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Modeling cumulative overall prevention efficacy for the VRC01 phase 2b efficacy trials

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ABSTRACT

The Antibody Mediated Prevention trials are assessing whether intravenously-administered VRC01 (10 mg/kg or 30 mg/kg vs placebo) can prevent HIV infection. In a modeling exercise, we used two models to predict the overall prevention efficacy (PE) of each VRC01 dose in preventing HIV infection. For the first per-exposure PE model, parameters were estimated from studies where nonhuman primates (NHPs) were administered high-dose intra-rectal simian-human immunodeficiency virus challenge two days post-VRC01 infusion at various dosages ("NHP model"). To account for the fact that humans may require greater VRC01 concentration to achieve the same level of protection, we next assumed that a 5-fold greater VRC01 serum concentration would be needed to provide the same level of per-exposure PE as seen in the NHP data ("5-fold model"). For the 10 mg/kg regimen, the 5-fold and NHP models predict an overall PE of 37% and 64%, respectively; for the 30 mg/kg regimen, the two models predict an overall PE of 53% and 82%, respectively. Our results support that VRC01 may plausibly confer positive PE in the AMP trials. Given the lack of available knowledge and data to verify the assumptions undergirding our modeling framework, its quantitative predictions of overall PE are preliminary. Its current main applications are to supplement decisions to advance mAb regimens to efficacy trials, and to enable mAb regimen ranking by their potential for PE in humans.

Introduction

Human immunodeficiency virus (HIV) remains a major global public health crisis and thus the search for an effective vaccine to prevent HIV infection remains an important, albeit challenging, task. Antiretroviral therapy (ART) is highly effective in reducing HIV transmission and acquisition[1,2]; however, the cost of ART, the resources required to identify newly infected patients and rapidly initiate treatment, the cost of patient monitoring, the risk of long-term side effects, and significant challenges related to adherence limit the use of ART in broad enough populations to halt the HIV pandemic using ART alone. Arising from the long history of using passive administration of antibodies to treat and/or prevent disease,[3] passive administration of HIV broadly neutralizing monoclonal antibodies (mAbs) represents a promising new HIV prevention modality. mAbs isolated from chronically infected individuals have shown impressive breadth, inhibiting 80-90% or more of HIV-Env pseudoviruses in in vitro neutralization assays at bnAb concentrations as low as 1 μg/mL[4–6,8–10]

VRC01 is an IgG1 HIV broadly neutralizing mAb that was isolated from a "slow progressor" who had been infected with HIV for more than 15 years at the time of serum and peripheral blood mononuclear cell collection. VRC01 targets the conserved CD4 binding site of the HIV envelope[7,8] and has been demonstrated to prevent HIV infection in non-human primate (NHP) challenge studies.[11–13,30] Building on these NHP results, the first efficacy studies of VRC01 – termed the Antibody Mediated Prevention (AMP) trials – for HIV prevention were launched in 2016, with an estimated total study duration of 5 years including enrollment and follow up.[14] Together, the two AMP trials were designed to enroll and randomize 4200 HIV-negative volunteers in 1:1:1 allocation to receive a total of ten intravenous infusions (8-weekly) of VRC01 at a dose of 10 mg/kg, 30 mg/kg, or placebo. The 4200 volunteers are enrolled into two cohorts in harmonized protocols: HVTN 704/HPTN 085 (ClinicalTrials.gov #NCT02716675) in the United States, Peru, Brazil, and Switzerland (2700 HIV-uninfected men and transgender persons who have sex with men); and HVTN 703/HPTN 081 (ClinicalTrials.gov #NCT02568215) in

Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe (1500 HIV-uninfected sexually active women). The primary efficacy objective of the AMP trials is to assess whether intravenously-delivered VRC01 prevents HIV infection.[14]

In this report, we describe an approach to modeling the cumulative overall prevention efficacy (PE) of each of the two mAb regimens tested in the AMP study. PE is defined as one minus the relative risk of HIV infection between a given VRC01 dosage group and the placebo group. Briefly, the prediction of PE is primarily based on two input functions: (1) bivariate per-exposure prevention efficacy $PE^{pe}(s, v)$ as a function of the concentration of VRC01 in participants' serum at the time of exposure, $S = s$, and of the in vitro 80% inhibition concentration (IC80) of the mAb against the exposing virus, $V = v$; and (2) the joint probability distribution $P(s, v)$ of (S, V) at HIV exposures for participants in a mAb group (Figure 1). For (1), $PE^{pe}(s, v)$ estimated from NHP high dose intra-rectal challenge data for VRC01[11,30] is used as the basis for a range of per-exposure PE models, indexed by the "NHP model" that assumes the per-exposure efficacy derived from NHP is applicable to humans. Based loosely on human explant experiments that suggest that some human genital tissues require greater concentrations of VRC01 for protection against HIV challenge than others,[28,29] we also use a "5-fold model" that assumes that 5-fold greater mAb concentration would be needed to provide the same level of PE as seen in the NHP challenge data. For example, Lemos et al. demonstrated that a 5.1-fold higher concentration of VRC01 was required to protect human inner foreskin compared to outer foreskin explant tissue against ex vivo HIV challenge[28] and Scott et al. reported that a higher concentration of VRC01 was required to reduce transmission in ectocervical tissue compared to colonic tissue.[29] For (2), assuming independence of S and V such that $P(s, v) = P(s) \times P(v)$, where $P(s)$ and $P(v)$ are the probability distributions for S and V, respectively, pharmacokinetics (PK) data from earlier phase 1 trials of VRC01[15–17] are used to estimate $P(s)$ for each of the mAb dose groups, and TZM-bl[18] IC80 data for VRC01 against

a panel of 177 HIV-1 Env pseudoviruses across multiple genetic subtypes of the virus are used to estimate $P(v)$ that is common across the two mAb groups and the placebo group. The TZM-bl VRC01 IC80 neutralization data were described in more detail in Wu et al.[8] Different distributions of S and V are also considered in sensitivity analyses. The formula for prediction of PE also depends on a model for the distribution of the number of exposures to HIV-1 that occur for AMP trial participants. Because estimating this distribution in an efficacy trial is a challenging problem without satisfactory solutions, our approach specifies simplifying assumptions that make the PE formula independent of this distribution (see Methods).

Results

Input 1: Per-exposure prevention efficacy, $PE^{pe}(s,v)$

Under the NHP model, Figure 2 shows the estimated per-exposure PE as a joint function of the VRC01 plasma level measured immediately before challenge (S), and the IC80 of the challenge virus (V). These estimates are obtained from a logistic regression model of the NHP challenge data[11,30] with S and V as main effect terms and assuming no interaction of S and V, with a per-exposure infection odds ratio of 0.14 (95% CI: 0.02, 0.81) per-$\log_e$ increase of s and a per-exposure infection odds ratio of 3.42 (95% CI: 0.92, 12.73) per-$\log_e$ increase of v (Figures S1–S3). Estimated $PE^{pe}(s, v)$ for the 5-fold per-exposure PE model is shown in Figure 3, where the effect of V remains the same as the NHP model, but the per-exposure infection odds ratio per-$\log_e$ increase of s is 0.31, instead (Figure S4).

Input 2: Probability mass functions of S and V, P(s) and P(v)

Figure 4 shows the empirical distribution of S, for the two VRC01 dose groups, based on a random sample of 1000 simulated concentrations at exposures for AMP participants
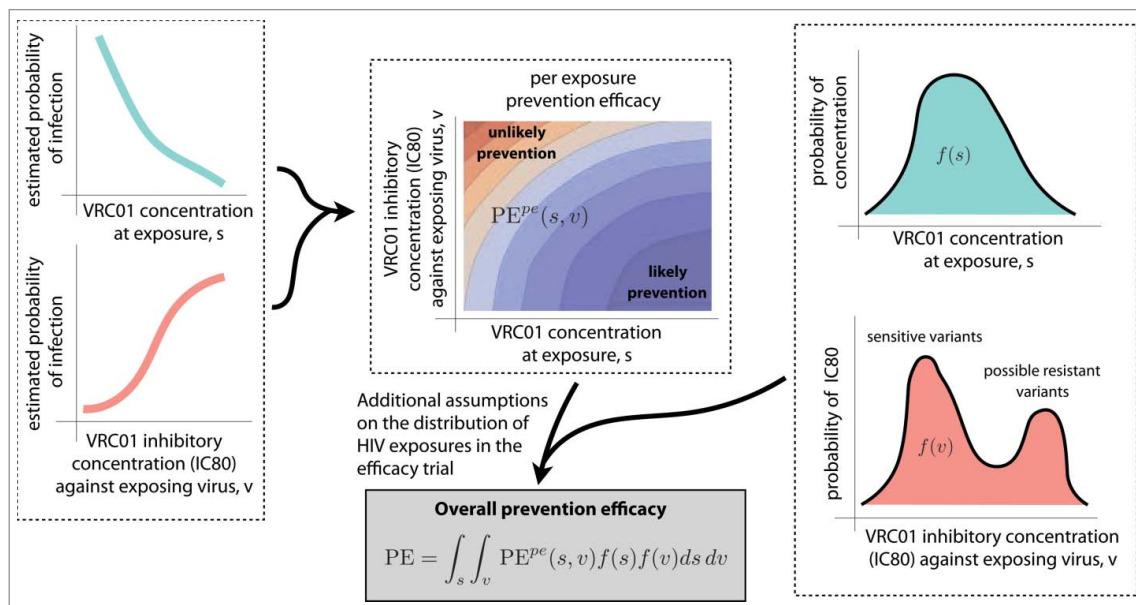

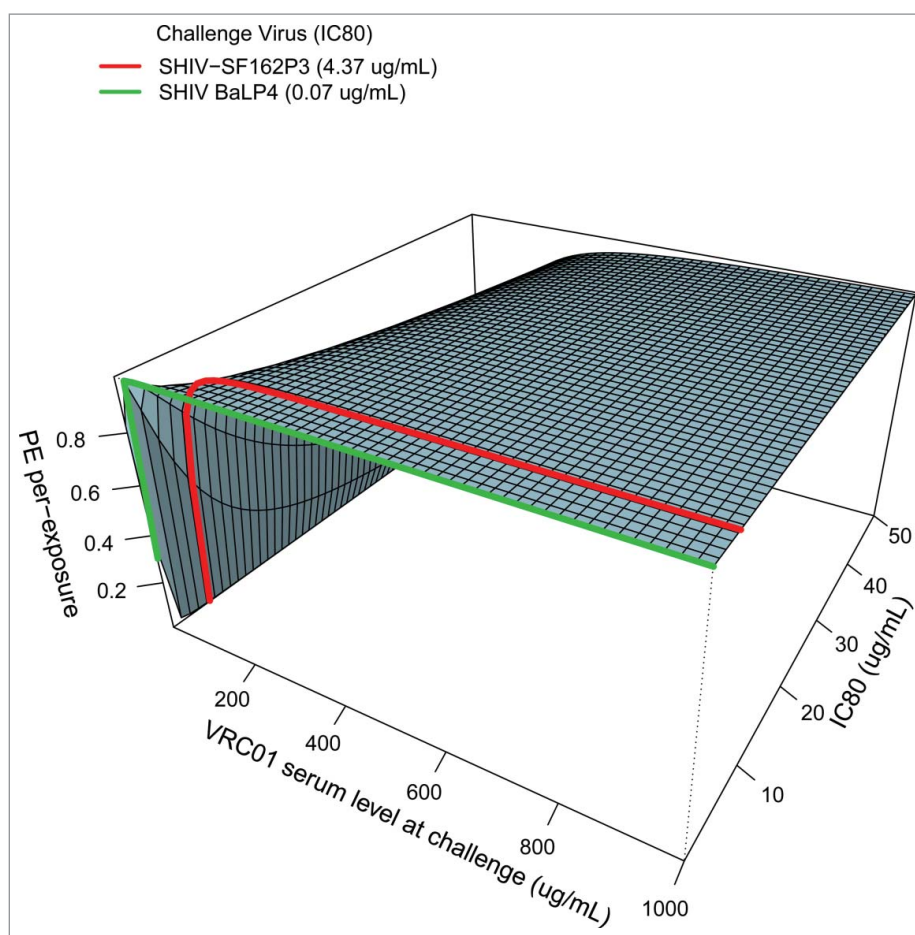**Figure 1.** Schematic of the proposed modeling approach.

Figure 2. Estimated per-exposure prevention efficacy (PE), PE^{pe}(s, v), as a function of VRC01 serum level at exposure and IC80 of the exposing virus based on the NHP challenge data.

accounting for inter-individual and intra-individual variability in concentrations over time where exposure times are sampled uniformly over the 80-week follow-up AMP period (Figure S5). In sensitivity analysis 1, the VRC01 serum levels at exposure are assumed to be lower and distributed according to a segmented uniform distribution as shown in Figure 5. Figure 6 shows the empirical distribution of V, based on IC80 values of VRC01 against a panel of 177 HIV-Env pseudoviruses. The median (range) IC80 is 1.30 (0.04, 50) μg/mL and 24% of the HIV-Env pseudoviruses have an IC80 > 5 μg/mL. In sensitivity analysis 2, a larger proportion of putatively resistant exposing viruses with IC80 > 5 μg/mL is assumed as shown in Figure 7.

Predicted overall PE

Based on the formula of overall PE described in the Methods section in terms of the input functions, PE^{pe}(s, v) and P (s, v), Figure 8 shows the predicted overall PE for the two dosing regimens of VRC01 in AMP under both the NHP and 5-fold models, as well as a gradient of models in between as indicated by the odds ratio of per-exposure acquisition risk of a VRC01 recipient per-log$_e$ increase of s. Specifically, for the 10 mg/kg regimen, the 5-fold and NHP models predict an overall PE of 37% and 64%, respectively. For the 30 mg/kg regimen, the 5-fold and NHP models predict an overall PE of

53% and 82%, respectively. Table 1 summarizes the predicted overall PE under different modeling scenarios.

In sensitivity analysis 1, the VRC01 serum levels at exposure are assumed lower than those observed in the phase 1 trials of VRC01,[15–17] and a lower PE is predicted under each scenario (Figure 9). For the 10 mg/kg regimen, the 5-fold and NHP models predict an overall PE of 32% and 55%, respectively. For the 30 mg/kg regimen, the 5-fold and NHP models predict an overall PE of 48% and 76%, respectively.

In sensitivity analysis 2, a higher proportion of resistant exposure viruses (i.e., IC80 > 5 μg/mL) is assumed than what is observed in the panel of 177 HIV-Env pseudoviruses. As expected, a lower PE is predicted under each scenario (Figure 10). Specifically, when the proportion of resistant viruses reaches 50% (last panel in Figure 10), for the 10 mg/kg regimen, the 5-fold and NHP models predict an overall PE of 25% and 49%, respectively. For the 30 mg/kg regimen, the 5-fold and NHP models predict an overall PE of 37% and 69%, respectively.

Discussion

Modeling exercises were conducted to predict the overall HIV prevention efficacy of the two VRC01 dose regimens (10 mg/kg and 30 mg/kg, each administered every 8 weeks)
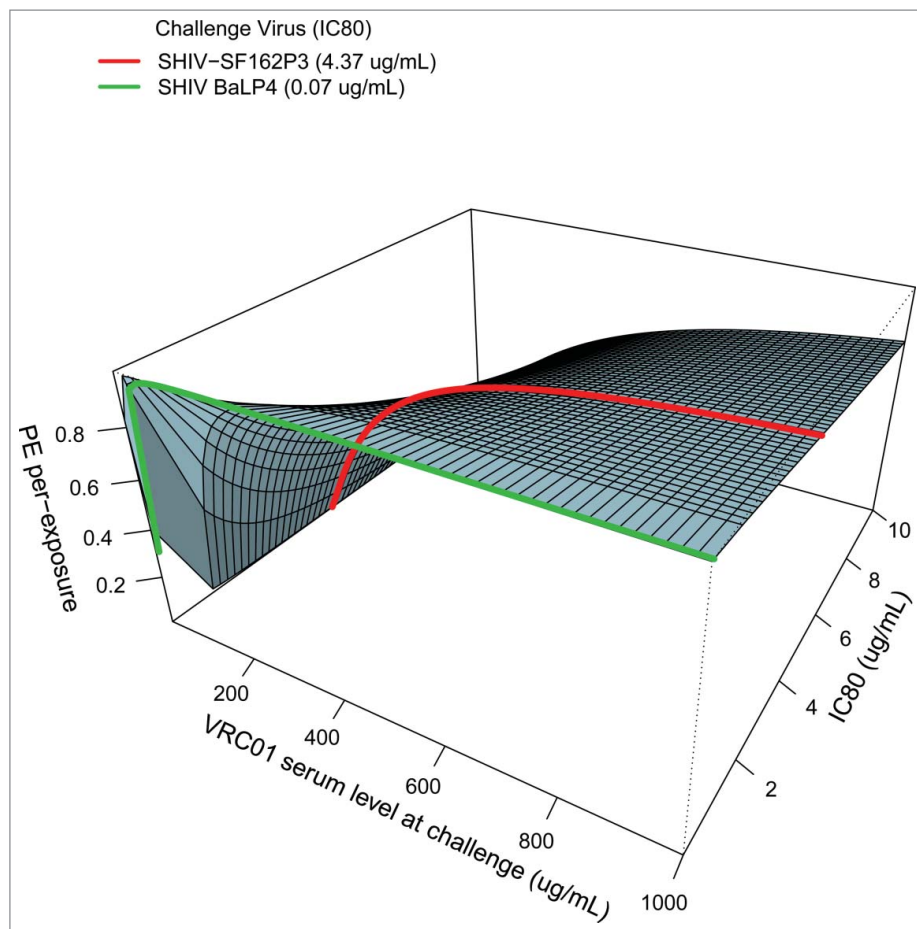
Figure 3. Estimated per-exposure PE, $PE^{pe}(s, v)$, as a function of VRC01 serum level at exposure and IC80 of the exposing virus based on the 5-fold model, which assumes 5-fold greater VRC01 serum level would be needed to provide the same level of $PE^{pe}(s, v)$ as observed in the NHP challenge data.

being evaluated in the ongoing AMP Phase 2b placebo-controlled prevention efficacy trials. Under certain assumptions a simple formula—independent of the background HIV incidence rate in the study population—was derived for prevention efficacy (PE) with two main input functions : per-exposure PE of VRC01 at a given level of VRC01 serum concentration at exposure ($S = s$) and the IC80 of the exposing virus ($V = v$), and the distributions of S and V for HIV exposures that occur in the AMP trials. Two models, and a spectrum of models bounded by them, were considered to estimate the functional form of per-exposure PE of VRC01 to cover a range of possible exposure models. The NHP per-exposure PE model assumes per-exposure PE measured in NHPs is exactly applicable to humans, whereas the 5-fold per-exposure PE model provides a more conservative prediction where a higher VRC01 concentration would be needed to provide the same level of protection as observed in the NHP model. These two models were chosen as two possible bounds for an illustration of our modeling approach; alternative per-exposure PE models outside of these bounds can be readily accommodated and may offer additional insights. Sensitivity analyses were also performed to account for different distributions of S and V from what the selected data on VRC01 concentrations and in vitro neutralization profile suggest. Across all the modeling scenarios considered, for the 10 mg/kg VRC01 dose group,

overall PE is predicted to be in the range of 49–64% under the NHP per-exposure model, and 25–37% under the 5-fold per-exposure model. For the 30 mg/kg VRC01 dose group, overall PE is predicted to be in the range of 69–82% under the NHP per-exposure model, and 37–53% under the 5-fold per-exposure model. These results support the concept of passive administration of HIV broadly neutralizing mAbs as a promising new HIV prevention modality. While the HIV research field awaits the final efficacy results from the AMP trials, these results provide model-based evidence for continued research in this area.

Our model makes several assumptions. First, it assumes that each trial participant has at most one HIV exposure during the trial. In reality, some high risk participants would very likely have multiple exposures. However, the same modeling formula applies allowing an arbitrary number of exposure if these repeated exposures do not change the per-exposure acquisition risk of placebo recipients and conditional prevention efficacy is invariant to the number of exposures. More data from multiple-challenge studies could be incorporated to adjust this assumption if needed. Second, we do not attempt to correlate neutralization sensitivity of the virus with its probability of infection in the placebo cohort. Yet, the assumption of homogeneous per-exposure acquisition risk of placebo recipients for all in vitro neutralization sensitivities V of exposing HIVs may be
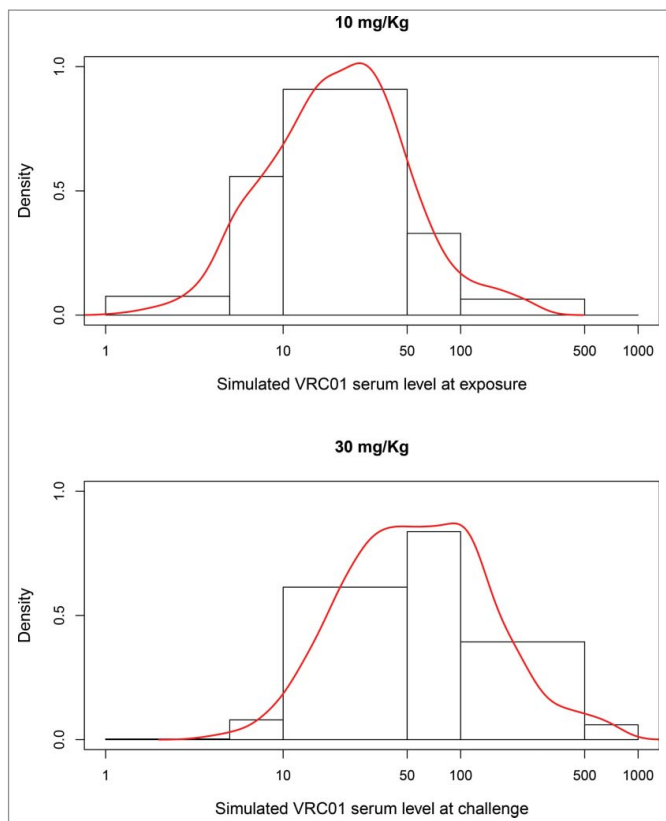
Figure 4. Distribution of the simulated VRC01 serum level at the time of HIV-1 exposure.

violated. There is some evidence for such an association (e.g.,[27]). These simplified assumptions about the amount of exposure and homogeneity of per-exposure risk allow the PE formula to be specified without needing to estimate the distribution of exposures in an efficacy trial, which is a hard problem given the difficulty in accurately measuring exposure to HIV. Further, simplification allowed us to avoid making assumptions about the background HIV incidence rate in these cohorts because PE is calculated as a ratio of infections in treated to placebo groups. Allowing identical incidence in both groups means incidence can be canceled out in the ratio. Eliminating incidence is advantageous because the PE formula immediately applies to both AMP trials without needing to specify the different background HIV incidence rates, although as mentioned below different per-exposure PE models may be needed for the two trials with different exposure routes or target tissues. Third, we assumed that the timing of exposure for participants with an HIV exposure is uniformly distributed over the trial follow-up period. In future work, it would be straightforward to modify the exposure model. For example, participants might be less likely to engage in high risk behaviors after a study visit (especially after a risk reduction counseling session), and the distribution of exposure times could be derived after accounting for the study visit schedule in AMP. However, since there is risk reduction counseling (RRC) at both the infusion visit and at the 4-week post-infusion visit, each month of post-infusion "exposure" (before the next infusion is received at 8 weeks) would have

approximately equal distribution of times from RRC sessions.

The modeling approach also assumes that the panel of 177 HIV-1 Env pseudoviruses used to obtain the VRC01 IC80 neutralization data faithfully represents the circulating viruses to which the participants in the AMP trials are exposed. Different HIV-1 subtypes predominate in the two AMP trials, with a clade C epidemic in sub-Saharan Africa and a clade B epidemic in the Americas and Switzerland.[19] While VRC01 does have broad neutralization activity, there is some variation across clades, with clade C viruses more resistant to neutralization.[20–22] In future work it would be of interest to re-run the models for the two AMP trials separately, for each trial using VRC01 IC80 data restricted to an up-to-date panel of viruses restricted to the HIV-1 subtype of the trial (e.g., for the 200-virus clade C panel of Wagh et al.[25]) and possibly restricted to other features relevant to the trial. It is also unknown how well the composition of the HIV-1 Env pseudoviruses in the panel, which were generated by using Env sequences cloned from HIV isolates derived from acute and chronic stages of HIV-1 infection, represent the distribution of infection stage of exposing partners that occurs in the AMP trials. This is relevant because, at least for clade B, there is evidence that sequences from individuals with acute HIV infection are more sensitive to VRC01-mediated neutralization than those from individuals with chronic HIV infection.[23] Moreover, the model does not account for the fact that AMP participants are exposed to HIV-1 quasispecies and VRC01 may need to neutralize all resistant variants or at least all resistant variants of some unknown minimum prevalence in the quasispecies.[26] Our sensitivity analyses in Figure 6 address the possibility that AMP participants are exposed to viruses (or virus variants) more resistant to VRC01-mediated neutralization than those in the panel.

Another source of uncertainty in our modeling approach stems from the lack of knowledge regarding how per-exposure PE in NHPs can be applied to per-exposure PE in humans and how per-exposure PE varies across different target tissues in humans, since the explant challenge studies suggest that such variation will exist.[28,29] Part of this uncertainty is due to the fact that the NHP work employed high dose intra-rectal challenges and included two challenge viruses, representing less diversity than the challenges in human trials. Moreover, the two challenge viruses used had higher transmission probabilities than those common in human trials. While the modeling approach could use alternative functional forms of per-exposure PE other than the logistic model (e.g., including interactions between S and V), this would not address the fundamental uncertainty in extrapolating between species and across exposure tissue types. Our modeling approach is dominantly statistical/empirical; additional modeling that accounts for viral and transmission dynamics at and near the time of HIV exposure may potentially yield different predictions of PE as well as provide mechanistic insights into prevention efficacy. This is particularly relevant in the context of the AMP trials, which are enrolling participants at risk of HIV
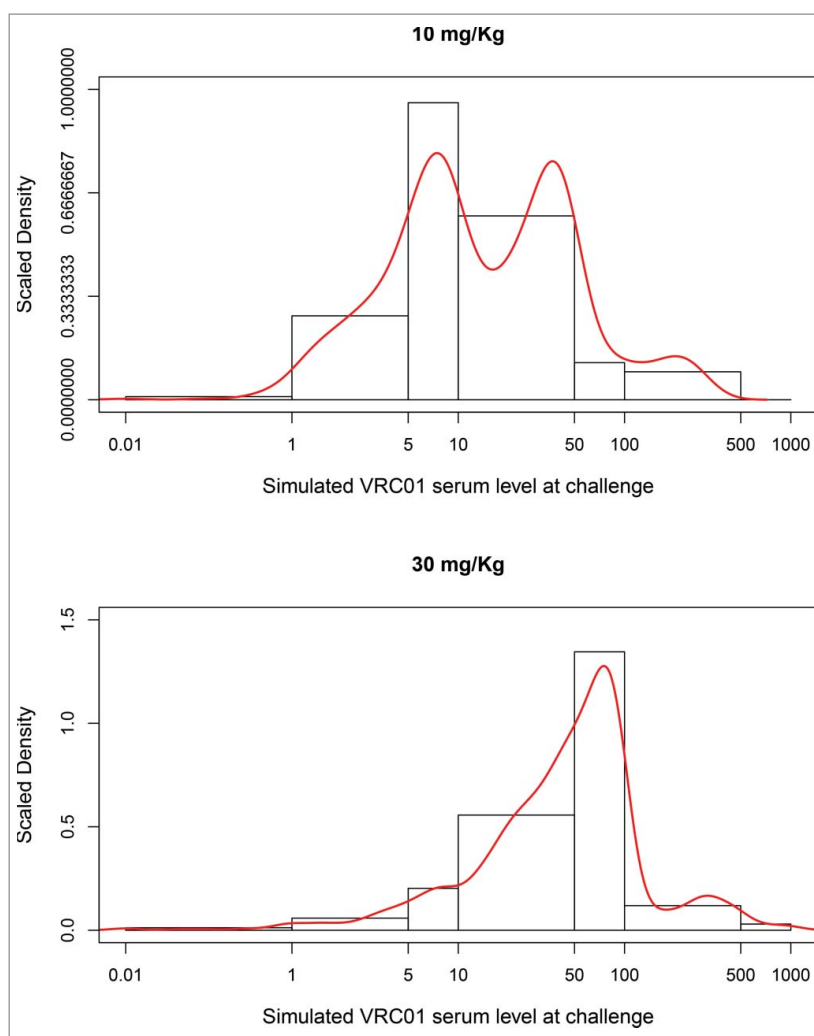
Figure 5. Sensitivity analysis 1: distribution of the simulated VRC01 serum level at time of HIV-1 exposure based on a segmented uniform distribution.

acquisition via two distinct modes: heterosexual acquisition, which predominates in the African cohorts, and male-to-male sexual acquisition, which predominates in the American and European cohorts.

Given the many uncertainties in the modeling assumptions that undergird the predictions of PE and the limited ability to fully test the assumptions, we suggest that the utility of our model is not primarily in providing a defensible quantitative prediction of PE that can then be empirically checked with the AMP results. Rather, the primary value of our model lies in (1) [Efficacy Trial Design] As supplemental information for Go/No-Go efficacy trial decision-making, in demonstrating (or not) that it is rationally plausible that an efficacy trial design is configured such that the specified design alternative of PE that the trial is powered to detect could be achievable. We note that it is important to point out the limitations of the predicted PE model in the supplemental information given that the requisite knowledge and data do not exist to adequately validate all of the modeling assumptions, or to accurately specify the parameter values in the PE model. The primary value of our model also lies in (2) [Rank-and-select + Down-Selection] Providing defensible rankings of predicted PE among multiple mAb regimens. For (1), the modeling was used as supplemental data in decisions to launch the AMP trials. Had predicted PE been considerably lower, then the AMP trials could have been re-designed. For (2), the essence of our formula is that the predicted overall PE of a mAb regimen is monotone increasing with the average per-exposure prevention efficacy values over the distributions of mAb concentration crossed with HIV neutralization sensitivity at HIV exposures in an efficacy trial. This monotonicity holds even if individual terms in the formula are estimated in a biased fashion, as long as the bias is similar across the mAb regimens being compared, and should hold under mis-specified assumptions on the distribution of the number of HIV exposures, given these assumptions apply uniformly to all mAb regimens. Therefore, as combination and multi-specific mAb regimens are tested in phase 1 trials and considered for future efficacy testing, this modeling approach could be applied to each regimen, assuming available standardized data on the distributions of S and V and on NHP challenge conditional efficacy data. The potential applications of this modeling approach include ranking and selecting regimens by predicted overall PE in an envisaged efficacy trial and down-selecting the most promising
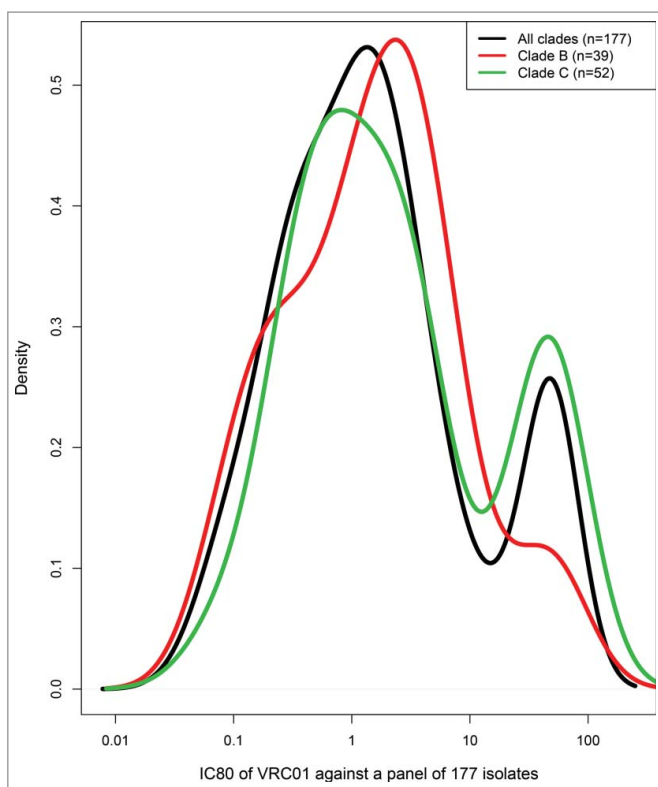
Figure 6. Empirical distribution of TZM-bl IC80 values based on a panel of 177 HIV-Env pseudoviruses.

regimen(s) to the efficacy trial. This application is of high value because multiple phase 1 trials evaluating dozens of different single-mAb regimens and combination- or multi-specific-mAb regimens administered at different dose levels, dosing schedules and administration routes are currently being evaluated or will soon be evaluated. Moreover, as the results from AMP and other mAb efficacy trials become available, the modeling approach could be refined based on the PE results to iteratively make the model more accurate, and be updated to integrate results on correlates of prevention efficacy from the efficacy trial(s).

Our modeling approach can be approximately interpreted as predicting overall PE in terms of serum neutralization titer against the challenge virus and IC80 of the challenge virus (V). This is because neutralization-effective serum concentration, which has been observed to be highly correlated with serum concentration measured by binding activity (S) for VRC01 (Supplementary Figure S6), can be estimated as the product of serum neutralization titer (i.e., as an inverse dilution factor of the serum inhibiting 80% of the virus from a neutralization assay) and the IC80 of the clinical lot of the mAb against the same virus in the same neutralization assay. In other words, the PE modeling formula detailed in Methods can be indexed by S defined as the serum neutralization titer to the challenge virus at exposure instead of as the binding concentration S, and because V is the IC80 of the challenge virus (using the same neutralization assay) the same formula applies. Alternatively, the PE model can be expressed as a function of serum neutralization titer to a virus (S) that differs from the challenge virus for which the IC80 (V) is measured. Due to the use of

different viruses for defining the host marker S and the challenge SHIV stock, the latter model may provide a less accurate modeling formula.

An application of the modeling is to help prepare for Phase 1 clinical trials of candidate HIV-1 vaccines designed to induce broadly neutralizing antibodies. For such trials a likely study endpoint will be the level at which a vaccine recipient's serum sample neutralizes a panel of HIV-1s representing potentially exposing viruses in a future efficacy trial, e.g., a vaccine recipient's geometric mean IC80 to the panel of viruses. Our modeling approach applies generally for any host marker S that is linked to per-exposure prevention efficacy in the NHP challenge model. Therefore selecting the host marker at challenge S to be the same geometric mean neutralization endpoint that is planned for use as a study endpoint in future Phase 1 HIV-1 vaccine clinical trials may link the PE model more closely to vaccine development, and it may be useful to compare the predicted overall prevention efficacy based on magnitude and breadth of serum neutralization versus that based on binding concentration.

Methods

Notation

The following notations are used throughout the derivations below. Let $Z = 1$ or 0 denote treatment assignment to a given mAb group or placebo, $Y = 1$ if infected or 0 if not infected during the trial follow-up period (80 weeks for AMP), $E = 1$ if exposed and 0 if never exposed during the trial, $P(s)$ or $f(s)$ denote the probability mass or density function for discrete or continuous S, and $P(v)$ or $f(v)$ denote probability mass or density function for discrete or continuous V. Consequently, the overall PE for a given mAb group is defined as $\text{PE} = 1 - \frac{P[Y=1|Z=1]}{P[Y=1|Z=0]}$, and the per-exposure PE for a given mAb group is defined as

$$\text{PE}^{pe}(s, v) = 1 - \frac{P[\text{Infection}|Z=1, E=1, S=s, V=v]}{P[\text{Infection}|Z=0, E=1, V=v]},$$

where the probabilities are for whether HIV is acquired upon a single exposure $E = 1$ with an HIV of phenotype v while the concentration of the mAb is s (if assigned to an mAb group). The notations $P(s)$, PE and $\text{PE}^{pe}(s, v)$ may be given a subscript 10 or 30 to denote the 10 or 30 mg/kg mAb group.

Assumptions

The following assumptions are used in the derivations.
(1) PE is predicted in a randomized placebo-controlled trial, where observed and unobserved confounding factors are balanced between the treatment groups.
(2) Each trial participant has exactly 0 or 1 HIV exposures during the trial (i.e., $E = 0$ or $E = 1$).
(3) Independence of S and V so that $P(s, v) = P(s)P(v)$ or $f(s, v) = f(s)f(v)$.
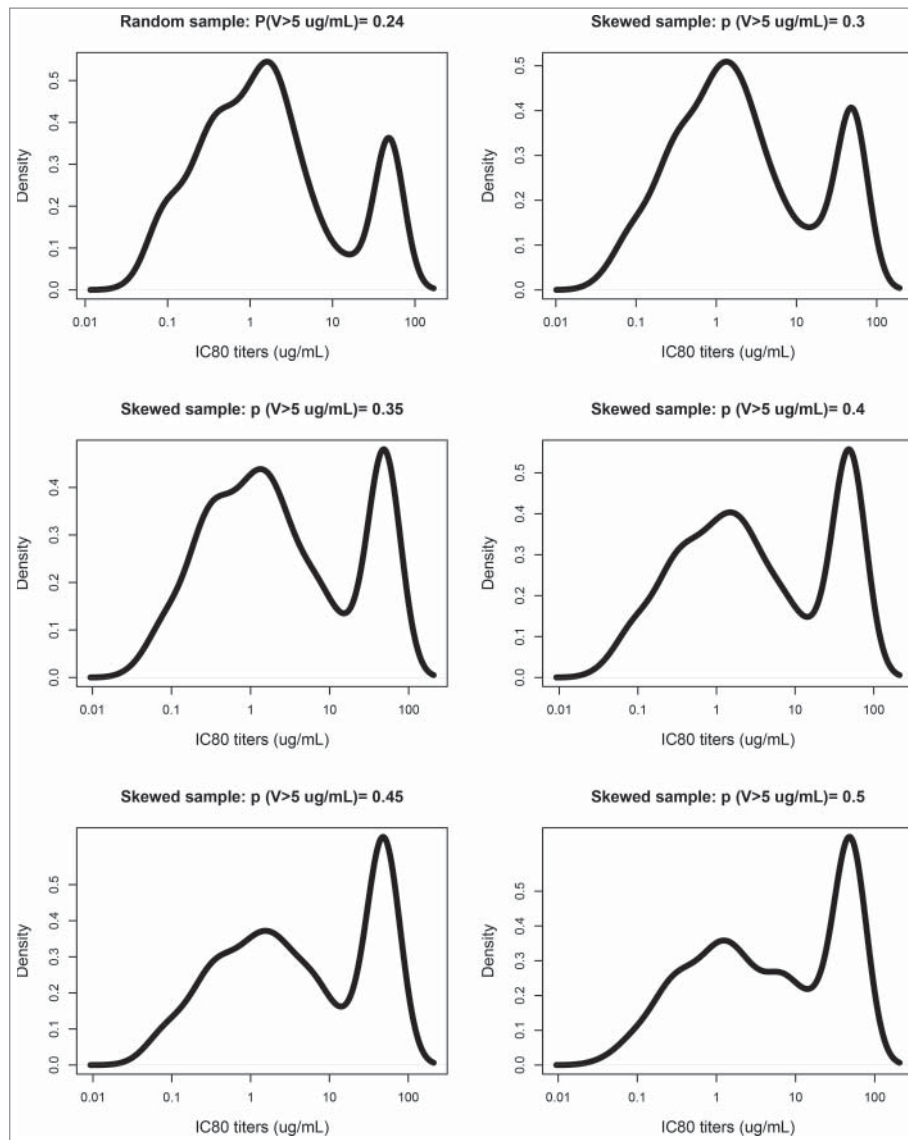
Figure 7. Sensitivity analysis 2: Empirical and alternative distributions of IC80 values based on assuming a higher proportion of resistant viruses than observed in the panel of 177 HIV-Env pseudoviruses.

(4) For participants with an HIV exposure, the timing of exposure is uniformly distributed during the period of the trial follow-up.

(5) Homogeneity of per-exposure acquisition probabilities in the placebo group: $P^{pe}[\text{Infection}|Z = 0, E = 1, V = v]$ is constant ($= \theta$) for all v.

(6) The effects of S and V on per-exposure acquisition probabilities in mAb group participants follow a logistic regression model and their effects are additive, i.e., there is no interaction between S and V: $\text{logit}(P^{pe}[\text{Infection}|Z = 1, E = 1, S = s, V = v]) = \beta_0 + \beta_1 * s + \beta_2 * v$, where β_0 is the log odds of infection at $s = 0$ and $v = 0$ and $\exp(\beta_1)$ and $\exp(\beta_2)$ are odds ratio of per-exposure infection per-$\log_e$ increase in s and v, respectively.

The identical formula below holds if Assumption 2 is changed to allow an arbitrary number of HIV exposures for participants, but then alternative assumptions are needed; one sufficient set is: (2.1) In the placebo group the risk of infection is memoryless, i.e., $P(Y = 1|Z = 0, E = e, V = v)$

$= 1 - (1 - \theta)^e$ for all counting numbers e; (2.2) V is independent of the number of exposures; and (2.3) $P(Y = 1|Z = 1, E = e, S = s, V = v)/P(Y = 1|Z = 0, E = e, V = v)$ is constant in e.

Prevention efficacy formula

We provide the formula for discrete S and V; the formula is the same for continuous S and V with $P(s)$ and $P(v)$ replaced with $f(s)$ and $f(v)$ and sums replaced with integrals. First, the cumulative risk of HIV infection during the trial follow-up period in the placebo group, $P[Y = 1|Z = 0]$, equals θ. This follows because:

$$P[Y=1|Z=0] = \sum_{s,v} P_0^{pe}(s,v)P(s,v) \ (\because \text{Assumption 2})$$
$$= \theta \sum_{s,v} P(s,v) \ (\text{Assumption 5}). \qquad (1)$$
$$= \theta$$
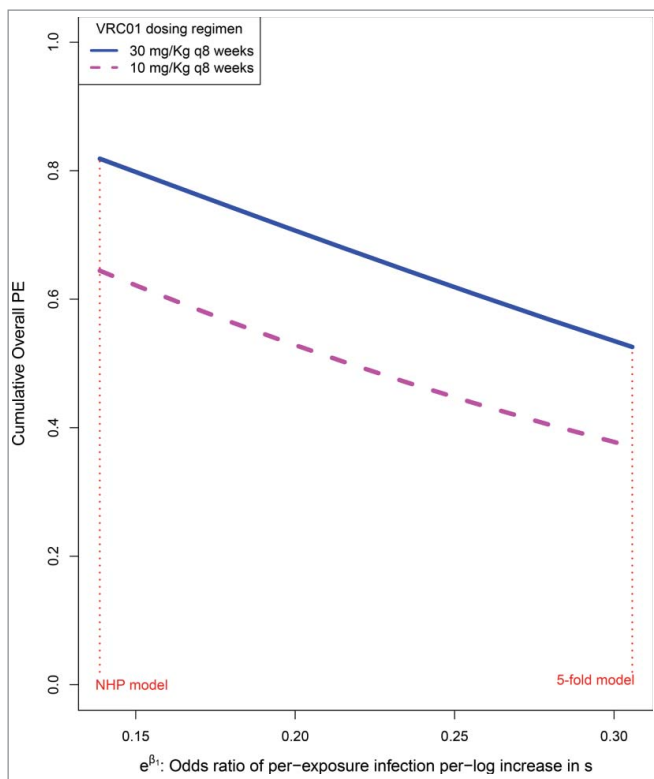
Figure 8. Predicted cumulative overall PE for the two VRC01 dosing regimens.

Figure 9. Sensitivity analysis 1: Predicted cumulative overall PE for the two VRC01 dosing regimens under the alternative segmented-uniform distribution of S.

Second, the cumulative risk of infection in an mAb group can be expressed as

$$P[Y = 1|Z = 1]$$

$$= \sum_{s,v}[1 - \mathrm{PE}^{pe}(s,v)]P_0^{pe}(s,v)P(s,v)\left(\mathrm{PE}^{pe}\text{ definition \& Assumption 2}\right)$$

$$= \theta\sum_{s,v}[1 - \mathrm{PE}^{pe}(s,v)]P(s,v)(\text{Assumption 5})$$

$$= \theta\left[1 - \sum_{s,v}\mathrm{PE}^{pe}(s,v)P(s,v)\right] \tag{2}$$

Consequently, we have

$$
\begin{aligned}
PE &= 1 - \frac{P[Y=1|Z=1]}{P[Y=1|Z=0]}(\text{Assumption \#1})\\
&= 1 - \frac{\theta\left[1 - \sum_{s,v}\mathrm{PE}^{pe}(s,v)P(s,v)\right]}{\theta}(\text{Equations (1) \& (2)}) \tag{3}\\
&= \sum_{s,v}\mathrm{PE}^{pe}(s,v)p(s,v)\\
&= \sum_{s,v}PE^{pe}(s,v)P(s)P(v)(\text{Assumption 3})
\end{aligned}
$$

or, for continuous S and V:

$$PE = \int_s\int_v PE^{pe}(s,v)f(s)f(v)\,ds\,dv. \tag{4}$$

This provides a simple formula mapping inputs $\mathrm{PE}^{pe}(s,v)$ and $P(s,v)$ (or $f(s,v)$) to the output PE.

Specification of parameters in the model for PE

In the following we describe how to specify each of the input functions and model PE based on formula (3) or (4).
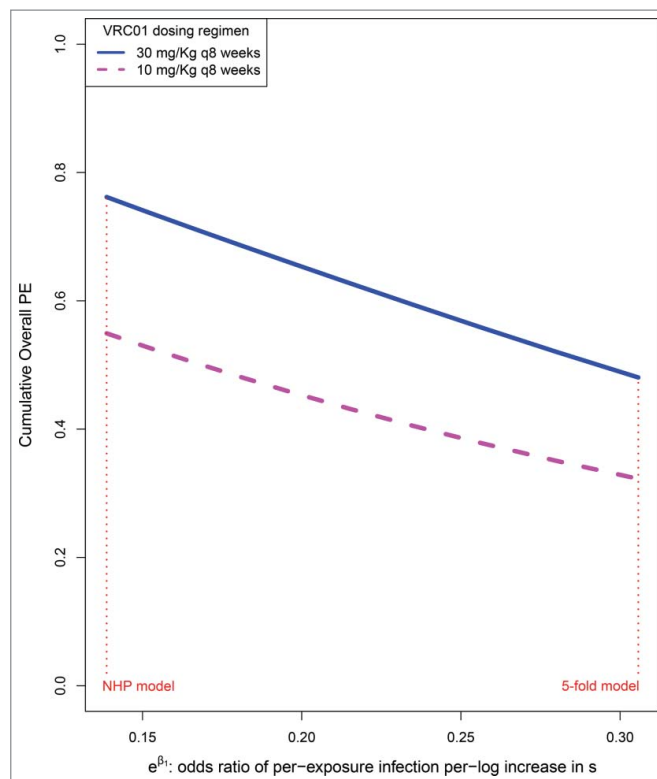
Specifying the input $PE^{pe}(s,v)$

This function is independent of the mAb dose group. Two models are considered for the specification of $\mathrm{PE}^{pe}(s,v)$: the non-human primate (NHP) model and the 5-fold model. Under the NHP model, this function is specified based on observed data from non-human primate challenges,[11,30] in which a total of 40 healthy male and female animals were challenged intra-rectally with a single 100% infectious SHIV inoculation two days after an infusion of VRC01 at various dosage levels. The infection status was recorded for eight animals challenged with SHIV-SF162P3, and 32 animals challenged with SHIV BaLP4, along with the animals' VRC01 plasma level on the day of challenge. The IC80 titers of VRC01 were 4.37 ug/mL and 0.07 ug/mL, respectively, for SHIV-SF162P3 and SHIV BaLP4.

Specifically, a logistic regression model (Assumption 6) is fitted to estimate the probability of infection among VRC01 treated animals as a function of VRC01 serum level on the day of challenge (S) and the IC80 of VRC01 against the challenge virus (V) as follows:

$$\frac{P_{\mathrm{NHP}}(\text{Infection}|Z=1, E=1, S=s, V=v)}{1 + \exp(-(\beta_0 + \beta_1\log(s) + \beta_2\log(v)))}$$

In the NHP model, we assume that control animals would be infected with probability 1 once exposed, i.e., $P(\text{Infection}|Z=0, E=1, V=v)=1$ for all values of v. Hence,

$$
\begin{aligned}
PE_{\mathrm{NHP}}^{pe}(s,v) &= 1 - P_{\mathrm{NHP}}(\text{Infection}|Z=1, E=1, S=s, V=v)\\
&= \frac{1}{1 + exp\left(\beta_0 + \beta_1 log(s) + \beta_2 log(v)\right)},
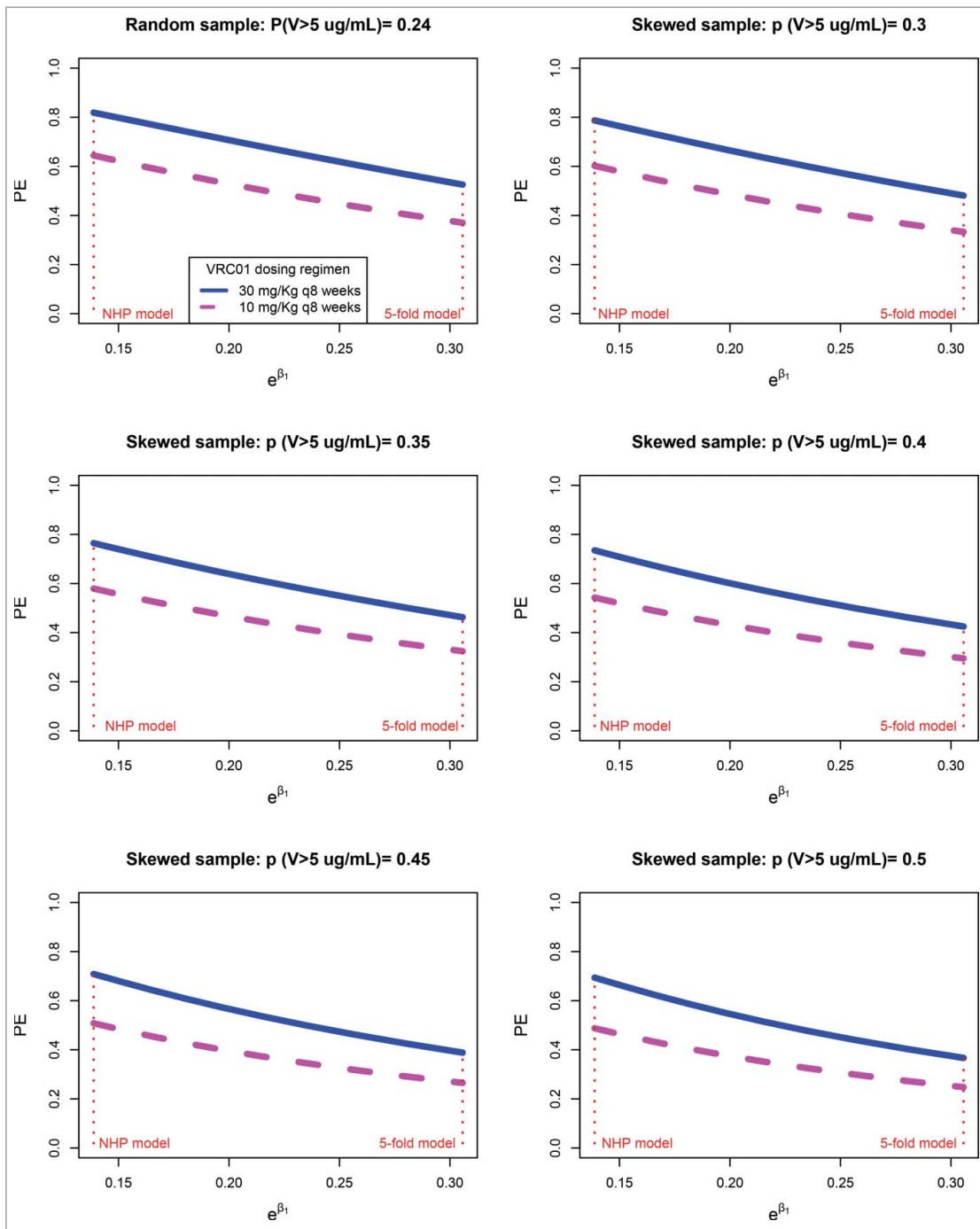\end{aligned}
$$

Figure 10. Sensitivity Analysis 2: Predicted cumulative overall PE for the two VRC01 dosing regimens under alternative distributions of *V*.

where $exp(\beta_1)$ can be interpreted as the decrease in per-challenge odds of infection per $\log_e$ increase in *s*. This is the parameter being plotted on the x-axis of Figures 8, 9 and 10. Based on the NHP model, $\widehat{\beta}_1 = -1.98$ indicates that there is an estimated 0.14 $(= exp(-1.98))$ fold decrease in the odds of getting infected per-$\log_e$ increase in *s*, and $\widehat{\beta}_2 = 1.23$ indicates that there is an estimated 3.41 $(= exp(1.23))$ fold increase in the odds of getting infected per-$\log_e$ increase in *v*.

Under the 5-fold model, we assume that 5-fold greater VRC01 serum level would be needed to provide the same level of PE as seen in the NHP intra-rectal challenge results. The

parameter $PE^{pe}(s, v)$ is specified as

$$
\begin{aligned}
PE^{pe}_{5-\text{fold}}(s, v) &= PE^{pe}_{\text{NHP}}(s/5, v) \\
&= \frac{1}{1 + \exp\left(\beta_0 + \beta_1^* \log(s) + \beta_2 \log(v)\right)}
\end{aligned}
$$

where $\beta^*_1 = \beta_1 \log(s/5)/\log(s)$ for all *s*. For simplicity, we choose $\beta^*_1 = \beta_1 \log(10)/\log(50) = 0.6^* \beta_1$.

Specifying the inputs f₁₀(s) and f₃₀(s)

The distribution functions of serum concentrations at exposure for the two dose groups, $f_{10}(s)$ and $f_{30}(s)$, are specified based on

uniform sampling (Assumption 3) of simulated VRC01 concentration levels over the trial follow-up period for the 10 mg/kg and 30 mg/kg 8-weekly dose groups using parameters estimated from a two-compartment PK model of observed time-concentration data in early phase trials of VRC01.[15–17] The simulated AMP trials assume participants received all ten infusions every 8 weeks. Thus far, this assumption seems to be holding close to true for the AMP trials.

In sensitivity analysis 1, we assume that S_{10} and S_{30} follow a continuous segmented uniform distribution, which, if collapsed, leads to, for the 10 mg/kg group, $P(S \in (Low, Med, High)) = (50\%, 40\%, 10\%)$, and, for the 30 mg/kg group, $P(S \in (Low, Med, High)) = (10\%, 40\%, 50\%)$, where Low, Med and High indicate $s \leq 10$ μg/mL, $10 < s \leq 50$ μg/mL, and $s > 50$ μg/mL, respectively.

Specifying the input f(v)

The distribution $f(v)$ is specified based on observed IC80 data reflecting how well VRC01 neutralizes a panel of 177 HIV-Env pseudoviruses, as measured by a validated TZM-bl assay, as described in[18]. The panel of 177 HIV-Env pseudoviruses was derived from the panel in[8] but has minor differences; a full listing of the 177 HIV-Env pseudoviruses used in this analysis is given in Supplemental Table 1. An empirical distribution of V is used, assuming the observed IC80 values represent a random sample from the circulating viruses to which trial participants are exposed. The median IC80 titer is 1.30 μg/mL, with a range of (0.04, 50) μg/mL across all clades of HIV-Env pseudoviruses included in the panel. The observed proportion of HIV-Env pseudoviruses with IC80 titer > 5 μg/mL is $p = 0.24$.

In sensitivity analysis 2, alternative distributions of V are specified by assuming a larger proportion of resistant exposing viruses with $p = 0.3, 0.35, 0.4, 0.45$ and 0.5.

PE modeling

In the modeling exercise, $f_{10}(s)$, $f_{30}(s)$, and $f(v)$ are held fixed. The Monte Carlo method is used to simulate 1000 realizations of each of S_{10}, S_{30} and V according to the specifications described above. We consider a gradient of $PE^{pe}(v, s)$ shapes

between the NHP and 5-fold models governed by $exp(\beta_1)$, i.e., the decrease in odds of infection per-$\log_e$ increase in s as described in Section 4.1. Under each $PE^{pe}(s, v)$ scenario, the overall PE predicted from the model is then calculated as the integrated $PE^{pe}(s, v)$ over all values of s and v based on Formula (3) or (4).

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Table 1. Predicted overall prevention efficacy of VRC01 for the 10 mg/kg and 30 mg/kg regimens. Observed S refers to simulated concentrations at exposure based on [16], and observed V refers to in vitro IC80 data of VRC01 against a panel of 177 HIV-1 Env pseudoviruses described in [8].

NHP per-exposure PE model	10 mg/kg	30 mg/kg
Observed S & V	64%	82%
Sensitivity Analysis 1: alternative $P(s)$	55%	76%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.3$	60%	79%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.35$	57%	77%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.40$	54%	73%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.45$	51%	72%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.50$	49%	69%

5-fold per-exposure PE model	10 mg/kg	30 mg/kg
Observed S & V	37%	53%
Sensitivity Analysis 1: alternative $P(s)$	32%	48%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.3$	34%	48%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.35$	31%	45%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.40$	29%	42%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.45$	26%	39%
Sensitivity Analysis 2: $P(V > 5\mu g/mL) = 0.50$	25%	37%

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