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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.

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 vaginalor 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.

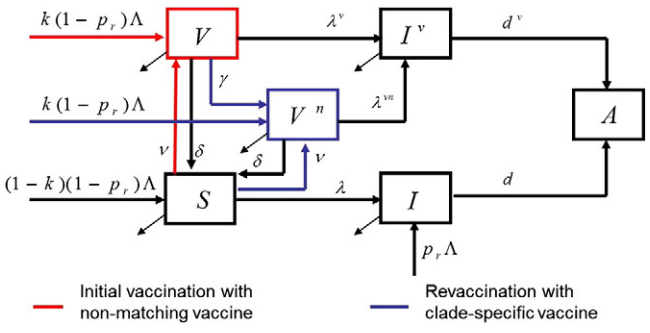

Fig. 1. Flow diagram of the model of HIV transmission under the replacement vaccination strategy. Simulated population is stratified in compartments by HIV and vaccination status as susceptibles (S), susceptibles vaccinated with non-matched (V) or clade-specific vaccines (V^n), HIV-positive who become infected when unvaccinated (I) or vaccinated (I^v), 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 ν) and revaccinations (revaccination rate γ).

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%