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The cost-effectiveness of a modestly effective HIV vaccine in the United States

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ABSTRACT

Background: The recent RV144 clinical trial showed that an ALVAC/AIDSVAX prime-boost HIV vaccine regimen may confer partial immunity in recipients and reduce transmission by 31%. Trial data suggest that efficacy may initially exceed 70% but decline over the following 3.5 years. Estimating the potential health benefits associated with a one-time vaccination campaign, as well as the projected benefits of repeat booster vaccination, may inform future HIV vaccine research and licensing decisions.
Methods: We developed a mathematical model to project the future course of the HIV epidemic in the United States under varying HIV vaccine scenarios. The model accounts for disease progression, infection transmission, antiretroviral therapy, and HIV-related morbidity and mortality. We projected HIV prevalence and incidence over time in multiple risk groups, and we estimated quality-adjusted life years (QALYs) and costs over a 10-year time horizon. We assumed an exponentially declining efficacy curve fit to trial data, and that subsequent vaccine boosters confer similar immunity. Variations in vaccine parameters were examined in sensitivity analysis.
Results: Under existing HIV prevention and treatment efforts, an estimated 590,000 HIV infections occur over 10 years. One-time vaccination achieving 60% coverage of adults could prevent 9.8% of projected new infections over 10 years (and prevent 34% of new infections in the first year) and cost approximately $91,000/QALY gained relative to the status quo, assuming $500 per vaccination series. Targeted vaccination strategies result in net cost savings for vaccines costing less than $750. One-time vaccination of 60% of all adults coupled with three-year boosters only for men who have sex with men and people who inject drugs could prevent 21% of infections for $81,000/QALY gained relative to vaccination of higher risk sub-populations only. A program attaining 90% vaccination coverage prevents 15% of new HIV cases over 10 years (and approximately 50% of infections in the first year).
Conclusions: A partially effective HIV vaccine with effectiveness similar to that observed in the RV144 trial would provide large health benefits in the United States and could meet conventionally accepted cost-effectiveness thresholds. Strategies that prioritize key populations are most efficient, but broader strategies provide greater total population health benefit.

1. Introduction

Despite dramatic increases in the availability of antiretroviral therapy for HIV in resource-limited settings, approximately two new infections occur worldwide for every person placed on treatment [1]. This observation highlights the urgent need for expanded HIV prevention efforts, including use of an HIV vaccine. After many years of disappointing results, several promising developments have provided more cause for optimism [2]. In 2009, a large phase III trial of an ALVAC and AIDSVAX vaccine (RV144) demonstrated modest protection from infection with HIV, with a 31% reduction among trial volunteers [3]. More recently, investigators have reported the development of broadly neutralizing antibodies, which provides potential new targets for vaccine development [4,5].

The modest success of the RV144 trial prompted renewed interest in understanding whether the use of a partially effective HIV vaccine would improve health outcomes sufficiently to justify its use [6–11]. In particular, although the RV144 trial showed an overall effectiveness of 31%, vaccine efficacy was likely higher (approximately 70%) in the first year and rapidly declined over time. Given such a modestly effective vaccine, it is unknown to what extent a universal vaccination campaign, or one that prioritizes key populations, will reduce overall HIV incidence in the population.

As part of a collaboration established by the Centers for Disease Control and Prevention (CDC) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), we evaluated the health and

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economic outcomes resulting from broad use of a partially effective HIV vaccine in the United States. Our analysis assumed declining vaccine efficacy as observed in the RV144 trial. We evaluated three strategies: one-time vaccination; vaccination followed by booster vaccinations at three- or five-year intervals; and a hybrid strategy, in which sub-populations at higher risk of HIV exposure received booster vaccinations. We evaluated the effect of these strategies on HIV incidence, infections averted, life expectancy, quality-adjusted life expectancy, costs, and cost-effectiveness.

2. Methods

Applying our previously published HIV vaccine model [6], we incorporated the 2009 ALVAC/AIDSVAX randomized clinical trial results to consider the effects of such a modestly effective HIV vaccine on population health outcomes and cost-effectiveness [3]. Additional model details can be found elsewhere [6,12]. The model was implemented in the mathematical programming language Matlab 2010b.

2.1. Study overview

We implemented a mathematical model of HIV transmission and disease progression in the adult US population aged 15–64 years. The key model components are (1) specific populations defined by risk of HIV exposure, (2) HIV transmission, progression, and treatment, (3) HIV vaccination, (4) initial conditions, and (5) health and economic outcomes. In our base case, we calculated outcomes over a 10-year time horizon. Appendix A contains further details about model structure, inputs, and assumptions.

The population was stratified based on sex and risk of HIV exposure: men who have sex with men (MSM), male and female persons who inject drugs (PWID), MSM/PWID, and male and female low-risk heterosexuals. Each group was further sub-divided into compartments based on HIV-infection status (uninfected or infected), HIV-identification status (status-aware or status-unaware), and disease and antiretroviral treatment (ART) status, if infected (Appendix A Fig. A1).

After specifying a set of initial conditions for reach risk group (e.g., population size, HIV prevalence, fraction receiving ART, etc.) based on published data, we numerically simulated the projected course of the HIV epidemic over time, under the status quo of no vaccination and under alternative HIV vaccination scenarios. In our prior analyses [6], we considered a range of values for vaccine efficacy and duration of protection; in the present study, we modeled vaccine efficacy as estimated from the ALVAC/AIDSVAX clinical trial, as well as the effects of offering a vaccine booster in the future.

2.2. Disease transmission and progression

For each population sub-group, we estimated average risk behavior, including number of homosexual and heterosexual partners, consistency of condom use, and partners with whom non-sterile injecting equipment was used. The likelihood of selecting an HIV-infected partner assumes proportional mixing in the population (i.e., persons with many partners are more likely to select partners who also have many partners). We then calculated the probability of HIV transmission between HIV sero-discordant partners, adjusting for sex, HIV disease status, antiretroviral treatment status, and HIV vaccination status. Finally, we incorporated risk behaviors and transmission probabilities to estimate new HIV infections over time in each risk group. Importantly, our dynamic modeling framework allows us to estimate *secondary HIV infections*, or the number of future infections caused by new primary infections.

For persons who were initially HIV-infected at the model's start or who became infected over the time horizon simulated, we accounted for HIV disease progression based on the natural history of HIV [13–18]. We calculated total quality-adjusted life years (QALYs) by summing the time spent in each health state and adjusting this by a quality of life factor based on utility estimates in published literature [19–26]. We also included the benefits of ART on reduced morbidity and mortality, as well as the effects of suppressive ART on reduced HIV transmission.

2.3. Vaccine characteristics

In the base case analysis, we assumed an exponentially declining vaccine efficacy, $\varepsilon(t) = 0.78e^{-0.06t}$, where t (measured in months) is time post-vaccination. The parameter $\varepsilon(t)$ refers to the instantaneous vaccine efficacy, or the reduction in the likelihood of HIV transmission in uninfected vaccine recipients, at time t.

2.4. Intervention strategies

To assess the potential costs and benefits of alternative vaccination campaigns, we considered a one-time vaccination, as well vaccination followed by a booster vaccine every three or five years. Although not yet tested in a clinical trial, a future booster could extend the effectiveness of a vaccine with rapidly declining efficacy. We also considered a *hybrid* strategy offering one-time vaccination to all adults, and subsequent booster vaccines only to sub-populations at higher risk of HIV exposure (i.e., MSM and PWID).

Although the uptake of a mass vaccination program is uncertain, we assumed a base case coverage level of 60%, where vaccination *coverage* refers to the fraction of eligible adults who complete a vaccination series. We also considered pessimistic (30% coverage) and optimistic (90% coverage) scenarios. To evaluate the hypothetical cost-effectiveness, we conservatively assumed that a primary vaccination series costs $500 per recipient and each subsequent booster series also costs $500, but we varied this assumption in sensitivity analysis.

2.5. Health outcomes

By using a dynamic HIV epidemic model, we simulated the change in population compartment sizes over time, due to persons receiving a vaccine, acquiring HIV infection, progressing to a later disease stage, initiating treatment, dying, or entering or exiting the adult population. From these projections, we calculated the number of new infections occurring per year, HIV prevalence in each risk group, overall population health benefits, which are measured in QALYs, and total vaccination and healthcare costs, under a variety of HIV vaccination scenarios. We then calculated the incremental cost-effectiveness ratio (ICER) of each vaccination program, relative to no vaccination or the next-best alternative. Our analysis was performed using a societal perspective, and costs and QALYs were discounted at 3% annually [27], with costs given in 2009 US dollars.

3. Results

With no HIV vaccination program, we estimated that approximately 590,000 new HIV infections will occur in the United States over the next 10 years, with 47% of cases occurring among MSM, 20% among PWID, 6% among MSM/PWID, and 27% among heterosexually exposed populations.

Table 1
Health and economic outcomes of alternative HIV vaccination strategies.

Vaccination strategy [a]	Coverage	HIV infections prevented (% of status quo)		Incremental costs (billions)[b]	Incremental life years (millions)	Incremental QALYs (millions)	ICER ($/QALY) relative to[c]	
		Over 1 year	Over 10 years				Status quo	Next-best
Universal (one-time)	30%	10,520 (16.9%)	29,341 (5.0%)	$28.9	0.36	0.32	$90,424	Dominated
Universal (one-time)	60%	20,923 (33.7%)	58,123 (9.8%)	$57.9	0.71	0.63	$91,355	Dominated
Universal (one-time)	90%	31,208 (50.3%)	86,356 (14.6%)	$86.9	1.07	0.94	$92,294	Dominated
Universal (five-year booster)	60%	20,923 (33.7%)	95,933 (16.2%)	$153.7	1.12	0.99	$155,858	Dominated
Universal (three-year booster)	60%	20,923 (33.7%)	142,742 (24.2%)	$206.4	1.61	1.42	$145,077	$645,292
Higher risk sub-populations (one-time)	60%	15,534 (24.7%)	46,009 (7.8%)	−$0.9	0.56	0.47	Cost-saving	Cost-saving
Hybrid: Universal (one-time) and higher risk sub-populations (three-year booster)	60%	20,923 (33.7%)	122,447 (20.7%)	$58.1	1.42	1.19	$48,693	$81,480

Dominated = dominated strategy (i.e., the strategy is not on the cost-effectiveness efficient frontier).

[a] All results in this table assume an exponentially declining vaccine efficacy, $\varepsilon = 0.78\, e^{-0.06t}$. Universal includes vaccination of adults aged 15–64. Higher risk sub-populations include only men who have sex with men and people who inject drugs. One-time vaccination occurs immediately, and boosters occur at subsequent time intervals. Hybrid strategy includes vaccination of all adults, followed by boosters only for higher risk sub-populations.

[b] Incremental costs, life years, and quality adjusted life years (QALYs) are relative to the status quo (no vaccination).

[c] Incremental cost-effectiveness ratio (ICER) is relative to the status quo or the next-best alternative.

3.1. One-time vaccination, waning efficacy

One-time vaccination of 60% of the adult US population with an HIV vaccine that has waning efficacy could prevent 58,123 infections over 10 years, or 9.8% of the projected total (Table 1, Fig. 1). In the first year following vaccination, approximately 34% of new infections are prevented, but the downstream benefits of a one-time vaccination decrease as efficacy wanes.

If vaccination coverage only reaches 30% of eligible persons, incidence is reduced by only 5.0% over 10 years (or 17% over one year). Conversely, an effective vaccination campaign reaching 90% of adults prevents nearly 15% of infections over 10 years. In the first year alone, this imperfect vaccine prevents more than 50% of new infections. Even after vaccine efficacy has completely waned, overall annual incidence is reduced by approximately 6% because of reduced secondary infections (i.e., persons who avoid infection in the first year cannot infect others in subsequent years).

At $500 per vaccination series, universal HIV vaccination costs less than $95,000 per QALY gained, relative to no vaccination (Fig. 2). A targeted strategy that instead vaccinates key populations only (MSM and PWID) with 60% coverage, prevents 7.8% of infections over 10 years (compared to 9.8% with universal vaccination), but requires 95% fewer vaccinations. Of note, this strategy is the most economically efficient, resulting in a net *cost savings* compared to no vaccination, assuming a price of $500 per vaccination series (Table 1, Fig. 2).

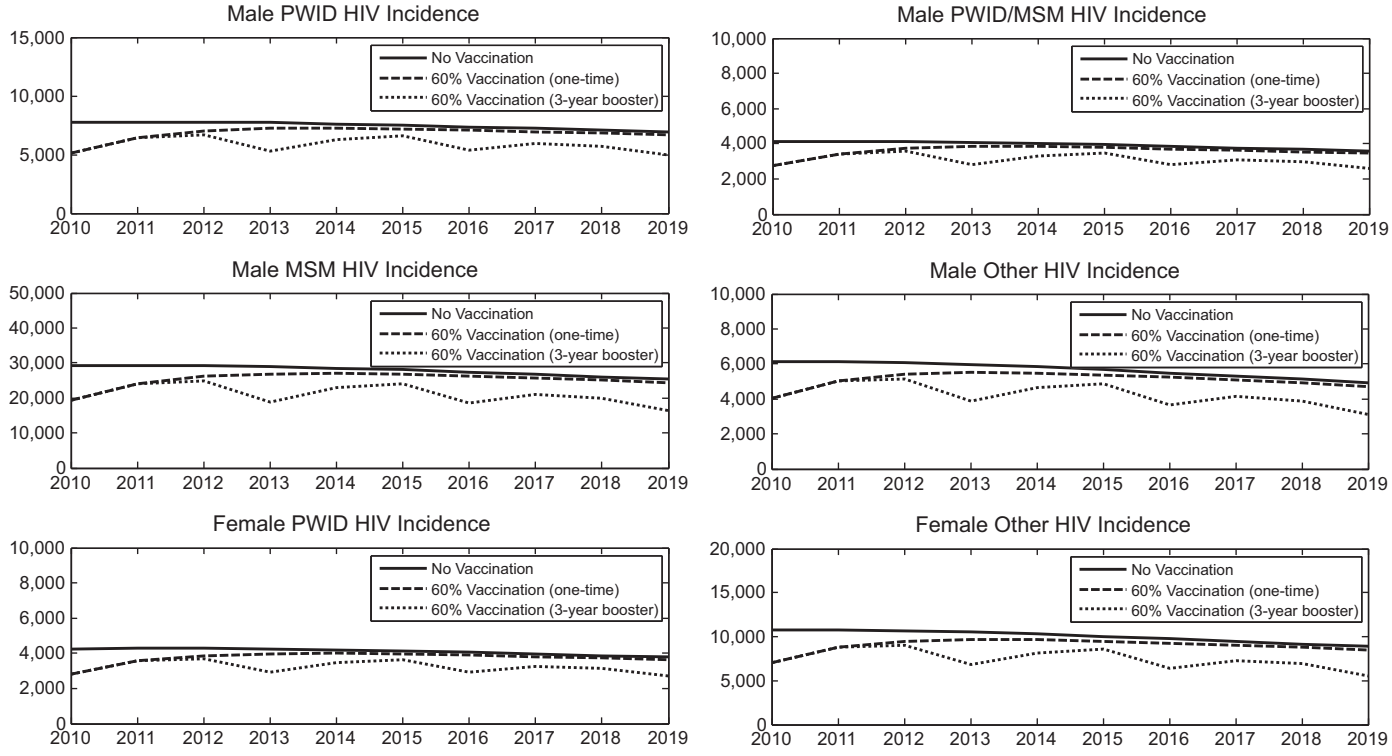

Fig. 1. HIV incidence over 10 years under HIV vaccination strategies. Projected HIV incidence in each risk group is shown assuming no vaccination (solid line), universal one-time vaccination with 60% coverage (dashed line), or universal vaccination with 60% coverage and three-year booster (dotted line). Assumes exponentially declining vaccine efficacy. MSM = men who have sex with men; PWID = people who inject drugs; Other = heterosexual population.

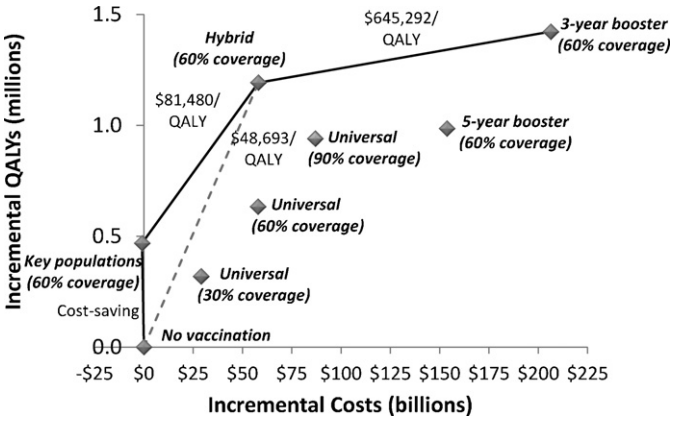

Fig. 2. Cost-effectiveness of alternative HIV vaccination strategies. The incremental costs and QALYs (discounted over 10 years) and cost-effectiveness ratios of HIV vaccination strategies are shown. Universal = one-time universal vaccination with 30%, 60%, or 90% coverage; key populations = one-time targeted vaccination of key populations (MSM and PWID) with 60% coverage; five-year booster = universal vaccination with 60% coverage and booster every five years; three-year booster = universal vaccination with 60% coverage and booster every three years; hybrid = universal vaccination with 60% coverage and booster every three years for MSM and PWID only. Assumes exponentially declining vaccine efficacy and price of $500 per vaccination or booster series. MSM = men who have sex with men; PWID = people who inject drugs; QALY = quality adjusted life year.

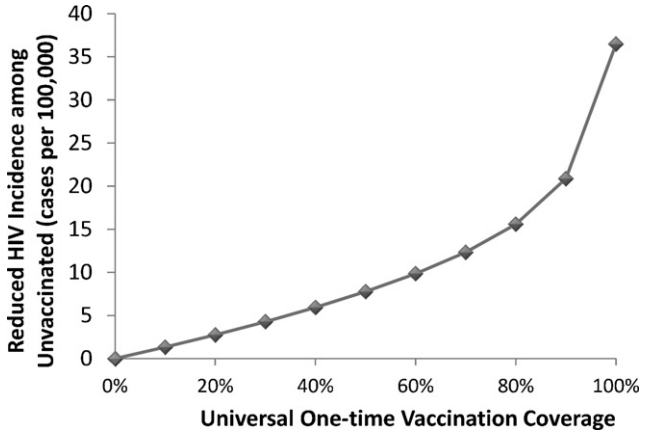

Fig. 3. Effect of herd immunity. Reduction in HIV cases among unvaccinated individuals over 10 years for varying levels of vaccination coverage is shown. Even with 100% one-time vaccination coverage, adolescents who later enter the sexually active population remain unvaccinated and thus benefit from reduced HIV transmission. Assumes exponentially declining vaccine efficacy.

3.2. Booster vaccination strategies

Offering a booster vaccine with a similar declining efficacy profile to all adults every five years improves long-term outcomes substantially: 16% of infections are prevented over 10 years, compared to 9.8% with no booster. Increasing the vaccine booster frequency to once every three years prevents 24% of infections over 10 years. Although one-year outcomes are identical, a frequent vaccine booster program offers more downstream benefit in terms of reduced incidence (Fig. 1). However, at a price of $500 per vaccination series, these strategies cost more than $145,000 per QALY gained, compared to the status quo (Fig. 2).

A more economically attractive strategy would be to offer universal vaccination to all adults initially, and a subsequent booster vaccine to higher risk sub-populations (MSM and PWID) only. This *hybrid* strategy prevents more than one-fifth of new infections over 10 years, and 34% of new infections in the first year. Compared to the cost-saving targeted vaccination strategy prioritizing only these two populations, a hybrid strategy costs $81,480 per QALY gained. However, if the former strategy is impractical, the hybrid strategy costs less than $50,000 per QALY gained versus no vaccination. This is significantly more cost-effective than a universal vaccine campaign with frequent boosters but no prioritization, assuming a price of $500 per vaccination series (Fig. 2). Of note, this strategy adds 84% of the QALYs that a universal three-year booster strategy offers, but uses only 27% of the requisite number of vaccines.

Although booster vaccination characteristics are unknown, we assumed similar coverage levels (60% in the base case) as with primary vaccination. If multiple vaccine doses are required for boosters, lower compliance levels would attenuate infections prevented and costs.

3.3. Effect of herd immunity

One benefit of a broad HIV vaccination campaign is herd immunity, resulting in reduced HIV infections among the unvaccinated population. Our epidemic modeling framework enables us to estimate the extent of this positive externality (Fig. 3). In the base case, one-time vaccination with 60% coverage prevents 9450 infections among *unvaccinated* persons over 10 years, a reduction of 9.8 cases per 100,000 people. Greater vaccination coverage increases the protective benefit to the initially unvaccinated population and unvaccinated adolescents entering the sexually active population.

3.4. Sensitivity analysis

In addition to considering variations in vaccine efficacy, we also varied key model parameters in sensitivity analysis.

3.4.1. Baseline rate of new infections

In general, if baseline HIV incidence is greater than we initially estimated, the cost-effectiveness of universal vaccination becomes more favorable. If HIV prevalence among each sub-population is 25% greater than in our base case assumption, universal vaccination costs $76,000 per QALY gained, compared to $91,000 in the base case. Similarly, if the probability of HIV transmission (due to sexual contact and use of non-sterile injecting equipment) is 25% greater, this strategy costs $64,000 per QALY gained. We also find the reverse effect: if HIV prevalence or transmission probabilities are 25% lower, then vaccination costs $117,000 or $138,000 per QALY gained, respectively. However, in all scenarios, the fraction of HIV infections prevented due to vaccination remains between 9% and 11%. These findings are generally consistent with the notion that offering HIV vaccination in higher incidence settings is more economically efficient.

3.4.2. Catch-up vaccination

In the base case, we assumed a one-time vaccination policy with 60% coverage of the adult population aged 15–64 years. Including annual catch-up vaccination for 15-year-olds entering the model slightly improves outcomes: 12.4% of HIV infections are prevented (compared to 9.8%), and cost-effectiveness improves to $89,000 per QALY gained (compared to $91,000).

3.4.3. Behavioral risk compensation

One concern with implementing a mass HIV vaccination is the possibility that some individuals may reduce their condom use or increase their number of sexual partners post-vaccination. If only vaccinated individuals increase their number of sexual partners by 25% then infections prevented are reduced from 9.8% to 6.7% (Appendix A Fig A4). This implies that vaccinated individuals are predominantly increasing contact with other vaccinated persons, in order for sexual partnerships to balance. A worst-case scenario where vaccinated individuals increase sexual contact

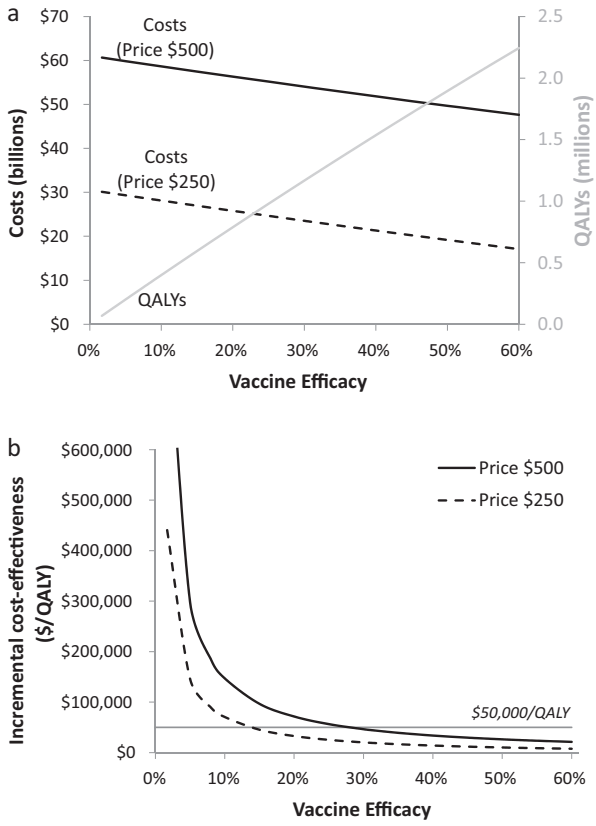

Fig. 4. Sensitivity analysis of vaccine efficacy. Sensitivity analysis of variations in constant vaccine efficacy on (a) incremental costs and QALYs, and (b) incremental cost-effectiveness ratios, assuming a price of $500 (solid line) or $250 (dashed line) per vaccination series. Assumes universal one-time vaccination with 60% coverage, and constant vaccine efficacy with lifetime duration of protection. QALY = quality adjusted life year.

with only unvaccinated persons substantially worsens the epidemic: a 25% increase in sexual partners leads to an 18% *increase* in new infections, even with 60% vaccination coverage. This suggests that comprehensive counseling programs and campaigns aimed at altering sexual norms should augment large-scale vaccination programs.

3.4.4. Vaccine cost

Given that an HIV vaccine has not been licensed or manufactured, the expected price per dose is unknown. We initially assumed a conservative price of $500 per vaccination series. At $250 per series, universal vaccination with 60% coverage costs $43,000 per QALY gained; at $100 per series, this strategy costs $21,000 per QALY gained. Adding a booster vaccine for higher risk subpopulations (hybrid strategy) costs less than $21,000 per QALY gained with a vaccine price less than $250.

If the vaccine booster regimen requires fewer doses, and is thus less expensive, than the primary series, then vaccination with three-year boosters for *all* adults should be re-evaluated. For example, the cost-effectiveness of this strategy improves to $125,000 per QALY gained (compared to $645,000 in the base case) given a booster cost of $100 and primary series cost of $500.

3.4.5. Constant vaccine efficacy

We considered an alternative scenario where vaccine efficacy is constant over time, in case such a vaccine becomes available in the future (Fig. 4). With this assumption, the relationship between vaccine efficacy and health outcomes is more mathematically straightforward than with a waning efficacy vaccine. The change in number infections occurring over the modeled time horizon is proportional to the size of the vaccinated population and vaccine efficacy:

$$\Delta \text{Infections} = -\alpha_1 \times \text{population} \times \text{coverage} \times \text{efficacy}$$

The parameter α_1 depends on background epidemic characteristics and based on our model's results we estimated that $\alpha_1 \approx 0.003$. Life years and quality-adjusted life years increase proportionately with the number of infections prevented (Fig. 4a):

$$\Delta \text{QALYs} = \alpha_2 \times \text{population} \times \text{coverage} \times \text{efficacy}$$

We estimated that $\alpha_2 \approx 0.03$, suggesting that approximately 10 QALYs (discounted) are gained for each HIV infection prevented. This value reflects advances in antiretroviral therapy prolonging life expectancy and quality of life for HIV-infected persons.

The incremental costs of vaccination include a fixed vaccination costs and a variable cost corresponding to healthcare costs saved per averted HIV infection (Fig. 4a):

$$\Delta \text{Costs} = \text{population} \times \text{coverage} \times \text{price} - \alpha_3 \times \text{population} \times \text{coverage} \times \text{efficacy}$$

We estimated that the parameter $\alpha_3 \approx 180$, suggesting that there are savings of approximately $60,000 (=180/0.003) per HIV infection prevented, because HIV infected persons utilize more health services but live a shorter period of time.

Finally, the incremental cost-effectiveness ratio is the incremental cost per QALY gained:

$$\text{ICER} = \frac{\Delta \text{Costs}}{\Delta \text{QALYs}}$$

The ICER is thus proportional to *1/efficacy*, implying that cost-effectiveness rapidly improves for very low efficacy vaccines up to approximately 20% efficacy (Fig. 4b). With a price of $500 per vaccination series, one-time universal vaccination with 60% coverage costs less than $50,000 per QALY gained if efficacy exceeds 28%. At a vaccine price of $250, this threshold decreases to a vaccine efficacy of 14%. As efficacy improves, the cost-effectiveness of universal vaccination continues to improve.

4. Discussion

In this model-based analysis for the United States, we estimated the population health and economic outcomes that would result from use of an HIV vaccine with efficacy similar to that observed in the RV144 trial. Over the three years of the RV144 trial, use of the vaccine reduced new infections by 31%. However, the efficacy of the vaccine was potentially higher during the first year and subsequently declined rapidly, and our analysis was designed to reflect this declining efficacy. Because of the short-lived efficacy, we also evaluated vaccination strategies that included booster vaccination at three- and five-year intervals. Booster vaccination was not evaluated in the RV144 trial and thus our analyses of booster vaccination are hypothetical.

Our analyses indicated that an HIV vaccine with the modest efficacy observed in the RV144 trial could provide substantial health benefit and meet generally accepted thresholds for cost-effectiveness in the United States, particularly with vaccination strategies that prioritize key populations. These findings are of particular importance because the modest efficacy observed in the RV144 trial would be considered a failure by many observers, and is certainly poor compared to vaccines that are in use for other diseases. Our analyses emphasize that even a modest and temporary reduction in new HIV infections offers substantial benefits at the population level.

A key finding of our study is that prioritized vaccination of certain key populations (MSM and PWID) results in net *cost savings* for vaccines costing less than $750 per person, assuming exponentially declining efficacy. The expense of vaccination is more than outweighed by the savings associated with prevention of HIV infections among these persons at higher risk of HIV exposure and their partners. The drawback of targeted strategies is that the total health benefit is not as great as with broader vaccination strategies, because fewer individuals are vaccinated. In practice, strategies that prioritize vaccination of MSM and PWID may also be challenging because individuals may be criminalized, stigmatized, and marginalized, making these populations more difficult to reach with vaccination programs. Targeted HIV screening strategies have had minimal success, leading to recommendations for routine screening in the United States [28,29]. Nonetheless, vaccination of certain sub-populations at higher risk of HIV exposure would be particularly economically efficient. We did not model the impact of vaccinating other sub-populations, such as heterosexual discordant couples, sex workers, clients of sex workers, or transgendered people.

Vaccination strategies that include all of the adult population offer greater total health benefits than do targeted strategies. The hybrid strategy we evaluated (vaccination of 60% of all adults followed by booster vaccination every three years for higher risk sub-populations) is particularly attractive, as it confers 84% of the total benefit of the most effective strategy (vaccination of all adults every three years) but requires only 28% of the incremental expenditures (Fig. 2). This strategy prevents 21% of new HIV infections over a 10-year period. As shown in Fig. 2, the hybrid strategy is both *more effective* and *less expensive* than universal vaccination of all adults with 60% or even 90% coverage, or with five-year boosters.

The total health benefit in the population is determined by the efficacy and duration of protection, and the proportion of the population that is vaccinated. Even a low efficacy vaccine provides some benefit to the unvaccinated population through herd immunity. Duration of protection is also a key determinant of population benefit. Our analyses indicate that the total benefit from vaccination could double with booster vaccination at three-year intervals if the booster provides the same protection as the original vaccine. How often vaccination should be done depends on the rate of decline in efficacy, thus indicating the importance of assessing the duration of protection in vaccine clinical trials.

A vaccine that confers constant immunity over the 10-year simulated time horizon remains cost-effective for even low efficacies. For less than $50,000 per QALY gained, a conservative cost-effectiveness threshold, universal vaccination (with 60% coverage) could prevent over 10,000 HIV infections per year if efficacy exceeds 28% and the vaccination series costs $500. At $250 per vaccination, a low 14%-efficacy vaccine results in such a favorable cost-effectiveness ratio.

Our analysis has several limitations. The actual efficacy of an HIV vaccine is, of course, unknown. Our analysis reflects the available data from the RV144 trial, and a vaccine with lower efficacy is unlikely to be used. Thus, our analysis likely provides a lower bound on the health benefit from an HIV vaccine. Likewise, the cost of an HIV vaccine is unknown. Our base-case assumption of $500 for the vaccination series is plausible given the price of vaccines currently on the market, but the price will have a direct bearing on the cost-effectiveness of the vaccine. Our model simplifies the complex process of sexual partnership formation and dissolution (see Appendix A). In addition, we do not stratify the population into multiple age groups, so we cannot evaluate vaccination strategies that prioritize specific age groups. Because HIV incidence varies with age, such analyses would be useful. Finally, we do not assess other HIV prevention interventions such as male circumcision. In practice, use of multiple prevention interventions simultaneously may be the most useful approach, and analysis of such portfolios would be an important extension of our analyses.

In conclusion, a partially effective HIV vaccine with effectiveness similar to that observed in the RV144 trial would provide large health benefits in the United States and could meet conventionally accepted thresholds for cost-effectiveness. Strategies that prioritize key populations at higher risk of HIV exposure, such as men who have sex with men and people who inject drugs, are most efficient, but broader strategies provide greater total population health benefit. More realistic estimates of the population health and economic outcomes from an HIV vaccine will depend on a more detailed understanding of the efficacy, duration of protection, and cost of the vaccine.

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Appendix A. Technical appendix

We extended a previously published model of HIV transmission, and additional model details can be found elsewhere [6,12]. Parameters used in the mathematical model are given in Table A3.

A.1. Risk groups

By subdividing the adult population aged 15–64 into risk stratifications (Table A1), we accounted for variations in baseline demographic characteristics (population size, HIV prevalence, mortality rate, population entry and exit rates), sexual behavior (annual number of sexual partners, condom use), drug using behavior (annual number of drug injections, use of non-sterile injecting equipment), and HIV transmission probabilities (male to male, male to female, female to male).

A.2. HIV transmission, progression, and treatment

We next sub-divided each risk group based HIV infection status, disease stage, screening status, antiretroviral treatment status, and preventive vaccination status (Fig. A1). We modeled HIV transmission as a binomial process, where individuals in compartment i select partners in compartment j with probability p, where p depends on the number of people in compartment j as well as the number of partners each person in j has. This is known as proportional mixing. If a susceptible person selects an HIV-infected partner, the probability of transmission depends on both sexes, the mode of transmission, disease stage, antiretroviral treatment status, and vaccination status (for the uninfected partner only). Individuals in compartment i then repeat this partnership selection process n times per year, for each type of partnership (heterosexual or homosexual). HIV transmission via injection drug use was modeled in a similar manner, except the number of injections, use of non-sterile injecting equipment, and the appropriate transmission probabilities are substituted.

Table A1
Population risk groups and modes of HIV transmission.

	Male				Female	
	MSM	MSM/PWID	PWID	Other	PWID	Other
Male						
MSM	Homosexual	Homosexual			Heterosexual	Heterosexual
MSM/PWID	Homosexual	Homosexual, Inject eqmt	Inject eqmt		Heterosexual, Inject eqmt	Heterosexual
PWID		Inject eqmt	Inject eqmt		Heterosexual, Inject eqmt	Heterosexual
Other					Heterosexual	Heterosexual
Female						
PWID	Heterosexual	Heterosexual, Inject eqmt	Heterosexual, Inject eqmt	Heterosexual	Inject eqmt	
Other	Heterosexual	Heterosexual	Heterosexual	Heterosexual		

MSM = men who have sex with men; PWID = people who inject drugs; Other = low-risk general population; Inject eqmt = use of non-sterile injecting equipment.

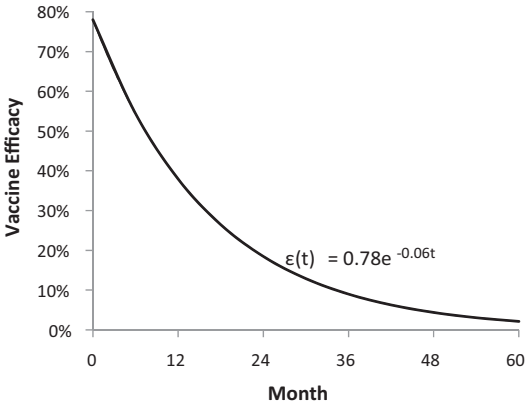

Fig. A2. Exponentially declining vaccine efficacy curve.

Upon becoming HIV infected, individuals progress through a continuum of disease states, ultimately ending in death. At various intervals, individuals may be screened for HIV or initiate an antiretroviral treatment regimen, which further adjusts the probability of infecting others (either through a reduced viral load due to suppressive ART, or through fewer sexual partners following HIV screening). We estimated disease progression rates and disease-related mortality based on a model of the natural history of HIV [24].

A.3. HIV vaccination

We considered alternative HIV vaccination strategies that vary the prioritized population (universal, sub-populations at higher risk of HIV exposure), coverage level (30%, 60%, 90%), and frequency of a booster vaccine (no booster, every three years, every five years). We assumed an exponentially declining vaccine efficacy, $\varepsilon(t) = 0.78e^{-0.06t}$, where t (measured in months) is time post-vaccination, based on the RV144 trial results (Fig. A2) [3]. This function implies that efficacy is initially 78% at the time of vaccination, 38% at 12 months post-vaccination, 19% at 24 months, and 9% at 36 months. We included the effects of a preventive vaccine by adjusting the appropriate transmission probabilities by $1 - \varepsilon(t)$.

Most of the efficacy of such a vaccine wanes within three to four years post-vaccination. Hence, we considered a hypothetical scenario where a vaccine booster enhances vaccine efficacy up to the original levels. As future trial data on the feasibility of a booster vaccine become available, we will update this assumption.

We also explored an alternative scenario in which constant vaccine efficacy, ε, is conferred over the duration of the simulation (10 years). We modeled how variations in constant efficacy and vaccination coverage levels affect the projected health outcomes (Fig. A5). In our prior published study, we considered simultaneous variations in vaccine efficacy and duration of protection [6].

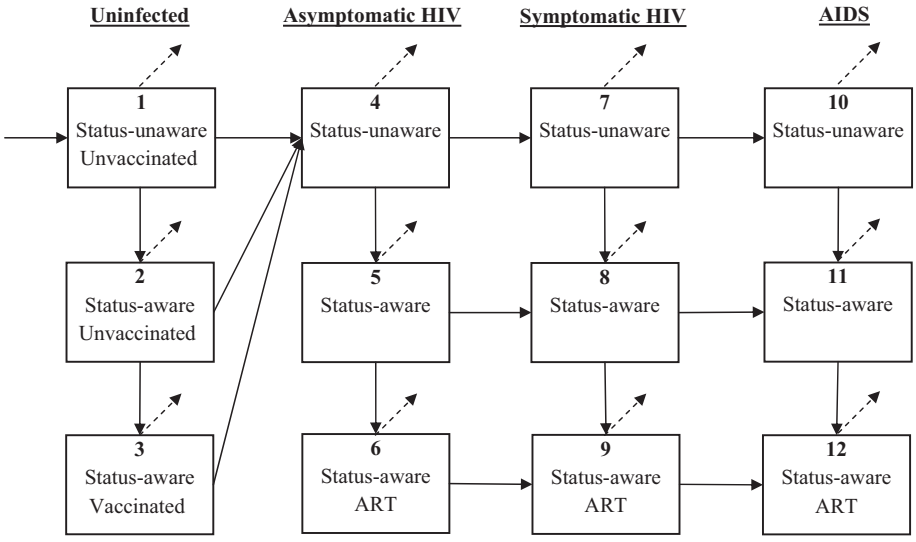

Fig. A1. Schematic model diagram. The boxes represent disease-stage compartments and the arrows represent transitions between compartments. Individuals enter into the unvaccinated population and may die or exit the population at various disease stages (dashed arrows).

Table A2
Annual HIV incidence with model (average over 10 years) and CDC estimates.

Transmission category	CDC estimate [31] (2006)	Model projection (2009–2019)
Men who have sex with men (MSM)	28,700 (53%)	27,904 (47%)
People who inject drugs (PWID)	6,600 (12%)	11,466 (20%)
MSM/PWID	2,100 (4%)	3,925 (7%)
Heterosexual	16,800 (31%)	15,687 (27%)
Total	56,300 (100%)	59,082 (100%)

A.4. Model calibration

We parameterized our model using the best available demographic, epidemiologic, and behavioral data from published literature (Table A3). Additionally, we calibrated the model to past estimates of the number of people living with HIV (Fig. A3), which suggests that our model approximates observed data reasonably well. Additionally, we compared our model's projected HIV incidence over the next 10 years with the most recent estimates from 2006 (Table A2). Here we find that our model's projections of HIV transmission among MSM and heterosexuals are very close to the CDC's estimates, and together these categories account for 75–85% of all new cases. Our model projects more HIV infections occurring among people who inject drugs over the next 10 years, which may be due to misestimates in our parameter values (e.g., overestimate of transmission probabilities, underestimate of fraction of PWID receiving antiretroviral therapy) or under diagnosis of HIV infection in these risk groups.

A.5. Initial conditions

Our mathematical model is characterized by a set of nonlinear differential equations, which calculate the size of each model compartment over time. After instantiating the model with a set of initial conditions using 2009 data, we numerically solved the system using the mathematical programming language Matlab 2010b. Initial population sizes and HIV prevalence levels are given in Table A3.

A.6. Health and economic outcomes

We applied the model under various vaccination strategies to estimate future HIV infections, HIV prevalence over time, quality-adjusted life years (QALYs) in the population, costs, and incremental cost-effectiveness ratios (ICERs). QALYs were calculated by applying a quality of life factor to each health state and integrating the total time spent in each health state. Similarly, HIV-related health costs were computed and added to the overall cost of the vaccination program. All costs and QALYs were discounted to the present at 3% annually [27]. Finally, we calculated the ICERs of each vaccination strategy relative to the status quo and next-best alternative.

A.7. Additional sensitivity analyses

A.7.1. Behavioral risk compensation

We expanded the sensitivity analysis on behavioral risk compensation following vaccination. The extent of the effect on the epidemic depends on assumptions about assortative or random sexual mixing in the population (Fig. A4). A best-case scenario

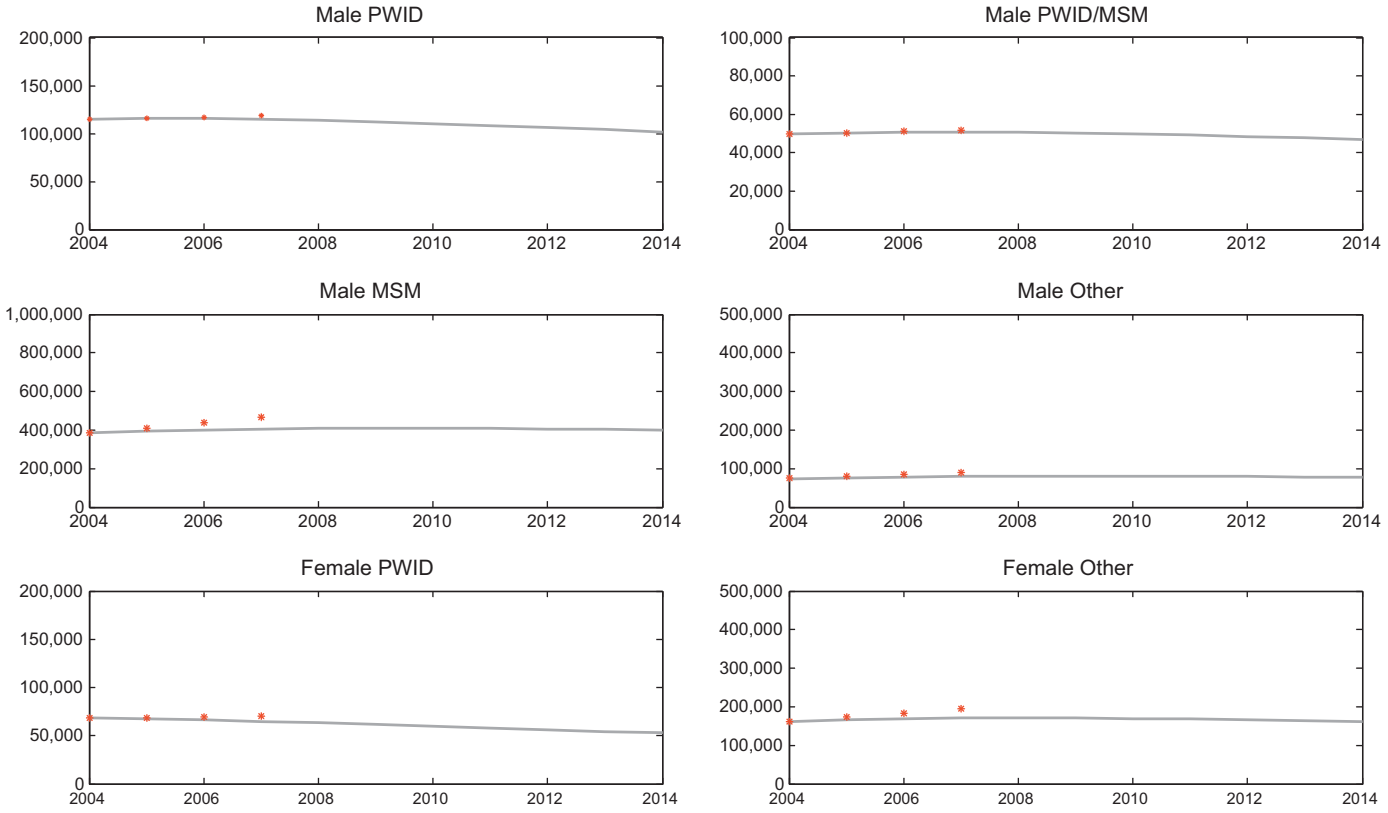

Fig. A3. Number of people living with HIV, 2004–2014. The model's projections are shown by the solid line, and CDC estimates from 2004 to 2007 are shown by the red asterisks. The CDC estimates are calculated based on the total number of people living with HIV and the percent of cases due to each transmission mode [30].

Table A3
Summary of key model parameters.

Parameter	Value	Range	Source
Demographics			
Total population (15–64 years)			
Male PWID	1,000,000	0.5–1.5 million	Calculated [32–36]
Male MSM	4,057,194	3–6 million	Calculated [32–34,37]
Male MSM/PWID	300,000	200,000–500,000	Calculated [30,32–38]
Male other	96,022,652	95–100 million	Calculated [32–34]
Female PWID	450,000	300,00–600,000	Calculated [32–36]
Female other	101,632,781	100–105 million	Calculated [32–34]
HIV prevalence			
Male PWID	12.9%	10–20%	Calculated [32–36]
Male MSM	12.6%	5–20%	Calculated [32–34,37]
Male MSM/PWID	18.8%	15–30%	Calculated [32–38]
Male other	0.10%	0.05–0.25%	Calculated [32–34]
Female PWID	17.3%	15–30%	Calculated [32–36]
Female other	0.22%	0.10–0.40%	Calculated [32–34]
Annual mortality rate			
Male	0.0041	0.002–0.005	[39]
Female	0.0024	0.002–0.005	[39]
PWID (excess)	0.025	0–0.05	[26]
Annual maturation rate			
Male	0.0111	0.01–0.02	[34]
Female	0.0122	0.01–0.02	[34]
Annual entry rate			
Male	0.0227	0.01–0.05	[34]
Female	0.0213	0.01–0.05	[34]
Sexual transmission			
Transmission probability per partnership			
Heterosexual ($F_{HIV+} \rightarrow M_{HIV-}$)			
Asymptomatic HIV	0.02	0.01–0.04	[40–48]
Symptomatic HIV	0.03	0.01–0.04	[40–48]
AIDS	0.05	0.03–0.06	[40–48]
Heterosexual ($M_{HIV+} \rightarrow F_{HIV-}$)			
Asymptomatic HIV	0.03	0.02–0.05	[40–48]
Symptomatic HIV	0.04	0.02–0.05	[40–48]
AIDS	0.08	0.05–0.10	[40–48]
Homosexual ($M_{HIV+} \rightarrow M_{HIV-}$)			
Asymptomatic HIV	0.04	0.03–0.06	[44,49–51]
Symptomatic HIV	0.05	0.03–0.06	[44,49–51]
AIDS	0.10	0.08–0.15	[44,49–51]
Annual number of same-sex partners			
Male MSM	3.0	2.0–5.0	[52–55]
Male MSM/PWID	3.0	2.0–5.0	[52,53,55]
Condom usage with same-sex partners			
Male MSM	40%	30–60%	[38,52–55]
Male MSM/PWID	40%	30–50%	[55]
Annual number of opposite-sex partners			
Male PWID	3.0	2.0–5.0	[56]
Male MSM	0.1	0–1.0	[54]
Male MSM/PWID	0.1	0–1.0	[57]
Male other	1.1	0.5–2.0	[54,58–61]
Female PWID	3.5	2.0–5.0	[62]
Female other	1.1	0.5–2.0	[58,59,61,63]
Condom usage with opposite-sex partners			
Male PWID	25%	15–35%	[38,57]
Male MSM	30%	20–50%	[38,55]
Male MSM/PWID	30%	30–50%	[55,57]
Male other	20%	10–40%	[58]
Female PWID	25%	20–50%	[56,62]
Female other	20%	10–40%	[58]
Reduction in heterosexual HIV transmission due to male circumcision	50%	48–60%	[64–66]
Injection drug use transmission			
Transmission probability per non-sterile injection			
Asymptomatic HIV	0.002	0.001–0.005	[26,67,68]
Symptomatic HIV	0.003	0.001–0.005	[26,67,68]
AIDS	0.003	0.001–0.005	[26,67,68]
Average injections per year	200	100–500	[26,69]
Use of non-sterile injecting equipment	20%	10–40%	[26,55,56,70]
HIV screening			
Fraction of population tested in past 12 months			
Higher risk sub-populations	23%	10–30%	[33]
Other	10%	5–20%	[33]
Annual probability of symptom-based case finding			
HIV	10%	0–30%	[24]
AIDS	20%	10–60%	[24]

Table A3 (*Continued*)

Parameter	Value	Range	Source
Reduction in sexual behavior among HIV + identified individuals due to screening	20%	0–50%	[71–74]
Antiretroviral therapy (ART)			
Fraction starting ART at CD4 = 350 cells/mm^3	50%	25–75%	Assumed [75,76]
Annual ART entry rate if CD4 < 350 cells/mm^3	0.05	0–0.10	Assumed [76]
Reduction in injection infectivity due to ART	50%	25–75%	[24,25]
Reduction in sexual infectivity due to ART	90%	50–99%	[47,77–82]
Circumcision			
Fraction of males circumcised	70%	50–80%	[83]
Reduction in HIV transmission due to circumcision	50%	48–60%	[65,66]
Disease parameters			
Quality-of-life factors			
Uninfected	1.0	–	[19]
Asymptomatic HIV – Unaware	0.91	0.85–0.95	[20–23]
Asymptomatic HIV – Aware (Year 1)	0.84	0.85–0.95	[20–24]
Asymptomatic HIV – Aware (Years 2+)	0.89	0.85–0.95	[20–24]
Symptomatic HIV – Unaware	0.79	0.70–0.80	[20–23]
Symptomatic HIV – Aware	0.72	0.70–0.80	[20–23]
Symptomatic HIV – Treated with ART	0.83	0.82–0.87	[20–23]
AIDS – Unaware	0.72	0.60–0.75	[20–23]
AIDS – Aware	0.72	0.60–0.75	[20–23]
AIDS – Treated with ART	0.82	0.82–0.87	[20–23]
PWID (multiplier)*	0.90	0.80–1.0	[25,26]
Annual disease progression rate			
Asymptomatic HIV	0.11	0.10–0.20	[14,15,17]
Symptomatic HIV – Untreated	0.33	0.20–0.50	[14,15,17]
Symptomatic HIV – Treated with ART	0.06	0.05–0.10	[13–18]
AIDS – Untreated	0.40	0.20–1.00	[14,15,17]
AIDS – Treated with ART	0.25	0.10–0.50	[13–18]
Costs (2009 USD)			
Annual HIV-related healthcare costs			
Asymptomatic HIV – Untreated	$4,125	$3,000–$6,000	[84,85]
Symptomatic HIV – Untreated	$6,925	$5,000–$9,000	[84,85]
Symptomatic HIV – Treated with ART	$6,174	$5,000–$7,000	[84,85]
AIDS – Untreated	$21,838	$15,000–$25,000	[84–86]
AIDS – Treated with ART	$9,938	$6,000–$17,000	[24,85]
Annual non-HIV-related healthcare costs	$7,576	$5,000–$8,000	[87]
Annual cost of ART	$15,571	$12,000–$18,000	[24,85,86,88]
Cost of HIV ELISA antibody test	$12	$10–20	[89]
Cost of confirmatory Western Blot test	$19	$10–50	[89]
Cost of behavior counseling	$60	$50–$100	[24,88,90]
Annual cost of ancillary services for PWID	$2,500	$1,000–$4,000	[26]
Annual discount rate	3%	0–5%	[27]

ART = antiretroviral therapy; ELISA = enzyme-linked immunosorbent assay; MSM = men who have sex with men; PWID = people who inject drugs; $F_{HIV+} \rightarrow M_{HIV-}$ = HIV transmission between HIV + female partner and HIV- male partner; $M_{HIV+} \rightarrow F_{HIV-}$ = HIV transmission between HIV+ male partner and HIV− female partner; $M_{HIV+} \rightarrow M_{HIV-}$ = HIV transmission between HIV+ male partner and HIV− male partner; USD = United States dollars.

* Quality of life for all people who inject drugs is multiplied by this quantity.

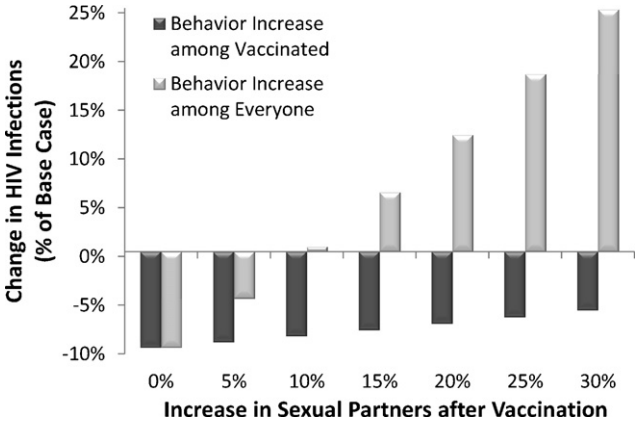

Fig. A4. Change in HIV infections with increased behavioral risk compensation. Change in HIV infections over 10 years relative to the status quo (590,852 new infections) is shown for varying levels of behavioral risk compensation among vaccinated individuals only (dark grey) or all adults (light grey). In the base case, a declining efficacy vaccine with 60% coverage of all adults prevents 9.8% of new infections.

is that vaccinated individuals only increase sexual contact with other vaccinated individuals. In this case, behavioral risk compensation has only a modest adverse effect on the epidemic because most of the additional partnerships are between vaccine-protected individuals (dark grey bars). On the other hand, if increased risk compensation prompts unvaccinated persons to increase their partnerships, then the epidemic would substantially worsen (light grey bars).

A.7.2. Constant vaccine efficacy

We extended our analysis on constant vaccine efficacy to explore the relationship between efficacy, vaccination coverage levels, and HIV infections prevented. A 31% (constant) efficacy vaccine, similar to the average efficacy observed in the RV144 trial, could prevent more than 20% of new infections over 10 years, assuming 60% vaccination coverage is achieved (Fig. A5). Increasing (or decreasing) vaccine efficacy or vaccination coverage prevents more (or fewer) infections, with the relative gain in infections prevented similar for both parameters.

Given a low-efficacy vaccine, coverage needs to be increased substantially to attain a small increase in infections prevented. For example, with a 20% efficacy vaccine, coverage must increase

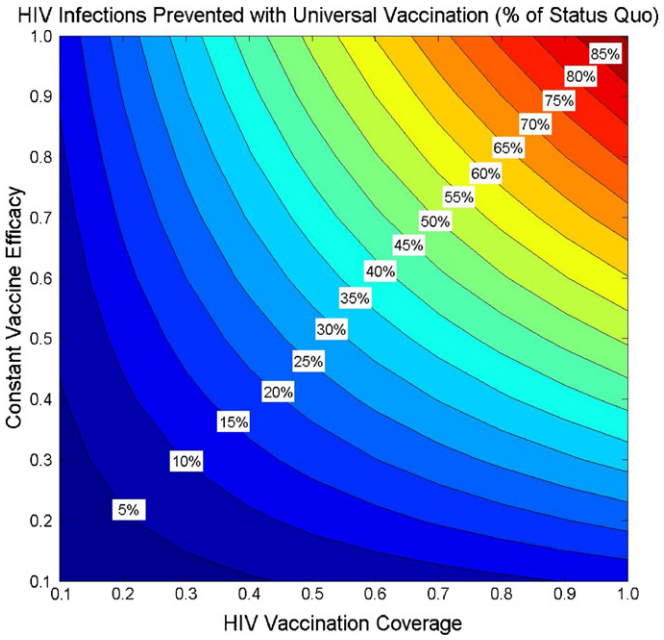

Fig. A5. Sensitivity analysis of vaccine efficacy coverage levels on infections prevented. Fraction of HIV infections prevented over 10 years relative to the status quo (590,852 new infections) is shown for varying levels of vaccination coverage (*x*-axis) and constant vaccine efficacy (*y*-axis). Assumes constant vaccine efficacy with lifetime duration of protection. In the base case, a 31%-efficacy vaccine with 60% coverage of all adults prevents 20.6% of new infections.

from 60% to nearly 90% to prevent an additional 5% of infections. However, with a highly effective 80% efficacy vaccine, coverage only needs to increase from 60% to 69% to achieve the same gain in infections averted. Hence, use of a low-efficacy vaccine necessitates expanding vaccination coverage as much as possible.

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