

# STATISTICAL ISSUES IN THE DESIGN OF HIV VACCINE TRIALS<sup>1</sup>

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## ABSTRACT

HIV vaccine trials present significant challenges related to trial endpoints, vaccine efficacy measurement, and the role of nonvaccine interventions. Infection is a valid endpoint for detecting sterilizing immunity. But if the vaccine prevents AIDS without preventing infection, infection may be a misleading surrogate. Appropriate endpoints must be defined for other mechanisms of vaccine action. Direct, indirect, behavioral, and biological effects all determine vaccine efficacy. False security among HIV-vaccine recipients may make negative behavioral effects an important component of vaccine performance. Both biological potency and a more comprehensive program effectiveness should be measured. These goals may require unblinded designs or community randomization. Nonvaccine interventions are currently the only HIV-prevention strategy. Support for larger scale implementation requires more rigorous

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evaluation that is less dependent on self-reported behavioral changes. The vaccine trial cohorts provide a unique opportunity to cost-effectively evaluate behavioral interventions.

## BACKGROUND

Acquired immune deficiency syndrome (AIDS), which is caused by the human immunodeficiency virus (HIV), has been reported to the World Health Organization (WHO) in 411,907 people in the United States and 985,119 worldwide as of June 30, 1994, but the WHO estimates that the actual number of AIDS cases worldwide is closer to 4 million (95). Estimates of current HIV infections range from greater than 13 million (9) to greater than 19 million (69). The WHO estimates that by the year 2000, 30 to 40 million individuals will have been infected since the beginning of the pandemic. As yet there is no cure for the disease.

HIV/AIDS research has included development of therapeutic interventions aimed at individuals already infected and preventive interventions aimed at individuals not yet infected. Therapeutic interventions investigated so far consist of treatments with drugs and biologics and therapeutic vaccines. Preventive interventions under investigation include prophylactic vaccines and nonvaccine interventions designed to reduce infection risk for uninfected individuals. Currently, no single one of these intervention types is capable of halting the epidemic.

A number of therapeutic interventions have been developed that inhibit the activity of the virus. Despite some successes in advanced AIDS patients, the overall success has been meager (58). Zidovudine (ZDV), an anti-retroviral drug, is the treatment that has been most extensively tested. It has shown success in extending the lives of advanced AIDS patients (36). In patients with early or no symptoms, however, it slows the progression to AIDS (37, 53, 92) but does not appear to improve overall survival time (1, 53). The initial results of the Concorde trial (1) have caused the medical establishment to reevaluate the role of ZDV in the fight against AIDS (26, 43, 80).

Two other anti-retroviral drugs have been widely examined in clinical trials. Didanosine (ddI) and zalcitabine (ddC) have been compared to ZDV and each other in a variety of trials (2, 35, 42, 60). There are settings in which ddI and ddC have been established to be effective, but they are still not close to being cures for AIDS. Combination therapies are also in the early stages of testing (24), but early results (34, 73) have not been impressive. Clumeck (22) reviews the current use of anti-HIV drugs.

An alternative approach for inhibiting the activity of the virus is the use of therapeutic vaccines. Since late 1988, a number have been evaluated in clinical trials (59, 93). Most have proved to be safe and many have induced immune

responses to HIV. However, the responses seen so far have been on biological measures such as antibody responses rather than clinical measures such as prevention of symptomatic AIDS-defining events and death. At present it is still unclear whether the biological responses will translate into clinical efficacy. Since most of these trials are small, it will be some time before the efficacy of these therapeutic vaccines can be assessed.

There has been more success treating and preventing the opportunistic infections that take advantage of the HIV-infected individual's weakened immune system. Prior to the advent of prophylaxis, most HIV-infected individuals had pneumocystis carinii pneumonia (PCP) episodes (18) and up to 40% developed mycobacterium avium complex (MAC) (19). By significantly decreasing the risk of both PCP and MAC episodes, successful prophylaxis has had an impact on the morbidity and mortality of the HIV-infected community. For other AIDS-defining opportunistic infections, a wide variety of drugs is being tried for prophylaxis (46), although the bulk of these are still in the testing phase.

The cost of treatment and care of HIV-infected individuals is extremely high. In the United States, it has recently been estimated that the cost of treating an HIV-infected individual from the time of infection to death is approximately \$119,000 (56) and that \$10.4 billion will be spent in 1994 treating all HIV-infected individuals (55). In the developing world where most existing cases are and most new cases are expected, this level of expense is out of reach of most individuals and governments. The search for treatments that inhibit the activity of the virus and prevent opportunistic infections remains of utmost importance. However, the challenges in developing such treatments and the cost of their use make it imperative that strategies for prevention of HIV infection also be explored.

The AIDS epidemic has spread rapidly since it was first identified. The rate at which epidemics spread is governed by the basic reproductive number,  $R_0$ , which measures the expected number of individuals who become infected from a single infected individual in a completely susceptible population (4, 29). If  $R_0$  is less than 1, the epidemic will die out because each infected individual is giving rise to fewer new infected individuals. Using data available through the mid-eighties, Anderson & May (4) present basic reproduction numbers for HIV that range from 2 to 11. These high rates help explain the rapid progress of the virus. HIV/AIDS prevention research is aimed at lowering these basic reproductive numbers to stop the onslaught of the epidemic. Two prevention strategies are the development of efficacious prophylactic vaccines and the development and implementation of effective nonvaccine prevention strategies.

The first generation of prophylactic vaccines is currently undergoing Phase I and II clinical trials, which are devoted primarily to testing vaccine safety

and immunogenicity. Almost 30 (93) vaccine candidates are currently in clinical trials, of which 2 are in Phase II trials. These were anticipated to be the first vaccine candidates available for full-scale Phase III efficacy testing. However, based on various data available from the Phase I/II trials, animal studies, and cross-neutralization studies, the AIDS Research Advisory Committee recommended on June 17, 1994, that the National Institute of Allergies and Infectious Diseases (NIAID) not go ahead with immediate Phase III testing of these two vaccines. There are currently no other vaccines in NIAID-sponsored Phase II trials. In its June 17, 1994, press release, the NIAID estimated that it would take between one and three years to gather the data necessary before they could propose expanded trials of suitable vaccine candidates.

There is still tremendous uncertainty about many areas of HIV vaccine development, of which we mention five. First, there are questions about the appropriate composition of the vaccine. Both of the initial Phase II candidates are based entirely on the gp-120 envelope protein of the virus. However, numerous other approaches (33, 54, 83, 93) are also undergoing clinical or preclinical testing, including other vaccines based on recombinant subunits of the virus, DNA vaccines, as well as vaccines based on whole killed viruses or live attenuated viruses. Second, there are questions about how the vaccine should be presented to the immune system (3, 11, 47). Novel adjuvants are being evaluated to increase the magnitude, breadth, and duration of immune responses. Third, there are questions regarding what component of the immune system to stimulate and how to elicit long-lasting immune responses. This uncertainty relates to whether it is necessary to stimulate both the humoral and cell-mediated arms of the immune system and whether it is necessary to elicit both systemic and mucosal immunity (10, 11, 45, 71). Fourth, a major question relates to how to achieve protection against a wide variety of strains of the virus (11, 45). HIV exhibits extensive genetic variation, particularly in its most antigenic region. Recent reports have suggested that while vaccines in various stages of testing have shown some success in protecting against strains of HIV similar to that used to make the vaccine, little success has been recorded in protecting against different strains, particularly the "wild" strains to which most people are exposed worldwide (25). Addressing the issues related to HIV variation is currently a major focus of basic scientific research. Fifth, concerns regarding the safety of the vaccines include fears that the vaccine may in fact increase susceptibility to infection, or possibly worsen the impact of HIV once an individual has become infected (70). Safety fears are also the primary reason why early efforts have concentrated on vaccines based on envelope proteins and other recombinant subunits of the virus rather than live attenuated viruses or whole killed viruses.

These uncertainties make it imperative that the early vaccine trials, even if not providing sufficiently efficacious vaccines for widespread use, should at

least provide information relative to these questions. They also necessitate increased focus on rigorous evaluation of nonvaccine prevention methods since these are currently the only weapon in HIV prevention and will be so for some time.

HIV infection can be prevented. Most HIV infections around the world result from high-risk behavior, so effective nonvaccine interventions that reduce high-risk behavior could theoretically lower HIV-transmission rates. A wide variety of nonvaccine interventions has been investigated in different communities (7, 38, 57), including needle-exchange programs, promotion of the use of barrier methods such as male and female condoms, use of topical virucides and microbicides, as well as more general health services and counseling programs. However, few nonvaccine interventions have received rigorous evaluations. Fisher & Fisher (38) note that "exhortations to intervene and recommendations for interventions far outnumber credible interventions that have been subject to statistical evaluation." Coates (23) notes that there is a "remarkable dearth of information on the effectiveness of behavioral change interventions" and Kelly & Murphy (61) observe that "the paucity of carefully evaluated studies of AIDS risk behavior change interventions is immensely troubling." Vaccine trials could provide an excellent opportunity to undertake rigorous controlled evaluation of nonvaccine interventions.

The trials raise ethical issues related to informed consent, exploitation of third-world and other vulnerable populations, potential risk increases for participants caused by perceived immunity to HIV, and possible discrimination against trial participants in areas such as health insurance, employment, and travel. Substantial effort is going into attempts to solve these difficult ethical questions (84); these efforts are not discussed here.

A final issue that potentially affects the feasibility of mounting vaccine-efficacy trials is the fear of government in the populations that will be needed for evaluating the vaccines (68). These considerations also motivate some of the statistical issues in designing the trials.

Because of the challenges in development of interventions for prevention of HIV infection, and the effort that will go into implementation of the pivotal field trials, the methods used to design and analyze these trials must be appropriate and must allow for reliable assessment of the proper role of these interventions. We review some of the more important issues in trial design and analysis.

## CHOICE OF ENDPOINTS

A vaccine could have three basic mechanisms of action that would confer benefit to the individual: (a) it could prevent an individual who comes into contact with HIV from becoming infected at all, thus providing "sterilizing

immunity;" (b) it could allow individuals to seroconvert but not have chronic infection, hence allowing only "transient infection;" and (c) it might not prevent chronic infection, but instead could prevent or delay the onset of AIDS and the death of the individual. One further mechanism of vaccine action that might not confer direct benefit to the vaccinated individual but might have considerable public health consequences is reduction in an infected vaccinee's level of infectiousness.

The goal of vaccine research is development of a vaccine that saves lives or at least provides some tangible benefit to individuals who become HIV-positive in spite of being vaccinated. Since potential benefits could arise from a vaccine that works according to any of the mechanisms described above, the methods used to evaluate vaccines should be able to detect success according to any of these mechanisms. This would require using death or onset of symptomatic AIDS-defining events as trial endpoints, but, since the incubation period for the virus is so long, this would result in very long trials. Because it may be unrealistic to wait for results from such long-term trials, surrogate endpoints such as HIV infection may need to be used.

A surrogate marker is usually a measure of biological activity that is meant to substitute for a measure of efficacy, where effects on efficacy endpoints should unequivocally reflect tangible benefit to the participant. These measures of biological activity can usually be determined over a shorter period than the measures of efficacy. However, some serious problems are associated with using surrogate markers; these have been discussed in different medical contexts (32, 39, 40).

Prentice (77) provided a criterion for what constitutes a valid surrogate: an endpoint that yields a valid test of the null hypothesis of no association between the treatment and the clinical endpoint. This criterion is satisfied if the surrogate fully captures the effect of the treatment on the endpoint, and is informative about the clinical endpoint. Unfortunately, it is rarely possible to establish that markers satisfy the Prentice conditions (39). An example is provided by CD4 lymphocyte counts, which were used as surrogates in HIV/AIDS clinical trials of nucleoside analogs. Although CD4 counts predict time to death in a natural history setting, intervention-induced changes in CD4 counts are not generally predictive of intervention-induced changes in survival time or in time to AIDS (27, 40, 67); CD4 count is therefore a less than ideal surrogate.

Most discussion relating to the evaluation of prophylactic HIV vaccines in definitive field trials has focused for two principal reasons on the occurrence of an initial infection (30, 87) as the measurement endpoint, which is appropriate for evaluating the sterilizing immunity mechanism of action. First, the nature of HIV's attack of the immune system and the ability of HIV to persist in host-cell DNA might make it impossible for a vaccine to cope with the virus once it has become established (64). Second, the time to initial infection is a well-defined

endpoint that can be readily documented and that will be observable in a three- to five-year clinical trial with high enough frequency to make evaluation feasible. However, most effective vaccines for other diseases have not prevented initial infection but have allowed only transient infections to occur (64). If, rather than providing sterilizing immunity, the vaccine allows only transient infection, suppresses chronic infection, or reduces infectiousness, using initial HIV infection as the endpoint could lead to false-negative conclusions. As a result, a vaccine that prevented everyone from developing AIDS but did not prevent initial infection would possibly be discarded as worthless. Since AIDS rather than HIV infection is the problem, we could be discarding the solution to the problem by focusing on the initial infection. Motivated by these considerations and studies of vaccines in animals that have shown reduced viral burden even though they have not prevented initial infection, the appropriateness of initial infection as the endpoint is being questioned (24, 83).

Defining endpoints that allow initial infection but measure some other protective property requires a definition of what constitutes protection for an individual with an initial infection. A vaccine might be considered a success according to this endpoint if it allowed an initial infection but resulted in no detectable virus in subsequent serial viral cultures or PCR assessments after a period of, say, three to six months. Using transient infection as the trial endpoint will require the development of sensitive culture or PCR techniques able to detect low levels of virus. However, no technique is completely sensitive and so, for example, endpoints based on assays for transient infection must be interpreted as suppressed levels of virus rather than complete clearance of infection. It remains to be seen whether levels of virus that are suppressed by vaccine action translate into delay or prevention of symptomatic AIDS-defining events and death.

Although there are undeniable weaknesses with the use of either sterilizing immunity or transient infection as trial endpoints, the need to use surrogate markers in vaccine trials is much more acute than in treatment trials because the true endpoint of interest is further into the future. Acknowledging these weaknesses, continued long-term follow-up of all individuals will be essential to determine whether reduction in the rate of HIV infection translates into tangible benefits such as reduction of symptomatic disease or increases in survival time. Extended follow-up of all participants would pay special attention to those becoming infected, and where necessary record linkages to AIDS and death registries would be used to determine the effect of the vaccines on the real endpoints of interest, either onset of symptomatic AIDS or death. Meanwhile, better markers are being sought (90) and more reliable uses of surrogate marker information are being explored. The latter includes research into using marker information as auxiliary information, rather than as replacement endpoints, to improve efficiency of clinical trials (39–41, 65).

## MEASURING VACCINE EFFICACY

The extensive literature on assessing vaccine efficacy, which goes back to Greenwood & Yule (49), has focused largely on efficacy measurement in vaccination programs rather than randomized field trials (74). We review the literature relevant to the situation of a randomized field trial. Throughout, we assume that a suitable endpoint has been specified.

### *Effects of Vaccination*

The effects of vaccination are best understood by examining the factors that determine the risk of infection during some time period, from the perspective of an individual called the index participant. Because certain unsafe acts are riskier than others, the overall infection risk will depend on the various types of risk activities in which the index participant engages. However, to simplify exposition, we assume a single type of risk activity. The infection risk depends on the following four parameters: the number of unsafe contacts in the time period; the fraction of unsafe contacts with infected individuals; the probability that an infected individual transmits the virus at a single contact (infectivity probability); and the probability that an uninfected individual acquires the virus at a single contact with an infected individual transmitting virus (susceptibility probability). Note that the risk of infection increases as any one of these parameters increases. The product of the first two determines the number of contacts with infected individuals and of the second two determines the probability of HIV transmission on a single contact with an infected individual. Of the four parameters, the susceptibility probability and the number of unsafe contacts are specific to the index participant, whereas the fraction of contacts with infected individuals and the infectivity probability reflect the environment in which the index participant is active.

The intended effect of a vaccine is to provide biological protection against the virus. However, the act of vaccination may have the additional unintended effect of changing the vaccinee's behavior if he or she perceives immunity to the virus as a result of being vaccinated. If the index participant is the only individual in the population who is vaccinated, then the vaccine can affect the risk of infection for that participant only through effects on the two index participant-specific parameters. These effects constitute the direct effects of the vaccine for the index participant. However, if the index participant is part of a vaccination program, the vaccine could affect the risk of infection for that specific participant through effects on all four parameters. Then the effects for the index participant consist of the direct effects on the index participant-specific parameters, and the indirect effects on the parameters reflecting the environment in which the index participant is active.

The direct biological effect of the vaccine on risk of infection for the index



participant is its effect on the susceptibility probability. The direct behavioral effect is on the number of unsafe contacts in which the index participant engages. The effect of vaccination on the infectivity probability represents an indirect biological effect. The effect of vaccination on the fraction of the index participant's contacts with infected individuals represents a combination of indirect biological and behavioral effects because either the vaccine's biological or behavioral effects could prevent infection in the index participant's partners. From the perspective of the index participant, the indirect biological and behavioral effects are experienced simultaneously. Together they make up what is typically called herd immunity.

### *Measurement Objectives*

In an actual vaccination program, the vaccine's direct, indirect, biological, and behavioral effects all play a role. Since it is anticipated that the initial vaccines will be significantly less than 100% effective, behavioral changes could induce effects that would be an important component of overall program effectiveness. In particular, if individuals increase their exposure in response to vaccination, a vaccine that is not fully effective could result in an increase of HIV infections even though the biological activity of the vaccine is positive (85). Therefore, a measure of *program effectiveness* that accounts for the vaccine's biological and behavioral effects, as well as all direct and indirect effects, should ultimately drive decisions about the use of the vaccine in clinical practice.

One drawback of including behavioral effects in a measure of vaccine success is that they will depend on the particular community in which the vaccine is delivered. For example, the changes in risk behavior among gay men who know that they are receiving the vaccine may be different from those of injecting drug users (IDUs). Measures of program effectiveness estimated from vaccine trials will reflect the particular environment in which the trial is offered. Since the trials will be undertaken in the highest-risk communities, the behavioral effects of the trial will approximate these effects in the communities most at need of the vaccine. However, the behavioral effects may be different in lower-risk communities not participating in the trial. The behavioral effects may also change as better nonvaccine intervention programs are discovered. Therefore, in addition to having measures of program effectiveness, it will be important to obtain some measure of the vaccine's effect that is less influenced by the particular population in which the program is provided. Such a measure might concentrate entirely on the direct biological effect on the susceptibility probability—in other words, on the *biological potency* of the vaccine.

Two principal measurement objectives are therefore needed in comparative HIV vaccine trials:

- the effect the vaccine would have on the spread of HIV if used in a vaccination program; and,
- the effect the vaccine would have on reducing the susceptibility probability.

We use the terms *program effectiveness* and *biological potency*, respectively, to characterize these effects.

Greenwood & Yule provide criteria for evaluation of vaccines: in the context of HIV vaccine trials, the participants must be alike in all material respects; and the effective exposure to HIV must be identical among the vaccinated and unvaccinated participants.

For estimating either program effectiveness or biological potency, random assignment of individuals to the vaccine and the control groups in a randomized field trial will satisfy the first of these criteria. The measure of biological potency attempts to estimate direct biological effects controlling for all indirect effects as well as direct behavioral effects. Therefore, the second condition is appropriate for estimating biological potency. The combination of randomization and blinding of participants to their vaccine status will meet the second criterion. For measuring biological potency, it will be necessary to ensure that unblinding does not occur, since unblinding could cause changes in the behaviors in the two arms of the trial and result in confounding of biological effects with exposure differences (52).

For measuring program effectiveness of an HIV vaccine, the second criterion is not appropriate. This measurement should ideally include all direct and indirect effects, including the direct effect on risk behavior for a participant in a vaccine program. To measure the direct effects related to behavioral changes, the conditions in a vaccination program must be simulated as closely as possible. If a vaccine program were undertaken, individuals would know they were receiving the vaccine. Thus, it would be inappropriate to conduct a blinded randomized trial because individuals, if they remain blinded, would not know their vaccination status and would not make the same behavioral changes as if they did know their status. Therefore, the evaluation of program effectiveness will require the use of unblinded randomized trials. Since measuring biological potency requires a blinded trial, whereas measuring program effectiveness requires an unblinded trial, both measurement goals cannot be met with the same simple trial. The actual design of trials will therefore depend heavily on the relative importance of the different measurement goals.

### *Estimability of Measurement Objectives*

Although we have just argued the need for blinded and unblinded randomized field trials to assess a vaccine's biological potency and program effectiveness respectively, neither quantity will be fully estimable in the type of blinded or unblinded vaccine trials currently being planned. We discuss how biological

potency and program effectiveness are related to the respective estimable quantities of *vaccine efficacy* and *vaccine field efficacy*.

**PROGRAM EFFECTIVENESS** Haber et al (50) point out that, even for an unblinded trial, the effect of herd immunity is not measurable in a cohort study such as a field trial in which the individual is the unit of randomization, because both the vaccinated and unvaccinated groups experience the same indirect effects. Even if the vaccinated and unvaccinated groups could be separated, a vaccine trial consisting of a small fraction of the total contact population is not a realistic environment in which to calculate estimates of the type of herd immunity that might be expected in a full-scale program. A vaccine's beneficial effect could substantially be through a reduction in infectivity of breakthrough cases rather than through reduction in susceptibility. To obtain direct evidence of such effects on infectivity, one would need to design trials that capture both indirect and direct effects of the vaccine. These could be large-scale pre-marketing controlled field trials with essentially contained communities as the unit of randomization. Such trials might need to be of long duration if the vaccine does not reduce infectivity of individuals who are in the community and already have HIV at the time of trial initiation.

We denote the direct behavioral and biological effects measurable by an unblinded randomized vaccine trial as the *vaccine field efficacy*. Although this parameter is not equivalent to the program effectiveness parameter, it will capture that component of the vaccine's effects with the greatest potential to undermine the biologic potency of the vaccine, namely the direct behavioral changes. A primary weakness will be its insensitivity to detecting vaccines that would reduce the spread of HIV by reducing infectivity rather than susceptibility.

**BIOLOGICAL POTENCY** When the effective exposure to HIV is identical between the vaccinated and unvaccinated persons, Greenwood & Yule define *vaccine efficacy* (*VE*) by:

$$VE = 1 - AR_v/AR_u,$$

where  $AR_v$  and  $AR_u$  are the attack rates in the vaccinated and unvaccinated groups, respectively. The attack rate is defined to be the probability of becoming infected. Note that  $\{1 - AR_v/AR_u\}$  would yield vaccine efficacy in a blinded trial and vaccine field efficacy in an unblinded trial that has individuals as the unit of randomization.

The use of randomization and blinding in a vaccine trial would result in approximately comparable exposure to the HIV virus in the vaccinated and unvaccinated groups. However, to estimate biological potency, it would be necessary to adjust for the *specific* amount of exposure experienced by the

individual trial participants, not just to ensure comparable exposure (51). For HIV vaccine trials, amount of exposure means number of unsafe contacts with an infected individual transmitting virus. Because individuals will not know whether a partner is infected with HIV and transmitting virus, it will be impossible to accurately estimate exposure to HIV. Since adjustment would have to take place at the individual level, even if the two groups have comparable but heterogeneous exposure such as might be expected in a randomized blinded trial, the *VE* measure defined above will only approximate the biological potency.

Although alternatives to the *VE* measure have been proposed (50), these depend on assumed underlying models. As pointed out by Greenland & Frerichs (48), *VE* as defined above "is of straightforward utility in evaluating the benefit of a vaccination program, regardless of the model of effect." A further argument in favor of using the *VE* measure is that when the probability of infection from a single contact is low, as is the case with HIV (15), the *VE* statistic provides a reasonable approximation to the biological potency parameter.

### *Heterogeneity in Susceptibility and Vaccine Effectiveness*

Another issue that arises in HIV trials is the heterogeneity in different individual's susceptibility to acquiring the virus from a single contact. Considerable evidence from various partner studies indicates that susceptibility to HIV varies across individuals (15). Svensson (89) considers variability in susceptibility and examines situations that could lead to either overestimation or underestimation of vaccine efficacy.

Heterogeneity can also arise in effectiveness of the vaccine. Smith et al (88) describe two models for the imperfect action of the vaccine: (a) the vaccine reduces the susceptibility probability for all individuals in the population by a fixed quantity but does not totally eliminate risk; or (b) the vaccine works perfectly for a fraction of the population and not at all for the rest. Any number of mechanisms of vaccine action between these two is also conceivable. Vaccines can also fail in the "duration" of protection they offer (72). The different ways in which a vaccine fails can have quite different effects on epidemics (50, 72, 88).

Developing an understanding of vaccine action could have useful implications for future vaccine development. It might be possible to identify measures of immunogenicity that are correlated with occurrence of HIV infection. By comparing biological and immunologic parameters of trial participants for those who do with those who do not become infected, we might obtain leads as to the type of immune responses that future vaccines should aim to stimulate (78). However, one should be very cautious about the reliability of such leads. These measures of immunogenicity might simply be markers identifying the

intrinsic heterogeneity in different individual's susceptibility to acquiring the virus. For example, occurrence of a specific type of antibody response might simply provide identification of participants intrinsically at low risk of HIV infection rather than evidence of a causal mechanism by which the vaccine achieves a protective effect.

## EVALUATING NONVACCINE INTERVENTIONS

Currently, nonvaccine interventions are the only tool for preventing HIV infection. At least for some individuals, they may remain the only prevention strategy for the near future since early HIV-vaccine candidates are unlikely to provide universal complete protection, and may never do so given the variation in the virus. The objective of nonvaccine interventions is to modify people's behavior to eliminate or at least reduce their risk of infection. These interventions vary as to their target audience, their promotion strategy and whom they use to communicate the message (31). Most interventions consist of some combination of suggested behavioral modifications, including recommendations for complete elimination of certain activities such as suggestions of sexual abstinence, or modification of existing behaviors through the use of technologies such as condoms or spermicides.

The complexity of nonvaccine interventions has presented many challenges for their evaluation. These challenges have made rigorous evaluation difficult and rare (23, 38, 61). Although numerous interventions have received evaluation with seemingly positive results (7, 38, 57), there remains ambiguity because of the evaluation method (38). We focus on two common shortcomings of existing evaluation of nonvaccine interventions—specifically, the observational nature of the studies and the endpoints used—and discuss the role of vaccine trials in addressing these shortcomings.

### *Study Design*

Ideally, nonvaccine prevention interventions should be evaluated in a randomized, controlled field trial (RCT). All too frequently, RCTs have not been viewed to be feasible either due to perceived difficulties with achieving compliance/noncompliance of a prescribed behavior or because of beliefs that the intervention would provide some benefit without causing any harm. Observational studies provide an alternative approach to using RCTs and have had a long history in epidemiology. Unfortunately, because of lack of a randomized control group, "it is rare ... for a single study to provide convincing evidence of causality" (14); numerous studies reporting similar results are required before reliable conclusions might be reached.

An example of the need for observational studies is provided by the evaluation of latex condoms as an intervention technology. It would be difficult to

identify a setting in which randomization could be used to determine condom use. Also, early studies provided positive although limited evidence in support of latex condoms as a device for reducing infection risk. Many studies over many years were required to establish efficacy for condoms. While Weller concluded on the basis of 16 studies up to mid-1990 that "a consistent association across studies remain[s] to be demonstrated" (94), two large European observational studies (28, 81) have recently demonstrated a strong association between infection and lack of consistent condom use. These and earlier studies form the basis for the CDC's statement that "condoms are highly effective for preventing HIV infection and other STDs when used consistently and correctly" (20).

Observational studies served a useful role in evaluating the efficacy of condoms, but the results from such studies have been less reliable for most other interventions. For example, an evaluation of pre- and post-HIV test counseling (75) suggested possible negative effects, although the conclusions of this observational study are unclear (44, 76) and must be considered along with numerous other evaluations of counseling, many of which have yielded positive results (57).

The evaluation of the spermicide, nonoxynol-9, provides another example of a technology for which efficacy remains uncertain. An observational study (96) was conducted to evaluate the effect on seroincidence rates of nonoxynol-9 administered in the form of vaginal suppositories. The investigators designed an observational study rather than a RCT because they felt "ethically bound to offer spermicides to all participants" based on the belief that use of the suppository would provide some protection from HIV. The study demonstrated a reduction in risk from the use of the nonoxynol-9 vaginal suppository. However, it is difficult to infer causality from this seemingly positive result because this study had no randomized controls and women were using condoms in addition to nonoxynol-9. Contrary findings were obtained in a placebo-controlled RCT of a commercially available nonoxynol-9 contraceptive sponge (66). Data from this trial indicated slightly higher rates of HIV infection associated with nonoxynol-9 use; however, the investigators noted two important issues that limit the generalizability of their results (66). First, the failure of the intervention may be due to the delivery mechanism, in this case the sponge, rather than the nonoxynol-9. Second, a number of women on the nonoxynol-9 arm of the trial experienced lesions in the vaginal mucosa, which may increase susceptibility to HIV. It is suspected that these lesions may be due to high doses of nonoxynol-9, and a lower dose might therefore be more efficacious.

Further examples of RCTs being used to evaluate nonvaccine interventions do exist (63, 82), but most have not been evaluated using RCTs (7). In some settings there may appear to be ethical reasons in favor of observational studies,

nevertheless extreme care is required when determining whether it would be ethical to withhold an intervention from control arm participants; inappropriate reliance on observational studies could lead to negative consequences being undetectable, while at the same time could greatly weaken the strength of any positive results. Nonoxynol-9 as delivered in the RCT appeared to increase vaginal lesions and thus caused harm. These negative effects on the vaginal mucosa and on risk of HIV infection would have been much more difficult to detect in an observational study. In such studies, effects of a modest size, either positive or negative, can be difficult to ascribe to the intervention because they may be of the same order of magnitude as methodological biases that can arise in even the most carefully conducted observational study.

RCTs are the gold standard for evaluating interventions due to many well-known advantages that relate to the unbiasedness and reliability of such evaluations. Some examples of interventions that might be evaluated in a RCT include needle-exchange programs for IDUs and approaches for reducing HIV-infection risk from sexual intercourse through the use of mechanisms over which the female partner has control. In the latter setting, trials could include evaluation of female condoms, or of new delivery methods and dosing of nonoxynol-9 or, alternatively, of other spermicides such as gramicidin, which has shown a 1000% increase in anti-HIV activity relative to nonoxynol-9 in recent *in vitro* studies (12, 13).

### *Endpoints*

Nonvaccine interventions aim to reduce the risk of symptomatic AIDS-defining events and death by reducing the risk of HIV infection. Thus, prevention of HIV infection might be an appropriate study endpoint in most definitive RCTs. However, alternative endpoints would be required when evaluating nonvaccine interventions that may have serious negative consequences, especially if these are not related to the occurrence of HIV. One example is the use of formula-feeding instead of breast milk as an intervention in developing countries for preventing HIV transmission from HIV-infected mothers to their babies. The use of potentially contaminated water in formula, and the loss of immunogens usually passed through the mother's breast milk, can have very serious negative consequences, including death, for the baby. Symptomatic disease and infant mortality must be considered to be key elements of the primary endpoints in such a trial.

Trials using HIV infection as the endpoint will typically be of long duration and require large numbers of participants because the endpoint of HIV infection is a rare event, even in communities at high risk (7). This fact previously has led to widespread use of self-reported changes in risk behavior as surrogate endpoints for evaluating nonvaccine interventions. Reviews list many examples of nonvaccine interventions with promising results as measured by self-

reported endpoints (7, 38, 57). Unfortunately, the well-recognized difficulties associated with self-reported data (17, 79) have caused ambiguity in study conclusions (38).

As is usually true with surrogates, self-reported endpoints should not be used as primary endpoints in definitive trials. However, they remain an essential component of the evaluation process. In trials providing a definitive evaluation of the effect of nonvaccine interventions on the risk of HIV infection, self-reported risk-behavior endpoints provide valuable insight into participant compliance and into the impact of the intervention on behavior. Self-reported endpoints are also the appropriate primary outcome measures in smaller Phase I/II or screening evaluations (7), which are designed to rapidly screen promising interventions for potential evaluation in large definitive Phase III field trials. Because of their importance, there has been extensive research in recent years to improve the reliability of self-reported endpoints (91).

Some studies have attempted to overcome certain problems associated with self-reported changes in behavior. Changes in sexual behavior and injecting drug use have been measured by redeemed condom coupons and number of needles exchanged (38). Both suggest adherence to the behavioral recommendations, but neither is a perfect measure of actual adherence. In an evaluation of pre- and post-HIV-test counseling, Otten et al (75) use the presence of STDs as a measure of risk activity. This is useful in being not only a marker of sexual activity, but also an objective efficacy endpoint that represents occurrence of symptomatic disease and that is known to be correlated with occurrence of HIV infection.

To motivate much-needed implementation of interventions on a scale large enough to have significant public health impact (62), evaluations must demonstrate that "new infections have been averted by such change" (7). Since such support will likely be based on some cost-benefit analysis (7), with benefits measured in terms of prevented HIV infections, "hard" evidence is needed on the efficacy of the interventions. To increase rigor and gather harder evidence, it has been recommended that evaluation of nonvaccine interventions be undertaken in the same three-step process that is used in drug trials and would be used in HIV vaccine trials (5, 6, 76). For nonvaccine interventions, Phase I could examine issues like feasibility of intervention schedules, Phase II could include larger studies like those evaluations that have been carried out so far, and Phase III trials could be RCTs that use the relevant endpoint of infection (6). Phase II would typically use self-reported behavioral endpoints to provide preliminary rather than definitive evidence for the efficacy of the intervention.

The vaccine trials provide a unique opportunity to circumvent significant impediments usually associated with the use of HIV infection as the endpoint in evaluations of nonvaccine interventions. Since the vaccine cohort would already be assembled with HIV-infection status being measured for vaccine



evaluation, the sample size/cost argument against using HIV infection as the endpoint in a RCT would become moot. There would be costs associated with implementing the interventions, but, as long as they do not detract from the evaluation of vaccine efficacy, they may be far outweighed by the value of the definitive results attainable in this setting.

### *Factorial Designs*

One way to incorporate evaluation of nonvaccine interventions into the vaccine trials is through factorial designs, which have previously received limited consideration in the clinical trial setting (16). A factorial design with the factors being vaccine/no vaccine and intervention/no intervention would allow the evaluation of the main effects, i.e. the respective efficacies of the vaccine and nonvaccine intervention, as well as the interaction between the two.

Slud (86) has developed methods for 2 by 2 factorial designs based on the proportional hazards model, where relative risk parameters are defined to represent the main effects of the two interventions and the possible interaction. Slud compares a 2 by 2 factorial design to a 3-group design containing a control group, a group receiving only the vaccine, and a group receiving only the nonvaccine intervention. He concludes that the power for testing the main effects in a factorial design usually is comparable to or better than that of the 3-group design. The exact gain from a factorial study depends on the extent of treatment interactions. Factorial designs are most advantageous if these interactions are nonexistent or modest (16). If the nonvaccine intervention is directed at preventing exposure, whereas the vaccine is directed at preventing infection given exposure, their interaction may be modest. In that situation, factorial designs would allow rigorous evaluation of nonvaccine interventions without significant loss of efficiency for evaluating vaccine efficacy. Larger sample sizes will be needed if each intervention has some positive effect, because the overall number of endpoints is likely to be smaller (78).

## CONCLUSION

Several important issues in the design of HIV vaccine trials remain controversial: the choice of endpoints, the role of blinding, and the type of behavioral interventions to be offered in the trials. Although approaches to vaccine evaluation in other disease areas provide useful guidance in resolving some of these controversies, unique aspects of the HIV-prevention setting will often require new approaches.

Many diseases for which vaccines have been developed have relatively short intervals between infection and disease symptoms. With these diseases, even if an infection occurs, the vaccine's ability or inability to assist in overcoming the infection will be observable during the course of the RCT. By contrast,

the median time from infection with HIV until the onset of AIDS is about 10 years (15). In a three- to five-year field trial, this time lag forces at least partial reliance on surrogates such as sterilizing immunity or prevention of transient infection. The latter requires defining some level of infection that is considered to be transient, such as no detectable virus in subsequent viral cultures for a duration of at least three months. However, it may not be known at the end of the trial whether such measures reliably ensure reduction in risks of AIDS-defining events or death. As a result, long-term follow-up of participants will be required in order to validate the use of the surrogates or as a way to observe potential effects of the vaccine on disease progression.

We have discussed the difference between evaluating biological potency and program effectiveness. Traditional vaccine evaluation often has concentrated on evaluating biological potency in controlled trials and has left evaluation of program effectiveness to postmarketing surveillance (8). This approach may not be appropriate when evaluating HIV vaccines. Vaccines for diseases such as mumps, measles, rubella, diphtheria, pertussis, tetanus, smallpox, and polio have resulted in 100- to 1000-fold reduction in occurrence rates (21). Effects of this magnitude can easily be identified, even with the imprecision inherent in postmarketing observational studies. By contrast, HIV vaccines may provide reductions of only twofold or less. Unlike other disease settings, the act of vaccination in HIV-prevention settings may also have the unintended effect of changing the vaccinee's risk behavior owing to a false sense of security, which further reduces or completely eliminates the small potential benefit achieved by vaccine-induced reductions in susceptibility. A blinded trial looking only at biological potency would provide no information about how these increases in risk behavior could impact the HIV-infection rate, and postmarketing surveillance would not provide a sensitive instrument for reliably estimating such small overall effects of the vaccine on the rate of HIV infection. It is therefore important to consider evaluation of program effectiveness, through an unblinded component of a RCT, as part of the evaluation process prior to vaccine approval. Finally, if a vaccine's beneficial effect is anticipated to be substantially through a reduction in infectivity of breakthrough cases, then large-scale premarketing field trials might be required where community would be the unit of randomization, thereby accounting for direct and indirect effects of a vaccine in estimating the program effectiveness.

Another unique aspect of HIV vaccine trials will be the need for care in "matching" the strain(s) of HIV used in the vaccine with the circulating strains in a given area. This will be necessary to provide a fair evaluation of the vaccine system. However, an implication is that results of vaccine evaluation may not be relevant in regions removed from the trial.

Finally, HIV, unlike most other diseases for which vaccines have been developed, can be prevented by behavioral changes. If funding for large-scale

interventions to promote these behavioral changes is to be obtained, it will be extremely important to subject interventions to rigorous evaluation. Such evaluations could use HIV infection as endpoints in a randomized controlled setting. The vaccine trials represent an opportunity for such evaluations. Since no vaccines are available for immediate Phase III trials, nonvaccine interventions represent the only way to prevent new infections in the short term. It may therefore be appropriate to use the existing cohorts that have been assembled for vaccine trials to evaluate promising nonvaccine interventions alone.

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