Correspondence

Modeling the Potential Public Health Impact of Imperfect HIV Vaccines

To the Editor—I wish to clarify the literature with regard to a recent publication by Anderson and Hanson [1]. They present a mathematical model for an imperfect preexposure HIV vaccine with therapeutic effects (see the flow diagram in figure 3 and the equations in the Appendix). However, this model has already been published by Blower et al. [2–5].

In 1993, McLean and Blower were the first to model the population-level impact of imperfect (i.e., those with an efficacy of <100%) preexposure HIV vaccines [6]. They assumed that vaccinated individuals would receive only partial protection against infection. Their model included 3 mechanisms by which vaccines could fail: (1) by generating a low "take" (ε), (2) by providing a low degree of protection against infection (ψ), and/or (3) by waning (ω) (figure 1). Thus, the efficacy *(e)* of an imperfect vaccine could be understood as the product of take and degree of protection: $e = \varepsilon\psi$ [3, 4, 6]. Furthermore, Blower and McLean showed that the population-level impact (Φ) of an imperfect preexposure HIV vaccine could be evaluated by multiplying *e* by the proportion of vaccinated individuals in whom the vaccine does not wane ($[\mu/(\mu+\omega)]$, where $1/\mu$ specifies the average time spent selecting new sex partners and $1/\omega$ specifies the average duration of vaccine-induced immunity) [2, 3, 6, 7]. Thus, $\Phi = \varepsilon\psi[\mu/(\mu+\omega)]$, and, if vaccine-induced protection is lifelong, then $\Phi = e$. Using their model [6, 7], Blower and McLean were the first to derive the expression for the critical vaccination coverage (p_c) necessary to achieve HIV eradication with an imperfect vaccine:

$$p_c = \left(\frac{1}{\phi}\right)\left(1 - \frac{1}{R_0}\right),$$

where R_0 is the average number of secondary infections caused by an infected individual.

Analysis of the model revealed that even imperfect vaccines could substantially decrease prevalence and incidence but that the rate of waning of vaccine-induced immunity is critical [3, 4, 6–8]. Blower and McLean also calculated the vaccine efficacy and vaccination coverage levels necessary to eradicate HIV in San Francisco [7]. They quantified the trade-off between coverage, efficacy, and potential changes in risky behaviors. They were the first to show that an imperfect preexposure vaccine could significantly curtail the HIV epidemic, provided that risky behaviors did not increase [7]. However, their analyses also indicated that it would be unlikely—unless risky behaviors were considerably reduced—that an imperfect vaccine could eradicate HIV in San Francisco. More importantly, they were the first to show that, if risky behaviors increased, mass vaccination with imperfect vaccines could have the perverse outcome of increasing the severity of the epidemic [7].

Blower et al. expanded their original model to develop a new one for predicting the impact of imperfect preexposure HIV vaccines that slow disease progression (i.e., disease-modifying, or therapeutic, vaccines) (figure 1*B*) [2–5]; this new model is the same as that which was recently presented by Anderson and Hanson [1]. The new model included a take, degree of protection, and duration effect. However, the key additional assumptions included were that the vaccine increases survival and reduces infectiousness (and, hence, decreases transmission) (figure 1*B*). An interactive Web-based version of this model can be found at: http://www.biomath.medsch.ucla.edu/faculty/sblower/applets/HIVVAC/hivvac.html. Blower et al. [4] derived the critical vaccination coverage necessary to achieve eradication with an imperfect preexposure disease-modifying vaccine:

$$P_c = \left(\frac{\mu+\omega}{\varepsilon\mu}\right)\left(\frac{1 - R_0}{(1-\psi)R_v - R_0}\right).$$

Smith and Blower further analyzed this model [5] and defined a new quantity, the fitness ratio *(f)*, as defined by $f = R_v/R_0$, where R_v and R_0 are the average number of secondary infections caused by a vaccinated-infected individual and an unvaccinated-infected individual, respectively. Disease-modifying vaccines will reduce transmission if they cause a reduction of 1.5 $\log_{10}$ copies/mL or more in viral load and if risky behaviors do not increase [5]. However, disease-modifying vaccines that provide only a low degree of protection against infection and/or generate high fitness ratios will increase transmission, even if risky behaviors do not increase [5]. High fitness ratios will be generated if the vaccine substantially increases survival times but does not substantially reduce infectiousness. Specifically, transmission will increase if $f > 1/(1-\psi)$ [5]. Smith and Blower derived 3-dimensional threshold surfaces to identify critical boundaries at which disease-modifying vaccines switch from causing a beneficial to causing a detrimental effect at the population level if risky behaviors change [5]. These surfaces are determined by the value of the fitness ratio, the proportion of the population that is successfully vaccinated, and the degree of

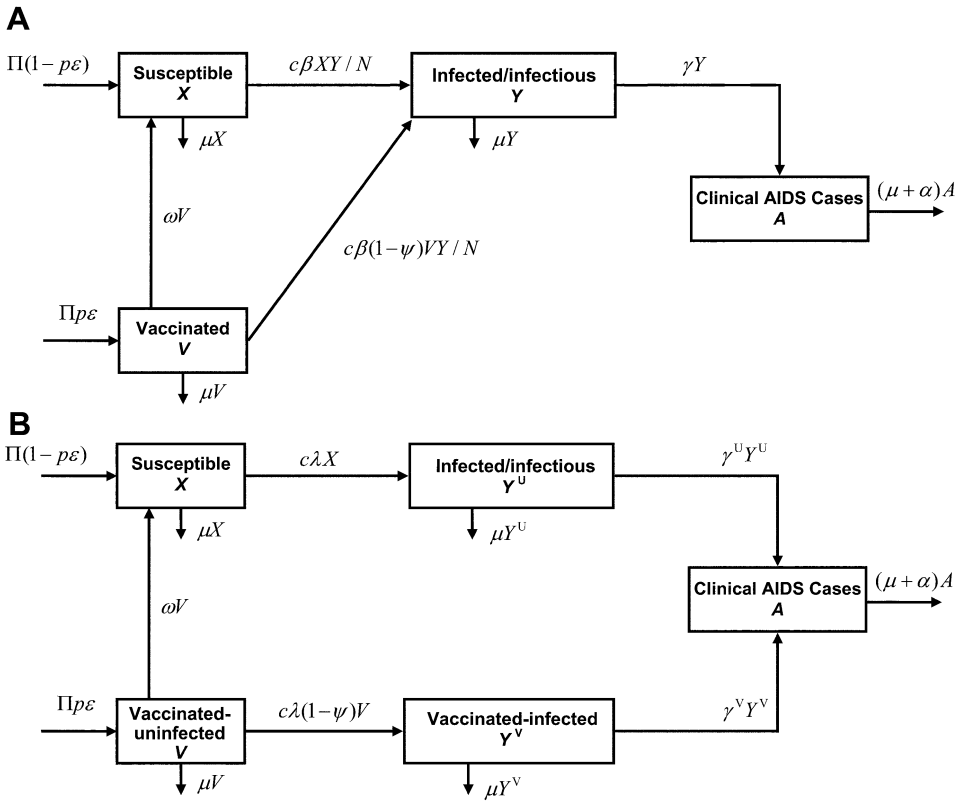

Figure 1. *A,* Flow diagram of an imperfect preexposure HIV vaccine model, designed by McLean and Blower (diagram is a modified version of that published in [6]). The population is divided into 4 states: susceptible individuals *(X),* infected/infectious individuals *(Y),* vaccinated individuals *(V),* and individuals with AIDS *(A).* The imperfect vaccine can produce a "take" effect, reduce susceptibility to a certain degree ($1 - \psi$), and wane (at rate $1/\omega$). *B,* Flow diagram of an imperfect preexposure HIV vaccine model with therapeutic effects, designed by Blower et al. [2–4]. This model is an extension, by 1 state, of the 4-state model shown in panel A, which was designed in 1993. The population is now divided into 5 states: susceptible individuals *(X),* infected/infectious individuals (Y^U), vaccinated-uninfected individuals *(V),* vaccinated-infected individuals (Y^V), and individuals with AIDS *(A).* The imperfect vaccine can produce a take effect, reduce susceptibility to a certain degree ($1 - \psi$), wane (at rate $1/\omega$), and both reduce infectivity and slow disease progression in vaccinated individuals who subsequently become infected.

change in risky behaviors in unvaccinated-infected individuals.

In summary, the model of an imperfect vaccine with therapeutic effects presented recently by Anderson and Hanson [1] was one that had been designed and analyzed previously by Blower et al. [2–5, 8].

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Reply to Blower

To the Editor—I wish to draw your readers' attention to an article by Anderson et al. that was published in *Nature* in 1991 [1], in particular to the equations and text on page 357. I hope your readers will draw their own conclusions as to the origins of both the first mathematical model (and associated analyses) of the potential population-level impact of imperfect HIV vac-

cines and the template described in Anderson and Hanson [2].

Blower falsely claims (e.g., see [3], p. 118) that her 1993 and 1994 articles included, to quote, "the first transmission model of HIV vaccines to assess the potential epidemic-level impact of imperfect vaccines." This is incorrect—the 1991 *Nature* article by Anderson et al. was the first.

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Breakthrough Zygomycosis and Voriconazole

To the Editor—Zygomycosis is an invasive fungal infection caused by various members of the class Mucorales and usually occurs in patients with ketoacidotic diabetes or hematological disorders. It most commonly occurs in patients with acute leukemia or lymphoma who develop neutropenia as a result of malignancy or chemotherapy and in transplant recipients receiving immunosuppressive treatment [1].

Recently, some reports have suggested an increase in the incidence of zygomycosis in association with prophylactic voriconazole (VRC) use in immunosuppressed patients [2–5]. In a recent article, Kontoyiannis et al. reported the results of an observational matched case-control study comparing consecutive patients with zygomycosis and 2 control groups, patients without an invasive mold infection and patients with invasive aspergillosis [6]. The authors identified 27 patients with zygomycosis; 13 (48%) of them had received previous VRC prophylaxis. In a multivariate analysis comparing the patients with zygomycosis and the patients without an invasive mold infection, VRC prophylaxis, diabetes, and malnutrition were found to be independent risk factors for zygomycosis. When the patients with zygomycosis and the patients with invasive aspergillosis were compared, VRC prophylaxis was found to be the most relevant factor favoring the onset of zygomycosis. Kontoyiannis et al. suggest that the increased incidence of zygomycosis might reflect the increasing and prolonged use of oral VRC versus parenteral agents with activity against Zygomycetes. However, it is important to determine whether the increased incidence of zygomycosis is due solely to an increase in oral VRC use or can also be attributed to improvement of the tools of diagnosis and to increased attention to this infection by physicians.

Certainly, an increase in breakthrough infections by opportunistic pathogens is a concern with any antimicrobial agent—VRC is no exception—and it is true that the increased incidence of zygomycosis stands in contrast to the previous breakthrough infections seen when fluconazole or itraconazole were used for prophylaxis [7, 8]. However, an increase in the incidence of zygomycosis over the past 20 years has already been described [9].

In a multicenter retrospective survey conducted over a 15-year period (1987–2001) by Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA), 59 cases of proven or probable mucormycosis in patients with hematological malignancies were registered [1]. It is noteworthy that 47 (80%) of the 59 patients had received oral antifungal prophylaxis, 35 (59%) of whom had received azole compounds (18 fluconazole, 15 itraconazole, and 2 ketoconazole); none of these patients had received VRC. In addition, in a study by Larkin and Montero in which all cases of zygomycosis in the Collaborative Exchange of Antifungal Research database were analyzed, 13 (23%) of 64 patients with zygomycosis had previously received fluconazole [10]. In an overview of case reports by Gleissner et al., data on previous antifungal prophylaxis were reported for only 12 of 120 patients with zygomycosis and underlying hematological disorders [11]. Prophylaxis with azoles was noted in 7 (58%) of the 12 patients (3 itraconazole, 3 fluconazole, and 1 ketoconazole).

These data suggest that breakthrough zygomycosis could occur with all prophylactic azoles that do not have activity against Zygomycetes. In our opinion, improved diagnostic tools play an important role in the increased incidence of this fungal complication. Finally, we completely agree with Kauffman, who has suggested in an editorial to wait for the results of a blinded, multicenter trial comparing VRC and fluconazole for prophylaxis in patients with hematological disorders before reconsidering the prophylactic use of VRC [4, 5].

Livio Pagano,[1] Beate Gleissner,[2] and Luana Fianchi[1]

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Reply to Pagano et al.

To the Editor—I thank Pagano et al. for their interest in our work [1]. I agree that the increase in the incidence of zygomycosis preceded the introduction of voriconazole (VRC), as my colleagues and I have previously reported [2]. However, I disagree that the increase in reported cases of zygomycosis resulted from the reasons Pagano et al. have set forth. First, I am not aware of any improvement in diagnostic tools specific for the detection of Zygomycetes that have been widely implemented in clinics during the last decade. Such improvement would be most welcome, given that the yield of conventional culture methods is suboptimal and that early diagnostic markers by which infection with Zygomycetes and infections with other, more common opportunistic molds can be differentiated are not available [3]. Second, I take issue with the assertion that the increase in the number of reported cases of zygomycosis is largely an artifact of an increased awareness of this infection, for the very reasons stated above. The clinical presentation of zygomycosis is frequently indistinguishable from that of aspergillosis, and a definitive diagnosis is often made only via tissue biopsy [4]. In addition to several case series from single institutions reporting an increase in breakthrough zygomycosis in patients receiving VRC during the last 2 years, a recent multicenter prospective surveillance study in transplant recipients has also documented an association between zygomycosis and previous VRC use [5]. I believe that all patients with continuous and intense immunosuppression are at high risk for breakthrough fungal infection, irrespective of the antifungal used. In our study, diabetes mellitus, malnutrition (serum albumin level of $\leq$3 g/dL), and VRC use were found to be independent risk factors (along with an initial presentation of sinusitis) that favored an eventual diagnosis of zygomycosis over aspergillosis in our high-risk patient population [6]. Because zygomycosis is uniformly fatal if not accurately diagnosed early, I feel that it is critical for clinicians who are caring for highly immunosuppressed patients to recognize the risk factors associated with breakthrough infections with this multiantifungal-resistant mold. I agree that future prospective studies will help to clarify the roles played by the complex and often interrelated factors that contribute to the epidemiology of zygomycosis in highly immunosuppressed patients with cancer.

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Questioning Wawer et al.'s Estimated Rate of Sexual HIV Transmission from Persons with Early HIV Infections

To the Editor—Wawer et al. [1] use data from a prospective study of HIV incidence in Rakai, Uganda, to estimate rates of HIV transmission per coital act between HIV-discordant heterosexual partners, according to the stage of infection in the index

Table 1. HIV seroconcordance among couples with prevalent HIV infections.

Country, years [reference]	Population	Couples with HIV, no. (%)	
		In 1 or both partners	Seroconcordant
Democratic Republic of Congo, 1987–1988 [5]	Workers and wives	239	35 (15)
Malawi, 1981–1989 [6]	General population	78	22 (28)
Tanzania, 1991–1995 [4]	General population	60	17 (28)
Tanzania, 1991–1996 [7]	Workers and wives	120	27 (23)
Uganda, 1990–1991 [8]	General population	171	88 (51)
Uganda, 1989–1997 [2]	General population	48	117 (41)

partner. They use genetic testing to support intracouple transmission [1]. Their estimated rate of transmission—0.0082 transmissions/coital act—during the initial 5 months of the index partner's incident infection depends on 23 formerly seroconcordant HIV-negative couples with incident HIV, of whom 10 (43%) were seroconcordant HIV positive when the first infection was recognized after a 10-month follow-up period.

Three comparable studies that followed seroconcordant HIV-negative couples in sub-Saharan Africa observed a cumulative total of 51 couples with incident HIV, of whom only 7 (14%) were seroconcordant HIV positive when the first infection was recognized. Briefly, in Masaka, Uganda, 3 of 29 couples with incident HIV were seroconcordant after an average follow-up of nearly 2 years [2]; in Rwanda, 1 of 4 couples was seroconcordant after a 1-year follow-up [3]; and in Tanzania, 3 of 18 were seroconcordant after a 2-year follow-up [4].

Although we do not have information on numbers of coital acts in these other studies, we can compare rates of transmission per 100 person-years (PYs). Using Wawer et al.'s assumptions (that index partners seroconvert at the midpoint of the follow-up interval and transmit at the midpoint of the remaining half of the interval), we calculate for Rakai a rate of HIV transmission from 23 index partners with incident HIV to their spouses of 133 transmissions/100 PYs. For the 3 comparable studies summarized above, the cumulative rate of transmission from 51 index partners with incident HIV is 16 transmissions/100 PYs. Even if we overadjust for the longer follow-up period in these studies than in the Rakai study by assuming that all 51 index partners seroconverted only 5 months before their infections were recognized, the rate of transmission computes to 35 transmissions/100 PYs, less than one-third the estimated rate from the Rakai data.

Moreover, the 43% seroconcordance among 23 Rakai couples with incident HIV in the index partner is unexpectedly high, compared with seroconcordance among couples with prevalent HIV, for which we can assume that the mean duration of exposure to an infected index partner was much longer than 5 months. Wawer et al. report only 44% seroconcordance among 741 couples with prevalent HIV at enrollment into the Rakai study. In 6 comparable studies conducted in Africa (table 1), the median rate of seroconcordance among couples with prevalent HIV is 28% (range, 15%–51%). (We searched our records for data on prevalent HIV in couples from African studies that selected persons from the general population or from workers and wives. Because people with HIV-related symptoms may be more likely to volunteer for tests, studies of voluntary testers are not comparable.)

Several methodological aspects of Wawer et al.'s analysis deserve comment. First, they exclude data from 4 of 46 couples in whom the virus in the seroconverting partner did not match that of the index partner. The analysis should have included data from these nontransmitting couples as long as they remained seronegative or discordant, which would reduce estimated rates of HIV transmission.

Second, it is not clear why Wawer et al., who establish HIV transmission linkages through genetic sequencing, limit their analysis to couples in which the nonindex partner was monogamous. As a general rule, studies should present and analyze all relevant evidence, including, in this case, data from as many of the other 175 serodiscordant couples for whom partner-to-partner transmission could be confirmed by genetic sequencing.

Finally, insufficient attention to blood exposures undermines their conclusions. Wawer et al.'s report of 4 genetically unlinked incident infections in monogamous partners of HIV-positive spouses suggests nonsexual HIV acquisition. Moreover, the high rate of seroconcordance among 23 couples with incident HIV in the index partner draws attention to blood exposures in the home. In a 1990s study, more than half of Ugandan families owned injection equipment [9]; sharing of razors, etc., should also be considered. Wawer et al. cite another study [10] to show a lack of association between injections and HIV in Rakai; this is less satisfying than a presentation of available (if limited) information on blood exposures, exploring associations with 4 reportedly nonsexual HIV transmissions and curiously high seroconcordance. In sum, Wawer et al.'s estimated rate of HIV transmission of 0.0082 transmissions/coital act during early HIV infection depends crucially on what appears to be an exceptionally high rate of seroconcordance among couples with incident HIV in the index partner.

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Reply to Gisselquist and Potterat

To the Editor—Gisselquist and Potterat [1] suggest that our Rakai data [2] overestimate the increased risk of HIV transmission per coital act during acute HIV infection. However, the 3 earlier studies that they cite [3–5] also reported higher rates of HIV acquisition in partners of new seroconverters compared with partners of seroprevalent persons. Direct comparison of transmission rates between these prior analyses and the Rakai study is problematic, given differences in the frequency and length of follow-up, rates of loss to follow-up, and condom use, and because of the absence of information on coital frequency and viral load in the earlier studies. Gisselquist and Potterat do not refer to other research that suggests that we may be conservative in our estimate [6] (which was based on an estimated mean period of 2.5 months between HIV acquisition and transmission to a partner), given what is now known regarding the effects of high viral load on increased transmission [7, 8] and the very high but transient spike in viral load observed during acute infection [9].

Gisselquist and Potterat's calculation that our data imply an HIV transmission rate of 133 transmissions/100 person-years during acute infection is misleading, because it assumes that the high risk of transmission associated with acute infection is evenly distributed over a year. However, one cannot extrapolate the acute short-term estimates to longer periods [9].

Their letter questions our "unexpectedly" low proportion of seroconcordant HIV-positive couples as a proportion of couples with at least 1 infected partner. However, mortality, out-migration of 1 or both partners, and marital dissolution are all more frequent in couples with HIV-positive partners [3, 10], which reduces the cross-sectional population prevalence of such unions. In the studies cited by Gisselquist and Potterat in their table 1, the 2 community-based cohorts with annual follow-up [3, 11] included a higher proportion of seroconcordant HIV-positive couples (41%–51% of all HIV-affected couples, similar to the 44% we reported in our article) than did the studies with less-frequent follow-up or more-mobile populations. However, it is not surprising that all of the studies, ours included, observed a lower proportion of seroconcordant HIV-positive couples than would be expected on the basis of our observed spousal transmission: 2 HIV-positive partners have a low probability of remaining together and being identified as a couple.

Gisselquist and Potterat question our removal of 4 couples in whom the originally HIV-negative partner acquired HIV from an external source. Since these individuals had already acquired the virus from an individual whose stage of HIV infection was unknown, they would not contribute to our analysis of their official partner's probability of *transmitting* HIV. Although superinfection from the official partner would theoretically be possible, it would imply complex immunological dynamics that were not the focus of our analysis. Removal of these 4 cases of new HIV infection (3 of which occurred in couples with prevalent HIV-infected index partners) had a negligible effect on the overall rates of transmission reported in the article.

We excluded couples with nonmonogamous HIV-negative partners, since individuals with multiple sexual exposures differ in behavioral and, possibly, immunological characteristics from those who are monogamous. Persons with molecular evidence of external HIV acquisition were removed from the analysis for the reasons discussed above. Removing nonmonogamous individuals from the numerator, while retaining them in the denominator, would result in bias.

Injections did not contribute substantially to the observed rates of HIV acquisition. Forty-five percent of HIV-negative partners in these couples reported receiving an injection, mainly from health-care providers, and their rate of HIV acquisition was slightly lower than that of the partners reporting no injections (adjusted incidence rate ratio, 0.72 [95% confidence interval, 0.29–1.82]), which is consistent

with previous Rakai analyses [12]. Furthermore, nonspousal household members residing with HIV-positive individuals did not exhibit high rates of HIV acquisition, regardless of the stage of the index infection, as would be expected if transmission occurred through domestic exposure to blood.

We thank Gisselquist and Potterat for their comments. However, we believe that the data support our original conclusions.

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