



## Research Article

# Are Clade Specific HIV Vaccines a Necessity? An Analysis Based on Mathematical Models



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## ABSTRACT

As HIV-1 envelope immune responses are critical to vaccine related protection, most candidate HIV vaccines entering efficacy trials are based upon a clade specific design. This need for clade specific vaccine prototypes markedly reduces the implementation of potentially effective HIV vaccines. We utilized a mathematical model to determine the effectiveness of immediate roll-out of a non-clade matched vaccine with reduced efficacy compared to constructing clade specific vaccines, which would take considerable time to manufacture and test in safety and efficacy trials. We simulated the HIV epidemic in San Francisco (SF) and South Africa (SA) and projected effectiveness of three vaccination strategies: i) immediate intervention with a 20–40% vaccine efficacy (VE) non-matched vaccine, ii) delayed intervention by developing a 50% VE clade-specific vaccine, and iii) immediate intervention with a non-matched vaccine replaced by a clade-specific vaccine when developed. Immediate vaccination with a non-clade matched vaccine, even with reduced efficacy, would prevent thousands of new infections in SF and millions in SA over 30 years. Vaccination with 50% VE delayed for five years needs six and 12 years in SA to break-even with immediate 20 and 30% VE vaccination, respectively, while not able to surpass the impact of immediate 40% VE vaccination over 30 years. Replacing a 30% VE with a 50% VE vaccine after 5 years reduces the HIV acquisition by 5% compared to delayed vaccination. The immediate use of an HIV vaccine with reduced VE in high risk communities appears desirable over a short time line but higher VE should be the pursued to achieve strong long-term impact. Our analysis illustrates the importance of developing surrogate markers (correlates of protection) to allow bridging types of immunogenicity studies to support more rapid assessment of clade specific vaccines.

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## 1. Introduction

While progress in the treatment and prevention of human immunodeficiency virus (HIV) in the past decade has resulted in significant reductions in the number of HIV-related deaths and new infections especially among infants, most authorities acknowledge that long term effective control will require the development of an effective HIV vaccine (Corey et al., 2011; Fauci and Marston, 2014). The promise of an HIV-1 vaccine received an important boost with the finding of partial efficacy in the RV144 trial (Rerks-Ngarm et al.,

2009). The initial results of this moderately effective pox-protein prime-boost strategy were met with considerable skepticism. However, additional investigations evaluating correlates of protection have shown persons with enhanced responses to several HIV-1 peptides or immunogens exhibit 58–75% efficacy (Rolland et al., 2012; Gartland et al., 2014; Li et al., 2014; Yates et al., 2014). Antibody responses to such proteins and peptides tend to be clade specific. As such, most candidate HIV vaccine regimens now entering efficacy trials are mainly based upon a single clade design. While expanding the breadth of vaccine responses by designing a more universal immunogen is under investigation; these approaches are primarily focused on expanding the T-cell rather than B-cell responses (Santra et al., 2010; Borthwick et al., 2014). Antibody responses to circulating strains of viruses in a population with such approaches still vary considerably by clade and strain and most immune correlates associated with HIV acquisition are antibody related (Tomaras et al., 2013; Gottardo et al., 2013; Haynes et al., 2012).

*Abbreviations:* HIV, human immunodeficiency virus; NHP, non-human primates; SF, San Francisco; SA, South Africa; VE, vaccine efficacy; ART, antiretroviral therapy.

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A likely scenario for the immediate future in the HIV vaccine field will be the development of an HIV vaccine with proven efficacy against a specific clade. One of the critical questions that emerges from this is whether to support the immediate introduction of a clade matched vaccine in regions where other clades are prevalent with possible loss of efficacy or to allocate resources toward the development of a new vaccine specific to each particular region. Given the time and financial cost required for vaccine development, it is important to consider the human and economic costs involved in immediate use of lower efficacy vaccination compared to waiting for vaccines specifically based on clade prevalence (Anon., 2010).

Mathematical models have been used to project the potential impact of moderately effective vaccines with waning protection and to study their cost-effectiveness along with the expected epidemiological impact (Andersson and Stover, 2011; Gray et al., 2011; Nagelkerke et al., 2011; Hontelez et al., 2011; Kaldor and Wilson, 2010; Long and Owens, 2011; Schneider et al., 2011; Stover et al., 2007; Andersson et al., 2011). We use a model to address the question of implementation of a clade specific vaccine by simulating the HIV epidemic in the men-who-have-sex-with-men (MSM) population in San Francisco (SF) and in the general population in South Africa (SA).

## 2. Materials and Methods

### 2.1. Transmission Model

Compartmental mathematical models of HIV transmission in heterosexual and MSM populations are developed to study the effectiveness of different vaccine development strategies (Fig. 1). We used these models to simulate HIV epidemics in the MSM population in SF and the general population in SA. Both populations have been extensively studied over time and data on the extent of the epidemics in these populations were available. Populations are stratified in compartments by gender (men and women), by HIV status as susceptible, infected with HIV and individuals who develop AIDS, and by vaccination status. Adolescents who become sexually active join the susceptible class at constant rates, which are selected to ensure the population growth observed in the simulated populations. Different immigration rates into the MSM community in SF are explored assuming that HIV prevalence among migrants is the average prevalence recorded in the largest 21 MSM populations in US (CDC, 2010). The rates at which individuals acquire HIV, i.e., forces of infections for different classes, are derived from standard binomial models based on the number of partners per susceptible person, the number of sex acts per partnership, the fraction of sex acts protected by condoms, the protection provided

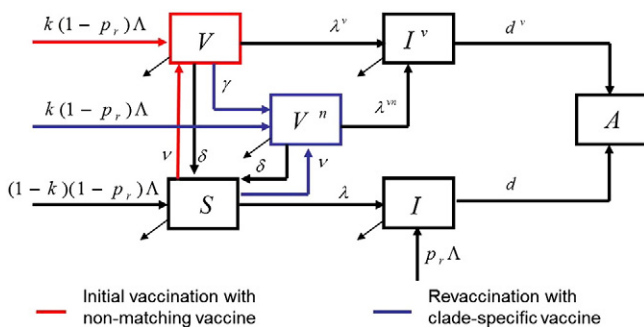
by the vaccine and the HIV acquisition risk per vaginal or anal intercourse for men and women. A complete description of the models is presented in the Supplementary Materials. The data for the SF model included a relatively high prevalence of antiretroviral therapy (ART) usage in the population and hence lower rates of transmission over time. As SA has a national plan for HIV and AIDS (South African National Aids Council (SANAC), 2011), our model includes a sensitivity analysis exploring the effects of circumcision in SA as well as modeling the increasing prevalence of ART use among those newly diagnosed with HIV infection.

### 2.2. Epidemic Settings and Public-Health Metrics

Demographic, behavior and epidemiological data representative for SA (UNAIDS/WHO, 2009; Morgan et al., 2002; Porter and Zaba, 2004; Johnson et al., 2009; Kalichman et al., 2009; Todd et al., 2009) and SF (CDC, 2010; McFarland, 2006; San Francisco Department of Public Health, 2012; Scheer et al., 2008; Volk et al., 2012) including population growth, number of partners per year, frequency of sex acts, fraction of protected sex acts, and time to remain sexually active is used to identify realistic ranges for the pre-intervention parameters of our models (see Tables S1 and S2). Acquisition probabilities per vaginal and anal sex acts with an HIV infected partner are obtained from meta-analyses of the observational data from developing and developed countries (Boily et al., 2009; Baggaley et al., 2010). The models are calibrated to fit the HIV prevalence and HIV incidence as well as population growth reported among the general population in SA and the MSM population in San Francisco (details in the Supplementary Materials). The effectiveness of different vaccine development strategies is measured in terms of the cumulative number and fraction of infections prevented as well as the reduction in HIV prevalence and incidence over up to 30 years using the simulated epidemics in the absence of a vaccine as a baseline. The economic impact of the vaccination is evaluated by calculating the lifetime treatment cost avoided for the prevented infections over 20 years. The cost of development of a novel clade specific vaccine and the implementation of an effective HIV vaccine on a country wide basis is currently unknown and implementation strategies vary greatly. As such, the economic analyses we present here are directed to inform how much could be spent on vaccine development based on the projected savings. We recognize that other biomedical interventions can be utilized to reduce acquisition; however their long-term population effect is under much study and debate (Abbas et al., 2013; Dimitrov et al., 2010). As such, our initial analysis has been conducted without modeling such interventions. Simulations defining such interventions can be performed once cost, utilization and effectiveness are known and then placed into our model.

### 2.3. Vaccine Efficacy and Vaccine Development Strategies

Licensure requirements with regulatory agencies have utilized a 50% reduction in acquisition over an 18–36 month time period as the requirement for regulatory approval (Rerks-Ngarm et al., 2009; Chen et al., 2011; Hankins et al., 2010). As such, we modeled a clade-specific vaccine that is 50% effective against the predominant circulating HIV strains in the two populations we analyzed: clade C for SA and clade B for MSM in SF. We assume reduced efficacy of the vaccine against other HIV strains and therefore explore the range of 20%–40% protection when the vaccine is used in regions with different dominant HIV subtypes, e.g., the clade C vaccine in SF and a clade B vaccine in SA. We evaluate and compare the effectiveness of three vaccine development strategies: i) *Immediate strategy*, in which a non-matched vaccine (20%–40% effective) is introduced immediately and used for 30 years; ii) *Delayed strategy* in which a matched vaccine (50% effective) is introduced after an initial period of development/testing and iii) *Replacement strategy* in which the original non-matched vaccine (20%–40% effective) is introduced immediately but replaced by a clade-specific vaccine (50%



**Fig. 1.** Flow diagram of the model of HIV transmission under the replacement vaccination strategy. Simulated population is stratified in compartments by HIV and vaccination status as susceptibles (S), susceptibles vaccinated with non-matched (V) or clade-specific vaccines (V<sup>n</sup>), HIV-positive who become infected when unvaccinated (I) or vaccinated (I<sup>v</sup>), and individuals with AIDS (A). Non-matched vaccine (red flows) is used initially and replaced with clade-specific vaccine (blue flows) when it becomes available in all new vaccinations (vaccination rate  $v$ ) and revaccinations (revaccination rate  $\gamma$ ).

effective) whenever it becomes available after an initial period of development. Comparable with the RV144 results, the protection provided by all vaccines is waning over time and a vaccine booster is required every three years. We assumed that the vaccine regimen was rolled out over an initial 3-year period with 20% of the uninfected population vaccinated per year. Afterward, an effort is made to vaccinate 50% of the adolescents who become sexually active and 5% of the uninfected population to secure stable level of vaccination coverage between 40% and 50% with an 80% revaccination rate (see Fig. S1). When the matched vaccine becomes available it is immediately used instead of the original vaccine in all vaccinations and revaccinations (see Fig. 1). Theoretically, a candidate HIV vaccine would reduce the viral load in unvaccinated individuals who acquire HIV and potentially decrease their transmission of the virus, adding an additional level of population effectiveness to an HIV vaccine program. However no evidence of this was seen in RV144 and as such this mechanism is not included in our models. All vaccination assumptions are summarized in Table S3.

### 3. Results

Without the implementation of an HIV vaccine, our model indicates that the HIV epidemics will remain relatively stable in SA and SF over the next 3 decades. We project 5.20, 10.37 and 15.55 million new HIV infections over the next 10, 20 and 30 years in SA (Fig. 2a) where an estimated 27 million people are in a sexually active age (15–49 years old), with HIV prevalence above 15% and HIV incidence between 2% and 2.4% over the entire 30-year period (Fig. 3c & e, solid black lines). In SF, with estimated 58,300 MSMs, we predict 8800, 18,700 and 29,600 new HIV infections over the next 10, 20 and 30 years (Fig. 2b) with HIV prevalence between 22% and 24% and HIV incidence around 1.7% (Fig. 3d & f, solid black lines). Our analysis suggests that vaccinating 50% of the population assuming a 50% vaccine efficacy will have a substantial impact on the HIV epidemics both in SA and among MSMs in SF (see Fig. 2).

#### 3.1. Immediate vs. Delayed Strategies

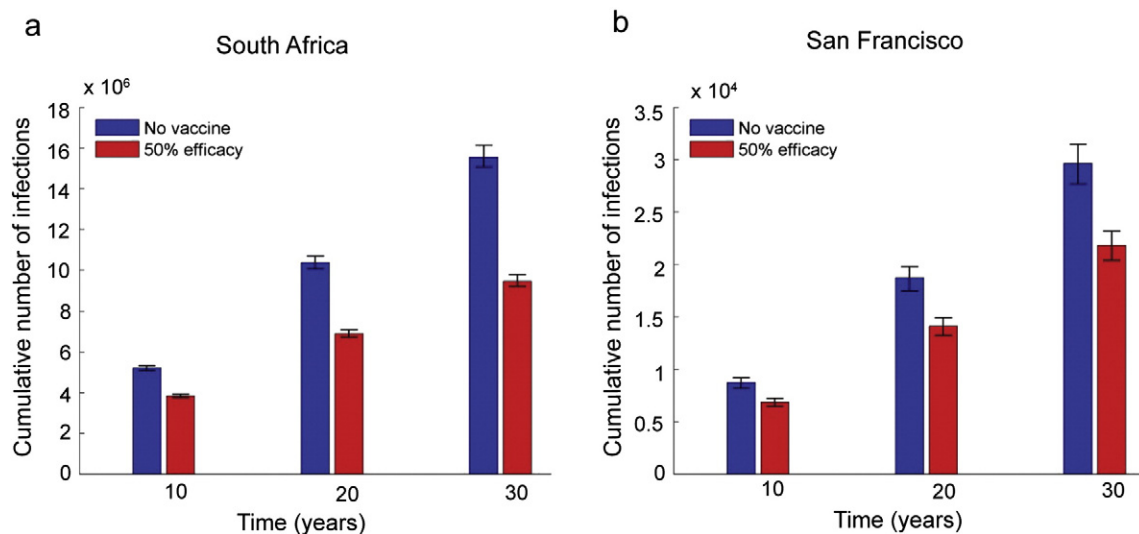
The immediate introduction of a non-matching vaccine with efficacy of 20%–40% will prevent 16.8%–32.2% of the infections in SA (Fig. 3a) and 10.7%–21.2% of the infections among MSMs in SF (Fig. 3b) over 30 years. Immediate vaccination with a non-matching vaccine is projected

to reduce the HIV prevalence 3–7 percentage points in SA versus 2–4 percentage points in SF (Fig. 3c & d) over the same period. It will also result in a 29–51% lower HIV incidence in SA versus a 15–29% incidence reduction in SF. A vaccination strategy in which a 50% effective clade-specific vaccine is introduced after delay for development is projected to achieve a better incidence reduction over 30 years but may not be able to prevent as many infections over 30 years as the non-matching vaccine introduced immediately, especially if the difference in the protection provided by the two vaccines is small (Fig. 3a & b, green vs. dashed black lines).

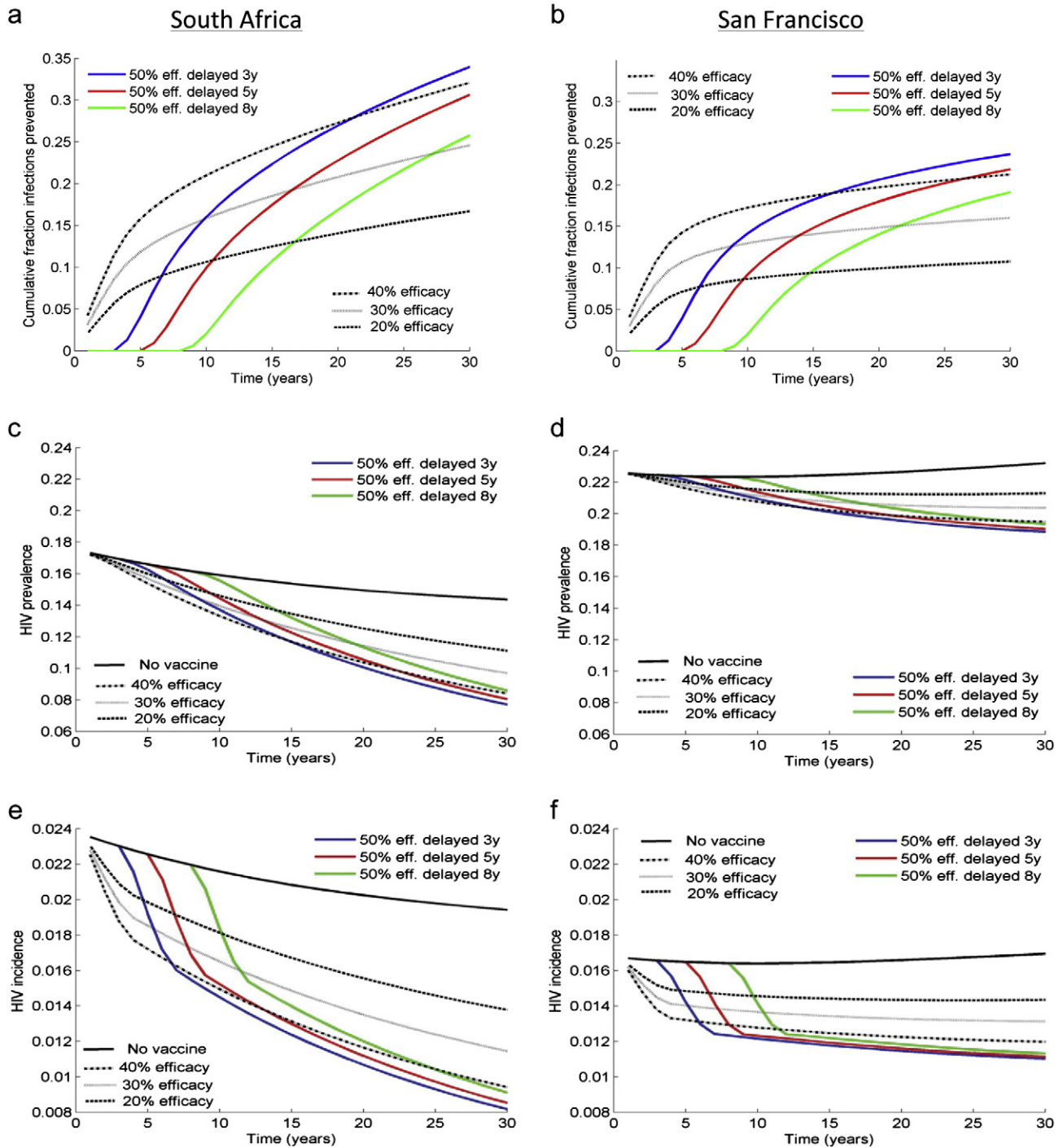
If the non-matching vaccine has low efficacy (20%) then a clade-specific vaccine delayed for five years will need only 5–6 years (total time of 10–11 years) to match the number of infections prevented (see Fig. 4). The break-even times increase significantly if the clade-specific vaccine does not provide substantial improvement in protection. For instance, after 18 years use (21 years in total) of a 50% effective vaccine in SA delayed only three years is still lagging behind a 40% effective vaccine in prevented infections, while a five-year delay makes it impossible to break even over the 30-year period (Fig. 4a, green). Similarly, if a clade-specific vaccine is introduced in SF after a five-year delay it needs 22 years (27 in total) to catch up with a 40% effective vaccine used immediately but only five years (ten in total) to match a 20% effective vaccine (Fig. 4b). Delayed vaccinations with a clade-specific vaccine need shorter time to match the reduction in HIV prevalence of the non-matching vaccine introduced without delay (Fig. 4c & d). Note that when a clade-specific vaccine provides little improvement in protection (50% vs. 40%) it is able to match the reduction in HIV prevalence substantially faster than the reduction in number of infections.

#### 3.2. Replacement Strategy

We find that the replacement strategy allows for additional time to develop a clade-specific vaccine without losing effectiveness (Fig. 5a & b). Assuming no changes in sexual behavior after the vaccine becomes available; the eight-year replacement strategy (light green) is as beneficial as a three-year delayed vaccination strategy (dark blue). The immediate use of a 30% effective vaccine, replaced by a 50% effective vaccine in three years, promises to have the greatest impact on the HIV epidemics in both SF and SA, preventing 10–12% more HIV infections than continuous use of a 30% effective vaccine for the entire 30-year



**Fig. 2.** Projected number of HIV infections over 10, 20 and 30 years in a) South Africa and b) San Francisco. Epidemic projections without vaccine (blue) are compared to scenarios in which 50% effective vaccine is available immediately (red) and vaccination coverage projected in Fig. S1. Bars (whiskers) represent mean (90% uncertainty interval) of the projections generated by 1000 epidemic simulations representative of each epidemic setting. All scenarios assume no changes in sexual behavior due to vaccine use.



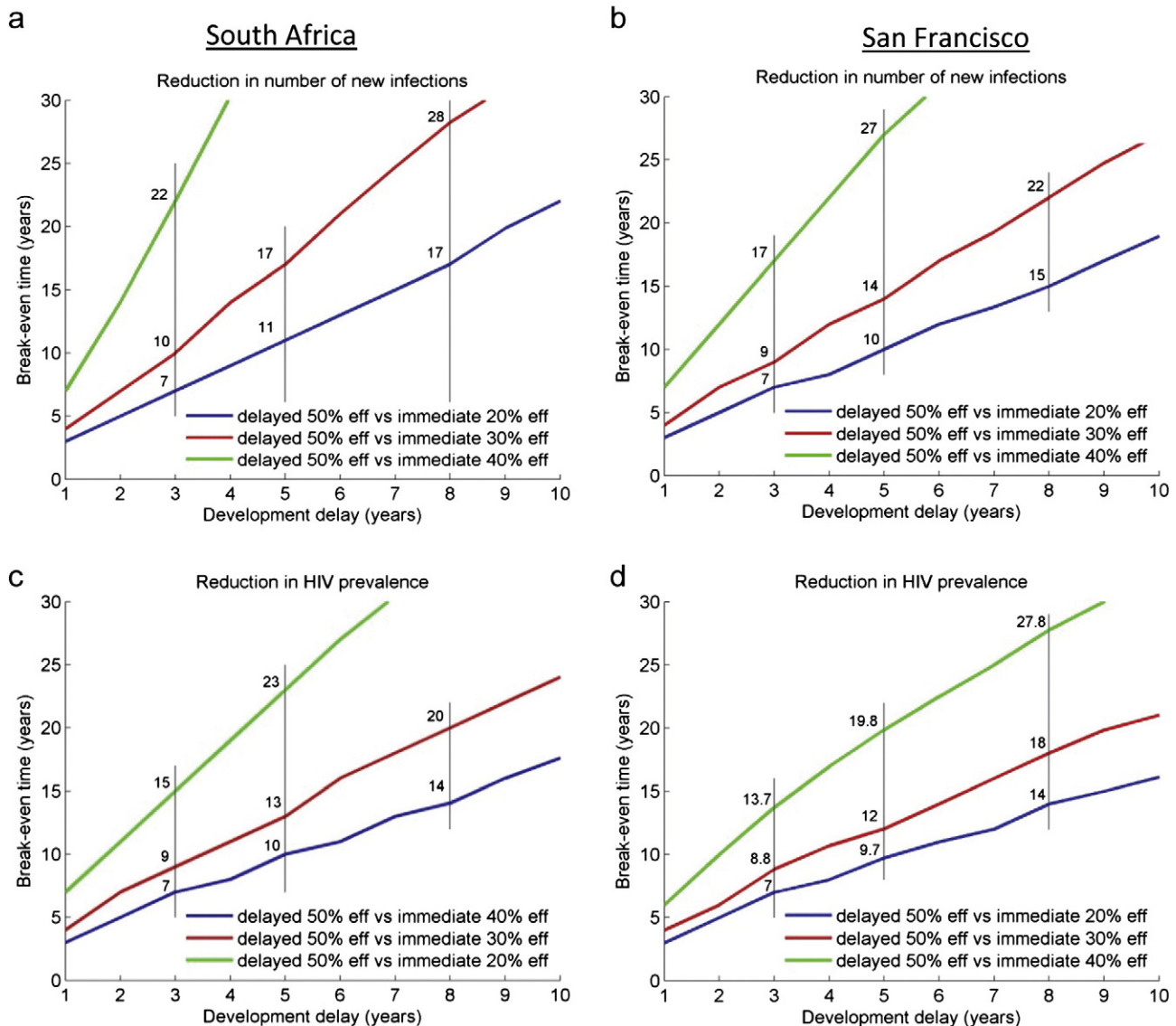
**Fig. 3.** Effectiveness of different vaccine interventions in South Africa (left) and San Francisco (right) measured by a–b) cumulative fraction of HIV infections prevented; c–d) reduction in HIV prevalence and e–f) reduction in HIV incidence over a period of 30 years. Epidemic projections without vaccine (solid black lines) are compared to scenarios in which 20–40% effective non-specific vaccine is available immediately (dashed and dotted black lines) and scenarios in which 50% effective clade-specific vaccine becomes available after a development delay of 3 to 8 years (colored lines). All lines represent median projections generated by 1000 epidemic settings representative of each epidemic setting. All scenarios assume no changes in sexual behavior due to vaccine use.

period (Fig. 5a & b, light blue vs. white). However, reduced condom use by vaccinated individuals may decrease the effectiveness of all vaccination programs and erase the advantage of the replacement strategy (see next section). A comparison of different impact metrics for the immediate, delayed and replacement vaccination strategies over 10, 20 and 30 years assuming no changes in sexual behavior is presented in Table 1. The economic savings based upon just ART cost avoided due to infections prevented over 20 years are shown in Table 2. We

estimate that the immediate vaccination strategy in SA could save between 5.1 and 19.5 billion USD over 20 years. The same strategy could save 0.7–1.1 billion USD in SF over the same period.

### 3.3. Sensitivity Analysis

The reduction in the number of protected sex acts by the vaccinated individuals has strongest impact when a less effective vaccine is



**Fig. 4.** Time needed (break even time) for a 50% effective clade-specific vaccine introduced in South Africa (left) and San Francisco (right) after a development delay of 1 to 10 years to surpass a 20–40% effective non-matched vaccine introduced immediately in a–b) number of new infections prevented and c–d) reduction in HIV prevalence. Mean projections generated by 1000 epidemic settings representative of the HIV epidemic in South Africa and San Francisco. Break-even times are consistent across simulated epidemics with all projections being within 1-year difference from the mean (not shown). All scenarios assume no changes in sexual behavior due to vaccine use.

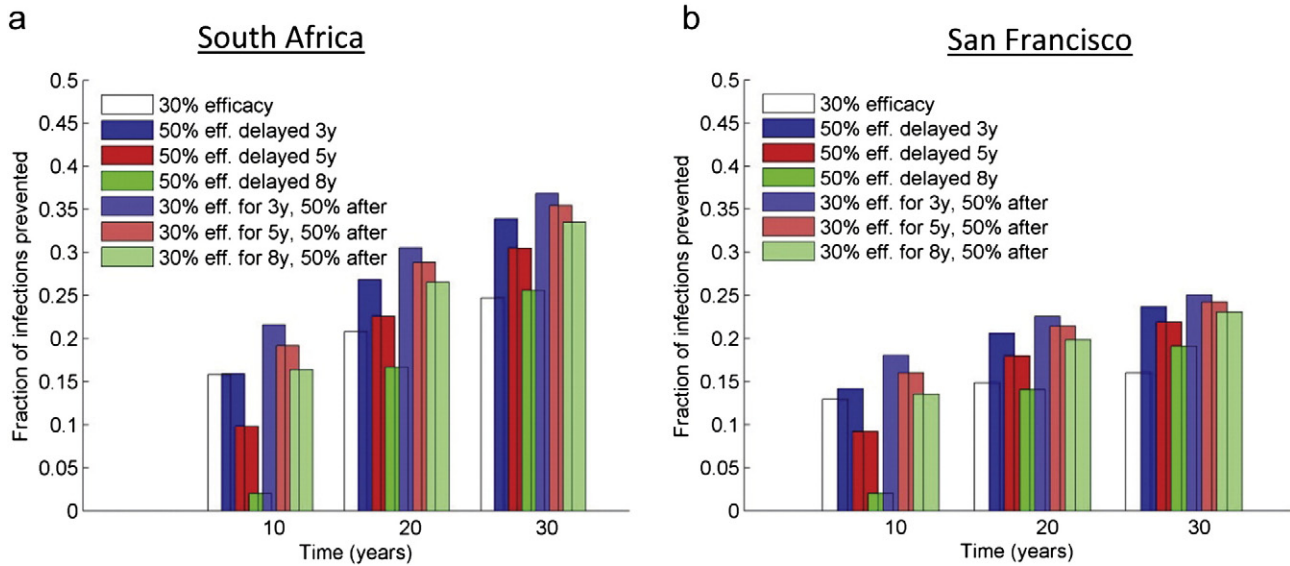
introduced immediately because in those scenarios a highly effective prevention method (condom) is replaced with another with significantly lower protection (vaccine) over long periods of time (Fig. S2 black box plots). For instance, 21% and 38% less infections will be prevented by a 30% effective vaccine over 30 years if vaccinated individuals reduce their condom use by 20% in SA and SF, respectively. The effectiveness of the vaccination will be reduced by 54% in SA and 92% in SF if condom use is half that compared to pre-vaccination with 10% of the simulations in SA and 42% of the simulation in SF projecting negative overall impact. In comparison, five-year delayed intervention with 50% efficacious vaccine will lose only 9% and 22% of its effectiveness in SA due to a 20% and 50% reduction in condom use, respectively (Fig. S2A, red boxes). Note that 50% condom replacement is enough to erase the projected advantage of the replacement over delayed vaccination (Fig. S2, yellow vs. white boxes). This suggests that the use of a vaccine with low efficacy may be justified only if an effort is made to prevent riskier sexual behavior by the vaccines.

Widespread use of ART in a population does not affect the model's conclusion (see Fig. S3). The total number of cases and HIV prevalence

over 30 years may be reduced substantially but the effectiveness of all vaccine regimens is slightly lower and the break-even times between vaccine strategies remain unchanged. Similarly, scenarios assuming improved circumcision coverage among South African males lead to smaller HIV epidemics over 30 years but do not alter the basic differences in vaccine strategies outlined above (see Fig. S4). If the vaccine provides longer protection, the expected reduction of the number of infections and in HIV prevalence is marginally better compared to the scenarios in the main text (see Fig. S5). The projected times needed for delayed clade specific vaccination to break-even with immediate non-matching vaccination in this scenario increased by a year.

#### 4. Discussion

Our model indicates that rapid deployment of a non-clade matched vaccine would be an effective public health strategy for reducing HIV infection in both high risk populations in the US and within a generalized epidemic in sub-Saharan Africa. We demonstrate that despite reductions in vaccine efficacy, a considerable number of HIV



**Fig. 5.** Comparison of immediate, delayed and replacement vaccination strategies. Projected effectiveness in terms of proportion of new infections prevented over 10, 20 and 30 years in a) South Africa and b) San Francisco. The bars represent the median projections generated by 1000 epidemic settings representative of the HIV epidemic in South Africa and San Francisco. All scenarios assume no changes in sexual behavior due to vaccine use.

acquisitions can still be prevented. Our analyses also indicate that the pursuit of large incremental increases (>20%) in vaccine efficacy is justified and will result in better long term effectiveness. Our data suggest that the most effective vaccination strategy is to employ non-clade

matched vaccines in highest risk populations immediately followed by the rapid development of a more effective clade matched prototype. We recognize that HIV vaccine efficacy trials are costly; typically enroll from 2000 to 4000 persons and take 4–5 years to conduct. Such trials

**Table 1**  
Long-term modeling projections of the HIV epidemics in South Africa and San Francisco under different vaccination scenarios.

		Epidemic projections (median [90% UI] <sup>a</sup> )								
		Over 10 years			Over 20 years			Over 30 years		
Strategy		Number of new infections (millions)	HIV prevalence at the end of the period (%)	HIV incidence at the end of the period (%)	Number of new infections (millions)	HIV prevalence at the end of the period (%)	HIV incidence at the end of the period (%)	Number of new infections (millions)	HIV prevalence at the end of the period (%)	HIV incidence at the end of the period (%)
<i>South Africa</i>										
No vaccination		5.20 [5.07–5.32]	15.9 [15.7–16.3]	2.16 [2.09–2.24]	10.4 [10.1–10.7]	14.9 [14.6–15.7]	2.03 [1.95–2.14]	15.5 [15.1–16.1]	14.4 [13.9–15.4]	1.94 [1.86–2.10]
Immediate <sup>b</sup>		4.39	14.0	1.65	8.21	11.4	1.35	11.7	9.7 [9.4–10.4]	1.14
(Effectiveness) <sup>e</sup>		[4.28–4.48] (16%)	[13.8–14.3] (12%)	[1.61–1.71] (24%)	[8.00–8.46] (21%)	[11.2–12.0] (23%)	[1.31–1.43] (33%)	[11.4–12.1] (25%)	[33%]	[1.10–1.24] (41%)
Delayed <sup>c</sup>		4.70	14.4	1.52	8.02	10.6	1.12	10.8	8.0 [7.8–8.6]	0.85
(Effectiveness) <sup>e</sup>		[4.58–4.80] (10%)	[14.3–14.8] (9%)	[1.48–1.57] (30%)	[7.83–8.26] (23%)	[10.3–11.1] (29%)	[1.08–1.18] (45%)	[10.5–11.2] (30%)	(44%)	[0.82–0.92] (56%)
Replacement <sup>d</sup>		4.21	13.5	1.42	7.38	9.9 [9.7–10.4]	1.05	10.0 [9.8–10.4]	7.6 [7.3–8.1]	0.81
(Effectiveness) <sup>e</sup>		[4.11–4.30] (19%)	[13.3–13.8] (15%)	[1.39–1.47] (34%)	[7.20–7.59] (29%)	[34%]	[1.02–1.11] (48%)	(35%)	(47%)	[0.77–0.87] (58%)
<i>San Francisco</i>										
Strategy		Number of new infections (thousands)	HIV prevalence at the end of the period (%)	HIV incidence at the end of the period (%)	Number of new infections (thousands)	HIV prevalence at the end of the period (%)	HIV incidence at the end of the period (%)	Number of new infections (thousands)	HIV prevalence at the end of the period (%)	HIV incidence at the end of the period (%)
No vaccination		8.81 [8.22–9.21]	22.3 [21.8–23.1]	1.64 [1.51–1.74]	18.8 [17.5–19.8]	22.7 [21.7–23.9]	1.66 [1.51–1.79]	29.7 [27.6–31.5]	23.2 [22.0–24.8]	1.69 [1.53–1.85]
Immediate <sup>b</sup>		7.67	21.1	1.37	16.0	20.5	1.33	24.9	20.3	1.31
(Effectiveness) <sup>e</sup>		[7.17–8.02] (13%)	[20.6–21.9] (5%)	[1.26–1.45] (16%)	[14.9–16.9] (15%)	[19.7–21.6] (10%)	[1.21–1.43] (20%)	[23.2–26.4] (16%)	[19.3–21.7] (13%)	[1.19–1.43] (22%)
Delayed <sup>c</sup>		8.00	21.4	1.23	15.4	19.8	1.16	23.2	19.0	1.11
(Effectiveness) <sup>e</sup>		[7.48–8.37] (9%)	[20.8–22.1] (4%)	[1.14–1.31] (25%)	[14.4–16.2] (18%)	[19.0–20.8] (13%)	[1.06–1.25] (30%)	[21.6–24.6] (22%)	[18.1–20.2] (18%)	[1.01–1.21] (34%)
Replacement <sup>d</sup>		7.40	20.8	1.22	14.8	19.5	1.15	22.5	18.8	1.10
(Effectiveness) <sup>e</sup>		[6.92–7.74] (16%)	[20.3–22.5] (7%)	[1.13–1.29] (26%)	[13.8–15.5] (21%)	[18.7–20.5] (14%)	[1.05–1.23] (31%)	[21.0–23.8] (24%)	[17.9–20.0] (19%)	[1.00–1.20] (35%)

<sup>a</sup> Median value and 90% uncertainty interval based on 1 000 simulations of epidemic settings representative for the HIV epidemics in South Africa and San Francisco.  
<sup>b</sup> Intervention with 30% effective non-matching vaccine introduced immediately.  
<sup>c</sup> Intervention with 50% effective clade-specific vaccine introduced after a development delay of 5 years.  
<sup>d</sup> Intervention with 30% effective non-matching vaccine introduced immediately replaced by 50% effective clade-specific vaccine after a development delay of 5 years.  
<sup>e</sup> The effectiveness of each vaccination strategy is measured as a percentage reduction in each metric compared to scenarios with no vaccination.

**Table 2**  
Infections prevented and ART cost averted by different vaccination strategies over 20 years.

Strategy	South Africa			San Francisco		
	Number of new infections prevented (millions)	ART cost avoided in billions USD (low estimate <sup>a</sup> )	ART cost avoided in billions USD (high estimate <sup>b</sup> )	Number of new infections prevented (thousands)	ART cost avoided in billions USD (low estimate <sup>c</sup> )	ART cost avoided in billions USD (high estimate <sup>c</sup> )
Immediate <sup>d</sup>	2.19	5.1027	19.491	2.8	0.7084	1.1256
Delayed <sup>e</sup>	2.38	5.5454	21.182	3.4	0.8602	1.3668
Replacement <sup>f</sup>	3.02	7.0366	26.878	4	1.012	1.608

<sup>a</sup> Based on \$2330 lifetime cost of care for HIV-infected person in South Africa assuming that HIV infection is detected via background screening (on average, every ten years) or with the development of severe opportunistic diseases (Walensky et al., 2011).

<sup>b</sup> Based on \$8900 lifetime cost of care for HIV-infected person in South Africa assuming that need for treatment begins eight years after infection and annual survival on first and second line is assumed to be 92% to 99% depending on the patient's CD4 count at treatment initiation (International AIDS Vaccine Initiative (IAVI), 2012).

<sup>c</sup> Based on \$253,000–\$402,000 lifetime cost of care for HIV-infected person in US, assuming all persons were infected at an average age of 35 years, CD4 count at infection was between 750 and 900 cells/mL and ART initiation for a CD4 count below 500 cells/mL (Farnham et al., 2013).

<sup>d</sup> Intervention with 30% effective non-matching vaccine introduced immediately.

<sup>e</sup> Intervention with 50% effective clade-specific vaccine introduced after a development delay of 5 years.

<sup>f</sup> Intervention with 30% effective non-matching vaccine introduced immediately replaced by 50% effective clade-specific vaccine after a development delay of 5 years.

would be even larger and more costly to demonstrate enhanced efficacy over a 40% effective vaccine and hence achieving maximal effectiveness for developing a clade matched vaccine within 3 years is a formidable hurdle. Developing surrogate markers of protection would greatly enhance the ability to plan, conduct and implement the optimal effectiveness strategy suggested by our model.

Developing an HIV vaccine that would have similar efficacy in all regions of the world and in all high risk groups would be optimal (Corey et al., 2011). Achieving such a goal for antibody mediated vaccination strategies appears at present challenging. Hence our article points to the creation of a mindset that recognizes the benefit of short term, non-clade matched vaccines and the long term advantages of developing an optimal highly effective vaccine (70–90% efficacy). Certainly for both the US and sub-Saharan Africa there is a mind set for developing clade B and C vaccines, respectively. Our analyses suggest that if a candidate HIV vaccine regimen is proven to be effective in a clade-matched population, its subsequent evaluation in a non-matched population should be considered.

Importantly, our analyses indicate that development of reliable surrogate markers of vaccine efficacy (correlates and/or surrogates of protection) would markedly speed the global development of incrementally effective HIV vaccines (Haynes et al., 2012). Efficacy trials of HIV vaccines should be conducted with the operational characteristics, sample collections and funding for defining such biomarkers. It is also possible that enhanced efficacy might be observed in the replacement vaccine in prior vaccinated versus newly vaccinated recipients. This may be especially important if immune escape and hence reduced efficacy to the initial vaccine occurs over prolonged time and use. One of the issues raised by our replacement strategy is the assumption that prior receipt of the non-clade matched vaccine would not reduce the efficacy of the next generation higher efficacy vaccine. We recognize that this may be an issue with some but not all approaches.

The mathematical models used here are simplistic representations of modeled epidemics and as such their projections, although comparable with the results of other modeling studies in similar populations (Gray et al., 2011; Hontelez et al., 2011; Andersson et al., 2011), shouldn't be perceived as comprehensive prediction of the epidemic dynamics over the next 20–30 years of HIV infection in SF or SA. Other simplifying assumptions, integrated in the model may also affect the epidemic projections. For instance, ART of the infected individuals was not modeled separately. It was incorporated indirectly in the model by reducing the average transmission probability per act and increasing the survival time on HIV. These parameters (among other) were selected to represent the observed population and epidemic dynamics. We have focused on modeling stable epidemics, which resemble the epidemics in South Africa and San Francisco. However, alternative scenarios exploring epidemics with decreasing

HIV prevalence and incidence showed similar to our main results (Figs. S3 and S4).

## 5. Conclusions

Our goal was to outline the issues associated with the deployment of what we hope are first generation HIV vaccines, which are likely to be partially effective, of reasonable durability and boostable, and allow predictive evaluation of reduced HIV acquisition over time. HIV is an active field of investigation and as population based therapy of HIV moves forward, some of the absolute numbers we quote may be reduced. However, the concept that emanates from our analyses that immediate deployment of non-clade specific vaccines should be seriously evaluated as an effective public health approach is still operant with other forms of biomedical intervention.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ebiom.2015.11.009>.

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