiveness. Campaign vaccination is consistently more effective and costs less than continuous vaccination across scenarios.

Results suggest that a partially effective HIV vaccine will have substantial impact on the HIV epidemic in South Africa and offer good value if priced less than \$145 per five-dose series. Vaccination campaigns every two years may offer greater value for money than continuous vaccination reaching the same coverage level.

## APPENDIX C: RELATED RESEARCH

This dissertation research relied on collaborations that resulted in the following manuscripts approaching publication:

1. Selinger C, Bershteyn A, Dimitrov D, Adamson B, Revill P, Hallett T, Phillips A, Bekker LG, Rees H, Gray G, and the P5 Global Access Committee. Targeting and Vaccine Durability Are Key for Population-level Impact and the Cost-Effectiveness of a Pox-Protein HIV Vaccine Regimen in South Africa. *Submitted*, 2017.
2. Projected Effectiveness of an Early Detection of Acute HIV Infections among MSM in Peru: A Modeling Study

# Targeting and Vaccine Durability Are Key for Population-level Impact and the Cost-Effectiveness of a Pox-Protein HIV Vaccine Regimen in South Africa

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Paul Revill<sup>4</sup>, Timothy B Hallett<sup>5</sup>, Andrew N Phillips<sup>6</sup>, Linda-Gail Bekker<sup>7</sup>, Helen  
Rees<sup>8</sup>, Glenda Gray<sup>8,9</sup>, for the Pox-Protein Public-Private Partnership Global  
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<sup>10</sup> The Pox-Protein Public-Private Partnership (P5) Global Access Committee (GAC) is comprised of representatives from the Bill & Melinda Gates Foundation, National Institutes of Health (DAIDS/NIAID), Sanofi Pasteur, GlaxoSmithKline and the South African Medical Research Council

## ABSTRACT

### Background

RV144 is to date the only HIV vaccine trial to demonstrate efficacy, albeit rapidly waning over time. The HVTN 702 trial (also known as Uhambo), supported by the Pox-Protein Public-Private Partnership (P5), is currently evaluating a similar vaccine formulation to that of RV144 for subtype C HIV with an additional 12-month booster. Here, we model population-level impact and potential cost-effectiveness of this regimen in South Africa.

### Methods and findings

Using a detailed stochastic individual-based network model of disease transmission calibrated to the HIV epidemic in South Africa, we investigate the population-level impact and maximum cost of an HIV vaccine to remain cost-effective in South Africa. Informed by RV144 results, we simulate vaccination programs in South Africa starting in 2027 under various vaccine targeting and HIV treatment scale-up and prevention assumptions. Consistent with the design of the pox-protein regimen, we model time-dependent vaccine efficacy for a primary series of five vaccinations meeting the goal of 50% cumulative efficacy 24 months after the first dose. We also consider two-yearly boosters that maintain durable vaccine efficacy over a period of 10 years.

Our analysis shows that this partially effective vaccine could prevent, at 60% catch-up vaccination, up to 655,000 new infections, or 12.8% of the total new infections between 2027 and 2047 averaged across a wide range of future treatment and prevention scale-up scenarios. A similar impact of 526,000 (or 10.2%) infections prevented could be achieved by targeting age cohorts of highest incidence, i.e. women aged 18 and men aged 23. Maximum cost for the vaccine to remain cost-effective ranged between 168 and 397

US\$ per person vaccinated (for a 10-year series, product and delivery) based on a 1xGDP per capita cost-effectiveness threshold.

### **Conclusions**

A partially effective vaccine with rapidly waning efficacy would only modestly reduce the number of new infections in South Africa, even if boosted every two years. Nonetheless, for the general population, it could be an adjunct to daily oral PrEP. Vaccination is expected to be most effective under targeted delivery to the age groups of highest HIV incidence. Although actual costs for purchasing and deploying the vaccine are unknown at present, our analysis indicates that vaccination could be cost-effective if the total cost were less than 400 US\$ per 10-year vaccine regimen. However, roll-out of a partially effective, rapidly waning vaccine will not eliminate HIV as a public health priority in sub-Saharan Africa. Therefore, vaccination must be performed in parallel with continued innovation in HIV prevention technologies, including continued research into vaccines with greater efficacy and durability

# Projected Effectiveness of an Early Detection of Acute HIV Infections among MSM in Peru: A Modeling Study

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## ABSTRACT

**Background:** SABES ('Do you know?' in Spanish), an ongoing study in Peru, is testing the hypothesis that intervening early, especially during acute HIV infection when viral load is high, will markedly reduce onward HIV transmission among high-risk populations such as men who have sex with men (MSM). We aim to investigate the potential benefits of detecting acute HIV infections and rapidly initiating antiretroviral treatment (ART).

**Methods:** A transmission dynamic model was designed to simulate the epidemic among MSM in Peru and calibrated to data on HIV prevalence and ART coverage from 2004 to 2011. We assess the impact of an intervention starting in 2018 in which up to 50% of the acute infections are diagnosed, linked to care and initiated on ART within 1 month of diagnosis. The intervention impact is estimated in terms of cumulative prevented fraction (CPF) of new HIV infections compared to scenarios without intervention over 20 years. Results are reported as median and 90% uncertainty interval (UI).

**Results:** Our model suggests that only 27% of the infected MSM are virally suppressed in 2017 and 35%-40% of the new HIV infections among MSM in Peru result from contacts with acutely infected partners. An intervention reaching 10% of the acutely infected MSM is projected to reduce the number of new infections by 7.6% [UI: 6.6%- 8.4%] and 13.1% [UI: 11.7%-14.1%] over 10 and 20 years, respectively. An intervention reaching 50% of the acutely infected MSM will increase the overall prevalence of viral suppression in 2038 to 60% and prevent about 40% of the expected infections over 20 years.

**Conclusion:** Early detection of HIV infections among MSM is desirable as it would increase the effectiveness of the HIV prevention program in Peru, especially if a high proportion of acutely infected MSM are diagnosed and rapidly initiated on ART. The importance of early detection will likely increase

with increases in ART coverage due to the larger proportion of new infections attributable to onward HIV transmission from acutely infected partners.

## VITA

Blythe Adamson uses health economics, epidemiology, and data science to research infectious diseases and identify high-value drugs, vaccines, and diagnostics in the research and development pipeline. By creating mathematical models of disease transmission and progression, she compares the costs and benefits of biomedical interventions to prioritize investment portfolios and inform efficient use of our scarce health care sector dollars. She studied at The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute at the University of Washington and was Chair of the Student Network for the International Society for Pharmacoeconomics and Outcomes Research from 2017-2018. Learn more about her research at [www.blytheadamson.com](http://www.blytheadamson.com).