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Endpoints and Regulatory Issues in HIV Vaccine Clinical Trials:

Lessons From a Workshop

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Summary

A successful HIV vaccine would have a substantial impact on acquisition of infection, progression of disease among the infected, or infectiousness of the infected. Current vaccine candidates are anticipated to have their major effect on viremia, however, with the expectation that this would induce or be concordant with a reduced rate of AIDS, death, or infectiousness. Although direct assessment of disease progression or infectiousness may be impractical, available potential surrogates for these endpoints may be misleading. This article summarizes the proceedings of a National Institute of Allergy and Infectious Disease–sponsored workshop to explore the use of surrogate endpoints for licensure of an HIV vaccine. Early, medium, and late endpoints were discussed, along with challenges such as surrogate validity, the confounding effect of antiretroviral therapy initiation, and potential selection bias in the vaccine and placebo recipients who become infected. Results from 5 hypothetical HIV vaccine clinical trials with ambiguously successful results were presented to an expert panel for interpretation and discussion of next steps. Key recommendations included assessing magnitude and durability of surrogate effects, generalization across populations, and directed improvement of vaccines. Use of acquisition and a postinfection surrogate as coprimary endpoints was supported, along with use of composite endpoints and exploration of heterogeneity in vaccine efficacy by characteristics of the host and virus.

Keywords

Clinical trials; epidemiology; HIV vaccine; surrogate endpoint

In the third decade of the HIV pandemic, its impact continues to increase in most of the world. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that 40 million people,

most of them residing in developing countries, are living with HIV/AIDS¹ despite ongoing prevention efforts, which include widespread distribution of condoms, safe blood supply, and increased access to treatment for other sexually transmitted diseases (STDs). During the past 5 years, there has been a significant increase in efforts to improve access to antiretroviral drugs in underserved populations. This increase is mainly because of the dramatic survival benefit seen in the developed and developing world² and because treatment is accompanied by targeted prevention counseling that may itself reduce HIV transmission to sexual partners. These prevention efforts, however, have not controlled the pandemic, and many scientists and policy makers believe that an effective preventive vaccine is the only way to halt the further spread of HIV.

It has proven difficult to construct immunogens capable of eliciting neutralizing antibodies. The first efficacy trials using an HIV subunit vaccine did not elicit broadly neutralizing antibodies and failed to show protection.³ Most of the current HIV vaccine candidates aim to induce CD8⁺ T cells with specificity for HIV as a critical component of the overall immune response. These so-called “cell-mediated immunity” (CMI) vaccines are widely expected to have little effect on acquisition of HIV but may result in a favorable shift in the battle between virus and T cells among individuals who become infected after vaccination.^{4,5} It is hoped that this shift, as reflected in reduced levels of viral replication, may reduce or delay disease progression among infected vaccinees and also perhaps limit transmission to their partners. Although the goal of a completely effective HIV vaccine may ultimately prove unachievable, it is important to reflect on what endpoint data should be presented in support of application for licensure.

This article summarizes a 2-day workshop sponsored by the Division of AIDS, National Institutes of Allergy and Infectious Diseases (NIAID), on endpoints and regulatory issues in HIV vaccine clinical trials. The workshop began with a series of presentations to illustrate current issues in preventive HIV vaccine trial design. This was followed by the presentation of 5 hypothetical HIV vaccine clinical trials whose outcomes were chosen to focus discussion on specific issues. A panel provided feedback on the presentations, and their views are summarized here. The panel was selected by the Planning Committee to provide expertise in a variety of areas, including HIV pathogenesis, HIV vaccines, statistics, developing world issues, and vaccine licensure.

DIFFICULTIES OF EVALUATING HIV VACCINES

Primary endpoints for preventive vaccine efficacy trials are ideally defined to reflect pathogen-specific morbidity and mortality directly as measured under standard conditions of clinical care. Use of this standard for the evaluation of HIV vaccines creates difficulties, however. The relatively low incidence of HIV infection combined with the long asymptomatic period from infection to clinical disease, especially in populations with access to highly active antiretroviral drug therapy, results in efficacy trial designs that require enrolling large numbers of participants and following them for long periods, possibly a decade or longer. Moreover, considerable efforts are currently being made to provide widespread access to antiretroviral drugs, although there is still doubt regarding the implementation of these initiatives. Thus, what constitutes “standard clinical care” as it relates to specifying vaccine trial endpoints is unclear. Finally, important beneficial effects of an HIV vaccine may not manifest primarily through direct benefits to vaccinees but might be realized at a population level through indirect effects (ie, reduced infectiousness of infected vaccinees). Although the standard efficacy trial endpoints reflect the vaccine’s direct effects, they do not capture such indirect effects.

The efficacy of an HIV vaccine could be evaluated using 3 parameters:⁶

1. Vaccine efficacy-susceptibility (VE_S): the reduction in risk of acquiring HIV

2. Vaccine efficacy-disease progression (VE_P): the reduction in the cumulative risk of progressing to AIDS or death from time of the infection diagnosis
3. Vaccine efficacy-infectiousness (VE_I): the reduction in the risk of transmitting HIV to others

In this typology of vaccine effects, the standard measure of a vaccine's direct effects on morbidity and/or mortality endpoints is decomposed into 2 parameters, VE_S and VE_P , and a key indirect effect of vaccines, VE_I , is added to complete this definition of an efficacy profile. Note that these 3 parameters are biologic; behavioral efficacy parameters such as the vaccine effect on the number of unsafe sexual contacts can also be considered.⁷

The endpoints used to estimate these efficacy parameters should be sensitive, clinically relevant, and easy to measure and interpret as well as being robust to the effects of potentially confounding variables. The feasibility of measuring certain endpoints is also affected by considerations such as the effect of treatment on outcomes among infected vaccinees, the length of follow-up required before effects on disease course can be reliably measured, and access to data on the partners of infected vaccinees to measure secondary HIV transmission.

It is anticipated that a typical efficacy trial should follow participants for 3 to 4 years, with periodic screening for HIV; these data allow the direct estimation of VE_S . The decomposition of an overall efficacy parameter into VE_S and VE_P separates the problem of estimating vaccine effects on infection rates from the much more complicated problem of estimating vaccine effects on morbidity and mortality end-points. For VE_P , participants who become infected during the trial are likely to be followed in a separate part of the protocol, possibly for 2 to 10 or more years; during this time, data on time to morbidity (HIV-related and AIDS-defining illnesses) and mortality are collected and used for the calculation of VE_P . Data on morbidity and mortality among HIV-infected participants that are sufficient to estimate VE_P are difficult to obtain, however, not only because most endpoints do not occur until many years after infection but because of the likelihood of antiretroviral therapy (ART) being provided to HIV-infected volunteers before the development of opportunistic infections (OIs) and death.

Data on VE_I would have to be collected in alternative study designs such as individually randomized trials, which allow for data collection on a spouse or partner,^{8,9} or community-randomized clinical trials (CRCTs), which would allow one to measure the aggregate effects of VE_S , VE_P , and VE_I .^{10,11}

USING SURROGATE ENDPOINTS FOR ACCELERATED APPROVAL

Because of the difficulties in direct assessment of VE_P (and VE_I), the use of biomarker-based postinfection surrogate endpoints rather than clinical endpoints has been proposed. This surrogate would likely be a coprimary endpoint along with acquisition. Such surrogate endpoints have been used to support application under the accelerated approval regulations for licensure of drugs and biologics, with the recognition that they establish biologic activity but not necessarily clinical efficacy. From a regulatory perspective, a surrogate endpoint is one that is reliably predictive of clinical benefit. Much attention has been focused on how to assess the reliability of specific predictions or, more generally, how to validate surrogate endpoints based on evidence from epidemiologic, clinical, and pathophysiologic studies.

Mechanistically, a surrogate endpoint is the measurement of an outcome that predicts clinical benefit when the pathway from intervention to the true clinical outcome is mediated through the surrogate and the intervention acts upstream of the surrogate. Successful prediction is less likely if the surrogate endpoint lies on only one of several causal pathways of disease. In this case, the intervention may affect the mediated pathway only or bypass it altogether. Uncertainty

as to the true nature of these pathways makes rigorous validation of surrogate endpoints challenging.

The US Food and Drug Administration (FDA) has used surrogate endpoints in an accelerated approval process for products that promise meaningful therapeutic benefit over existing options for serious or life-threatening illness. In contrast to the traditional approval process, which requires clinical endpoint data, the accelerated approval process allows consideration of surrogates—something less than the clinical endpoints of illness or death. Accelerated approval based on surrogate endpoints is provisional, however, and requires that the sponsor verify and characterize the clinical benefit before full approval for licensure. For HIV vaccine trials, this could be quite lengthy. Procedures for drug applications are outlined in the Code of Federal Regulations (CFR) 314.500, and procedures for biologics are outlined in CFR 601.41.

Surrogate endpoints and the accelerated approval process have been used extensively for approval of antiretroviral drugs. In the early to mid-1990s, accelerated approval was based on CD4 cell count with clinical confirmation, whereas the later 1990s saw a greater reliance on HIV viral load (VL). Finally, in 1997, the requirement for traditional approval based on clinical endpoints (an AIDS-defining event or death) was dropped. The FDA accepted the HIV RNA level as a suitable endpoint for accelerated approval (24-week data) and traditional approval (48-week data). The rationale for the use of this endpoint is based on the association of treatment-induced decreases of greater magnitude (>0.5 log) and duration in HIV VL with lower risk of disease progression.¹² The widespread use of such drugs led to large reductions in HIV-related mortality. The use of this surrogate is also consistent with our broader understanding of the pathology of HIV infection. For antiretroviral drugs, the use of data from clinical endpoint studies (based on Centers for Disease Control and Prevention [CDC] AIDS-defining events) remains optional.

The benefit of using a similar accelerated approval process for HIV vaccines is the possibility of more timely evaluation of efficacy. This potential benefit is offset by the risk that the observed vaccine effects on biomarker endpoints do not reliably predict tangible clinical benefit, however. The prior use of VL as an endpoint in antiretroviral drug treatment studies may facilitate the use of similar data for preventive vaccine applications. Because the validation of a surrogate depends critically on mechanistic pathways, the analogy of a vaccine to an antiretroviral drug may be stronger for vaccines whose anticipated mechanism is through CMI as opposed to vaccines whose anticipated mechanism is through neutralizing antibodies that prevent infection. Although plasma VL is typically used to measure virus, other measures such as virus in cell DNA or in mucosal tissue may be complementary measures.

POSSIBLE SURROGATE ENDPOINTS IN VACCINE EFFICACY TRIALS

Based on their effect in animal models,^{4,5} it is anticipated that current vaccine candidates are capable of reducing peak viremia and VL setpoint. To the extent that such reductions are predictive of clinical outcomes in animal models, their use as plausible surrogate endpoints in human trials is suggested. Moreover, as discussed previously, prolonged reduction in VL in untreated and antiretroviral drug-treated human patients is associated with a reduced rate of progression to AIDS and increased survival.

Based on these nonhuman primate (NHP) and human studies, potential surrogate endpoints for VE_p could include laboratory assessments among HIV-infected individuals (eg, VL, CD4 count) or a surrogate clinical endpoint (eg, time to initiation of ART), especially if uniform guidelines for such initiation are used and if the studies were conducted in a reliably double-blind manner. Because sexual transmission of HIV increases with increasing VL,¹³ reduction in VL after vaccination might also serve as a surrogate for VE_i .

Early Endpoints

Peak VL, which occurs shortly after infection, and VL setpoint are potentially useful indices. Trial participants are likely to be tested for HIV infection only every 4 to 6 months, however, so few infected individuals are likely to be identified during the seroconversion period near the time of peak viremia. In addition, although peak VL seems to be a surrogate endpoint in animal model studies, it has not been validated in humans. Conversely, setpoint or VL measurements taken early after infection (1–3 months after diagnosis) have been shown in natural history studies of HIV-1 to be predictive of long-term outcome.¹³⁻¹⁵ Therefore, vaccine trials could potentially compare mean pretreatment VL during this period in vaccine versus placebo recipients. A strong initial viral suppression would suggest the potential for a vaccine to have significant effects on VE_P and VE_I , because early peak viremia is associated with transmission.¹³ Of course, early VL endpoints have not undergone validation as surrogates for clinical diseases in human vaccine trials. Further, trial participants are likely to be tested for HIV infections 2 to 3 times per year. Viremia after detection of infection is thus a mixture of peak viremia and setpoint.

One potential limitation of this approach is that the initial effect may not be durable because of immune escape, which could lead to increased viral replication and associated increases in rates of progression and secondary transmission relative to the period of suppression. Another limitation is the possibility that some infected persons may receive treatment during primary infection, making the measurement of pretreatment VL impossible. This is unlikely to play a large role, because prior vaccine trials suggest that few seroconverting trial participants are identified during primary infection. In addition, initiation of ART during this period is not currently recommended by any national treatment guidelines; thus, it would likely occur in only a few of those identified with primary infection.

Medium-Term Endpoints

Durability of VL reduction is a necessary requirement for reduced progression of HIV disease, and, as such, some aspect of durability of a vaccine's effect on VL is essential. Measurements made 6 to 24 months after infection may capture more information about the durability of vaccine effects on biomarkers and may be more predictive of ultimate effects on disease progression. The variability in HIV infection and its signs and symptoms may influence such measurements and, through them, the initiation of ART at later time points (>24 months after first detection of HIV infection), which may have a profound and possibly paradoxical effect on biomarker endpoints.¹⁶

To the extent that treatment initiation is based on standard criteria that are predictive of disease progression, the time to treatment initiation per se is an endpoint that may be used to judge vaccine effects. Unlike surrogate endpoints based solely on biomarker measurements, treatment initiation also indirectly captures some aspect of clinical effects associated with the toxicities and expense of antiretroviral drugs. For these reasons, it may be helpful to use composite endpoints, such as time to CD4 count <X or initiation of ART, for those "medium-term" vaccine trial endpoints for which the fixed failure threshold X is set equal to the treatment initiation trigger (eg, X = 350).

Another potential surrogate endpoint at later time points is median HIV VL. In calculating this surrogate endpoint, one could assume that the VL of individuals on therapy would have been higher than the median if treatment were not initiated. If fewer than 50% of individuals in each arm have begun therapy at a given time, we can interpret the median VL before ART in each arm for this time point as the median under the hypothetical situation of an untreated patient population. We can calculate this median as follows. For each patient who is on ART, we replace his or her measured VL with a large value, say 10^{100} . Thus, all infected patients in each

group are counted. Additional surrogate endpoints include early clinical markers other than AIDS-defining illness among all individuals, including those taking ART.

Late Endpoints

For populations in which ART is readily available, 2 types of clinical benefit should ultimately be considered. First is a delay in the initiation of ART, which would spare the expense and toxicity associated with treatment. Second is the overall reduction in HIV-associated morbidity and/or mortality. We note that although the first type of clinical benefit is readily assessable in vaccine trials, the latter is not because of the long delay from infection to disease or death in an ART-treated cohort. Thus, the ultimate impact of a vaccine on morbidity and mortality after the effects of ART are fully realized is hard to know. For populations in which ART is not available, the clinical benefit of vaccination would be realized by a reduction in HIV-associated morbidity and/or mortality. Because trial participants are likely to be provided ART, however, the long-term clinical benefits of vaccination in terms of morbidity and/or mortality are not directly observable. Such benefits to populations without access to ART must be inferred from observed vaccine effects on time to initiation of ART.

CHALLENGES OF USING SURROGATE ENDPOINTS

There are several important limitations to the use of surrogate endpoints in vaccine efficacy trials. First, at present, we do not know whether vaccine effects on biomarkers measured at early, intermediate, or late times after infection accurately predict vaccine effects on the clinical course of infection. For valid surrogates, the effect of the vaccine on clinical outcomes is reliably predicted by the effect of the vaccine on the surrogate endpoint. Validation of surrogate outcomes can be accomplished statistically, using meta-analysis of data from multiple vaccine efficacy trials to assess the association between vaccine effects on the surrogate and clinical endpoints, or clinically, based on a comprehensive understanding of the disease process and the vaccine's intended and unintended effects.

Second, ART may be initiated preferentially or earlier in one of the arms (dependent censoring by ART initiation), and thus bias the comparison between the vaccine and placebo groups. For example, if prior vaccination decreases the likelihood of symptomatic seroconversion, vaccinees are less likely to be identified at the time of seroconversion and may be less likely to receive ART during primary infection.

Third, postrandomization selection bias may occur for surrogate endpoints measured only in infected participants, because these groups are subsets of the originally randomized volunteers. This potential bias can be avoided by analyzing outcomes for all study participants in an intention-to-treat analysis,¹⁷ although this can have low statistical power. The extent of bias can also be explored by statistical sensitivity analyses.^{18,19}

Although biomarkers can likely be measured in sufficient quantity and quality to answer these questions and issues, it is unclear whether enough true clinical events such as AIDS-defining OIs can be accumulated in vaccine trials. Ethical issues make it imperative to initiate ART according to uniform locally approved guidelines. Because of this, only a limited number of persons become symptomatic with clinical AIDS-defining OIs before initiation of ART. Individual clinical outcomes that have been proposed for consideration in vaccine testing include loss of more than 10% of body weight, herpes zoster (acute), chronic diarrhea, and pulmonary tuberculosis.²⁰ Unfortunately, the background rate of morbidity associated with these infections differs by region, making the prognostic value of such clinical conditions problematic. Additionally, clinical outcomes such as diarrhea have a variety of causes, and this could make it difficult to see a difference between the infected placebo and vaccine recipients, because some of these causes would not be reduced by an HIV vaccine. Measurement and

quantitation of reduction in ART use and reduced side effects from such drugs may also be a potential marker of “clinical benefit” on a population basis.

FIVE SCENARIOS

To help highlight key issues regarding how the performance of a vaccine in an efficacy trial would be received, results from 5 hypothetical clinical trial scenarios were presented to the panel. Each scenario involved a randomized, placebo-controlled, phase 3 vaccine efficacy trial with 6000 volunteers in a 1:1 randomization between placebo and control. The vaccine viral subtype and the subtype of HIV circulating in the study populations were clade B. For simplicity, all patients were assumed to enroll on the same date, with follow-up visits every 6 months for 3 years. Infected participants were followed up for 2 years after diagnosis, with visits at 0.5, 1, 2, 4, 8, 12, 16, 20, and 24 months.

Trial endpoints included HIV acquisition, time to VL >55,000 copies/mL or ART initiation (VL/ART), time to CD4 count <350 cells/mm³ or ART initiation (CD4/ART), time to ART initiation, time to AIDS, and the trajectories of pre-ART VL and CD4 count in the infected volunteers. VEs (VE_p) was estimated as 1 minus the relative risk of infection (surrogate for disease progression) using a Cox regression model. For VE_p, time to VL >55,000 copies/mL or ART initiation was the primary endpoint used, and thus represents a relatively early surrogate for true clinical progression.

Infection times were generated according to an exponential distribution. The control group had a cumulative rate of 10% at 3 years; in the vaccine group, the hazard of infection was multiplied by 1 – VEs. The postdiagnosis pre-ART VLs and CD4 counts were generated by linear mixed models based on the VAX004 experience.³ The largest vaccine effect on VL was a drop of 2 logs (base 10) over the course of follow-up. The largest vaccine effect on CD4 count was to maintain the immediate preinfection value over the course of follow-up.

The simulations incorporated loss to follow-up of 20% at 3 years for the overall cohort and 10% at 2 years for the infected volunteers. The guideline for ART initiation was to trigger treatment at a CD4 count of less than or equal to 350 cells/mm³. Imperfect compliance with this guideline was simulated by setting the probability of ART initiation at 0.4 to 0.6 for each visit after a CD4 count ≤350 cells/mm³ was observed. No treatment was initiated at any visit with a CD4 count >350 cells/mm³. An AIDS-defining event occurred with a probability of 0.05 by the next visit when the CD4 count was ≤350 cells/mm³ but ≥200 cells/mm³; a CD4 count <200 cells/mm³ was considered an AIDS-defining event. The scenarios are summarized in Table 1.

For all scenarios, the panel was asked to consider the following possible interpretations:

1. The vaccine is unpromising, and further development and/or evaluation should be abandoned.
2. The results are not convincing, but further study of the vaccine is warranted.
3. The trial has demonstrated public health utility of the vaccine in some settings.

Also, for interpretations of (2) and (3), what further studies of this vaccine (if any) should be performed?

Scenario 1

This trial showed no significant effect on VEs but showed an immediate and dramatic effect on VL, with the infected vaccinees having approximately 2 logs less virus than the infected placebo recipients. This translated into a strong effect on the composite endpoint (time to VL

>55,000 copies/mL or ART) with an estimated VE_P of 75%. An increasing benefit of vaccine for CD4 counts was highest at 2 years; at that time, CD4 counts among vaccinees were approximately 130 cells higher than among placebo recipients. Overall, there were approximately 600 infections and approximately 60 cases of AIDS. Some of this information is displayed in Figures 1 and 2.

All agreed that this trial clearly demonstrated the vaccine had a potent effect. Because follow-up for infected participants stopped at 2 years, however, it was difficult to determine if the substantial benefit in VL would translate into real clinical events over the long term. It was considered advisable to continue follow-up of the cohort to obtain more information about the durability of the effect and to determine whether the trends were sustained. The frequent and appropriate initiation of ART at CD4 counts less than or equal to 350 cells/mm³ would, however, tend to diminish the difference in CD4 counts between groups.

It is interesting to speculate as to what effect the VL benefit would have on infectiousness. Quinn et al¹³ showed that secondary transmission rarely occurred if the VL is <1500 copies/mL. The mean VL in the infected vaccinees was <100 copies; thus, there is the possibility of a substantial effect on VE_I . Other infectious disease trials have shown impressive indirect effects. Conversely, in a trial of an antiviral drug to treat herpesvirus, viral shedding assessed by DNA polymerase chain reaction (PCR) decreased quite substantially (>90%); however, there was only an approximately 50% reduction in transmission.²¹ These examples make the point that it is difficult to predict what effect a vaccine might have on VE_I based on an unvalidated surrogate such as VL.

The panelists indicated that a subsequent trial to assess VE_I or population-level effects directly would be worth consideration for a vaccine with such a profound impact on VL setpoint but little or no demonstrated effect on VE_P or VE_S . They also considered broadening the definition of AIDS-related events to glean further information about clinical progression in the initial trial. Early events could provide additional useful evidence beyond VL and CD4 count because they might indicate a clinical consequence that parallels the effect on the surrogates. Early events may be partly attributable to causes that a vaccine could not possibly affect, however.

In summary, the panel's consensus was that the trial results were extremely promising; however, a consensus on defining the criteria for licensure was not reached. Accrual of early clinical endpoints and further follow-up were issues raised by the panelists. If signals emerged from such analyses (eg, effects on early endpoints, time to ART with a CD4 count <350 cells/mm³, time to AIDS), a new trial might be designed specifically to achieve licensure using these clinical endpoints.

Scenario 2

Scenario 2 described a vaccine that had a modest but definite impact on VE_S , with a point estimate of 31% and a 95% confidence interval (CI) of 17% to 43%. There was an immediate benefit on VL of approximately 2 logs, resulting in an initial assessment of VE_P of 60%. The VL benefit waned over time, however, and there was no significant effect on CD4 count. A standard threshold of licensure for VE_S based on previous HIV vaccine trials³ is a 95% CI that excludes 30%; thus, the vaccine fell well short of this standard. Furthermore, the initial VL benefit was not sustained, thereby making the prospect for downstream clinical benefits questionable.

The reason for the waning effect on VL was unclear, but possibilities include the waning of vaccine-induced immune response or the development of mutant viruses that escape the vaccine-induced immune response. One consequence of the latter on a population level might be that the vaccine becomes ineffective after a few years. To investigate possible reasons for

the waning VL benefit, it would be important to sequence the virus in infected individuals over time and also to measure immune responses over time.

A combined or unconditional analysis might be especially informative. A rough calculation suggests that the overall chance of developing AIDS among all randomized subjects is approximately 50% less among the vaccinees by the end of follow-up. One additional advantage of this unconditional analysis is that it includes all randomized participants (not just those who are infected); thus, it is consistent with the intent-to-treat principle.

In summary, the results of scenario 2 show statistically significant results for acquisition and VL, but the magnitude of these effects is probably less than required for licensure. The panel's opinion was that redesign of the vaccine should be attempted. Different analyses to inform redesign should be attempted, including the following: (1) search for an immune correlate of protection or progression, and then redesign the vaccine to strengthen this specific immune response; and (2) conduct sieve-type analyses to see if the vaccine only benefits against viruses that are similar to the immunogen, and then redesign the immunogen to cover more viruses. A vaccine with a 31% VE_S and a 2-log benefit on peak and/or setpoint viremia might be modeled to predict a substantial overall effect in a community-randomized trial. Although there are enormous challenges with HIV vaccine community-randomized trials, for such a vaccine, a community-randomized trial should at least be considered, especially if a redesigned vaccine was not promising.

Scenario 3

In this scenario, the estimate of VE_S was nearly 60% with a 95% CI (47% to 66%). Because the lower bound of this interval exceeds 30%, a threshold for licensure, there was unanimity that licensure was warranted for this vaccine. The facts that there were slightly higher VLs among infected vaccinees and a trend toward harm with VE_P were not so concerning because the benefit on VE_S was so strong.

There are a variety of reasons that might explain the higher VL in infected vaccinees. One possibility is that the vaccine has no effect after infection but that the infected placebo and vaccine participants are different, because the vaccine prevents infection in those who would be better equipped immunologically to control the virus.^{19,22} Perhaps those who develop neutralizing antibodies are also those who would develop better T-cell responses in response to the virus if infected. In the placebo group, these T-cell virus responders are infected and achieve good viremic control, whereas in the vaccine group, these T-cell virus responders are uninfected and the infected vaccinees are those who have a poor T-cell response to the virus. Another possibility is that although the placebo and vaccine infected groups are inherently similar, the vaccine somehow causes enhancement of infection. Exactly how this might occur is unknown, but one speculation is that the vaccine might induce enhancing and neutralizing antibodies. The neutralization antibodies would cause a favorable VE_S , whereas the enhancing antibodies might allow for more efficient viral replication in those who were infected.

From a practical point of view, however, what matters is the overall effect of the vaccine. An unconditional analysis that evaluates time to VL failure or ART initiation in all subjects, thereby synthesizing the effects of VE_S and VE_P , would clearly show that the vaccine had an overall favorable effect.

In summary, the panel's consensus was that the trial results on VE_S make an immediate and compelling case for licensure in the population that was studied. Such a vaccine might be applied to other populations as well. If so, it would be desirable to conduct phase 4 studies of vaccine effectiveness. One possibility is to compare infection rates before and after mass vaccination. Another possibility is a stepped wedge design, where the vaccine is sequentially

introduced into a country by randomizing the order that communities (eg, provinces or cities) receive mass vaccination.²³

Scenario 4

This successful trial showed a clear and strong vaccine effect on VE_S and VE_P (using the composite VL/ART initiation endpoint) and a trend toward better CD4 counts in infected vaccinees. All infecting viruses were genetically sequenced, and their distance from the immunogen, as assessed by percent amino acid mismatch, was calculated. The distribution of distances was roughly the same in the vaccine and placebo groups, which is consistent with the idea that the vaccine is equally efficacious against all viral strains with subtype B. In this scenario, immune responses to subtype C antigens were measured in vaccinees and found to be comparable to responses to subtype B antigens. These immune responses were categorized into quartiles, and, for each quartile, the VE_S relative to the entire placebo group was calculated. The value of VE_S did not vary across quartiles of immune responses to subtype B or subtype C antigens. Thus, the vaccine has a strong and durable effect that seems to be uniform across subtype B viruses. The estimated VE_S is not predicted by measured immune response, however.

The primary question for this vaccine was whether the demonstrated efficacy could be generalized to a subtype C viral population with (1) the same vaccine construct or (2) a re-engineered construct that replaced subtype B inserts with those from subtype C virus. A second issue was the type of data that would be required to infer reliable comparable public health benefits in subtype C settings with the same or different routes of transmission.

It seemed clear that an additional prospective study in the subtype C population was necessary, especially because there was no immunologic correlate of protection for this vaccine. Several different studies could be considered. Because the efficacy of a subtype B immunogen in a population exposed primarily to subtype C virus is unknown, one may argue that a placebo-controlled trial would be appropriate. In this case, a controlled trial that evaluates subtype B and C immunogens would be most informative. There was no consensus among the panel that a placebo-controlled trial would be possible in such circumstances, however. In lieu of a placebo-controlled trial, a large equivalence trial comparing the original B-immunogen with a C-immunogen might be considered. Although a positive result would be strong evidence for the new C-immunogen, a null result would raise difficult questions, because both immunogens might be efficacious or both might be useless in the subtype C population. Given the possibility that subtypes may be completely irrelevant for characterizing vaccine efficacy, a phase 4 trial (in which the subtype B vaccine would be used in a population in which subtype C HIV predominates) might be an option. Another possibility would be to anticipate success in the initial subtype-matched trial and to perform 2 simultaneous studies: a phase 3 trial of a B-immunogen in a B population and a large phase 2 or phase 2b trial of the B-immunogen in a C population. One could look at the consistency of vaccine effects by testing whether VE_S was the same in the clade-matched and clade-mismatched subgroups. To be convincing, such an analysis would need to be specified a priori and justified by power calculations.

In summary, the panel's consensus was that evidence for licensure for use in subtype B populations, in the absence of other immunologic or virologic correlations of protection, was immediate and compelling. There was no consensus on how to proceed with vaccine evaluation for other settings.

Scenario 5

This trial described a vaccine with a dramatic effect on VE_S , a strong effect of approximately 2 logs on VL setpoint, and a strong effect on VE_P . As in scenario 4, it is clear that the vaccine works in the clade B setting. Unlike scenario 4, however, there is strong selective efficacy,

with the vaccine preventing infections from subtype B viruses that are close to the immunogen (Fig. 3). There is also a strong correlation between clade B immune response and vaccine efficacy, with poor clade B immune response being associated with little efficacy (Fig. 4). The efficacy of the vaccine is not dependent on the immune response to subtype C antigens (see Fig. 4).

Although the vaccine showed an overall benefit in the subtype B setting, there are 2 ways in which it might be improved. The subtype B immune response might be improved so that those with the worst response (ie, quartile 1 in Fig. 4) would see an improvement to a higher quartile, and thus, presumably, also benefit in terms of protection against acquisition. The second improvement would be to generalize or bridge the vaccine to a subtype C population. Even if a phase 2 trial of a vaccine with a C-immunogen showed a similar immunogenicity profile, it was unclear whether this would be persuasive. It seemed that a new efficacy trial of a C-immunogen in a subtype C population would be necessary.

To improve on a successful vaccine with narrow applicability, 2 different strategies might be attempted: multiple single-valent vaccines or 1 multivalent vaccine. The multivalent strategy is appealing, provided that there is no interference and that a relatively small number of inserts would cover the circulating strains in the target population.

In summary, the panel's consensus was that the vaccine was a great prototype and that refinements in the vaccine (ie, improvement of the immune response for subtype B and C populations) would be aggressively pursued. These improved candidates would be tested in new efficacy trials. Testing the new subtype B immunogen in a subtype B population would require a large trial with the old subtype B vaccine used as a comparator. The comparator for the new subtype C-immunogen in a subtype C population might be a placebo or the old subtype C vaccine.

CONSENSUS THEMES FROM SCENARIOS

The scenario discussions led to several points of consensus, all of which are summarized in this section. Given the anticipated effect of CMI vaccines on VE_p , standardized ART initiation guidelines are important to ensure that exposure to ART is systematic. If patients begin ART initiation early and haphazardly, it is difficult to discern the effect of vaccination on postinfection endpoints. Trial participants who become infected should be followed for a long period so as to achieve the best possible assessment of true clinical benefit. Ideally, sufficient AIDS or death events would accrue to have sufficient power to ensure meaningful assessment of vaccine effects and also to evaluate surrogates such as VL or CD4 counts. Long-term follow-up would allow short-term endpoints, such as VL and CD4 counts, to be examined as possible surrogates. In addition, early clinical endpoints may provide supportive secondary information. It would also be desirable to use uniform treatment regimens to the extent that is possible to evaluate response to treatment and the possible differences in these responses over the long term between those with and without prior vaccination.

The use of coprimary endpoints that separately represent vaccine effects on rates of HIV acquisition (VE_S) and on rates of disease progression among those infected (VE_p) was viewed as preferable to a single primary endpoint that represents vaccine effects on overall rates of morbidity and mortality. The HIV acquisition endpoint is the easiest to interpret, and trial scenarios that statistically demonstrated reduction in infection rates of at least 30% over a 3-year period were deemed sufficient to support licensure, albeit with specific postmarketing study plans to assess long-term durability of protection against infection.

A composite endpoint that integrates information on VL or CD4 counts along with time to treatment initiation (eg, time to ART or CD4 count <350 cells/mm³) was viewed as the best

approach to capture potential vaccine effects on morbidity and mortality. Most workshop participants considered that a 1- to 2-log difference in mean VL sustained for 2 years would be sufficient to support licensure, although there was no consensus on this point. Although the presentation of the scenarios emphasized conditional analyses of VE_p (ie, analyses in which infected vaccine and placebo recipients are compared in terms of postinfection endpoints), unconditional analyses that include all randomized participants are also important because they offer a simple and rigorous way to synthesize any beneficial effects of the vaccine on acquisition and postinfection outcomes.

Scenarios 4 and 5 demonstrated a clearly efficacious vaccine for a specific viral subtype (B). It was unclear whether the results would apply to a different viral subtype, however. If a successful study is conducted in a population with a relatively homogeneous distribution of subtypes and if immunogenicity studies of the newly constructed vaccine are similar to the original one, it may be difficult to have a placebo arm for volunteers from other regions with a different subtype. This is particularly true if vaccine protection does not vary with genetic distance to the immunogen within a subtype. To avoid this dilemma, a parallel trial strategy might be adopted (eg, a subtype B vaccine phase 3 trial in a subtype B population concurrent with a phase 2 study of the same vaccine in a subtype C population). The panel thought that bridging to another HIV subtype would at least require some efficacy data. It would also be desirable to see efficacy outcomes so as to feel comfortable about bridging across viral subtypes.

The public health utility of a vaccine is best assessed via the combination of direct (VE_S and VE_p) and indirect (herd immunity and disruption of secondary transmission) effects. To the extent that indirect effects are needed to inform licensure or guide application of an approved vaccine, they should be studied in an experimental setting. The 2 main methods for assessing indirect effects are studying partners of trial participants^{8,9} and CRCTs.¹⁰ Both offer challenges beyond a standard individual-randomized trial and can be difficult to execute.

ACCELERATED APPROVAL, POSITIVE TRIALS, AND INTERNATIONAL ISSUES

The topic of “accelerated approval” was discussed by the workshop participants. Accelerated approval would allow provisional approval of a vaccine but would not provide a definitive efficacy profile. The provision is that further study of the vaccine be expeditiously completed to provide a definitive efficacy profile in terms of clinical outcomes. The experience of the FDA in other areas (eg, oncology, ART trials of HIV-infected patients) suggests that for this to be practical, a confirmatory trial needs to be in place at the time of accelerated approval for practical reasons. For a phase 3 trial of an HIV vaccine, this might be accomplished by extended follow-up of the infected trial participants, possibly by accumulating postinfection outcomes for participants who become infected subsequently as well.

If a less than perfect vaccine were licensed, there would be debate about what settings and communities might accrue the largest benefit from such a vaccine. To inform such a debate, a CRCT could provide valuable information.^{24,25} A more proactive approach would be to consider (1) combining classic phase 3 trials that randomize individuals with study designs that obtain information about partners or (2) embedding individual-level randomized design within community-based trials. Practical thinking and additional research into which designs would be useful to follow up on a modestly positive vaccine are required. If such trials were impossible to perform, mathematic modeling of the population-level impact of a vaccination campaign would be the only way to attempt to estimate overall effects of a vaccine licensed on the basis of direct effects.

The level of evidence for licensure might be different from the level of evidence required to maintain equipoise about new vaccine candidates. For example, if a vaccine had a mildly positive efficacy profile or a dramatic effect on an unanticipated endpoint, it is possible that this would be insufficient for licensure. Institutional Review Boards or researchers might think that it would be unethical to enroll patients in a subsequent trial with a placebo control in this situation, however. In a similar vein, if a phase 2b trial demonstrated a dramatic drop in VL (eg, 2 logs over 2 years as in scenario 1), it might be difficult to launch a phase 3 trial with a placebo control.

SUMMARY

A key issue in licensing an HIV vaccine with expected effects on postinfection endpoints is the validity of using early change in VL as a surrogate. It is not known whether effects on VE_S (for acquisition) and VE_P (for progression) occur in a concordant fashion and whether a vaccine with modest benefit on VE_P would be effective in reducing VE_I (infectiousness). The use of coprimary endpoints in efficacy trials that separately assess vaccine effects on VE_S and VE_P is a useful design strategy, and criteria for support of licensure based on VE_S are relatively straightforward. A composite endpoint that incorporates information about VL and treatment initiation provides a balanced approach to assessing vaccine effects on disease progression, provided that it is supplemented by an array of additional analyses and secondary endpoints. Nevertheless, one must anticipate that clinical endpoints such as AIDS or death take a long time to occur. The identification of minimal criteria for support of licensure based on VE_P is complicated by issues of surrogacy of VL, and such criteria likely need to be determined in the context of specific vaccine candidates. Licensure decisions are likely to be based on some aspects of information from surrogate endpoints. The issue to be resolved is the magnitude and durability of effects on such endpoints that are suitable for support of licensure. Effects on VL of 1 to 2 logs in magnitude that persist for at least 2 years after infection represent a “middle ground,” which some have considered to be too strict and others too lenient. Ultimately, the risks associated with use of surrogate endpoint information need to be balanced against the potential benefits of delivering even a partly efficacious vaccine.

It would not be surprising if a vaccine's efficacy varied with differences in human and viral populations. How to modify a vaccine that shows efficacy in a specific population of hosts and viruses to other populations of hosts and viruses depends on whether there is evidence of selective efficacy by HIV genetics, whether there is a putative correlate of protection, and whether the correlate applies to a subset of viral subtypes. Even if selective efficacy and/or an immune correlate of protection is identified, use of this information to infer efficacy observed in a specific population (human and/or viral) to a different population without a direct assessment of efficacy is fraught with risk. At least 1 direct demonstration of efficacy in a second different population would provide some evidence for generalization and was considered advisable. A trial that shows evidence of some vaccine efficacy would make conducting future trials with a placebo group more difficult, however, making it important to identify a specific integrated strategy to assess vaccine candidates in heterogeneous populations as part of the overall development plan.

Historically, vaccines have been licensed on the basis of demonstrated protective effects on clinically significant acquisition. With HIV, however, potential vaccine effects on VL may have uncertain implications for long-term direct effects on disease progression but may have considerable potential for population-level impact on the HIV epidemic through indirect effects. General strategies for assessing indirect and total vaccine effects at the population level have been described but have not been specifically incorporated into an overall evaluation strategy for HIV vaccines. Such an expansion of the evaluation strategy for HIV vaccines requires consideration of more challenging trial designs such as a region-by-region rollout of

a vaccine as was done for a hepatitis vaccine.^{23,26} An incremental rollout would be necessary because of the time it takes to manufacture large lots of a vaccine. Elucidation of specific strategies for evaluating population-level effects of HIV vaccines and preparation for their implementation for suitable HIV vaccine candidates should be given a high priority.

The process for licensure of an HIV vaccine in the developing world is currently performed on a country-by-country basis without coordination. A more unified international process for assessment of trial results and their public health relevance in different populations would be helpful. The World Health Organization (WHO) has draft guidelines for evaluation of vaccine products for countries without a licensure process, but these are less developed for HIV vaccines than for other vaccines. A natural next step would be for interested parties such as the National Institutes of Health (NIH), CDC, WHO, IAVI, and Gates Foundation to help establish a process to foster the development of such guidelines. Such a process should directly involve relevant countries from the developed and developing world.

This article has summarized the proceedings of a 2-day workshop sponsored by the Division of AIDS, NIAID, to explore regulatory issues and endpoints in HIV vaccine clinical trials. Similar workshops have been conducted over the years to explore these issues.^{27,28}

APPENDIX

Panel members were as follows: Marie-Claude Boilly, Susan Ellenberg, Patricia Fast, Tom Fleming, Karen Goldenthal, Scott Hammer, Peter Lachenbruch, Gary Nabel, Bill Pape, James Whitworth, and Larry Corey. Presenters were as follows: Marie-Claude Boilly, Tom Fleming, James Whitworth, Ram Rangsins, Dale Hu, Scott Hammer, Jeff Murray, Visanu Thamlikitkul, and Peter Gilbert. Planning Committee members were as follows: Massimo Cardinali, Therese Cvetkovich, Ann Duerr, Alan Fix, Jorge Flores, Dean Follmann, Mary Foulkes, Antonia Geber, Scott Hammer, Joseph Heyse, Steven Self, Stephen Tabet, and Joseph Toerner.

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FIGURE 1.

Kaplan-Meier plots of the time from randomization to diagnosis of HIV infection (left panel) and from time of infection diagnosis to initiation of ART or virologic failure (right panel) for scenario 1.

FIGURE 2.

VL trajectories from time of detection of infection to 2 years for scenario 1.

Distribution of HIV distance to the immunogen

FIGURE 3.

Distribution of the distance, percent amino acid mismatch, from the consensus infecting virus to the immunogen for scenario 5. The difference in shapes suggests that the vaccine works better against viruses that are close to the immunogen.

FIGURE 4.

VE_S by immune response quartile along with 95% CIs for scenario 5. Immune response to clade B and clade C peptides is measured in the vaccine shortly after immunization. The vaccine group is split into quartiles of immune response, and the VE_S of each quartile to the entire control group is calculated.

Summary of the Observed Vaccine Effects for All 5 Hypothetic Clinical Trials

TABLE 1

VE _S % (95% CI)	VL	CD4 Cell Count	VE _P % (VL/ART)	Time to CD4 Count/ ART	Time to AIDS	Secondary Analysis
1 -3 (-22 to 14)	Immediate 2-log vaccine benefit sustained for 2 years	No CD4 count decline among vaccinees with 130-cell difference from placebo by 2 years	75	No significant effect	No significant effect	
2 31 (17 to 43)	Immediate 2-log vaccine benefit, wanes after 18 months to 0 by 2 years	No significant effect over 2 years	60	No effect	No effect	
3 58 (47 to 66)	Immediate 0.5-log vaccine detriment sustained for 2 years	No effect over 2 years	-25 (NS)	No effect	No effect	
4 60 (50 to 68)	Immediate 2-log vaccine benefit sustained for 2 years	Trend for vaccine benefit over 2 years	75	Vaccine benefit	Vaccine benefit	No selective efficacy, no differential efficacy by immune response to subtype B or subtype C
5 67 (58 to 74)	Immediate 2-log vaccine benefit wanes to 1 log by 2 years	No effect over 2 years	70	No effect	No effect	Strong selective efficacy, positive (flat) relation between VE _S and immune response to subtype B (subtype C)

Each trial involved 6000 patients randomized 1:1 to placebo/vaccine. Both the vaccine and study population are subtype B.

Selective efficacy occurs when VE_S differs across viral types.

NS indicates not significant.