Designing HIV Vaccination Policies: Subtypes and Cross-immunity

TRAVIS C. PORCO

San Francisco Department of Public Health
Community Health Epidemiology Section
25 Van Ness Avenue, Suite 710
San Francisco, California 94102

SALLY M. BLOWER

Department of Microbiology and Immunology
University of California, San Francisco
513 Parnassus, Rm HSE 401
Box 0414
San Francisco, California 94143-0414

We developed and used mathematical models to assess vaccine programs for controlling two subtypes of HIV, both for developing countries where more than one subtype is present and for countries where only one subtype is present but other subtypes may invade. We began by formulating a model of the intrinsic transmission dynamics of the two HIV subtypes and then extended this model to include the effects of a prophylactic vaccine that provides a degree of protection against infection by one subtype and vaccine-induced cross-immunity against infection by the second subtype. Using these models, we assessed the potential impact of using a prophylactic vaccine when one subtype of HIV is endemic and a second subtype is introduced into the community. In each case, mass vaccination could result in one of four possible outcomes: (1) both subtypes are eradicated, (2) the endemic subtype persists and the invading subtype is eradicated, (3) the endemic subtype is eradicated and the invading subtype persists, or (4) both subtypes coexist.

The human immunodeficiency virus (HIV) exhibits considerable genetic heterogeneity [Burke and McCutchan 1997; McCutchan, Salminen et al. 1996; Saag et al. 1988]. The first of two major types of HIV, HIV-1, is of worldwide dis-

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tribution and is responsible for the global pandemic; the second major type, HIV-2, occurs almost exclusively in Africa. Construction of phylogenetic trees from DNA sequences from isolates of HIV-1 has led to the recognition of over 15 subtypes (or clades), where each subtype is composed of a multitude of variants (or strains); isolates assigned to a particular subtype are considered to be more closely related to other isolates of the same subtype, though considerable variability exists among variants of a given subtype [Fisher et al. 1988; Hu et al. 1996; Kuiken et al. 1993; Rojas et al. 1994].

Most HIV infections in the world are caused by only five of the subtypes of HIV-1 [Burke and McCutchan 1997]; these subtypes differ significantly in their geographic distributions. In most developed countries, only a single subtype—subtype B—predominates, while in many developing countries, at least two subtypes are cocirculating (such as subtypes B and E in Thailand [McCutchan, Hegerich et al. 1992; WHO 1994] or subtypes A and D in Uganda [Sánchez-Palomino et al. 1995; WHO 1994]). Recent evidence suggests that some of the HIV-1 subtypes differ from each other in their cell tropisms and transmission efficiencies [Kunanusont et al. 1995; Mastro et al. 1994; Soto-Ramirez et al. 1996].

This genetic heterogeneity complicates efforts to develop effective HIV vaccines [Bloom 1996; Grady and Kelly 1996; Kalish et al. 1995; Mascola, Louwagie et al. 1994; Rowe 1996; Verani et al. 1993] and suggests that HIV vaccines should be developed that will be effective against more than one subtype. To date, several candidate vaccines have been developed based on a single subtype, subtype B [Cohen 1994; Levy 1996]. These vaccines did not prove effective against new isolates of the same subtype [Mascola, Snyder et al. 1996], and current efforts are underway to design vaccines that are effective against other isolates of the same subtype and across subtypes. Recent evidence suggests that vaccines that induce cross-immunity between subtypes may be possible (for example, Ferrari et al. [1997]).

Mathematical models have been developed and used to assess vaccine programs for controlling HIV transmission when only a single subtype is circulating in a community [Blower and McLean 1994, 1995; McLean and Blower 1993, 1995]. However, we need to consider the case of controlling more than one subtype, both for developing countries where more than one subtype is present and for countries where only one subtype is present but other subtypes may invade. We extended the earlier models to assess the control of two subtypes of HIV by vaccination. We began by formulating a model of the intrinsic transmission dynamics of two HIV subtypes in a homosexual community and then extended this model to include the effects of a prophylactic vaccine that provides a degree of protection against infection by one subtype and vaccine-induced cross-immunity against infection by the second subtype.

Using these models, we assessed the potential epidemiological impact of use of a prophylactic vaccine when one subtype of HIV is endemic and a second subtype is introduced into the community. Using the basic reproductive number of the subtype

as a measure of evolutionary fitness, we considered the case of invasion by a subtype that has a higher fitness than the endemic subtype and also the case of invasion by a subtype that has a lower fitness than the endemic subtype. We show that in each case, mass vaccination could result in one of four possible outcomes: (1) both subtypes are eradicated, (2) the endemic subtype persists and the invading subtype is eradicated, (3) the endemic subtype is eradicated and the invading subtype persists, or (4) both subtypes persist indefinitely, approaching a coexistence equilibrium. We derived analytical criteria that specify the conditions for which each of these outcomes is to be expected, and we simulated the temporal dynamics for illustrative special cases.

A Model of the Intrinsic Transmission Dynamics of Two HIV Subtypes

We first formulated a model of the intrinsic transmission dynamics of two HIV subtypes in a homosexual community (Figure 1, Appendix). In this model, individuals are part of a community of potential sexual partners. Individuals enter this community at a constant rate (for brevity, we refer to this as the *inflow rate*); individuals leave the community at a constant per capita rate when they cease acquiring new sexual partners (for brevity, we refer to the rate at which individuals leave the sexually active community as the *rate of sexual attrition*). The model projects the number of susceptibles, the number of individuals in the community who are infected with either of two subtypes but who have not developed AIDS, and the number of individuals who have developed AIDS as a result of each of the two subtypes. We assume that individuals with AIDS do not acquire new sex partners, so that the total size of the sexually active community is the sum of the number of susceptibles, the number of individuals infected by subtype 1 who have not progressed to AIDS, and the number of individuals infected by subtype 2 who have not progressed to AIDS. The total community size is then the size of the sexually active community plus the number of individuals who have AIDS.

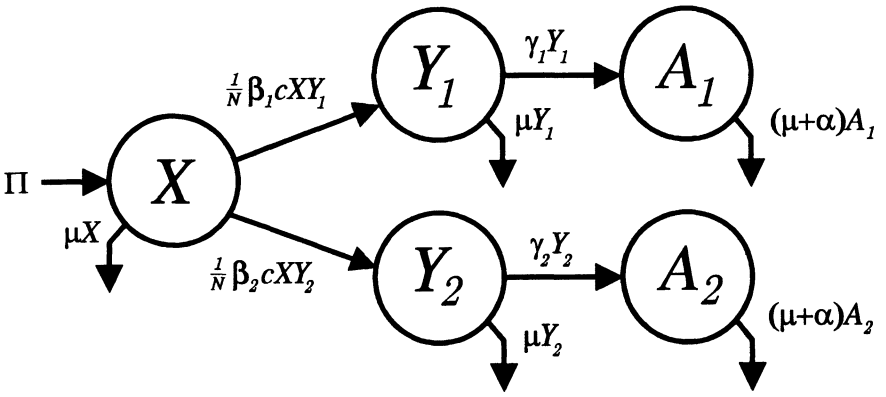

Figure 1: In this flow diagram of the two-subtype model without vaccination, X—susceptibles, Y_1—infective individuals who are infected by subtype 1, Y_2—infective individuals who are infected by subtype 2, A_1—individuals with AIDS caused by subtype 1, A_2—individuals with AIDS caused by subtype 2.

Individuals, including infectives of both subtypes, in the sexually active community acquire new sexual partners, infective or susceptible, randomly from this community at a constant rate per unit time. Infectives transmit the infection to susceptible partners with a given probability per partnership. The number of new partners per unit time, times the probability of transmission per partnership, will be called the *effective contact rate;* it is the number of new infections per unit time that a single infective will cause in an otherwise completely susceptible population. When the population is not completely susceptible, the number of new infections per unit time that each infective causes is the effective contact rate times the probability that a partner is a susceptible. The number of new infections per unit time that each infective causes times the number of infectives then gives the incidence of infection—the number of new infections per unit time in the population as a whole [Anderson and May 1991; Kermack and McKendrick 1927].

We formulate the equations (shown in the appendix) for the instantaneous rate of change of each of the state variables of the model as follows: The instantaneous rate of change of the number of susceptibles is the rate of arrival of new susceptibles, minus the rate of sexual attrition, minus the incidence of infection by each subtype. The instantaneous rate of change in the number of individuals infected with each subtype is the incidence of new infections minus the rate of sexual attrition and the rate of progression to AIDS. We assume that individuals infected by one subtype do not become infected at a later stage by the other subtype. Although coinfection by two subtypes has been observed [Artenstein et al. 1995], the epidemiological significance of this process is currently unknown. Recent empirical evidence that infection by HIV-2 provides a degree of protection against infection by HIV-1 [Travers et al. 1995] suggests that a high degree of natural cross-immunity at the level of the subtype is plausible. Finally, the instantaneous rates of change of the number of AIDS cases due to each subtype are given by the rate of progression to AIDS minus the rate of sexual attrition and the total death rate from AIDS. Finally, we calculate the prevalence rate of disease due to a subtype at any given time as the fraction of the total community that has AIDS as a result of that subtype. The prevalence rate of infection due to each subtype is defined as the fraction of the total community size that is infected by the given subtype.

Reproductive Numbers for the Two-Subtype Model Without Vaccination

We derive two reproductive numbers for each subtype, the basic reproductive number and the invasion reproductive number.

The *basic reproductive number* of a subtype is defined as the average number of secondary cases that will be produced by a single infective, who is infected with that subtype, when the entire community is susceptible [Anderson and May 1991; MacDonald 1957]; it is given by the effective contact rate times the duration of infectivity. If an infective individual who is infected with a given subtype is introduced into the community, then that subtype will become established if and only if

the basic reproductive number for that subtype exceeds one; that is, the initial infective individual must be expected to produce more than one new infective in the population before the initial infective dies or otherwise ceases to transmit the infection. According to Equation (8) given in the appendix, the value of the basic reproductive number equals the average length of time that an individual is infectious multiplied by the number of new infections that individual will cause per unit time. If the basic reproductive number is greater than one, and only subtype 1 is introduced into the community, then subtype 1 will become established and eventually an endemic equilibrium will be reached (appendix) with the proportion of susceptible individuals given by the reciprocal of the basic reproductive number.

However, if an individual infected by the second subtype is introduced when the first subtype has attained equilibrium, then the second subtype can increase only if the initial infective (infected with subtype 2) can cause at least one new infection (due to subtype 2) on average. We define the *invasion reproductive number* of subtype 2 when subtype 1 is at equilibrium to be the average number of new infections caused by a single individual infected with the second subtype, when the first subtype is at equilibrium in the community. In the appendix, we show that the invasion reproductive number of subtype 2 at the equilibrium of subtype 1 is given by the basic reproductive number of subtype 2 multiplied by the proportion of the population that remains susceptible at the equilibrium of subtype 1; this in turn equals the basic reproductive number of subtype 2 divided by the basic reproductive number of subtype 1. Since the first subtype is at equilibrium, fewer individuals are available for the second subtype to infect; the number of susceptibles is smaller than at the no-disease equilibrium, and so the number of new infections that a subtype-2 infective can cause is reduced by the same factor from its value at the no-disease equilibrium.

For this model, which does not include vaccination, the invasion condition for subtype 2 when subtype 1 is at equilibrium is that the invasion reproductive number of subtype 2 when subtype 1 is at equilibrium is greater than one; this condition is equivalent to the condition that the basic reproductive number of subtype 2 is greater than that of subtype 1. Thus, if subtype 2 has a larger basic reproductive number than subtype 1, subtype 2 will eventually replace subtype 1; if subtype 2 has a smaller basic reproductive number than subtype 1, subtype 2 will eventually be replaced by subtype 1. Equilibrium coexistence of the competing subtypes is not possible unless the basic reproductive numbers are exactly equal. Since the subtype with the largest basic reproductive number competitively excludes the other, maximization of the basic reproductive number is an evolutionary stable strategy. We use the basic reproductive number as a measure of evolutionary fitness (as others have done, for example, Anderson and May [1991]), so that we say that a subtype that has a higher basic reproductive number in a given community than another subtype has a higher fitness than the other subtype.

Temporal Dynamics for the Two-Subtype Model Without Vaccination

We considered the temporal dynamics that result from the introduction of two subtypes into a community at different times. While the analytical threshold expression (Equation (8)) determines the long-term outcome, the realization of this long-term outcome may require decades. We numerically simulate the model for particular parameter values (Table 1) to determine how the time delay in introducing the subtype with the higher fitness affects the temporal dynamics. Figure 2 shows five different scenarios for the prevalence rate of infection for hypothetical subtypes 1 and 2 for the first 80 years after subtype 1 is introduced. In all five scenarios, the basic reproductive number of subtype 1 is 3.04 and the basic reproductive number of subtype 2 is 4.72; thus subtype 2 eventually eradicates subtype 1 (the prevalence rate of subtype 2 approaches a positive equilibrium value and the prevalence rate of subtype 1 will approach zero). In each scenario, one infective individual with subtype 2 is introduced at a different time (10, 15, 20, 25, or 30 years after subtype 1 is introduced); but all of the other parameters remain the same in all five scenarios.

It may take many decades for the subtype with the higher fitness (subtype 2) to reduce the prevalence rate of infection by subtype 1 to very low levels, and the longer the time delay in introducing subtype 2, the longer it will take for subtype 2 to predominate. Even though the more fit subtype will eventually exclude the less fit subtype, the two subtypes will continue to cocirculate for many decades. If subtype 2 is introduced 10 years after subtype 1, the

Symbol	Interpretation	Parameter Values	
Π	Number of new individuals added to community per unit time	2,000 per year	McLean and Blower 1993
$1/\mu$	Average amount of time a person acquires new sexual partners from the community	32 years	McLean and Blower 1993
β_i	Transmission probability of subtype i per partnership	~0.05–0.1	McLean and Blower 1993; Grant et al. 1987
c	Rate of acquisition of new sexual partners	3–6 per year	McLean and Blower 1993; Grant et al. 1987
$1/\gamma_i$	Average time of asymptomatic period	10 years	McLean and Blower 1993
$1/\alpha$	Average survival time with AIDS	2.5 years	McLean and Blower 1993
p	Vaccination coverage level	0–1	
e	Vaccine take	0–1	
ζ_i	Degree of protection against infection by subtype i	0–1	

Table 1: The model parameter values are derived from probability samples of gay men in San Francisco [Grant, Wiley, and Winkelstein 1987; Osmond et al. 1994].

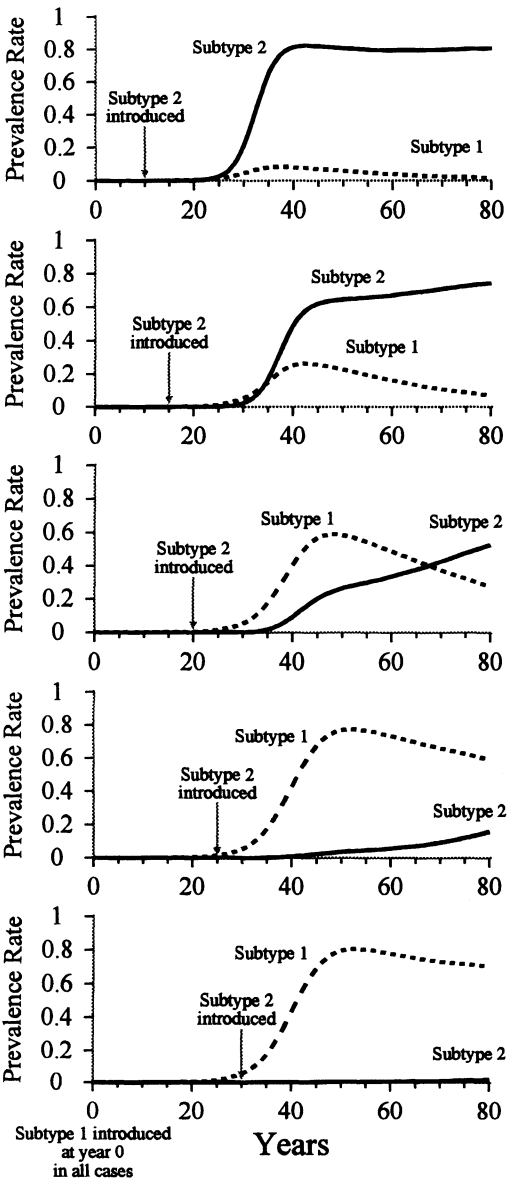

Figure 2: Prevalence rate of HIV infection for the two subtypes for 80 years after the introduction of subtype 1 varies it the more fit subtype 2 is introduced 10, 15, 20, 25, or 30 years afterwards. The parameter values are as follows: the rate of sexual attrition is $\frac{1}{32}$ per year, the inflow rate is 2,000 persons per year, the rate of progression to AIDS is 0.1 per year, the effective contact rate of subtype 1 is 0.4, and the effective contact rate of subtype 2 is 0.62.

initial rise in infection (and hence also of AIDS cases) will be largely due to subtype 2, with subtype 1 never causing more than a small fraction of the infections (see Figure 2). If subtype 2 is introduced 15 years after subtype 1, subtype 1 very briefly causes more infection than subtype 2 in the early years of the epidemic but will be overtaken by subtype 2 at approximately year 35; if subtype 2 is introduced 20 or 25 years after subtype 1, most of the initial rise in infection will be due to subtype 1. If subtype 2 is introduced 30 years after subtype 1, subtype 2 will not make an appreciable contribution to the epidemic even after 80 years; but by year 134 (not shown) the prevalence rate of infection caused by subtype 2 will equal that caused by subtype 1. The temporal dynamics also depend upon the number of infectives that initiate the epidemic; for instance, introducing 100 infectives of subtype 2 at year 30 (rather than a single infective) will accelerate the rise of subtype 2 by nearly six decades (results not shown).

Vaccine Model with Cross-immunity

We generalized the model presented in the previous section to include the effects of vaccination with a prophylactic vaccine (Figure 3, appendix, Table 1). We assumed that a fraction of the individuals entering the sexually active community are vaccinated and that a protective immune response is induced by the vaccine (that is, the vaccine takes) in a fraction of these vaccinated individuals. The fraction of individuals who are effectively vaccinated then is the product of the fraction of individuals who are vaccinated and the fraction of vaccinated individuals in whom the vaccine takes. Uninfected individuals

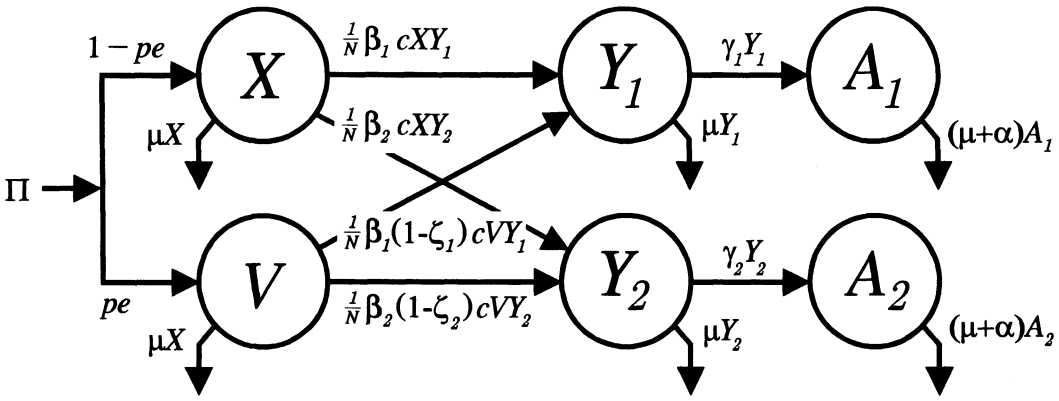

Figure 3: In this flow diagram for the two-subtype vaccine model, effectively vaccinated individuals receive a degree of protection ζ_i against subtype *i*. *X*—completely susceptible individuals, *V*—effectively vaccinated individuals, Y_1—infective individuals who are infected by subtype 1, Y_2—infective individuals who are infected by subtype 2, A_1—individuals with AIDS caused by subtype 1, A_2—individuals with AIDS caused by subtype 2.

who were either not vaccinated or who were vaccinated but in whom the vaccine did not take will be referred to as being completely susceptible. In this model then, we simulated the number of effectively vaccinated individuals over time in addition to the number of individuals who are completely susceptible, the number of individuals who are infected with each subtype but who have not yet developed AIDS, and the number of individuals with AIDS.

We assumed that an effectively vaccinated individual is less likely to be infected by one of the subtypes than a completely susceptible individual. The degree of protection that the vaccine confers against infection in the individuals who are effectively vaccinated is between zero and one, with zero corresponding to no protection, and one corresponding to a vaccine that completely prevents infection in effectively vaccinated individuals who are exposed to a given subtype. This model of the transmission dynamics of two subtypes in the presence of vaccination can be interpreted in two ways: (a) assuming that the vaccine has been developed against one of the two subtypes (subtype 1 without loss of generality), so that the degree of protection against subtype 1 represents the direct protection conferred by the vaccine, and the degree of protection against subtype 2 represents the degree of vaccine-induced cross-immunity against infection by the second subtype, or (b) assuming that the vaccine has been developed against a third subtype, so that, in this case, both the degrees of protection against subtype 1 and subtype 2 represent vaccine-induced cross-immunity. For example, when considering a vaccine developed against subtype B, the first interpretation (interpretation (a)) could be used to assess the effects of a vaccine campaign in Thailand (where subtypes B and E are cocirculating), and the second interpretation (interpretation (b)) could be used to assess the effects of a vaccine campaign in Uganda (where subtypes A and D are

cocirculating). For definiteness, we base the following discussion on the first of these interpretations.

In the vaccination model, the instantaneous rate of change of the number of completely susceptible individuals is the same as in the model without vaccination presented in the previous section, except that only the noneffectively vaccinated fraction of the individuals entering the community per unit time is completely susceptible. The instantaneous rate of change of the number of effectively vaccinated individuals is the rate at which new individuals enter the community multiplied by the fraction of these individuals who are effectively vaccinated minus the rate at which individuals leave the community due to sexual attrition and the rate at which individuals become infected with either subtype 1 or subtype 2. The instantaneous rate of change of the number of individuals infected with subtypes 1 or 2 is given by the sum of the incidence of infections from both the class of completely susceptible individuals and the class of effectively vaccinated individuals, minus the rate of sexual attrition and the rate of progression to AIDS. Finally, the instantaneous rates of change of the number of AIDS cases due to each subtype are the same as given in the previous section.

Reproductive Numbers

We derived two reproductive numbers for each subtype in the vaccine model (as we did previously for the model without vaccination); for the vaccine model, the two reproductive numbers are the vaccinated reproductive number and the vaccinated invasion reproductive number.

The *vaccinated reproductive number* of a subtype when a given fraction of the community is vaccinated is defined as the average number of secondary cases produced by a single infective at the no-disease equilibrium in the presence of a vaccination campaign [McLean 1995]. Vaccination will eradicate a subtype whenever the vaccinated reproductive number of that subtype is less than one (appendix). The vaccinated reproductive number consists of two terms; the first is the basic reproductive number multiplied by the fraction of the community that is completely susceptible; this term represents the contribution from the completely susceptible individuals. The second term is the basic reproductive number times the fraction effectively vaccinated, multiplied by the relative risk of infection of an effectively vaccinated individual; this term represents the contribution made by the effectively vaccinated individuals, where their degree of protection against infection by a particular subtype is specified. Equation (18) in the appendix shows that the vaccinated reproductive numbers depend on the basic reproductive number, the vaccine coverage level, and on three characteristics of the vaccine: the take, the degree of protection against infection by subtype 1, and the degree of vaccine-induced cross-immunity against infection by subtype 2. Therefore Equation (18) shows that as the basic reproductive number of the subtype increases, greater coverage levels, higher degrees of protection against infection by subtype 1, and higher levels of vaccine-induced cross-immunity against infection by subtype 2 will be needed to eradicate HIV.

We defined the *vaccinated invasion repro-*

ductive number of subtype 1 at the equilibrium of subtype 2 to be the average number of secondary infections of subtype 1 that an initial infective would cause when introduced into a community in which subtype 2 is at equilibrium and when a vaccination campaign is in place. When subtype 2 is at equilibrium in a community, the fraction of completely susceptible individuals and the fraction of effectively vaccinated individuals remain constant over time, and are the host resources available for subtype 1 if subtype 1 is introduced. Exactly analogous to the expression for the vaccinated reproductive number, the vaccinated invasion reproductive number of subtype 1 when subtype 2 is at equilibrium is given by the sum of the completely susceptible fraction and the effectively vaccinated fraction times the relative risk for infection by subtype 1 in an infected individual, all multiplied by the basic reproductive number of subtype 1 (appendix). An analogous expression holds for the vaccinated invasion reproductive number for subtype 2 at the equilibrium of subtype 1.

Using the expressions for the vaccinated reproductive number and for the vaccinated invasion reproductive number, we find that four equilibrium outcomes are in general possible: eradication, persistence of subtype 1, persistence of subtype 2, and coexistence of both subtypes. In general, which outcome will occur will depend upon the basic reproductive numbers of each subtype, specific characteristics of the vaccine and the achieved coverage level (appendix). Figure 4 shows a numerical example of the four possible equilibrium outcomes that can occur as the result of mass vaccination when an endemic subtype is at equilibrium and a less fit subtype is introduced (the basic reproductive number of subtype 1 is 3.15, and the basic reproductive number of subtype 2 is 2.36); Table 2 gives the mathematical conditions under which these outcomes occur. Figure 5 shows temporal dynamics of four scenarios, each of which illustrates one of the four possible outcomes, based on the same parameters used in Figure 4. The temporal dynamics are shown beginning at time 0, when subtype 1 is at an endemic equilibrium and subtype 2 is introduced at year 0; mass vaccination occurs at year 5 and continues thereafter.

Eradication of Both Subtypes

When the vaccinated reproductive number is less than one for both subtypes, then both subtypes will be eradicated, as shown in the black region in Figure 4. Eradication will be possible only if a vaccine has a high take, induces a high degree of cross-immunity, and is applied at a high coverage level. Figure 5B shows a temporal sequence leading to eradication; here the fraction that is effectively vaccinated (which is calculated as the product of take and coverage) is 0.9, and the vaccine-induced cross-immunity is 0.9. In this scenario, the endemic subtype is eradicated, and the invading subtype 2 never causes any appreciable level of disease.

Persistence of the Invading Subtype Only

The mathematical condition that results in this outcome is given in Table 2 and discussed in the appendix. Only the invading subtype will persist if the fraction effectively vaccinated is moderate to high and the degree of vaccine-induced cross-

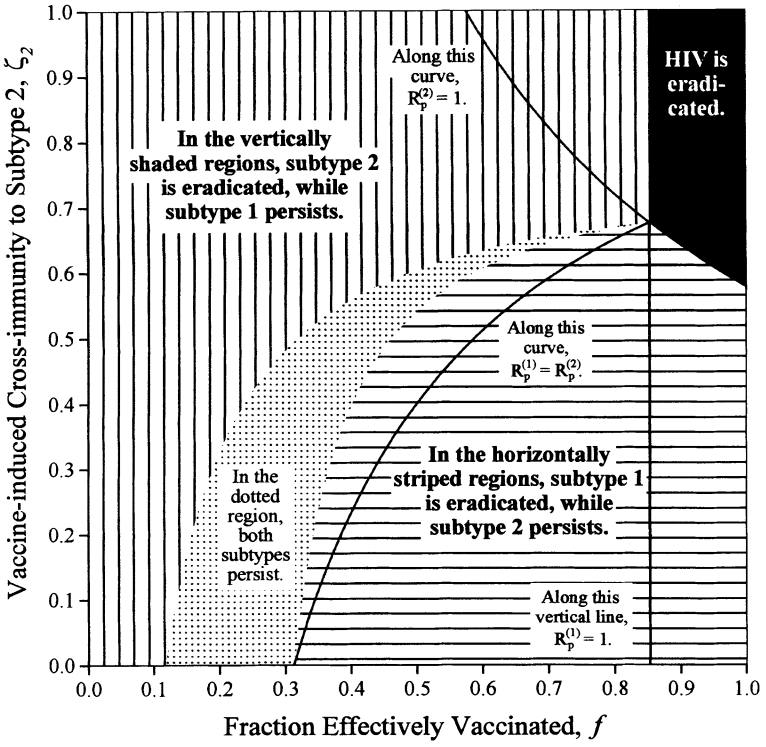

Figure 4: The long-term outcome of a vaccination policy with effective coverage level f and degree of protection ζ_2 against subtype 2 is shown by the shading at each point; dots indicate that both subtypes coexist, vertical stripes indicate that only subtype 1 persists, horizontal stripes indicate that only subtype 2 persists, and black indicates that neither subtype persists (Table 2). In this figure, the degree of protection against the endemic subtype, subtype 1, is 0.8; the basic reproductive number of subtype 1 is 3.15, and the basic reproductive number of subtype 2 is 2.36, so that subtype 2 is less fit than subtype 1. The vertical axis is the degree of cross-immunity that the vaccine induces against the less fit subtype 2; the horizontal axis is the fraction f effectively vaccinated, which is calculated as the product of the take and the coverage.

$R_p^{(1)}$	$R_p^{(2)}$	$R_p^{(1:2)}$	$R_p^{(2:1)}$	Outcome	Shade in Figure 3
$R_p^{(1)} < 1$	$R_p^{(2)} < 1$	any	any	Both subtypes eradicated.	Black
$R_p^{(1)} > 1$	$R_p^{(2)} < 1$	any	any	Only subtype 1 persists.	Vertical
$R_p^{(1)} < 1$	$R_p^{(2)} > 1$	any	any	Only subtype 2 persists.	Horizontal
$R_p^{(1)} > 1$	$R_p^{(2)} > 1$	$R_p^{(1:2)} > 1$	$R_p^{(2:1)} < 1$	Only subtype 1 persists.	Vertical
		$R_p^{(1:2)} < 1$	$R_p^{(2:1)} > 1$	Only subtype 2 persists.	Horizontal
		$R_p^{(1:2)} > 1$	$R_p^{(2:1)} > 1$	Both subtypes persist.	Dotted

Table 2: Outcomes of vaccination model for Figure 4.

immunity is low. This outcome would occur because such a vaccine would provide little protection against invasion by subtype 2 yet would provide sufficient protection against infection by subtype 1. Figure 5D shows a temporal sequence in which

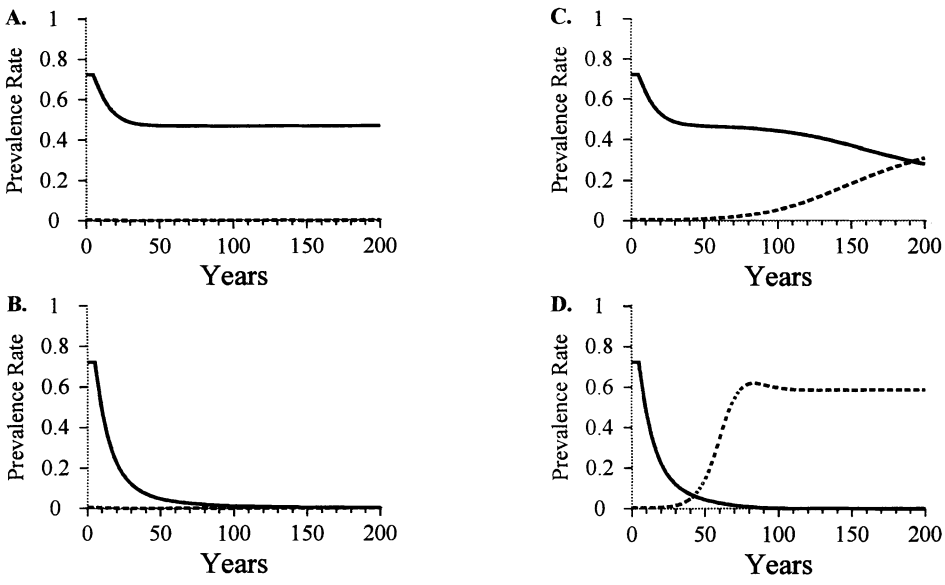

Figure 5: This figure shows the prevalence rate of HIV due to each subtype following a vaccination campaign. Each scenario begins with subtype 1 at endemic equilibrium, and the less fit subtype 2 is introduced at year 0; mass vaccination begins at year 5. In each scenario, the degree of protection against subtype 1 is 0.8, the rate of sexual attrition is $\frac{1}{32}$, the inflow rate is 2,000 persons per year, the effective contact rate of subtype 1 is 0.4133, the effective contact rate of subtype 2 is 0.31, the rate of development of AIDS is 0.1 per year, the vaccine take is 1, and the AIDS death rate is 0.4 per year; the basic reproductive number of subtype 1 is 3.15 and the basic reproductive number of subtype 2 is 2.36. A. Effective coverage level $f = 0.3$, degree of protection against the second subtype $\zeta_2 = 0.9$. B. Effective coverage level $f = 0.9$, degree of protection against the second subtype $\zeta_2 = 0.9$. C. Effective coverage level $f = 0.3$, degree of protection against the second subtype $\zeta_2 = 0.1$. D. Effective coverage level $f = 0.9$, degree of protection against the second subtype $\zeta_2 = 0.1$.

subtype 2 displaces subtype 1; in this scenario, the fraction effectively vaccinated is 90 percent and the vaccine-induced cross-immunity against infection by subtype 2 is 10 percent.

Both Subtypes Coexist

The mathematical condition that results in this outcome is given in Table 2 and discussed in the appendix. Both subtypes will coexist only if a low to moderate fraction are effectively vaccinated and the vaccine induces a low level of cross-immunity. In this case, the vaccine cannot eradicate either subtype, but it controls the first subtype enough to allow subtype 2 to invade. Figure 5C shows a scenario is shown in which a coexistence equilibrium is approached (however, it will take several hundred more years to reach this equilibrium); in this scenario, the fraction effectively vaccinated is 0.3 and the degree of vaccine-induced cross-immunity is 0.1.

Persistence of the Endemic Subtype Only

As in the other cases, we give the mathematical conditions that result in this outcome in Table 2 and discuss them more fully in the appendix. An effective vaccination program that utilizes a vaccine that induces high levels of cross-immunity and that results in a moderate to high fraction

effectively vaccinated would allow only the endemic subtype to persist. This outcome occurs because the vaccine exerts much greater control on the invading subtype than on the endemic subtype. Figure 4 also shows that an ineffective vaccination program that results in a low fraction effectively vaccinated (with a vaccine that induces any level of cross-immunity) would also allow only the endemic subtype to persist. This outcome occurs because subtype 2 is less fit than the endemic subtype and the ineffective vaccination program has little impact on the endemic subtype. Figure 5A shows a scenario in which subtype 1 persists and subtype 2 cannot invade; the fraction that is effectively vaccinated is 30 percent and the vaccine induces 90 percent cross-immunity. Although subtype 1 is not eradicated, the vaccination program reduces the seroprevalence rate due to subtype 1 from 73 percent to 45 percent.

Figure 6 is similar to Figure 4, except

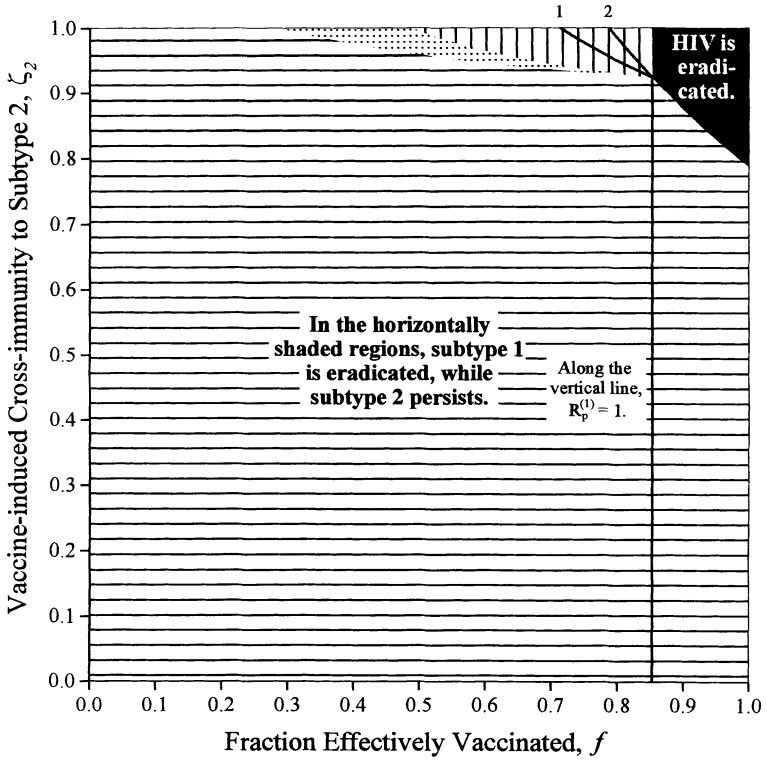

Figure 6: The long-term outcome of a vaccination policy with effective coverage level f and degree of protection against subtype 2 ζ_2 is shown by the shading at each point; in the dotted region, long-term coexistence occurs, and in the vertically striped region, subtype 1 excludes subtype 2. Along the curve labeled 1, each subtype has the same vaccinated reproductive number. Along the curve labeled 2, the vaccinated reproductive number of subtype 2 equals 1, so that above this curve, subtype 2 would be eradicated even in the absence of subtype 1. For this figure, the degree of protection against subtype 1 is 0.8; the basic reproductive number of subtype 1 is 3.15 and the basic reproductive number of subtype 2 is 4.72, so that subtype 2 is more fit than subtype 1.

that Figure 6 shows the four possible equilibrium outcomes that can occur due to mass vaccination if the introduced subtype has a greater fitness than the endemic subtype (the basic reproductive number of subtype 1 is 3.15 and the basic reproductive number of subtype 2 is 4.72, with all other parameters the same as in Figure 4). Although all four equilibrium outcomes are still possible, under a wide range of conditions, the more fit subtype will competitively replace the endemic subtype. Because the invading subtype has a higher basic reproductive number (higher fitness) than the invading subtype in Figure 4, a higher fraction of susceptibles must be effectively vaccinated and the vaccine must induce a greater degree of cross-immunity if HIV is to be eradicated.

Discussion

We developed mathematical models of homosexual transmission of two subtypes of HIV, in the presence and absence of a vaccination campaign. In these models, we assumed that natural cross-immunity is complete; at this time, the true degree of subtype-specific cross-immunity to reinfection is not known. Although coinfection by two subtypes has been observed in some studies [Artenstein et al. 1995], the epidemiological significance of this process is currently unknown. The partial protection that HIV-2 infection provides against HIV-1 infection [Travers et al. 1995] suggests that a substantial degree of natural cross-immunity at the level of the subtype is a possibility. We also assumed that the two subtypes have different probabilities of sexual transmission per partnership; recent evidence suggests that some of the HIV-1 subtypes may indeed have different transmission efficiencies [Kunanusont et al. 1995; Mastro et al. 1994; Soto-Ramirez et al. 1996]. Evidence that HIV-1 and HIV-2 differ in their efficiency of sexual transmission (and also cause disease to progress at different rates) [Kanki et al. 1994; Marlink et al. 1994; Mertens and Piot 1997; Travers et al. 1995] further suggests the possibility that HIV-1 subtypes may possess different biological properties (though HIV-1 and HIV-2 are more distantly related each other than any two subtypes of HIV-1 are related to each other). When an effective vaccine becomes available, quantitative design of a specific vaccination strategy in a particular location would require including additional refinements, such as partial natural cross-immunity among subtypes, heterogeneity in sexual activity, nonrandom sexual mixing, and several different subtypes. We designed our model to assess the use of a prophylactic vaccine when the subtypes have different transmissibilities, but these models can also be straightforwardly extended to include the possibility that the incubation period is different for different subtypes and other mechanisms of vaccine action (such as vaccine-induced transmissibility reduction and a limited duration of vaccine protection). However, our models are not applicable for designing vaccination strategies against the many different variants within any given subtype.

In the absence of vaccination, our models show that the number of individuals infected with any subtype will approach zero if the basic reproductive number of that subtype is less than one. If the basic reproductive number of both subtypes is greater than one, then in the absence of

vaccination, the subtype with the largest basic reproductive number will eventually exclude the other. However, this competitive exclusion takes place slowly, and according to our models, two subtypes can continue to cocirculate for many decades; thus, the predictions of our models are consistent with the observed cocirculation of more than one subtype in many countries. In fact, in some countries, such as Thailand, the subtypes are at present largely found in different risk groups [Ou et al. 1993], so that determining how long it would take for competitive exclusion to occur would require a model that explicitly included the different risk groups.

In the presence of vaccination, the analysis revealed that in order to eradicate both subtypes (that is, to eradicate the endemic subtype and to prevent a second subtype from invading) it is necessary for the vaccine to be sufficiently efficacious and for the vaccine coverage levels to be high enough to eradicate each subtype independently. Our analysis shows that the interaction between the two subtypes plays no role in the eradication criterion, and thus a vaccine must induce high levels of cross-immunity between subtypes to eradicate HIV. Our results suggest further that HIV eradication is likely to take decades.

In general, the vaccination model yields four possible outcomes: (1) both subtypes are eradicated, (2) only the endemic subtype is eradicated, (3) only the invading subtype is eradicated, and (4) neither subtype is eradicated and the two subtypes permanently coexist. Thus, when mass vaccination is unable to eradicate the two subtypes, it may nevertheless alter the competitive dynamics between the subtypes (as McLean [1995] showed for vaccination against two strains of measles virus). In the case of invasion by a less fit subtype against which the vaccine is less effective, long-term coexistence of the two subtypes or the replacement of the endemic subtype by the invading subtype is possible if the vaccine-induced cross-immunity against the weaker invading subtype is low to moderate. When the invading subtype is more fit than the endemic subtype and the vaccine is less effective against the invading subtype, the invading subtype will eventually replace the endemic subtype if eradication does not occur. Equilibrium coexistence of the two subtypes cannot occur unless the vaccine is more efficacious against the subtype that has the higher basic reproductive number in the absence of vaccination. Thus, even though the vaccine program may reduce the number of cases, the vaccine program creates a niche in which an ordinarily less fit subtype can persist, even though it would eventually be excluded in the absence of vaccination.

In this analysis, we have assumed that the vaccination campaign will not alter the risk behavior in the community receiving the vaccine; however, it is possible that risk behavior could change as the result of mass vaccination [Blower and McLean 1994]. If individuals respond to the vaccine campaign by reducing their high-risk behavior, HIV eradication by vaccination becomes easier; if individuals respond by increasing their high-risk behavior, then HIV eradication becomes harder. In fact, if risk behavior increases beyond a critical level, then a mass-vaccination campaign

can cause a perverse effect and increase the severity of the epidemic [Blower and McLean 1994]. Since any vaccine that is developed is likely to be less than perfect, efforts to reduce high-risk behavior should be used in conjunction with mass-vaccination campaigns to control the epidemic of HIV [Porco and Blower 1997]. Furthermore, as we have shown in this analysis, it would be important to use even imperfect vaccines at noneradicating control levels, because such vaccines could prevent significant numbers of new infections.

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APPENDIX

In this appendix, we give the differential equations that specify the models discussed in the text and provide a more detailed analysis of those equations.

Two-Subtype HIV-Transmission Model

The two-subtype HIV-transmission model (without vaccination) consists of five ordinary differential equations (see text for discussion and Figure 1 for a flow graph). The state variables are X—the number of susceptible individuals, Y_1 and Y_2—the numbers of individuals infected with subtype 1 and subtype 2, respectively, who have not developed AIDS, and A_1 and A_2—the numbers of individuals infected with subtype 1 and subtype 2, respectively, who have developed AIDS. The parameters are listed in Table 1. Note that $\beta_i c$, the probability that an infective will transmit infection to a susceptible times the number of new partners per unit time, equals the effective contact rate, that is, the rate at which an infective would produce new infectives if the population were completely susceptible. The size of the sexually active community is $N_{sa} = X + Y_1 + Y_2$; the total number of individuals is $N_{tot} = X + Y_1 + Y_2 + A_1 + A_2$. The model, then, is specified by the following five equations:

$$\dot{X} = \Pi - \mu X - \frac{1}{N_{sa}}\beta_1 c X Y_1 - \frac{1}{N_{sa}}\beta_2 c X Y_2, \tag{1}$$

$$\dot{Y}_1 = \frac{1}{N_{sa}}\beta_1 c X Y_1 - (\mu + \gamma_1) Y_1, \tag{2}$$

$$\dot{Y}_2 = \frac{1}{N_{sa}}\beta_2 c X Y_2 - (\mu + \gamma_2) Y_2, \tag{3}$$

$$\dot{A}_1 = \gamma_1 Y_1 - (\mu + \alpha) A_1, \tag{4}$$

and

$$\dot{A}_2 = \gamma_2 Y_2 - (\mu + \alpha) A_2. \tag{5}$$

We next give details of the analysis of the two-subtype model specified by Equations (1)–(5). Observe that the behavior of the system is determined solely by Equations (1)–(3). Let $x = X/N_{sa}$, $y_1 = Y_1/N_{sa}$, and $y_2 = Y_2/N_{sa}$ denote the fractions of the sexually active community that are completely susceptible, infective with subtype 1, and infective with subtype 2, respectively.

The Jacobian matrix of the system of Equations (1)–(3) is given by Equation (6) (Figure 7).

We begin by examining the no-disease equilibrium, for which the values of the state variables are given by $(X^*, Y_1^*, Y_2^*)^T = (\Pi/\mu, 0, 0)^T$, or $(x^*, y_1^*, y_2^*)^T = (1,0,0)^T$ with $N_{sa}^* = \Pi/\mu$. Evaluating the Jacobian matrix at this equilibrium gives

$$\mathbf{J} = \begin{bmatrix} -\mu - (\beta_1 c y_1 + \beta_2 c y_2)(1 - x) & -\beta_1 c x(1 - y_1) + \beta_2 c x y_2 & \beta_1 c x y_1 - \beta_2 c x(1 - y_2) \\ \beta_1 c y_1(1 - x) & \beta_1 c x(1 - y_1) - (\mu + \gamma_1) & -\beta_1 c x y_1 \\ \beta_2 c y_2(1 - x) & -\beta_2 c x y_2 & \beta_2 c x(1 - y_2) - (\mu + \gamma_2) \end{bmatrix} \quad (6)$$

Figure 7: The Jacobian matrix of Equations (1)-(3).

$$\mathbf{J}_0 = \begin{bmatrix} -\mu & -\beta_1 c & -\beta_2 c \\ 0 & \beta_1 c - (\mu + \gamma_1) & 0 \\ 0 & 0 & \beta_2 c - (\mu + \gamma_2) \end{bmatrix}. \quad (7)$$

The eigenvalues of $\mathbf{J}_0$ are $-\mu$, $\beta_1 c - (\mu + \gamma_1)$, and $\beta_2 c - (\mu + \gamma_2)$; the no-disease equilibrium is stable when and only when all eigenvalues of $\mathbf{J}_0$ have negative real parts. Equivalently, disease can invade if and only if at least one of these two eigenvalues has a positive real part, and this occurs when at least one of the basic reproductive numbers $R_0^{(i)}$ is greater than one, where

$$R_0^{(i)} = \frac{\beta_i c}{\mu + \gamma_i}, \quad (8)$$

is the basic reproductive number of subtype i, as given by Blower and McLean [1994]. If only one subtype, subtype i say, is introduced, then subtype i can invade and become established if and only if its basic reproductive number is greater than one. Since the average duration of infectivity (length of time spent in the Y_i-state) is $1/(\mu + \gamma_i)$, the basic reproductive number is the number of new infections produced per unit time by the initial infective times the expected amount of time the initial infective will have before leaving the infective state.

When only subtype i is present and $R_0^{(i)} > 1$, a subtype-i-only equilibrium exists. Without loss of generality, we calculate the values of the state variables at the subtype-1-only equilibrium assuming $R_0^{(1)} > 1$. In this case, the equilibrium fractions of susceptibles and of individuals infected by subtype 1 are given, respectively, by $\bar{x} = 1/R_0^{(1)}$ and $\bar{y}_1 = 1 - 1/R_0^{(1)}$, and the equilibrium size of the community is given by $\bar{N}_{sa} = \Pi/(\mu + \gamma_1 \bar{y}_1)$ [McLean and Blower 1993]. The stability of this equilibrium can be found by substituting these values into Equation (6) and calculating the eigenvalues of the resulting matrix in Equation (9) (Figure 8). Since this matrix is upper block triangular, the set of eigenvalues of the matrix is the union of the set of eigenvalues of the square matrices on the block diagonal (see, for example, Horn and Johnson [1985]). We first consider the two eigenvalues arising from the two-by-two matrix $\mathbf{C}$ in the upper left.

$$\mathbf{J}_1 = \left[\begin{array}{cc|c} -\mu - \beta_1 c\left(1 - \frac{1}{R_0^{(1)}}\right)^2 & -\beta_1 c\left(\frac{1}{R_0^{(1)}}\right)^2 & -\beta_1 c \frac{1}{R_0^{(1)}}\left(1 - \frac{1}{R_0^{(1)}}\right) - \beta_2 c \frac{1}{R_0^{(1)}} \\ \beta_1 c\left(1 - \frac{1}{R_0^{(1)}}\right)^2 & \beta_1 c\left(\frac{1}{R_0^{(1)}}\right)^2 - (\mu + \gamma_1) & -\beta_1 c \frac{1}{R_0^{(1)}}\left(1 - \frac{1}{R_0^{(1)}}\right) \\ \hline 0 & 0 & \beta_2 c \frac{1}{R_0^{(1)}} - (\mu + \gamma_2) \end{array}\right]. \quad (9)$$

Figure 8: Matrix from which eigenvalues are computed to determine stability of the subtype-1-only equilibrium.

Since, when $R_0^{(1)} > 1$,

$$\text{trace}(\mathbf{C}) = -\mu - \beta_1 c\left(1 - \frac{1}{R_0^{(1)}}\right)^2 - (\mu + \gamma_1)\left(1 - \frac{1}{R_0^{(1)}}\right) < 0$$

and

$$\det(\mathbf{C}) = \mu(\mu + \gamma_1)\left(1 - \frac{1}{R_0^{(1)}}\right) + \beta_1 c(\mu + \gamma_1)\left(1 - \frac{1}{R_0^{(1)}}\right)^2 > 0,$$

both eigenvalues of **C** have negative real parts whenever $R_0^{(1)} > 1$; this matrix determines the stability of the subtype-1-only equilibrium when $Y_2 = 0$, and thus whenever $Y_2 = 0$ and $R_0^{(1)} > 1$, the endemic equilibrium of subtype 1 is stable. The third eigenvalue of $\mathbf{J}_1$ is $\beta_2 c\, 1/R_0^{(1)} - (\mu + \gamma_2)$; when this eigenvalue is strictly positive, then subtype 2 can invade the equilibrium. Since the invasion reproductive number of subtype 2 when subtype 1 is at equilibrium is given by

$$R_0^{(2:1)} = R_0^{(2)}\bar{x} = \frac{R_0^{(2)}}{R_0^{(1)}}, \qquad (10)$$

the third eigenvalue of $\mathbf{J}_1$ exceeds 1 (and subtype 2 can invade the equilibrium) whenever the invasion reproductive number of subtype 2, when subtype 1 is at equilibrium, is greater than one. The corresponding result for the subtype-2 equilibrium follows similarly.

We next examine the condition for eradication of subtype i and show that if $R_0^{(i)} < 1$, then subtype i will be eradicated, that is, $\lim_{t\to\infty} Y_i(t) = 0$; without loss of generality, we show this result for subtype 1. Since $R_0^{(1)} < 1$, it follows that $\beta_1 c < \mu + \gamma_1$ and thus $c\beta_1 X/(X + Y_1 + Y_2) < \mu + \gamma_1$. But from Equation (2), $\dot{Y}_1 = Y_1 \times (c\beta_1 X/(X + Y_1 + Y_2) - (\mu + \gamma_1))$; thus $\dot{Y}_1 < 0$ when $Y_1 > 0$; note also that $\dot{Y}_1 = 0$ when $Y_1 = 0$. Thus, since $\dot{Y}_1$ is a continuous function of t, $\lim_{t\to\infty} Y_1(t) = 0$.

Two-Subtype Transmission Model with Vaccination

We next present the six ordinary differential equations that constitute the two-subtype transmission model with vaccination (Figure 3). The state variables are as follows:

X = the number of completely susceptible individuals (individuals who either have not been vaccinated or have been vaccinated but in whom the vaccination provided no protection against subsequent infection, that is, in whom the vaccine did not take);

V = the number of effectively vaccinated individuals (individuals who were vaccinated and in whom the vaccine took);

Y_1 = the number of individuals infected with subtype 1 but who have not developed AIDS;

Y_2 = the number of individuals infected with subtype 2 but who have not developed AIDS;

A_1 = the number of individuals who have developed AIDS as a result of infection by subtype 1;

A_2 = the number of individuals who have developed AIDS as a result of infection by subtype 2.

The fraction of individuals entering the sexually active community who are vaccinated is denoted p, the fraction of the vaccinated individuals in whom there is a protective response is denoted e, and the fraction of individuals who are effectively vaccinated is denoted f, where $f = pe$. The degree of protection that the vaccine confers against infection by subtype i in the individuals who are effectively vaccinated, denoted ζ_i, $\zeta_i = 1$, corresponds to a vaccine that completely prevents infection in effectively vaccinated individuals who are exposed to subtype i, and $\zeta_i = 0$ corresponds to a vaccine conferring no protection for effectively vaccinated indi-

viduals exposed to subtype i; an effectively vaccinated individual is $1 - \zeta_i$ times less likely to be infected by subtype i as an individual who has not been effectively vaccinated.

The model then consists of the following equations:

$$\dot{X} = \Pi(1 - pe) - \mu X - \frac{1}{N_{sa}}\beta_1 cXY_1 - \frac{1}{N_{sa}}\beta_2 cXY_2, \quad (11)$$

where the size of the sexually active community is now given by $N_{sa} = X + V + Y_1 + Y_2$;

$$\dot{V} = \Pi pe - \mu V - \frac{1}{N_{sa}}(1 - \zeta_1)\beta_1 cVY_1 - \frac{1}{N_{sa}}(1 - \zeta_2)\beta_2 cVY_2, \quad (12)$$

$$\dot{Y}_1 = \frac{1}{N_{sa}}\beta_1 cXY_1 + \frac{1}{N_{sa}}(1 - \zeta_1)\beta_1 cVY_1 - (\mu + \gamma_1)Y_1, \quad (13)$$

$$\dot{Y}_2 = \frac{1}{N_{sa}}\beta_2 cXY_2 + \frac{1}{N_{sa}}(1 - \zeta_2)\beta_2 cVY_2 - (\mu + \gamma_2)Y_2, \quad (14)$$

$$\dot{A}_1 = \gamma_1 Y_1 - (\mu + \alpha)A_1, \quad (15)$$

and

$$\dot{A}_2 = \gamma_2 Y_2 - (\mu + \alpha)A_2. \quad (16)$$

The total community size is now given by $N_{tot} = X + V + Y_1 + Y_2 + A_1 + A_2$. The dynamics of the system are determined by Equations (11)–(14). In general, the two-subtype model with vaccination admits four equilibria: a no-disease equilibrium, a subtype-1-only equilibrium, a subtype-2-only equilibrium, and a coexistence equilibrium; we neglect equilibrium solutions that exist only when equality constraints among the parameters are satisfied.

The no-disease equilibrium occurs when $x^* = 1 - f$, $v^* = f$, $y_1^* = 0$, $y_2^* = 0$, with $\bar{N}_{sa} = \Pi/\mu$. The stability of the no-disease equilibrium is determined by evaluating the Jacobian matrix of Equations (11)–(14) at this equilibrium. This yields Equation (17) in Figure 9, where $\zeta_i' = 1 - \zeta_i$, $f = pe$ and $f' = 1 - pe$. Since this matrix is triangular, the eigenvalues appear on the diagonal; the no-disease equilibrium is then stable when all of the eigenvalues have negative real parts. That is, setting

$$\beta_1 cf' + \zeta_1'\beta_1 cf - (\mu + \gamma_1) < 0$$

and rearranging yields the necessary condition for stability $R_p^{(1)} < 1$, where the vaccinated reproductive number of subtype i is defined as

$$R_p^{(i)} = R_0^{(i)}(x^* + (1 - \zeta_i)v^*); \quad (18)$$

$x^* = 1 - pe$ is the equilibrium fraction of the community that is completely susceptible when no disease is present, and $v^* = pe$ is the equilibrium fraction of the community that is effectively vaccinated when no disease is present. Substituting in these values gives the equation

$$J_0 = \begin{bmatrix} -\mu & 0 & -\beta_1 cf' & -\beta_2 cf' \\ 0 & -\mu & -\zeta_1'\beta_1 cf & \zeta_2'\beta_2 cf \\ 0 & 0 & \beta_1 cf' + \zeta_1'\beta_1 cf - (\mu + \gamma_1) & 0 \\ 0 & 0 & 0 & \beta_2 cf' + \zeta_2'\beta_2 cf - (\mu + \gamma_2) \end{bmatrix} \quad (17)$$

Figure 9: The Jacobian matrix of Equations (11)-(14) evaluated at the no-disease equilibrium.

$$R_p^{(1)} = \frac{\beta_1 c(1 - \zeta_1 pe)}{\mu + \gamma_1} = R_0^{(1)}(1 - pe) + R_0^{(1)} pe(1 - \zeta_1) \tag{19}$$

as given in McLean and Blower [1993] and Blower and McLean [1994]. An analogous result holds for $R_p^{(2)}$. Thus, the stability criterion shows that the no-disease equilibrium is stable when and only when both vaccinated reproductive numbers are less than one.

If the entire population were effectively vaccinated, the vaccinated reproductive numbers become $R_p^{(i)} = (1 - \zeta_i)R_0^{(i)}$. The quantity $(1 - \zeta_i)R_0^{(i)}$ can be interpreted as a measure of the fitness of subtype i in a completely vaccinated population.

Next, we show that if subtype i is initially present when $R_p^{(i)} < 1$, then subtype i will be eradicated. That is, if $R_0^{(i)} > 1$ and subtype i is endemic in a community and then a vaccination program is initiated such that $R_p^{(i)} < 1$, this vaccination program will eradicate subtype i. Thus, the condition that subtype i cannot invade the no-disease equilibrium is equivalent to the condition that subtype i will be eradicated if it is present. Because effective vaccination reduces the risk of infection per partnership, the presence of disease in a community increases the proportion of effectively vaccinated individuals among the uninfected, relative to a disease-free population in which a vaccination campaign is being undertaken. That is, when disease is not present in a population, the vaccinated fraction will be f; when disease is present, we expect the fraction of noninfected individuals who are vaccinated (that is, the fraction $\tilde{v} = V/(X + V)$) to be greater than f. This is shown as follows. Observe that Equation (11) is of the form

$$\dot{X} = \Pi f' - (\mu + \phi_1(t))X$$

and Equation (12) is of the form

$$\dot{V} = \Pi f - (\mu + \phi_2(t))V,$$

where $\phi_1(t) = \beta_1 c\, Y_1(t)/N_{sa}(t) + \beta_2 c\, Y_2(t)/N_{sa}(t)$ and $\phi_2(t) = \beta_1 c(1 - \zeta_1) Y_1(t)/N_{sa}(t) + \beta_2 c(1 - \zeta_2) Y_2(t)/N_{sa}(t)$. Note that $0 \le \phi_2(t) \le \phi_1(t) \le \beta_1 c + \beta_2 c$. Then

$$\dot{\tilde{v}} = \frac{\Pi f X - \Pi f' V + XV(\phi_1(t) - \phi_2(t))}{(X + V)^2} \ge \frac{\Pi f X - \Pi f' V}{(X + V)^2} = \frac{\Pi f X - \Pi f' V}{X + V} \frac{1}{X + V}$$

for all t. Since $\dot{X} + \dot{V} \le \Pi - \mu(X + V)$, $X(t) + V(t) \le (\Pi/\mu)(1 + ke^{-\mu t})$, where $k = (X(0) + V(0))(\mu/\Pi) - 1$. Since for $t > 0$, $X(t) + V(t) > 0$,

$$\dot{\tilde{v}} \ge \frac{\Pi f X - \Pi f' V}{X + V} \frac{\mu}{\Pi} \frac{1}{1 + ke^{-\mu t}} = (f - \tilde{v}) \frac{\mu}{1 + ke^{-\mu t}}.$$

Using the integrating factor $(e^{\mu t} + k)/(1 + k)$, integrating both sides from 0 to t yields

$$\tilde{v}(t) \ge \frac{1 + k}{e^{\mu t} + k} \tilde{v}(0) + f \frac{e^{\mu t} - 1}{e^{\mu t} + k},$$

so that $f \le \liminf_{t \to \infty} \tilde{v}(t)$. Then, since $R_p^{(1)} < 1$,

$$\frac{\beta_1 c - (\mu + \gamma_1)}{\beta_1 c \zeta_1} < f \le \liminf_{t \to \infty} \tilde{v}(t).$$

Thus, there exists $T > 0$ such that for all $t > T$, $\tilde{v}(t) > (\beta_1 c - (\mu + \gamma_1))/\beta_1 c \zeta_1$. Substituting $V/(X + V)$ for $\tilde{v}$ and rearranging gives

$$\frac{\beta_1 c}{\mu + \gamma_1} \frac{X + (1 - \zeta_1)V}{X + V} < 1,$$

and since $X + V + Y_1 + Y_2 \ge X + V$,

$$\frac{\beta_1 c}{\mu + \gamma_1} \frac{X + (1 - \zeta_1)V}{X + V + Y_1 + Y_2} < 1.$$

Therefore, using Equation (13), it follows that for $t > T_1$, $\dot{Y}_1 \le 0$, with equality only when $Y_1 = 0$, and hence $\lim_{t \to \infty} Y_1(t) = 0$. Similarly, $\lim_{t \to \infty} Y_2(t) = 0$ whenever $R_p^{(2)} < 1$.

We next determine the disease-1-only equilibrium. Let $\bar{x}$ denote the equilibrium proportion (of the sexual community) that is susceptible, that is, $\bar{x} = \bar{X}/N_{sa}$. Similarly, let $\bar{y}_1$ denote the equilibrium proportion (of the sexual community) that is infected with subtype 1, and let $\bar{v}$ denote the equilibrium proportion (of the sexual community) that has been effectively vaccinated. It can be shown by Equations (11)–(14) that $\bar{y}_1$ is the larger solution of

$$\begin{aligned}\bar{y}_1^2\beta_1^2c^2\zeta_1' + \bar{y}_1\beta_1c(-\beta_1c\zeta'1 + \gamma_1(1 + \zeta_1') \\ - f'\gamma_1 - \zeta_1'f\gamma_1 + \mu + \zeta_1'\mu) \\ + \mu(\mu + \gamma_1)(1 - R_p^{(1)}) = 0.\end{aligned} \tag{20}$$

Since the coefficient of $\bar{y}_1^2$ is positive, the larger root of (20) is real and positive when and only when the constant term $\mu(\mu + \gamma_1)(1 - R_p^{(1)}) < 0$, that is, when and only when $R_p^{(1)} > 1$. For no range of parameters is it ever possible for $\bar{y}_1 > 1$. Finally, the equilibrium fraction of the number of completely susceptible individuals is given by $\bar{x} = f'(\mu + \gamma_1\bar{y}_1)/(\mu + \beta_1c\bar{y}_1)$ and the equilibrium fraction of the number of effectively vaccinated individuals is given by $\bar{v} = f(\mu + \gamma_1\bar{y}_1)/((\mu + \beta_1c\,\zeta'_1)\bar{y}_1)$

To examine the stability of the subtype-1-only equilibrium, the calculated values for the values of the state variables at the subtype-1-only equilibrium must be substituted into the Jacobian matrix of the system (11)–(14). This leads to an expression of the form

$$\mathbf{J}_1 = \begin{bmatrix} \mathbf{A} & \mathbf{B} \\ 0 & \beta_2c\bar{x} + \zeta_2'\beta_2c\bar{v} - (\mu + \gamma_2) \end{bmatrix}, \tag{21}$$

where $\mathbf{A}$ is a 3×3 matrix. The set of eigenvalues of $\mathbf{J}_1$ is the union of the set of eigenvalues of $\mathbf{A}$ (which determine the stability of the subtype-1-only equilibrium in the absence of subtype 2) and the set containing only

$$\lambda_2 = \beta_2c\bar{x} + \zeta_2'\beta_2c\bar{v} \quad - (\mu + \gamma_2). \tag{22}$$

Denote the vaccinated invasion reproductive number of subtype 2 at the equilibrium of subtype 1 as $R_p^{(1:2)}$. Then subtype 2 can invade the subtype-1-only equilibrium if and only if $\lambda_2 > 0$, which is equivalent to the following condition:

$$R_p^{(2:1)} = R_0^{(2)}(\bar{x} + (1 - \zeta_2)\bar{v}) > 1, \tag{23}$$

with $\bar{x}$ and $\bar{v}$ denoting the values of the fraction of completely susceptible individuals and effectively vaccinated individuals at the subtype-1-only equilibrium. A similar argument shows that subtype 1 can invade the subtype-2-only equilibrium if and only if

$$R_p^{(1:2)} = R_0^{(1)}(\bar{\bar{x}} + (1 - \zeta_1)\bar{\bar{v}}) > 1, \tag{24}$$

with $\bar{\bar{x}}$ and $\bar{\bar{v}}$ denoting the values of the fraction of completely susceptible individuals and effectively vaccinated individuals at the subtype-2-only equilibrium; if subtype 1 is introduced when subtype 2 has reached equilibrium, then $\bar{\bar{x}}$ and $\bar{\bar{v}}$ represent the available host resources for subtype 1. Equation (24) can be seen to be analogous to the expression for the vaccinated reproductive number given in Equation (18). Similarly, the vaccinated invasion reproductive number $R_p^{(2:1)}$ of subtype 2 when subtype 1 is at equilibrium is given by

$$R_p^{(2:1)} = R_0^{(2)}(\bar{x} + (1 - \zeta_2)\bar{v}), \tag{25}$$

where $\bar{x}$ and $\bar{v}$ are, respectively, the proportion of completely susceptible and effectively vaccinated individuals when subtype 1 has attained equilibrium in the absence of subtype 2.

Finally, when a coexistence equilibrium exists, let $\hat{x}$ denote the fraction of unvaccinated susceptibles and let $\hat{v}$ denote the fraction of effectively vaccinated individuals. Then Equations (13) and (14) yield

$$\hat{x} = \frac{(1 - \zeta_2)R_0^{(2)} - (1 - \zeta_1)R_0^{(1)}}{(\zeta_1 - \zeta_2)R_0^{(1)}R_0^{(2)}}$$

and

$$\hat{v} = \frac{R_0^{(1)} - R_0^{(2)}}{(\zeta_1 - \zeta_2)R_0^{(1)}R_0^{(2)}},$$

and from these, Equations (11) and (12) yield cumbersome expressions for the equilibrium fractions $\hat{y}_1$ and $\hat{y}_2$ (omitted for brevity); the coexistence equilibrium exists provided $0 \le \hat{x} \le 1$, $0 \le \hat{v} \le 1$, $0 \le \hat{y}_1 \le 1$, and $0 \le \hat{y}_2 \le 1$.

Expanding and rearranging the inequalities $\hat{x} > 0$ and $\hat{v} > 0$ yields the following necessary condition for the existence of the coexistence equilibrium. If $R_0^{(i)} > R_0^{(j)}$, the coexistence equilibrium cannot exist unless the vaccine provides protection against the subtype with the larger basic reproductive number, that is, $\zeta_i > \zeta_j$. In other words, if subtype-1 has a higher fitness in a completely susceptible population, then subtype-2 must have a higher fitness in a completely effectively vaccinated population, but if subtype-1 has a lower fitness in a completely susceptible population, then subtype-2 must have a lower fitness in a completely effectively vaccinated population.

Determination of the stability of this equilibrium could be by performed substituting the values just given into the Jacobian of the system (11)–(14), but this procedure leads to extremely cumbersome expressions. Numerical simulations (not shown) suggest that the coexistence equilibrium is stable whenever $R_p^{(1:2)} > 1$ and $R_p^{(2:1)} > 1$.

References

Anderson, R. M. and May, R. M. 1991, *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, Oxford, England.

Artenstein, A. W.; VanCott, T. C.; Mascola, J. R.; Carr, J. K.; Hegerich, P. A.; Gaywee, J.; Sanders-Buell, E.; Robb, M. L.; Dayhoff, D. E.; Thitivichianlert, S.; Nitayaphan, S.; McNeil, J. G.; Birx, D. L.; Michael, R. A.; Burke, D. S.; and McCutchan, F. E. 1995, "Dual infection with human immunodeficiency virus type 1 of distinct envelope subtypes in humans," *Journal of Infectious Diseases*, Vol. 171, No. 4, pp. 805–810.

Bloom, B. R. 1996, "A perspective on AIDS vaccines," *Science*, Vol. 272, No. 5270, pp. 1888–1890.

Blower, S. M. and McLean, A. R. 1994, "Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco," *Science*, Vol. 265, No. 5177, pp. 1451–1454.

Blower, S. M. and McLean, A. R. 1995, "AIDS: Modeling epidemic control," *Science*, Vol. 267, No. 5202, pp. 1250–1253.

Burke, D. S. and McCutchan, F. E. 1997, "Global distribution of human immunodeficiency virus-1 clades," in *AIDS: Biology, Diagnosis, Treatment and Prevention*, eds. V. T. DeVita, Jr., S. Hellman, and S. A. Rosenberg, Lippincott-Raven, Philadelphia, Pennsylvania, pp. 119–126.

Cohen, J. 1994, "Are researchers racing toward success, or crawling?" *Science*, Vol. 265, No. 5177, pp. 1373–1375.

Ferrari, G.; Humphrey, W.; McElrath, M. J.; Excler, J.-L.; Duliege, A.-M.; Clements, M. L.; Corey, L. C.; Bolognesi, D. P.; and Weinhold, K. J. 1997, "Clade B-based HIV-1 vaccines elicit cross-clade cytotoxic T lymphocyte reactivities in uninfected volunteers," *Proceedings of the National Academy of Science of the United States of America*, Vol. 94, No. 4, pp. 1396–1401.

Fisher, A. G.; Ensoli, B.; Looney, D.; Rose, A.; Gallo, R. C.; Saag, M. S.; Shaw, G. M.; Hahn, B. H.; and Wong-Staal, F. 1988, "Biologically diverse molecular variants within a single HIV-1 isolate," *Nature*, Vol. 334, No. 6181, pp. 444–447.

Grady, C. and Kelly, G. 1996, "State of the science: HIV vaccine development," *Nursing Clinics of North America*, Vol. 31, No. 1, pp. 25–39.

Grant, R. M.; Wiley, J. A.; and Winkelstein, W. 1987, "Infectivity of the human immunodeficiency virus: Estimates from a prospective study of homosexual men," *Journal of Infectious Diseases*, Vol. 156, No. 1, pp. 189–193.

Horn, R. A. and Johnson, C. R. 1985, *Matrix Analysis*, Cambridge University Press, Cambridge, England.

Hu, D. J.; Dondero, T. J.; Rayfield, M. A.; George, J. R.; Schochetman, G.; Jaffe, H. W.; Luo, C. C.; Kalish, M. L.; Weniger, B. G.; and Pau, C. P. 1996, "The emerging genetic diver-

sity of HIV. The importance of global surveillance for diagnostics, research, and prevention," *Journal of the American Medical Association*, Vol. 275, No. 3, pp. 210–216.

Kalish, M. L.; Baldwin, A.; Raktham, S.; Wasi, C.; Luo, C.-C.; Schochetman, G.; Mastro, T. D.; Young, N.; Vanichseni, S.; Rübsamen-Waigmann, H.; von Breisen, H.; Mullins, J. I.; Delwart, E.; Herring, B.; Esparza, J.; Heyward, W. L.; and Osmanov, S. 1995, "The evolving molecular epidemiology of HIV-1 envelope subtypes in injecting drug users in Bangkok, Thailand: Implications for HIV vaccine trials," *AIDS*, Vol. 9, No. 8, pp. 851–857.

Kanki, P.; Travers, K. U.; Mboup, S.; Hsieh, C.-C.; Marlink, R. G.; Guèye-Ndiaye, A.; Siby, T.; Thior, I.; Hernandez-Avila, M.; Sankalé, J.-L.; Ndoye, I.; and Essex, M. E. 1994, "Slower heterosexual spread of HIV-2 than HIV-1," *Lancet*, Vol. 343, No. 8903, pp. 943–946.

Kermack, W. O. and McKendrick, A. G. 1927, "A contribution to the mathematical theory of epidemics," *Proceedings of the Royal Society of London, A*, Vol. 115, No. 772, pp. 700–721.

Kuiken, C. L.; Zwart, G.; Baan, E.; Coutinho, R. A.; van den Hoek, J. A.; and Goudsmit, J. 1993, "Increasing antigenic and genetic diversity of the V3 variable domain of the human immunodeficiency virus envelope protein in the course of the AIDS epidemic," *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 90, No. 19, pp. 9061–9065.

Kunanusont, C.; Foy, H. M.; Kreiss, J. K.; Rerks-Ngarm, S.; Phanuphak, P.; Raktham, S.; Pau, C.-P.; and Young, N. L. 1995, "HIV-1 subtypes and male-to-female transmission in Thailand," *Lancet*, Vol. 345, No. 8957, pp. 1078–83.

Levy, J. A. 1996, "HIV heterogeneity in transmission and pathogenesis," in *AIDS in the World II, Global Dimensions, Social Roots, and Responses*, eds. J. M. Mann and D. J. M. Tarantola, Oxford University Press, New York, pp. 177–185.

MacDonald, G. 1957, *The Epidemiology and Control of Malaria*, Oxford University Press, London, England.

Marlink, R.; Kanki, P.; Thior, I.; Travers, K.; Eisen, G.; Siby, T.; Traore, I.; Hsieh, C.-C.; Dia, M.; Gueye, E.-H.; Hellinger, J.; Guèye-Ndiaye, A.; Sankalé, J.-L.; Ndoye, I.; Mboup, S.; and Essex, M. 1994, "Reduced rate of disease development after HIV-2 infection as compared to HIV-1," *Science*, Vol. 265, No. 8903, pp. 1587–1590.

Mascola, J. R.; Louwagie, J.; McCutchan, F. E.; Fischer, C. L.; Hegerich, P. A.; Wagner, K. F.; Fowler, A. K.; McNeil, J. G.; and Burke, D. S. 1994, "Two antigenically distinct subtypes of human immunodeficiency virus type 1: Viral genotype predicts neutralization serotype," *Journal of Infectious Diseases*, Vol. 169, No. 1, pp. 48–54.

Mascola, J. R.; Snyder, S. W.; Weislow, O. S.; Belay, S. M.; Belshe, R. B.; Schwartz, D. H.; Clements, M. L.; Dolin, R.; Graham, B. S.; Gorse, G. J.; Keefer, M. C.; McElrath, M. J.; Walker, M. C.; Wagner, K. F.; McNeil, J. G.; McCutchan, F. E.; and Burke, D. S. 1996, "Immunization with envelope subunit vaccine products elicits neutralizing antibodies against laboratory-adapted but not primary isolates of human immunodeficiency virus type 1," *Journal of Infectious Diseases*, Vol. 173, No. 2, pp. 340–348.

Mastro, T. D.; Satten, G. A.; Nopkesorn, T.; Sangkharomya, S.; and Longini, I. M., Jr. 1994, "Probability of female-to-male transmission of HIV-1 in Thailand," *Lancet*, Vol. 343, No. 8891, pp. 204–207.

McCutchan, F.; Hegerich, P.; Brennan, T.; Phanuphak, P.; Singharaj, P.; Jugsudee, A.; Berman, P.; Gray, A.; Fowler, A.; and Burke, D. 1992, "Genetic variants of HIV in Thailand," *AIDS Research and Human Retroviruses*, Vol. 8, No. 11, pp. 1887–1895.

McCutchan, F. E.; Salminen, M. O.; Carr, J. K.; and Burke, D. S. 1996, "HIV-1 genetic diversity," *AIDS*, Vol. 10, Suppl. 3, pp. S13–S20.

McLean, A. R. 1995, "Vaccination, evolution and changes in the efficacy of vaccines: A theoretical framework," *Proceedings of the Royal Society of London, Series B*, Vol. 261, No. 1362, pp. 389–393.

McLean, A. R. and Blower, S. M. 1993, "Imperfect vaccines and herd immunity to HIV," *Proceedings of the Royal Society of London, Series B*, Vol. 253, No. 1336, pp. 9–13.

McLean, A. R. and Blower, S. M. 1995, "Modelling HIV vaccination," *Trends in Microbiology*, Vol. 3, No. 12, pp. 458–463.

Mertens, T. and Piot, P. 1997, "Global aspects of human immunodeficiency virus epidemi-

ology: General considerations," in *AIDS: Biology, Diagnosis, Treatment and Prevention*, eds. V. T. DeVita, Jr., S. Hellman, and S. A. Rosenberg, Lippincott-Raven, Philadelphia, Pennsylvania, pp. 103–118.

Osmond, D. H.; Page, K.; Wiley, J.; Garrett, K.; Sheppard, H. W.; Moss, A. R.; Schrager, L.; and Winkelstein, W. 1994, "HIV infection in homosexual and bisexual men 18 to 29 years of age: The San Francisco Young Men's Health Study," *American Journal of Public Health*, Vol. 84, No. 12, pp. 1933–1937.

Ou, C. Y.; Takebe, Y.; Weniger, B.; Luo, C. Y.; Kalish, M.; Auwant, W.; Yamazaki, S.; Gayle, H.; Young, N.; and Schochetman, G. 1993, "Independent introduction of two major HIV-1 genotypes into distinct high-risk populations in Thailand," *Lancet*, Vol. 341, No. 8854, pp. 1171–1174.

Porco, T. C. and Blower, S. M. 1997, "HIV vaccines: Subtypes, cross-immunity, and risk behavior change," working paper.

Rojas, J. M.; Dopazo, J.; Najera, I.; Sánchez-Palomino, S.; Olivares, I.; Martin, M. J.; Bernal, A.; Garcia-Saiz, A.; Najera, R.; and Lopez-Galindez, C. 1994, "Molecular epidemiology of HIV-1 in Madrid," *Virus Research*, Vol. 31, No. 3, pp. 331–342.

Rowe, P. M. 1996, "HIV subtypes raise vaccine anxieties," *Lancet*, Vol. 347, No. 9001, p. 603.

Saag, M. S.; Hahn, B. H.; Gibbons, J.; Li, Y.; Parks, E. S.; Parks, W. P.; and Shaw, G. M. 1988, "Extensive variation of human immunodeficiency virus type-1 in vivo," *Nature*, Vol. 334, No. 6181, pp. 440–443.

Sánchez-Palomino, S.; Dopazo, J.; Olivares, I.; Martin, M. J.; and López-Galíndez, C. 1995, "Primary genetic characterization of HIV-1 isolates from WHO-sponsored vaccine evaluation sites by the RNase-A mismatch method," *Virus Research*, Vol. 39, No. 2–3, pp. 251–259.

Soto-Ramirez, L. E.; Renjifo, B.; McLane, M. F.; Marlink, R.; O'Hara, C.; Sutthent, R.; Wasi, C.; Vithayasai, P.; Vithayasai, V.; Apichartpiyakul, C.; Auewarakul, P.; Cruz, V. P.; Chui, D.-S.; Osathanondh, R.; Mayer, K.; Lee, T.-H.; and Essex, M. 1996, "HIV-1 Langerhans' cell tropism associated with heterosexual transmission of HIV," *Science*, Vol. 271, No. 5253, pp. 1291–1293.

Travers, K.; Mboup, S.; Marlink, R.; Guèye-Ndiaye, A.; Siby, T.; Thior, I.; Traore, I.; Dieng-Sarr, A.; Sankalé, J.-L.; Mullins, C.; Ndoye, I.; Hsieh, C.-C.; Essex, M.; and Kanki, P. 1995, "Natural protection against HIV-1 infection provided by HIV-2," *Science*, Vol. 268, No. 5217, pp. 1612–1615.

Verani, P.; Buttò, S.; Taddeo, B.; Federico, M.; and Rossi, G. B. 1993, "HIV variability and perspectives for a vaccine," *Vaccine*, Vol. 11, No. 5, pp. 542–544.

WHO network for HIV isolation and characterization 1994, "HIV Type 1 variation in World Health Organization-sponsored vaccine evaluation sites: Genetic screening, sequence analysis, and preliminary biological characterization of selected viral strains," *AIDS Research and Human Retroviruses*, Vol. 10, No. 11, pp. 1327–1343.