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Article

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 by evaluating the potential cost-effectiveness of implementation that would support the design of clinical trials for 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 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. 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 (US) requires substantial societal resources and 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 US will, on average, suffer from lower quality and length of life and accumulate $229,800 (2012 USD) more in lifetime medical costs (2012 USD) 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® is a single-pill fixed-dose antiretroviral combination of tenofovir disoproxil fumarate and emtricitabine launched in 2004 to treat HIV (Gilead Sciences Inc.). The FDA approved expanded Truvada's® indication in 2012 as safe and effective daily oral medication to reduce the risk of sexually acquired HIV infection, a form of pre-exposure prophylaxis (PrEP). PrEP studies (iPrEX, PROUD, Ipergay, and Kaiser) have reported efficacy ranging from 42% to 99% with adherence strongly correlated with effectiveness [5–9]. Side effects in some patients include diarrhea, nausea, liver toxicity, and bone mineral density loss. By 2015, Truvada® had the largest market share (17%) of all HIV drugs with no competing HIV drugs on the market for prophylaxis. The potential market for PrEP is estimated as 1.2 million people, including 25% of the estimated 4.5 million men who have sex with men (MSM) in the US [10–12]. The

average wholesale price of Truvada® was $1,646 for a 30-day supply in 2015 whether used for prevention or treatment of HIV [13].

HIV vaccines in development and currently in Phase III clinical trials may eventually be used in place of or in combination with PrEP. A Phase III study in Thailand with more than 16,000 participants (labeled as RV144 and referred to as "the Thai trial" in this paper) established an HIV vaccine candidate with average 31% preventive efficacy over three years [14]. Immunogenicity results from a follow-on study of RV144 participants re-vaccinated years later suggested boosting may be effective [15]. A National Institute of Allergy and Infectious Diseases (NIAID)-funded confirmatory trial (HVTN 702) in South Africa evaluates the safety and preventive efficacy of ALVAC-HIV (vCP2438) vaccine prime with bivalent subtype C gp120/MF59 boosts (see descriptions in Table A1) [16,17]. Compared to the Thai trial, the HVTN 702 vaccine regimen, which matches the HIV sub-type circulating in Southern Africa, replaces alum with the potentially more potent adjuvant MF59, and it also adds a fifth dose at 12 months to the regimen schedule [17]. This pivotal HIV vaccine trial hypothesizes an average vaccine efficacy (VE) of 50% over 36 months, and is scheduled to be completed in 2021.

Previous economic evaluations have separately examined the cost-effectiveness of PrEP or HIV vaccines in the US, but none have modeled the potential outcomes when combining these products [18–23], as shown in a recent review of HIV vaccine cost-effectiveness studies [24]. For treatment of HIV, Truvada® is highly cost-effective when used in combination with other drugs, but the cost-effectiveness estimates for prevention are mixed in reviews [21,25,26]. If an HIV vaccine is launched in the US, experts may consider modifying PrEP clinical guidelines to inform the most efficient use in combination with HIV vaccines [27]. This analysis is the first to assess the potential cost-effectiveness of combining PrEP with an HIV vaccine in comparison to either alone for MSM in the US. Specifically, the objective of our study is to identify the potential cost-effectiveness of HIV vaccines co-administered with PrEP and to investigate thresholds for vaccine characteristics for efficient use in US MSM. The findings have implications not only for potential uptake but also for prioritization of PrEP and vaccine candidates progressing through clinical development pipeline.

2. Materials and Methods

This modeling study followed methodology recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine and, meets standardized reporting requirements from the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) statement [28,29].

2.1. Study Population

The analysis evaluated policy strategies for potential implementation of HIV prevention interventions in a cohort of HIV-negative MSM in the US. The base-case analysis models men of average age 30 until death, i.e., a lifetime horizon. A sub--group analysis focuses on a cohort of "high-risk" men, defined as having anal sex without a condom in the last 12 months: clinical practice guidelines recommend that they use PrEP [27].

2.2. Model Overview

We developed a Markov health-state transition model of HIV infection and disease progression and used the model to estimate clinical benefits, total costs, and the cost-effectiveness of strategies delivering HIV vaccines and PrEP alone or in combination. We developed a model based on previous work by Sanders *et al* and Bayoumi *et al* [30,31]. Importantly, we add functions to describe PrEP of varying duration and HIV vaccines with waning efficacy and boosting. Health states, seen in Figure 1, are connected by difference equations solved at monthly time steps. Parameter values were informed by the most recent peer-reviewed literature. The HIV prevention strategies evaluated include: PrEP alone, HIV vaccines alone, co-administration of PrEP and HIV vaccines, and a reference base-case of standard HIV prevention without PrEP or vaccines. An Impact Inventory (Table A2) catalogues the intervention costs and effects within and outside the healthcare sector and identifies components included in this analysis [28].

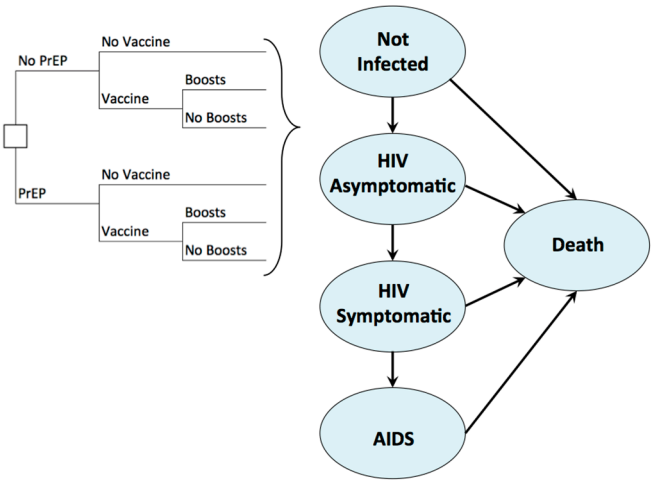

Figure 1. Simplified conceptual diagram of health states in Markov model.

2.3. Model Inputs

Table 1 summarizes key model inputs.

2.3.1. HIV Incidence

HIV-negative men entering the model had an age-dependent risk of infection. The input values for HIV incidence were calculated from Centers for Disease Control (CDC) surveillance data on newly detected cases and population sizes from the US Census Bureau (Table 1) [32,33]. Cross-sectional MSM incidence was extrapolated to future years. Given uncertainty in HIV-incidence among PrEP-indicated MSM, we scaled the observed trend by age to match the incidence levels observed in the PROUD study participants to represent the high-risk sub-group (Figure A1) [8]. For example, at the age of greatest average risk, 30-34 years, the HIV incidence input value for general MSM was 1.2 infections per 100 person-years and for high-risk MSM was 10.5 infections per 100 person-years. Incidence rates were converted into the probability of infection in a monthly time step.

2.3.2. Clinical Inputs

Newly infected HIV patients progressed over time through health states defined by CD4+ T-cell count categories (>500, 200-499, and <200 copies per mL). The probability of monthly transitions through progressing health states represent population averages based on published literature (Table 1). Age- and gender-specific baseline mortality rates were calculated from 2010 United States Life Tables [34]. Based on the SMART and ESPRIT clinical trials in well-controlled HIV infected individuals, patients with CD4 counts ranging of 200-500 had a 1.8 times increased hazard of non-AIDS death compared to the general population, but those with CD4 >500 had no increased risk of death [35]. Patients with CD4 <200 could die from AIDS in addition to their baseline risk of death from other causes [36].

2.3.3. Health State Utility

We identified preference-based utility weights (Table 1) corresponding to health men in the general population and CD4 t-cell count categories of infected persons (Figure 1) in published literature [30,37–40]. Utilities for uninfected MSM are stratified by age and based on healthy males in the general US population [37]. To account for the range of adverse events associated with PrEP, such as bone mineral density loss, time using PrEP had a utility decrement of 0.008 (ranging 0-0.1 in sensitivity analyses). To adjust for an assumed incidence of reactogenicity, men lost the equivalent of one quality-adjusted day at the time of each vaccine injection.

2.3.4 Intervention Effectiveness

We define the standard of care as routine HIV testing, risk reduction counseling, and no availability of PrEP or HIV vaccines. The base-case PrEP strategy assumed average adherence, five years duration, and 86% effectiveness in reduction in HIV incidence [8,41]. Ranges of PrEP duration (0-10 years) and effectiveness (40% - 99.9%) are explored in the sensitivity analysis. Base-case HIV vaccination resembled the HVTN 702 regimen with a five-dose series administered over 12 months (Figure A2). We modified the proportional hazards model Hankins et al. fitted to the 31% VE observed in the Thai study [42], to effectively describe the waning over time to 50% VE at 24 months as expected in HVTN 702 from a fifth dose at 12 months. The time-dependent reduction in likelihood of HIV acquisition following a complete HIV vaccine series followed the equation

$$VE_t = 1-\exp(-2.88+0.76*\log((t+0.001)*30))$$

where t is time in months since first dose of the most recent vaccination series (see Figure 2 and Figure A2). We assumed that re-vaccination five years later boosted immunity to the initial levels followed by the same rate of exponential decay in protection from infection [43]. The PrEP-Vaccine combination strategy assumes the cohort of MSM initiates PrEP at the time of vaccination, and then they continue PrEP for five years and receive HIV vaccine boosts every 5 years (varying 0-10 years in sensitivity analyses). Figure 2 shows the average efficacy for each strategy over time. We assume the combined effectiveness is multiplicative, with the monthly probability of HIV infection multiplied by

$$p_t = (1-RR_{PrEP})*(1-VE_t).$$

2.3.5. Costs

Cost inputs were derived from published literature and adjusted to 2015 US dollars using the medical consumer price index. Costs were projected from a US health care payer perspective and discounted 3% annually to reflect a greater value for present dollars compared to future gains, following guidelines from the Second US Panel on Cost-Effectiveness [44,45]. A study of US health care expenditures among HIV patients HIV care costs were specific to CD4-count defined health states and based on the distribution of health care expenditures for HIV-infected patients. The cost of living with HIV was based on a study of US health care expenditures among HIV-infected individuals [46].

PrEP users incurred costs from quarterly clinic visits with an HIV antibody test, other STI tests, and measurement of blood urea nitrogen and serum creatinine levels. PrEP drugs cost $1,646 per month, based on the average wholesale price for a 30-day supply of Truvada® in 2015 [13]. As the launch price for an HIV vaccine is unknown, we benchmarked on the price per dose of other FDA-approved vaccines to prevent other sexually transmitted infections [47] and consulted expert opinions. We assumed an HIV vaccine price of $500 per dose, totaling $2,500 for the five-dose series. The cost per vaccine dose ranged $100-$1,000 in the sensitivity analysis.

Table 1. Key model inputs.

Parameter	Value	Sensitivity Ranges		Reference
		Lower	Upper	
HIV Incidence (per 100 person-years)				
25-34 year old MSM in United States	0.66%	0.56%	0.76%	[32],[33]
35-44 year old MSM in United States	0.46%	0.38%	0.55%	[32],[33]
45-54 year old MSM in United States	0.24%	0.19%	0.29%	[32],[33]
High-risk scenario	2.0%	1.0%	4.0%	[48]
Intervention Efficacy				

Vaccine efficacy, 2 year average with 4 doses	31.2%	1.1%	52.1%	[14]
decay parameter, λ_{30}	-2.400	-2.037	-2.762	[42]
Vaccine Efficacy, 2 year average with 5 doses	50.0%	30.0%	70.0%	Assumed [49]
decay parameter, λ_{50}	-2.880	-2.400	-3.380	Calculated [42]
Vaccine boosting potential, ϱ	100%	80%	100%	Assumed
PrEP Efficacy	86%	39.4%	98.5%	[41]
Disease Progression				
Probability of HIV symptoms, monthly	0.008	0.000	0.015	[30], [50]
Probability of AIDS, monthly	0.081	0.009	0.700	[31]
Additional hazard of dying with HIV	1.770	1.170	2.550	[35]
AIDS mortality rate	0.43%	0.37%	0.51%	[36]
Utilities				
Healthy utility, age 30-39	0.918	0.912	0.925	[37]
Vaccine AE utility decrement	0.003	0.000	0.005	Assumed
PrEP AE utility decrement	0.008	0.000	0.020	Assumed
HIV Utility, CD4 >500	0.798	0.696	0.900	[40], [39], [30], [38]
HIV Utility, CD4 200-500	0.780	0.767	0.793	[40], [39], [30], [38]
AIDS Utility, CD4 <200	0.702	0.567	0.837	[40], [39], [30], [38]
Costs[1]				
Vaccine Price, per dose	$500	$100	$1,000	Assumed
PrEP drug cost, 30-day supply	$1,646	$893	$2,000	[13], [47]
PrEP visit cost, including lab tests	$208	$156	$260	[19]
HIV Care if CD4 >500, monthly	$1,634	$1,579	$1,689	[51]
ART drug cost	$1,211	$1,172	$1,251	[51]
Outpatient costs	$45	$43	$47	[51]
Other costs	$378	$364	$392	[51]
HIV Care, CD4 200-500, monthly	$1,924	$1,817	$2,032	[51]
ART drug cost	$1,158	$1,103	$1,212	[51]
Outpatient costs	$54	$51	$57	[51]
Other costs	$713	$663	$763	[51]
HIV Care, CD4 < 200, monthly	$2,558	$2,334	$2,783	[51]
ART drug cost	$1,162	$1,094	$1,229	[51]
Outpatient costs	$62	$58	$67	[51]
Other costs	$1,334	$1,182	$1,486	[51]

[1] Costs are presented in 2015 US dollars. Abbreviations: AE, adverse event; AWP, average wholesale price; ART, antiretroviral therapy; MSM, men who have sex with men; PrEP, preexposure prophylaxis.

2.4. Model Outputs

The hypothetical cohort of men was followed from the time of intervention until death. Patient outcomes are reported as per-person averages, and include lifetime discounted HIV-related health care costs, lifetime probability of HIV infection, expected life years (LYs), and expected quality-

adjusted life years (QALYs). Reflecting both survival length and quality of life, QALYs were calculated as the sum of the monthly survival time multiplied by the utility value for the corresponding health state. Costs and QALYs are discounted 3% annually to reflect the present value [44,45].

2.4.1 Cost-Effectiveness

For the primary economic endpoint, we estimated the incremental cost-effectiveness ratio (ICER) for each scenario using the equation

$$ICER = \frac{Costs_{intervention} - Costs_{standard\ care}}{QALYs_{intervention} - QALYs_{standard\ care}}.$$

To support facilitate the interpretation of the implications cost-effectiveness, we defined a cost-effectiveness threshold for the US health care payer. Consistent with recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine and several pharmaceutical value frameworks, we interpret ICERs < $50,000/QALY as highly cost-effective, $50,000 - $150,000/QALY as cost-effective, and > $150,000/QALY as unlikely to be cost-effective, given a threshold of 1-3 times the gross domestic product (GDP) per capita in the US [28,52]. If an intervention strategy had a lower ICER and greater total health gains, it ruled out the less cost-effective strategies by "extended dominance" [53]. HIV incidence and HIV vaccine price varied in threshold analyses to identify the maximum value at which the strategy remained cost-effective when all other parameter values remain fixed. As a secondary economic endpoint, the incremental cost per HIV infection averted was estimated for each strategy.

2.5. Sensitivity Analysis

One-way (univariate) sensitivity analyses were performed using the upper and lower ranges of each input, holding all other variables constant) to explore the model's sensitivity to uncertainty in individual parameters (Table 1). We explored more than 500 scenarios to evaluate policy relevant cases of interest to decision-makers. Scenarios projected impact at varying ages for initiation of each intervention, lengths of PrEP duration, levels of PrEP adherence, and frequency of vaccine boosting. A sub-group analysis estimated cost-effectiveness of the interventions for high-risk MSM.

A multi-variate probabilistic sensitivity analysis (PSA) evaluated the combined parameter uncertainty in the model. We selected and fitted distributions for each model parameter and followed gamma for costs, beta for utilities, and normal for risk reduction using the method of moments. Monte Carlo simulations generated a unique set of input values based on random draws from these distributions and re-estimation of model outcomes as 1000 simulations per strategy.

3. Results

3.1. Base Case

3.1.1. Clinical Outcomes

The cohort with standard preventive care (no PrEP or HIV vaccine) had a lifetime HIV risk of 171 cases/1000 MSM (Figure 2). Delivering PrEP for five years reduced the lifetime risk of HIV by 25% and gained an average 0.38 lifetime QALYs per person (Table 2). HIV vaccines alone (with waning immunity with average 50% VE over 3 years, boosting every 5 years) reduced risk of HIV in the cohort to 88 cases/1000 men (48% reduction compared to standard care) and gained an additional 0.14 lifetime QALYs compared to PrEP alone. The combination of PrEP with an HIV vaccine achieved the largest health gains and an incremental 0.19 lifetime QALYs per person compared to the vaccine alone.

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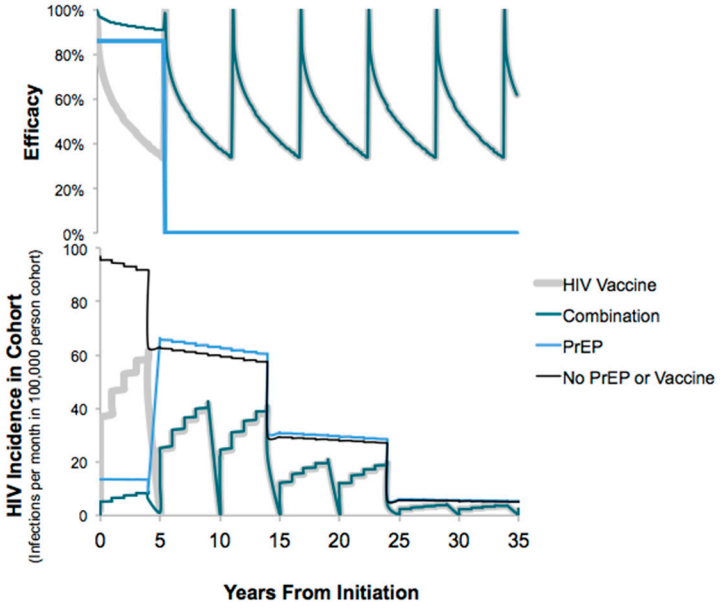

Figure 2. Efficacy and epidemic impact of HIV prevention strategies. The top panel shows the average efficacy over time given each strategy and the lower panel shows the number of new infections per month per 100,000 persons in the cohort of men. Baseline HIV incidence declines with age categories.

3.1.2. Costs

HIV prevention and treatment-related health care for the cohort using PrEP (duration of five years, 86% efficacy) cost an average $78,884 more per person than standard care over the lifetime (Table 2 and Figure 3). The HIV vaccine strategy cost $21,057 less per person than standard care. The combination of PrEP with vaccination cost $66,558 more than standard care and $12,326 less than PrEP alone. Over time as patients aged, the added cost of each re-vaccination had a smaller marginal return in terms of reducing ART drug costs.

Table 2. Base case outcomes per MSM receiving preventative care

HIV Prevention Strategy	Total Costs [1]	Total QALYs	HIV Infections	ICER [2] ($/QALY)
Standard Care	$51,926	22.057	170.7	Dominated
PrEP	$130,811	22.439	128.7	Dominated
HIV Vaccination	$30,870	22.580	88.3	Dominant
Combination: PrEP and Vaccine	$118,484	22.769	65.8	$463,448

[1] Costs presented in 2015 US$ and discounted 3%. [2] ICERs present a ratio of incremental costs to incremental QALYs as compared to the next best option. Abbreviations: ICER, incremental cost-effectiveness ratio; PrEP, preexposure prophylaxis; QALYS, quality adjusted life-years.

3.1.3. Cost-Effectiveness

HIV vaccination alone dominated PrEP, as the vaccine had greater health gains and lower total costs than PrEP (Table 2 and Figure 3). Vaccines dominated standard care by $40,224 per QALY. The combination of PrEP with HIV vaccines had an ICER of $463,448 per QALY gained, as compared to HIV vaccines alone, and would not be cost-effective even given the upper-bound threshold of a $150,000 per QALY.

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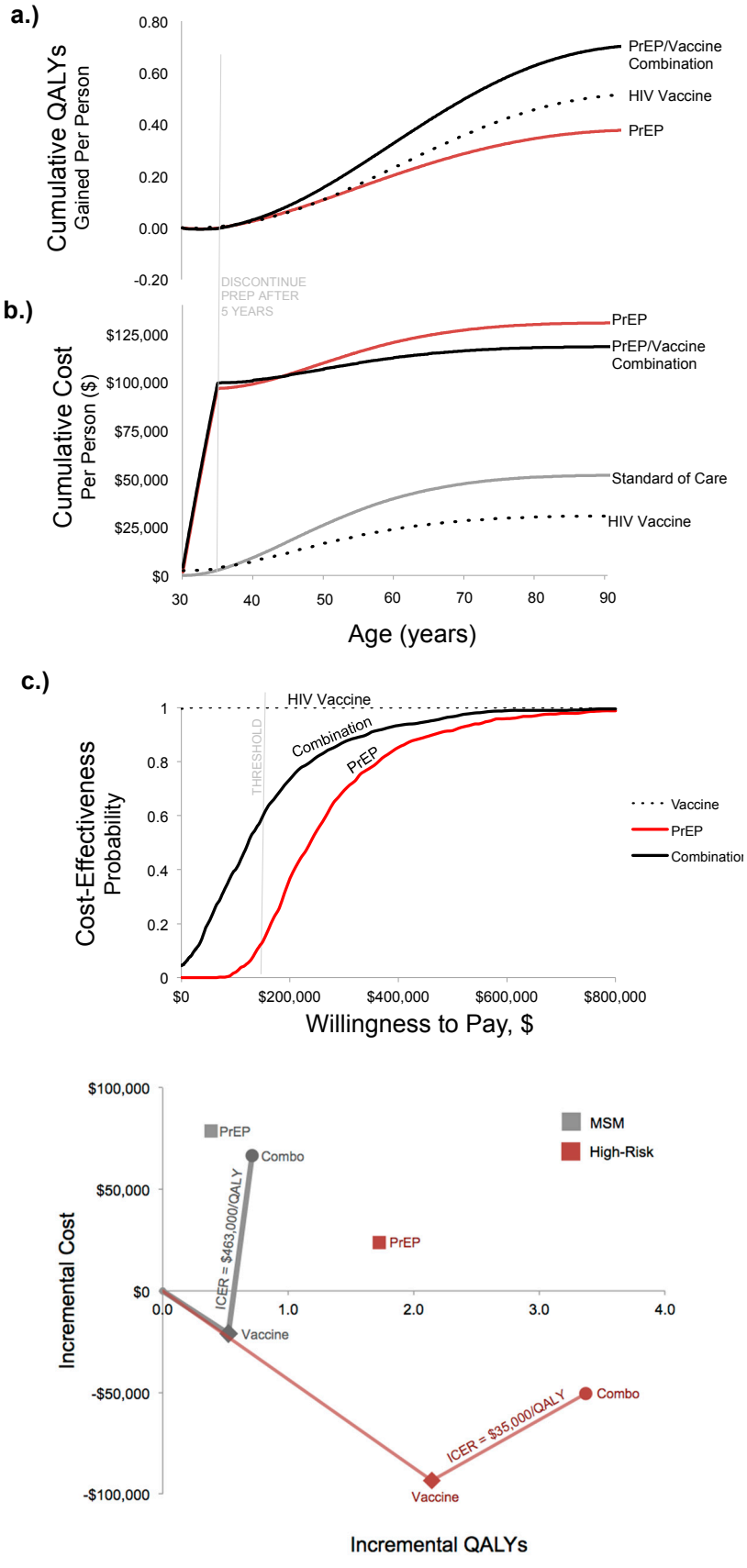

(d)

Figure 3. Cost-effectiveness of combination HIV prevention strategies. Panels include **(a)** cumulative QALYs gained over time for base case strategies of PrEP (red line), HIV vaccines (dashed

line), and a combination (black line) in pairwise comparison to standard care; **(b)** cumulative incremental costs for each strategy in pairwise comparison to the standard care; **(c)** cost-effectiveness acceptability curve showing the probability each strategy may be cost-effective given varying levels of willingness-to-pay; **(d)** cost-effectiveness plane where the origin represents standard preventative care, y-axes for the average lifetime discounted per-person incremental costs, and x-axis of QALYs gained for each policy strategy as compared to standard prevention. The cost-effectiveness frontier for all MSM using base-case assumptions is in grey line and for a high-risk scenario in. An HIV vaccine alone is cost-saving compared to standard prevention in the base case. Abbreviations: QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis.

3.2. Sensitivity Analysis

Cost-effectiveness findings were most sensitive to HIV incidence rates and PrEP drug costs in the univariate analyses (Figure 4). The cost-effectiveness of the PrEP/vaccine combination was more sensitive to the rate of decay in VE (also known as durability) than to the level of PrEP effectiveness. The threshold analysis estimated a maximum cost-effective price of PrEP drugs as $893 per 30-day supply, corresponding to a 50% drop in the average wholesale price of Truvada® in 2015. At the largest hypothesized range of HIV vaccine price—$5,000 per series and per boost—the vaccines resulted in lower lifetime health system costs than standard prevention.

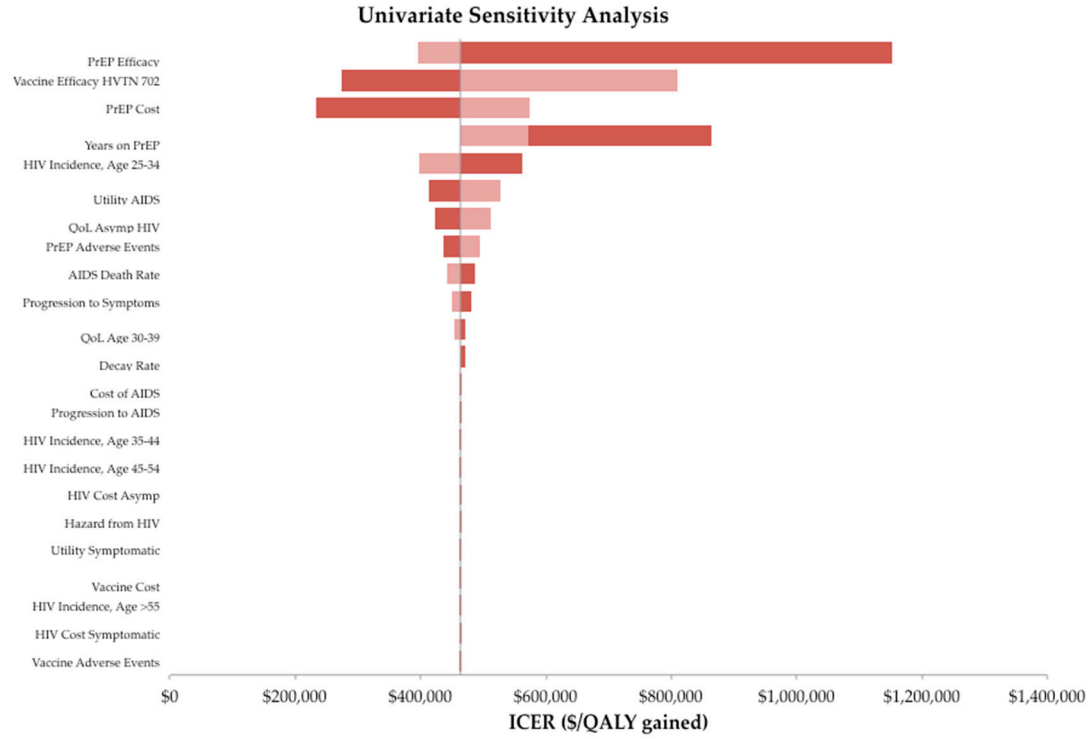

Figure 4. Tornado diagram of one-way sensitivity analysis showing the impact of minimum and maximum parameter ranges on the ICER of the combination strategy versus HIV vaccines alone. Univariate sensitivity of PrEP duration shows that 1 year or 10 years on PrEP in the combination strategy have larger ICERs than the base case assumption of 5 years duration, because the balance of lifetime PrEP costs and benefits is closer to optimization of duration at 5 compared to 1 or 10 years.

3.2.1. Scenarios

Pairwise comparisons of policy-relevant scenarios for PrEP, HIV vaccines, and combinations versus standard care are provided in Figure 5. Vaccines only dominated PrEP if boosting after the initial series resulted in waning protection similar to the initial series. Vaccination without boosting gained 37% fewer QALYs and cost 30% more in lifetime HIV-related health care than re-boosting

every 5 years. PrEP alone was cost-effective for high-risk men (with lifetime annual HIV incidence reaching a maximum of 8.9%) with an ICER of $13,713 per QALY compared to standard prevention. With PrEP duration extended to 10 years, vaccination alone no longer dominated PrEP and it had an ICER of $776,786/QALY compared to standard care. In this 10-year duration scenario, the PrEP-vaccine combination dominated PrEP alone by extension. In high-risk men, 10 years of PrEP was estimated to be cost-effective with an ICER of $64,159 per QALY vs. standard care. Figure 5 suggests these HIV prevention interventions offer greatest value in younger and higher-risk populations.

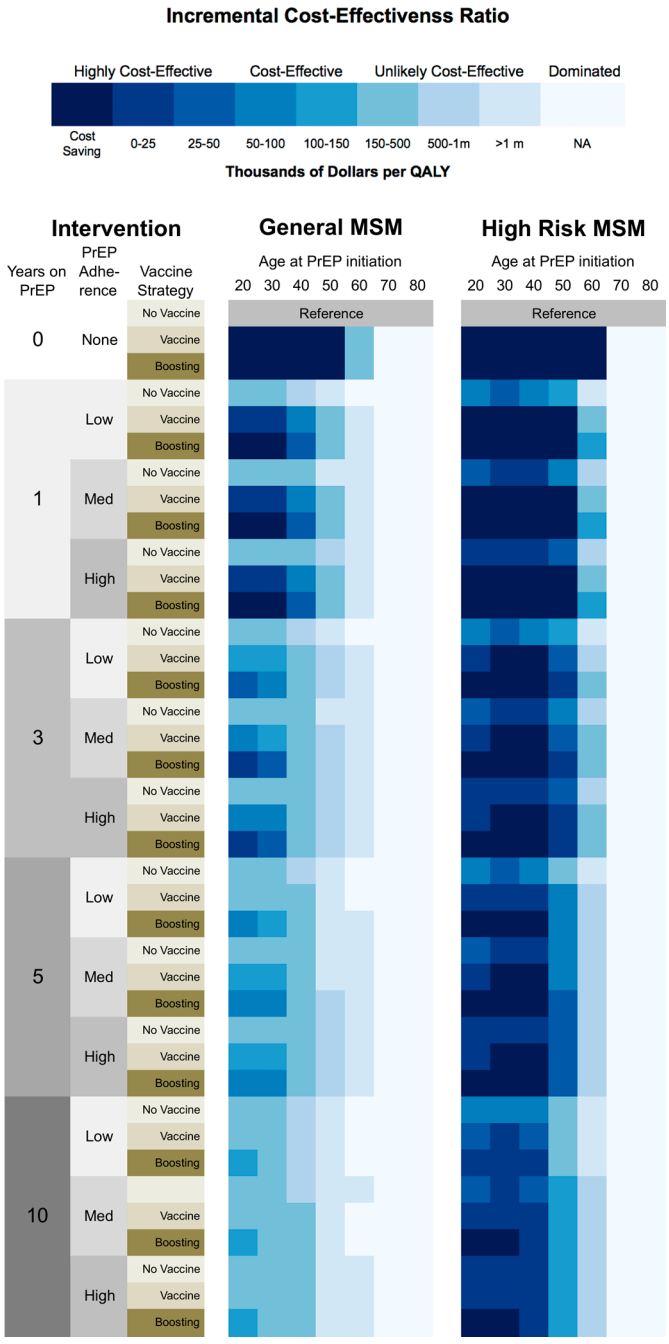

Figure 5. Sensitivity analyses of cost-effectiveness of pairwise comparisons of scenarios versus standard care suggest strategies would be more cost-effective with younger populations, higher-risk men, shorter duration on PrEP, and added HIV vaccine boosting. Darker blue color represents greater cost-effectiveness and lighter color represents scenarios dominated or unlikely cost-effective as compared to standard care.

3.2.3. Probabilistic Sensitivity Analysis

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Consistent with the deterministic findings, HIV vaccines dominated standard care and PrEP alone in the probabilistic sensitivity analysis (Figure 6). PrEP alone cost $77,895 (95% credible range [CR] $42,095 - $113,695) more per person than standard care and was the highest costing strategy. In comparison to HIV vaccines alone, adding PrEP for the combination strategy cost an additional $86,976 per person (95% CR $52,080-$121,853) and gained 0.19 QALYs (95% CR -0.06 – 0.44) per person on average. We estimated an average ICER of $696,318 per QALY (95% CR of -$584,780 - $2 million) for the combination strategy versus HIV vaccines alone. The distribution of simulations in each strategy shows a shift in the distribution of simulations down (lower costs) and to the right (greater health) for the combination compared to PrEP alone.

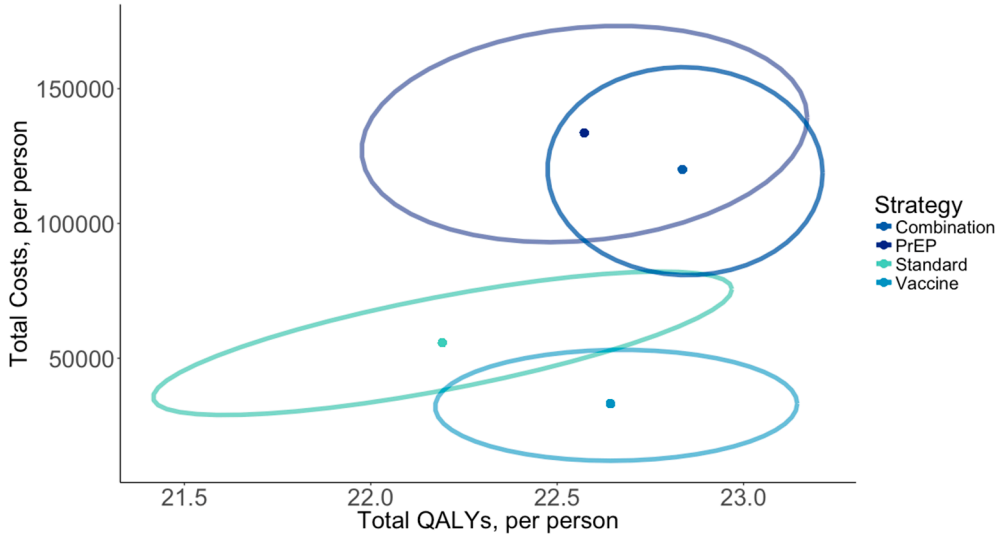

Figure 6. Distribution of incremental costs and QALYs per person among 1000 Monte Carlo simulations in the probabilistic sensitivity analysis. Ellipse represent 95% credible ranges around the average estimate for each strategy.

4. Discussion

We projected the potential cost-effectiveness of various HIV treatment strategies for MSM in the US after the future introduction of HIV vaccines. We found that HIV vaccination was estimated to dominate PrEP alone (i.e., provide increased QALYs and reduced costs). A combination of PrEP with HIV vaccination provided the highest total QALYs but at substantial additional cost versus the other interventions: and it was unlikely to be cost-effective. However, the sensitivity analyses suggest that the combination strategy may be cost-effective for high-risk men provided the estimates for vaccine effectiveness from previous trials remain consistent in the ongoing pivotal trials. PrEP alone is not projected to be cost-effective in general MSM at current PrEP prices.

PrEP costs too much to be cost-effective at current prices. Potential options for PrEP to be cost-effective could include discounting the price by 50%, restricting the indication to high-risk persons, introduction of indication-specific pricing, or the entry of PrEP generic medications. Indication-specific pricing could accommodate one value-based charge and reimbursement for Truvada® prescribed for HIV treatment and a second, lower, value-based price for Truvada® prescribed for prevention [54]. If implemented, a larger population would be recommended for cost-effective use of PrEP and HIV vaccines in combination. The anticipated reduction in PrEP costs with generic drug entry may be delayed if the recently approval drug tenofovir alafenamide fumarate (TAF, trade name Descovy®, Gilead Sciences Inc.) replaces TDF for PrEP. TAF may effectively extend the patent-life of Truvada®, capture new users, and help Gilead maintain its large market share of HIV drugs even after generic entry of TDF.

HIV vaccine success relies on either the durability of protection or the potential for boosting years later to elicit robust immunogenicity responses that correlate strongly with protection from infection. If PrEP drug costs are lowered, future HIV vaccine clinical trial designs may want to

consider increasing trial sample sizes to evaluate the combined safety, efficacy, and potential synergy of HIV vaccines administered with PrEP. If HIV vaccines can more effectively reach disproportionately affected high-risk groups with little PrEP use, such as young Black and Latino MSM in the Southeast [55], availability of both products could make a great impact on HIV incidence. Efficient implementation, defined as greatest health impact under constrained health care resources, may be achieved by recommending vaccination for all MSM and PrEP for only some.

Our estimates for the cost-effectiveness of PrEP and HIV vaccines alone are consistent with results from other models including dynamic transmission models. The PrEP-alone cost-effectiveness findings align with Juusola et al., who estimated PrEP for all MSM costs $216,480 per QALY gained (differing 5% from our ICER for this population) [19]. Similarly, PrEP for injection drug users in the US was estimated by Bernard et al. to cost $253,000 per QALY gained [20]. Our conclusion on the potential cost-savings with HIV vaccines is consistent with Long et al. in scenarios with similar assumptions [56]. The results from this analysis differ from a recent economic analysis of Canadian MSM where PrEP was cost-saving in almost all scenarios [57]. The different result may be due to lower Canadian drug costs and the selection of HIV incidence rates, as the Canadian study applied a constant number needed to treat (NTT) from a high-risk Peruvian population with 5% annual HIV incidence while our analysis parameterized baseline infection rates to age-specific CDC HIV incidence in the US. In the sensitivity analysis, if annual HIV incidence was increased to the same constant 5% rate, similar conclusions would be reached for PrEP-alone cost-effectiveness. As HIV incidence is frequently a driver of the value of HIV prevention, the different sources of baseline transmission rates in each model may explain why different analyses have reached very different conclusions.

Our analysis had a number of limitations that warrant mention. First and foremost is the hypothetical nature of the efficacy estimates and attrition rates for long-term vaccine boosting and the combination of PrEP with vaccines. We considered a healthcare payer perspective and so did not include transmission dynamics to capture the indirect benefits of vaccination to others. As a consequence, our results are likely to underestimate the population-level health benefits from the prevention interventions. The current incidence of HIV in MSM recommended to take PrEP is unknown, but we address this by scaling feasible ranges based on age trends in published data [32,58,59]. The model also assumes no behavioral disinhibition among intervention users, meaning an individual's perception of protection from HIV will not lead them to increase risky choices. Future modeling studies should examine HIV vaccine uptake and the potential the potential impact of impact of the interaction with PrEP utilization as a complement or substitute.

5. Conclusions

Balancing the high cost and high effectiveness of PrEP with the potentially low cost and moderately effective HIV vaccines calls for innovative design and testing of these products if combinations are planned for implementation. Achieving the ambitious milestones in the National Strategic Plan for the US requires efficient spending of limited health care resources and research dollars. Early identification of high-value vaccine candidates and planning for optimal combinations with PrEP could extend many lives and reduce the burden of HIV in the US.

Supplementary Materials: The following are available online at www.mdpi.com/link, Figure S1: title, Table S1: title, Video S1: title.

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Abbreviations

The following abbreviations and corresponding units are used in this manuscript:

ART: Antiretroviral Therapy
AWP: Average Wholesale Price, $
CEA: Cost-Effectiveness Analysis
CR: Credible Range
GDP: Gross Domestic Product, $ per capita
ICER: Incremental Cost Effectiveness Ratio, $/QALY
LY: Life Years
MSM: Men Who Have Sex With Men
PrEP: Pre-exposure Prophylaxis
QALY: Quality-Adjusted Life Year
VE: Vaccine Efficacy, %
WTP: Willingness to Pay, $

Appendix A

Table A1. Description of HIV vaccine candidates in clinical trials

	RV144 Thai Trial			**HVTN 702 South Africa Trial**		
Vaccine Component	DNA Prime	Protein Boost	Adjuvant	DNA Prime	Protein Boost	Adjuvant
Description	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
Manufacturer	Developed by Virogenetics Corporation (Troy, NY) and manufactured by Sanofi Pasteur (Marcy-l'Étoille, 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
Trial Funding	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.		

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Table A2. Impact inventory

Sector	Type of Impact (Unit of measure if relevant)	Included in this analysis from the perspective of			Notes
		Payer ☑	Health care Sector ☐	Societal ☐	
Formal Health-care sector	*Health outcomes (effects)*				
	Longevity effects (Life Years)	☑	☐	☐	
	Health-related quality of life (QALYs)	☑	☐	☐	
	Adverse events (QALYS)	☑	☐	☐	
	Secondary transmissions of infections	☐	☐	☐	
	Medical costs				
	Paid for by third-party payers ($)	☑	☐	☐	
	Paid for by patients out-of-pocket ($)	☐	☐	☐	
	Future related medical costs to payers ($)	☑	☐	☐	
	Future related medical costs to patients ($)	NA	☐	☐	
	Future unrelated medical costs to payers ($)	☑	☐	☐	
	Future unrelated medical costs to patients ($)	NA	☐	☐	
Informal Health-care sector	Patient time costs	NA	☐	☐	
	Unpaid caregiver time costs ($)	NA	☐	☐	
	Transportation costs ($)	NA	☐	☐	
Productivity	Labor market earnings lost ($)	NA	NA	☐	
	Cost of unpaid lost productivity due to illness ($)	NA	NA	☐	
	Cost of uncompensated household production ($)	NA	NA	☐	
Consumption	Future consumption unrelated to health ($)	NA	NA	☐	
Social Services	Cost of social services as part of intervention ($)	NA	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	NA	☐	

Abbreviation: NA, not applicable; QALYs, quality-adjusted life years.

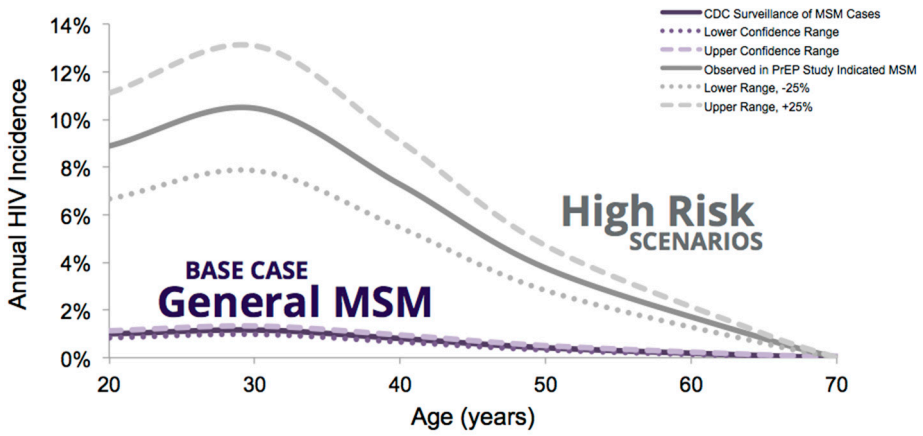
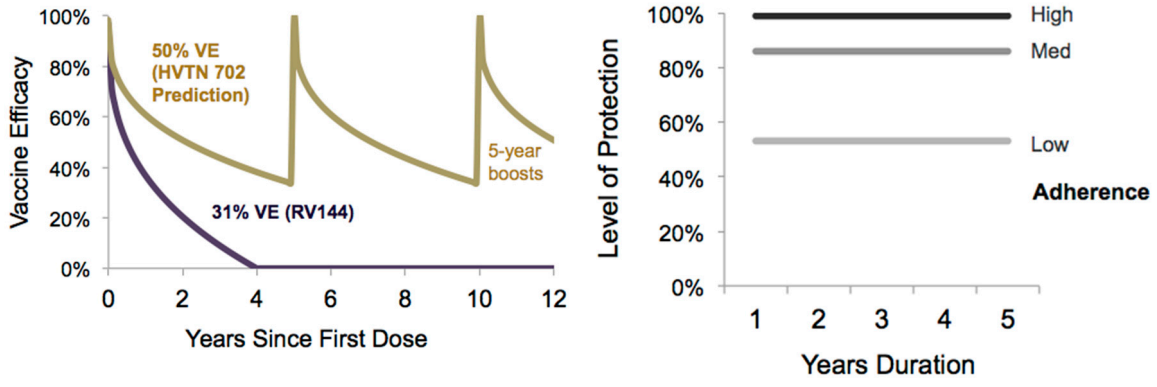


Figure A1. Incident HIV infections among men-who-have-sex-with-men (MSM) in the United States, based on 2012 CDC surveillance data [32].



(a) (b)

Figure A2. Percent reduction in HIV infection for HIV vaccines and PrEP as modeled in the analysis. Intervention efficacy assumptions for **(a)** HIV vaccine efficacy decaying over time with boosting every 5 years and **(b)** PrEP by level of adherence. Abbreviations: PrEP, Pre-exposure prophylaxis; VE, vaccine efficacy.

Model Validation

We compared the mean total remaining life years for the cohort and compared this to the life expectancy of US men. To support validation of the selected transition probabilities for HIV progression, we initialized HIV disease compartments with a cohort of newly infected patients and calculated the average remaining life-years. We subtracted this number from the average total life years for a scenario with no HIV infections and compared the difference to the estimated life years lost from HIV infection calculated by others. We validated costs by comparing our estimated average cost of HIV care per infection to the lifetime cost of HIV calculated by Franham in 2013 and Schackman in 2015 [61,62].

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