Web Supplementary Material for "Predicting Overall Vaccine Efficacy in a New Setting by Re-Calibrating Baseline Covariate and Intermediate Response Endpoint Effect Modifiers of Type-Specific Vaccine Efficacy"

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Appendix A: Comparison of Principal Stratification and Controlled Effects Frameworks for Transport Formulas

Our transport formula fits within the principal stratification framework, and at the end of this appendix we show how the formula can be modified to fit within the controlled direct effects framework. These frameworks lend themselves to transport formulas because they use causal parameters describing how vaccine efficacy varies over subgroups defined by the biomarker candidate surrogate endpoint response, for the former framework with the "happenstance" value of the biomarker and for the latter with the biomarker set to a given constant value. In contrast, the natural direct effects framework does not consider biomarker-specific vaccine efficacy, and therefore does not provide a means for mathematically translating how a change of the biomarker distribution in the new setting leads to an overall treatment efficacy that differs from that in the original setting. The Prentice framework could be used, with appeal that the bridging is based on observable subgroups, whereas in contrast the subgroups for the principal stratification and controlled effects approaches are challenging to identify and membership in the subgroups may not be directly measurable. Nevertheless, the principal stratification and controlled effects frameworks are useful because it may be difficult to express interpretable bridging functions in terms of statistical parameters, and the absence of interpretable bridging assumptions hinders the ability to conduct sensitivity analysis.

The context informs the pros and cons of using the principal versus controlled effects framework. The latter framework may be preferred if plausible identifiability assumptions exist, as the bridging assumptions needed for believing that intervened effects in one setting would carry over to another may be clearer and more plausible than those needed for believing that un-intervened principal effects would carry over,

given that the happenstance principal strata subgroups will be different in the original and new settings. However, in many applications including our motivating example the controlled effects framework cannot be used whereas the principal effects framework can, and we therefore focus most of the manuscript on the principal effects framework.

In general the controlled effects framework may apply if there are no or few clinical events before the intermediate biomarker response endpoints S are measured. Otherwise it may be difficult to use, because the definition of the controlled effects parameters requires setting all subjects to not experience the clinical endpoint before S is measured. This may be inconceivable. In addition, the controlled effects framework appears inapplicable in the scenario of our motivating application wherein S does not vary in the placebo/control group, a scenario we named Case Constant Biomarker (CB) (Gilbert and Hudgens, 2008). We have argued that controlled effects parameters cannot be meaningfully defined in Case CB (Gilbert, Hudgens, Wolfson, 2011), i.e., it is difficult to justify the existence of a structural causal model (Pearl, 2009) defining interventions on the biomaker. In addition, in Case CB the two central difficulties with the principal stratification approach are ameliorated, with identifiability achieved under weaker assumptions and the set of subjects within the principal strata of interest becoming known. Moreover, Case CB is prevalent and important– for example present in all vaccine efficacy trials that enroll subjects never previously infected with the pathogen under study, and such vaccine efficacy trials have been of great significance for public health.

We conclude this Supplement by describing how the principal stratification transport formula of the main article may be changed from being based on the vaccine efficacy curve to being based on controlled effects vaccine efficacy. Unlike principal stratification that statistically controls intermediate variables by conditioning on them, the controlled direct and indirect effects framework experimentally controls intermediate variables by physical control/manipulation/intervention. See Robins and Greenland

(1992) and Pearl (2001) for a rigorous exposition. To use this framework for the transport problem, we define $T(z, s_1)$ to be the potential outcome T under joint assignment of Z to z, $S(1)$ to s_1, and T to exceed τ, and similarly define $V(z, s_1)$. Then the "intervened" or controlled effects mark-specific vaccine efficacy curve is defined as

$$VE^{cont}(t, v|s_1, x) \equiv 1 - \frac{P(T(1, s_1) \leq t, V(1, s_1) = v|X = x)}{P(T(0, s_1) \leq t, V(0, s_1) = v|X = x)}.$$

Substituting $VE(t, v|s_1, x)$ with $VE^{cont}(t, v|s_1, x)$ into the transport formula of the main article yields the controlled effects version of the transport formula, where now $\phi(t, v|s_1, x)$ is modified to $\phi^{cont}(t, v|s_1, x) \equiv VE^{*cont}(t, v|s_1, x)/VE^{cont}(t, v|s_1, x)$. An advantage of this approach is that $\phi^{cont}(t, v|s_1, x)$ may be easier to specify because it is in terms of experimentally defined subgroups.

Appendix B: Selection of the Re-Calibration Variables X, $S(1)$, and V from the RV144 HIV-1 Vaccine Efficacy Trial and Details of Estimation of the Terms in the Immuno-Bridging Transport Formula

This appendix describes how each of the terms in the transport formula [equation (3) in the main article] are estimated for the application in the main article.

To apply the immuno-bridging transport formula, we need to estimate the input parameter $VE(t, v|s_1, x)$ based on the analysis of the RV144 HIV-1 vaccine efficacy trial data. The first task is determining the HIV-1 genetic mark variable V to use. Our approach considers the set of binary marks V^i defined as the indicators at each amino acid (AA) position i in the HIV-1 Envelope protein that were pre-specified as potentially relevant for protective antibodies. Specifically, V^i is the indicator of whether the AA at position i in an HIV-1 infected subject's virus sampled at diagnosis of infection mismatches the AA of a specified HIV-1 sequence contained in the vaccine at the same AA position (Rolland and Edlefsen et al., 2012). Three sets of indicators

are defined corresponding to the three HIV-1 vaccine sequences, totaling eight AA positions. For each indicator V^i, we tested the null hypothesis $H_0 : VE(t = 39, V^i = 1) = VE(t = 39, V^i = 0)$ using a cause-specific Cox model (Lunn and McNeil, 1995) and selected all indicators such that the 1-sided p-value for testing H_0 versus the alternative $H_1 : VE(t = 39, V^i = 1) < VE(t = 39, V^i = 0)$ was below 0.025.

This analysis yielded one AA position, number 169 in the V2 portion of HIV-1 Envelope, with 1-sided $p = 0.02$ and $\widehat{VE}(t = 39, V^i = 1) = -0.55$ (95% CI = -2.58 to 0.33) and $\widehat{VE}(t = 39, V^i = 0) = 0.48$ (95% CI = 0.18 to 0.66). This result was reported in Rolland and Edlefsen et al. (2012), with identical results for the two subtype AE HIV-1 sequences contained in the vaccine. The AA in the vaccine was Lysine (K); thus we take the mark V to be the indicator of non-K at position 169. Because the confidence interval for $VE(t = 39, V^i = 1)$ is wide and the data are consistent with no vaccine efficacy against $V^i = 1$ HIV, for the formula we use $\widehat{VE}(t = 39, V^i = 1|s_1, x) = 0$ for all s_1, x and use the available estimates of $\widehat{VE}(t = 39, V^i = 0|s_1, x)$, determined using the approach described below. Follow-up functional experiments supported that antibodies to 169K HIV-1 could be a mechanism of protection Liao et al. (2013), which is an important piece of evidence for specifying and evaluating the bridging assumptions. Functional experimentation of Liao et al. (2013) supported that a constellation of amino acid residues surrounding position 169 is a vulnerable epitope target of HIV-1 vaccines, with a K at site 169 required for immunological recognition (introducing a mutation K to V abrogated immunological recognition).

With $V = I$(Not K at position 169), next we need an approach for picking the immune response variable $S(1)$ to use in the curve $VE(t, v|s_1, x)$. Our approach considers the six primary immune response variables that were measured in vaccine recipients at the Month 6.5 visit after randomization (time point τ in the main article) and were assessed for their association with the subsequent HIV-1 infection through 39 months after randomization (Haynes et al., 2012). We select any variable among these six

such that $VE(t = 39, v = 0|s_1)$ significantly increases in s_1, based on a 1-sided p-value < 0.05. To estimate $VE(t = 39, v = 0|s_1)$, we use a multinomial logistic regression model for $mrisk_z(t = 39, v = 0|s_1)$ for $z = 0, 1$ under the assumption of average causal necessity (i.e., $VE(t = 39, v = 0|s_1 = 0) = 0$), which yields identifiability of $VE(t = 39, v = 0|s_1)$ under the multinomial logistic model and the typical assumptions in randomized clinical trials stated in Section 2.1, plus the No-early-VE assumption with $\tau =$ Month 6.5. Web Appendix D provides details of this modeling approach.

Of the six variables $S(1)$ that were assessed, one qualified (1-sided $p = 0.035$ for variation of $VE(t = 39, v = 0|s_1)$ in s_1)– the magnitude of binding antibodies to the V1V2 portion of a gp70-scaffolded HIV-1 envelope protein. The binding antibodies were measured both with ELISA (Haynes et al., 2012) and binding antibody multiplex array (BAMA) (Zolla-Pazner et al., 2014), yielding very similar vaccine efficacy curve estimates, and we base the bridging on the BAMA assay because it is planned for use in the HVTN 100 Phase IIa trial in South Africa.

Next, we need a strategy for determining the baseline covariates X to use in the curve $VE(t = 39, v = 0|s_1, x)$. Our approach systematically assesses several baseline covariates for whether $VE(t = 39, v = 0|s_1, x)$ varies in x, selecting covariates with 1-sided p-value < 0.05 for such effect modification. We assessed age, gender, HLA type, Fc-γ receptor genotype, Fc-α receptor genotype, and behavioral risk score, again under the average causal necessity assumption that is now expressed as $VE(t = 39, v = 0|s_1 = 0, x) = 0\%$ for all x. We found that the VE curve varied with a single nucleotide polymorphism (SNP) (rs114945036) located at position 126 in intron 2 of the Fc-γ receptor 2C gene locus. Figure 1 in the main article shows the estimated $VE(t = 39, v = 0|s_1, x)$ curves with 95% pointwise confidence intervals for the two subgroups carrying CC or carrying CT or TT (CT/TT) at the SNP position, where $x = 0$ denotes CC and $x = 1$ denotes CT/TT. Related to this result, recently this SNP was reported to significantly modify 169-matched vaccine efficacy in RV144 (estimated $VE(t = 39|x =$

$CC) = 0.15$ in the CC subgroup versus estimated $VE(t = 39|x = CT/TT) = 0.91$ in the CT/TT subgroup, $p = 0.05$ for different VE after family-wise error rate multiplicity correction) (Li et al., 2014).

We next consider how to estimate $mrisk_0^*(t = 39, v|s_1, x)$ for each $v, x \in \{0, 1\}$, which is accomplished by obtaining separate estimates of $w_{Inc}(t|x)$, $w_V(t, v|x)$, and $mrisk_0(t, v|s_1, x)$ according to the strategy laid out in the main article. Estimating the numerator of $w_{Inc}(t|x)$ is accomplished using data from placebo recipients at-risk at 6 months after enrollment into the recent HVTN 503 preventive HIV-1 vaccine efficacy trial in South Africa (Gray et al., 2014), which studied a similar population as will be studied in HVTN 702. From the HVTN 503 data we estimate $risk_0^*(t = 39) = P(T(0^*) \leq 39)$, the numerator of $w_{Inc}(t = 39|x)$, by the Kaplan-Meier estimator, yielding an estimate of 0.121. Because data on the host genotype X were not collected in HVTN 503, we set $\widehat{risk}_0^*(t = 39|x = 0) = \widehat{risk}_0^*(t = 39|x = 1) = 0.121$, which provide an estimate of the numerator. The denominator of $w_{Inc}(t = 39|x)$ is estimated based on RV144 placebo recipients at-risk at 6 months after enrollment using the inverse probability weighted Kaplan-Meier estimator, yielding $\widehat{risk}_0(t = 39|x = 0) = 0.00696$ and $\widehat{risk}_0(t = 39|x = 1) = 0.0119$.

Next, we estimate $w_V(t = 39, v|x)$, and we first consider estimation of the denominator $risk_0(t, v|x)/risk_0(t|x)$. This term can be estimated based on the RV144 data. In particular, we estimate each $risk_0(t, v|x)$ for $v, x \in \{0, 1\}$ by analyzing RV144 placebo recipients at-risk at 6 months, applying the Aalen and Johansen (1978) nonparametric maximum likelihood estimator extended to use inverse probability weighting to account for the fact that X was measured in a random sample that depended on subject characteristics (Haynes et al., 2012). This yields estimates $\widehat{risk}_0(t = 39, v|x)$ of 0.0047, 0.0078, 0.0011, and 0.0010 for $v, x = (0, 0), (0, 1), (1, 0), (1, 1)$, such that $\widehat{risk}_0(t = 39, v = 0) = 0.0047 + 0.0078 = 0.0125$ and $\widehat{risk}_0(t = 39, v = 0) = 0.0011 + 0.0010 = 0.0021$. This provides estimates for each denominator $risk_0(t = 39, v|x)/risk_0(t = 39|x)$ equal to

0.810, 0.886, 0.190, and 0.114 for $v, x = (0,0), (0,1), (1,0), (1,1)$.

However, for estimating the numerator, we use genomic epidemiological data on HIV-1 sequences in South Africa (as elaborated below), and for consistency in approach for estimation of the denominator, we adjust the above estimates to account for genomic epidemiological data on HIV-1 sequences in Thailand. This is advantageous not only for consistency but also because the database of HIV-1 sequences is much larger than the number of HIV-1 infection endpoint cases available in RV144 for estimation.

For both Thailand and South Africa the Los Alamos HIV-1 Sequence database (www.hiv.lanl.gov) is used. However, the database does not include information on the host genotype X, such that it yields estimates of $risk_0(t,v)/risk_0(t)$ and $risk_0^*(t,v)/risk_0^*(t)$ but not of the x-specific relative prevalences. To solve this issue for the denominator (RV144), we first consider the equality

$$\frac{risk_0(t,v)}{risk(t)} = D^{-1}\left[P(X=0)risk_0(t|x=0)\frac{risk_0(t,v|x=0)}{risk_0(t|x=0)} + P(X=1)risk_0(t|x=1)\frac{risk_0(t,v|x=1)}{risk_0(t|x=1)}\right] \quad (1)$$

with

$$D \equiv P(X=0)risk_0(t|x=0) + P(X=1)risk_0(t|x=1).$$

Next, we assume that the relative prevalences to solve for in (1) have the same ratio as observed with the initial estimates from RV144 as described above:

$$\frac{risk_0(t,v|x=1)}{risk_0(t|x=1)} \Big/ \frac{risk_0(t,v|x=0)}{risk_0(t|x=0)} = \\ = \frac{risk_0^{RV144}(t,v|x=1)}{risk_0^{RV144}(t|x=1)} \Big/ \frac{risk_0^{RV144}(t,v|x=0)}{risk_0^{RV144}(t|x=0)} \equiv \text{ratioRV144}(v). \quad (2)$$

Plugging (2) into (1), we solve

$$\frac{risk_0(t,v|x=0)}{risk_0(t|x=0)} \\ = \frac{risk_0(t,v)}{risk(t)} \frac{P(X=0)risk_0(t|x=0) + P(X=1)risk_0(t|x=1)}{P(X=0)risk_0(t|x=0) + P(X=1)risk_0(t|x=1)\text{ratioRV144}(v)} \quad (3)$$

and then also

$$\frac{risk_0(t, v|x=1)}{risk_0(t|x=1)} = \text{ratioRV144}(v)\frac{risk_0(t, v|x=0)}{risk_0(t|x=0)}. \quad (4)$$

Based on the relative fraction of all available HIV-1 sequences ($n = 207$) of infected individuals in Thailand from 2003 to 2009 (during the period of RV144 follow-up), 72% of sequences have a $v = 0$ (vaccine-matched), from which we set $\widehat{risk}_0(t = 39, v = 0)/\widehat{risk}_0(t = 39) = 0.72$ and $\widehat{risk}_0(t = 39, v = 1)/\widehat{risk}_0(t = 39) = 0.28$. Based on the above estimates we have 0.886/0.810=1.094 and 0.114/0.190=0.60 as estimates of ratioRV144(0) and ratioRV144(1), respectively, and the other terms in (3) and (4) also have estimates. The formulas yield answers

$$\frac{\widehat{risk}_0(t = 39, v = 0|x = 0)}{\widehat{risk}_0(t = 39|x = 0)}$$
$$= 0.72\frac{[0.72 * (0.0047 + 0.0011) + 0.28 * (0.0078 + 0.0010)]}{[0.72 * (0.0047 + 0.0011) + 0.28 * (0.0078 + 0.0010) * 1.094]} = 0.696$$
$$\frac{\widehat{risk}_0(t = 39, v = 0|x = 1)}{\widehat{risk}_0(t = 39|x = 1)} = 1.094 * 0.696 = 0.761$$
$$\frac{\widehat{risk}_0(t = 39, v = 1|x = 0)}{\widehat{risk}_0(t = 39|x = 0)}$$
$$= 0.28\frac{[0.72 * (0.0047 + 0.0011) + 0.28 * (0.0078 + 0.0010)]}{[0.72 * (0.0047 + 0.0011) + 0.28 * (0.0078 + 0.0010) * 0.60]} = 0.329$$
$$\frac{\widehat{risk}_0(t = 39, v = 1|x = 1)}{\widehat{risk}_0(t = 39|x = 1)} = 0.60 * 0.329 = 0.197.$$

Next, we estimate the numerator of $w_V(t = 39, v|x)$, $risk_0^*(t = 39, v|x)/risk_0^*(t = 39|x)$, based on the relative fraction of all available HIV-1 sequences ($n = 254$) of infected individuals in South Africa from 2008 to 2013 in the same Los Alamos HIV-1 Sequence database. This yields an overall fraction 0.60 with $v = 0$ (vaccine-matched), which estimates $risk_0^*(t = 39, v = 0)/risk_0^*(t = 39)$. Because no data are available about how this prevalence depends on X^* in South Africans, we assume homogeneity across the two X^* subgroups, such that $\widehat{risk}_0^*(t = 39, v|x)/\widehat{risk}_0^*(t = 39|x) = 0.60$, 0.60, 0.40, and 0.40 for $v, x = (0, 0), (0, 1), (1, 0)$, and (1,1), respectively.

Supplemental Table 1. Estimation of Terms $w_V(t=39,v|x)$ in the Transport Formula for Bridging RV144 to Estimation of $VE^*(t=39)$ in HVTN 702

	(v,x) Level			
Term	(0,0)	(0,1)	(1,0)	(1,1)
$\widehat{w}_V(t=39,v\|x)$ numer.				
$\widehat{risk}_0^*(t=39,v\|x)/risk_0^*(t=39\|x)$	0.60	0.60	0.40	0.40
$\widehat{w}_V(t=39,v\|x)$ denom.				
$\widehat{risk}_0(t=39,v\|x)/\widehat{risk}_0(t=39\|x)$	0.696	0.761	0.329	0.197
$\widehat{w}_V(t=39,v\|x)$	0.862	0.788	1.216	2.030

Supplemental Table 1 shows the final results for estimation of $w_V(t=39,v|x)$.

Estimates of the term $mrisk_0(t,v|s_1,x)$ for $v=0$ were already obtained via the method used to estimate the VE curve that was obtained via separate estimates of $mrisk_1(t=39,v=0|s_1,x)$ and $mrisk_0(t=39,v=0|s_1,x)$ (Figure 1 of the main article). Lastly, because of the choice to set $\widehat{VE}(t=39,v=1|s_1,x)=0$ for all s_1 and x, we set $\widehat{mrisk}_0(t=39,v=1|s_1,x)=\widehat{mrisk}_1(t=39,v=1|s_1,x)$, where $\widehat{mrisk}_1(t=39,v=1|s_1,x)$ for each $x=0,1$ separately was obtained via structural multinomial logistic regression as described in Web Appendix D.

Appendix C: Proof of the Transport Formula in the Main Article (Under No-Early-VE)

The proof of the transport formula in expression (3) of the main article is simple; it is based on averaging and invoking the No-early-VE assumption.

For fixed $t\in(\tau,\tau_1]$, write

$$
\begin{aligned}
&VE^{*d}(t)=P(T(1^*)\le t)-P(T(0^*)\le t)\\
&=P(T(1^*)\le t|T(1^*)>\tau)P(T(1^*)>\tau)+P(T(1^*)\le t|T(1^*)\le\tau)P(T(1^*)\le\tau)\\
&-[P(T(0^*)\le t|T(0^*)>\tau)P(T(0^*)>\tau)+P(T(0^*)\le t|T(0^*)\le\tau)P(T(0^*)\le\tau)]\\
&=P(T(1^*)\le t|T(1^*)>\tau)P(T(1^*)>\tau)-P(T(0^*)\le t|T(0^*)>\tau)P(T(0^*)>\tau)
\end{aligned}
$$

$$
\begin{aligned}
&= [P(T(1^*) \leq t | T(1^*) > \tau, T(0^*) > \tau) - P(T(0^*) \leq t | T(1^*) > \tau, T(0^*) > \tau)] \\
&\times P(T(0^*) > \tau) \\
&= \int\int\int [P(T(1^*) \leq t, V(1^*) = v | s_1, x) - P(T(0^*) \leq t, V(0^*) = v | s_1, x)] \, dv dF^*(s_1|x) dH^*(x) \\
&\times P(T(0^*) > \tau) \\
&= P(T(0^*) > \tau) \int\int\int \left[-1 + \frac{P(T(1^*) \leq t, V(1^*) = v | s_1, x)}{P(T(0^*) \leq t, V(0^*) = v | s_1, x)} \right] \\
&\times P(T(0^*) \leq t, V(0^*) = v | s_1, x) dv dF^*(s_1|x) dH^*(x) \\
&= -P(T(0^*) > \tau) \int\int\int VE(t, v | s_1, x) \phi(t, v | s_1, x) mrisk_0^*(t, v | s_1, x) dv dF^*(s_1|x) dH^*(x)
\end{aligned}
$$

where the third and fourth equalities both follow from the No-early-VE assumption (which states that $T(1^*) > \tau$ if and only if $T(0^*) > \tau$).

Appendix D: Constructing Bootstrap Confidence Intervals for $VE^*(t = 39)$

To construct a bootstrap confidence interval for the estimate of $VE^*(t = 39)$, we resample RV144 data stratified on treatment assignment for estimation of $mrisk_0(t = 39, v|s_1, x)$, $VE(t, v|s_1, x)$, and $F^*(s_1|x)$; resample HVTN 503 data stratified on treatment assignment for estimation of $P(T(0^*) \leq 39)$, $P(T(0^*) > \tau)$, and $risk_0^*(t = 39|x)$; resample from a Bernoulli distribution with success probability $P(X^* = 1) = 0.49$ and variance $0.49(1 - 0.49)/131$ for estimation of $H^*(x)$ (131 subjects were used for estimating the prevalence of the CT/TT genotype in South Africans; Lassauniere and Tiemessen, 2014); and resample from the 254 South African individuals with an HIV-1 sequence in the Los Alamos National Laboratory HIV-1 sequence database for estimation of $risk_0^*(t = 39, v|x)/risk_0^*(t = 39|x)$, the numerator of $w_V(t = 39, v|x)$.

Appendix E: Estimation of $VE(t, v|s_1, x)$ from the Previous Efficacy Trial RV144

We describe how

$$VE(t, v|s_1, x) = 1 - \frac{P(T(1) \leq t, V(1) = v|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)}{P(T(0) \leq t, V(0) = v|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)}$$

and

$$VE(t, v|s_1) = 1 - \frac{P(T(1) \leq t, V(1) = v|T(1) > \tau, T(0) > \tau, S(1) = s_1)}{P(T(0) \leq t, V(0) = v|T(1) > \tau, T(0) > \tau, S(1) = s_1)}$$

are estimated from RV144 data for a fixed failure time t, fixed binary mark $v = 0$ or 1, and fixed value of a univariable baseline covariate $X = x$.

Consider three different possible infection outcomes at time t among placebo or vaccine recipients:

(i) Not infected: $T(z) > t$

(ii) Infected by t with type $V = 0$

(iii) Infected by t with type $V = 1$.

We assume a multinomial logistic regression model:

$$\log \frac{P(T(z) \leq t, V(z) = v|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)}{P(T(z) > t|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)} = \alpha_{zv} + \beta_{zv} s_1 + \gamma_{zv} x,$$

for $z = 0, 1$, $v = 0, 1$.

To estimate α_{zv}, β_{zv}, and γ_{zv}, we fit two logistic models separately: one using data from categories (i) and (ii) to model

$$\log \frac{P(T(z) \leq t, V(z) = 0|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)}{P(T(z) > t|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)} = \alpha_{z0} + \beta_{z0} s_1 + \gamma_{z0} x,$$

assuming $\alpha_{00} = \alpha_{01}$ (Average Causal Necessity, ACN) (Part I), and the other using data from categories (i) and (iii) to model

$$\log \frac{P(T(z) \leq t, V(z) = 1|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)}{P(T(z) > t|T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x)} = \alpha_{z1} + \beta_{z1} s_1 + \gamma_{z1} x$$

assuming $\alpha_{01} = \alpha_{11}$ (ACN) (Part II).

We then estimate

$$\begin{aligned} & P(T(z) > t | T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x) \\ = & \frac{1}{1 + exp(\alpha_{z0} + \beta_{z0} s + \gamma_{z0} x) + exp(\alpha_{z1} + \beta_{z1} s + \gamma_{z1} x)}, \end{aligned}$$

and

$$\begin{aligned} & P(T(z) \leq t, V(z) = 0 | T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x) \\ = & P(T(z) > t | T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x) \times exp(\alpha_{z0} + \beta_{z0} s + \gamma_{z0} x), \\ & P(T(z) \leq t, V(z) = 1 | T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x) \\ = & P(T(z) > t | T(1) > \tau, T(0) > \tau, S(1) = s_1, X = x) \times exp(\alpha_{z1} + \beta_{z1} s + \gamma_{z1} x). \end{aligned}$$

In the RV144 example, we also make the additional assumption that $VE(t = 39, v = 1 | s_1, x) = 0$ for all s_1 and x, as discussed above. For a rare disease such as the HIV-1 infection endpoint in RV144, this corresponds approximately to $\alpha_{01} = \alpha_{11}$ and $\beta_{01} = \beta_{11}$ and $\gamma_{01} = \gamma_{11}$. To incorporate this extra assumption, we modify Part II by fitting a logistic regression model to $Z = 1$ (vaccine recipients) from categories (i) and (iii) to estimate α_{11}, β_{11}, γ_{11}, and then set $\widehat{\alpha}_{01} = \widehat{\alpha}_{11}$, $\widehat{\beta}_{01} = \widehat{\beta}_{11}$ and $\widehat{\gamma}_{01} = \widehat{\gamma}_{11}$.

Appendix F: Application of the Transport Formula to Go/No-Go Decisions for Which Candidate Treatments to Advance to Efficacy Trials

A common issue in many biomedical research fields is that several candidate treatments for efficacy testing are available, but due to resource constraints only a small number of the candidates that are studied in Phase I/II trials can be advanced to Phase III efficacy trials that directly assess treatment efficacy/vaccine efficacy. For example, in the HIV vaccine field, over a dozen candidate HIV-1 vaccine regimens are being tested

in Phase I/IIa clinical trials in Southern Africa, and based on a set of immune response biomarker endpoints in these trials, the most promising regimens will be advanced to the HVTN 701 efficacy trial in Southern Africa. The putative surrogate endpoints used for ranking the regimens for advancement are the immune response endpoints that were effect modifiers of vaccined efficacy [modifying $VE(t|s_1)$ and $VE(t,v|s_1)$ or $VE(t|s_1,x)$ and $VE(t,v|s_1,x)$] in the RV144 trial, where subgroups with higher marker levels had higher vaccine efficacy.

The transport formula can be applied based on the aggregated Phase I/IIa trial data combined with the other types of data sources described in the illustrative application of Section 5, to obtain an estimate of $VE^*(t)$ for each candidate HIV-1 vaccine regimen. Then, the regimen with the highest estimated $VE^*(t)$ is assigned the highest rank of 1, the regimen with the second highest estimated $VE^*(t)$ is assigned rank 2, and so on. The top-ranked vaccine regimen would be priortized for advancement to the efficacy trial, and according to their ranks other vaccine regimens may also be advanced, where these decisions would account for additional factors such as the precision of the estimation, safety data, and the distinctiveness of the immune response endpoint distributions among the different vaccine regimens.

Appendix G: The Transport Formula Relaxing No-Early-VE to No-Early-Harm Monotonicity

We now develop a new version of the transport formula (3) provided in the main article, replacing the No-early-VE assumption (that $P(I(T(1)>\tau)=I(T(0)>\tau))=1$) with the weaker No-early-harm assumption (that $P(T(1)\leq\tau,T(0)>\tau)=0$). This relaxed assumption is also used for the new setting. The No-early-harm assumption is quite plausible for studies where the vaccine or treatment has beneficial overall efficacy.

As noted in the main article, under No-early-harm the early-protected (EP) principal stratum may not be empty. Therefore, we need to consider conditional vac-

cine efficacy parameters in the EP principal stratum as well as in the early-always-survivors (EAS) principal stratum that was the focus of the main article. We define $VE^{EP}(t, v|s_1, x) \equiv 1 - P(T(1) \leq t, V(1) = v|T(1) > \tau, T(0) \leq \tau, S(1) = s_1, X = x)/P(T(0) \leq t, V(0) = v|T(1) > \tau, T(0) \leq \tau, S(1) = s_1, X = x)$ and $mrisk_0^{EP}(v|s_1, x) \equiv P(V(0) = v|T(1) > \tau, T(0) \leq \tau, S(1) = s_1, X = x)$. The latter term does not depend on t because it conditions on $T(0) \leq \tau$.

We develop a transport formula for $VE^{d*}(t) \equiv P(T(1^*) \leq t) - P(T(0^*) \leq t)$, as well as for $VE^*(t) = 1 - P(T(1^*) \leq t)/P(T(0^*) \leq t)$. For $t \in (\tau, \tau_1]$, define "bridging assumption functions"

$$\phi(t, v|s_1, x) \equiv VE^*(t, v|s_1, x)/VE(t, v|s_1, x), \tag{5}$$

$$\phi^{EP}(t, v|s_1, x) \equiv VE^{*EP}(t, v|s_1, x)/VE^{EP}(t, v|s_1, x), \tag{6}$$

$$\phi(\tau, v|x) \equiv VE^*(\tau, v|x)/VE(\tau, v|x). \tag{7}$$

For the new transport formula we make the same assumptions as used for the original formula except No-early-VE and No-early-VE* for the old and new settings are replaced with No-early harm and No-early-harm* for the old and new settings, respectively. (Here No-early-harm* is $P(T(1^*) \leq \tau, T(0^*) > \tau) = 0$.) We also make the following additional assumptions:

1. The two additional bridging assumption functions $\phi^{EP}(t, v|s_1, x)$ and $\phi(\tau, v|x)$ are known and correctly specified

2. $VE^{EP}(t, v|s_1, x)$ and $VE(\tau, v|x)$ are estimated consistently based on the original trial

3. $F^{*EP}(s_1|x)$, $H^{*EP}(x)$, and $H^*(x)$ are estimated consistently from the Phase I/II trial

4. $mrisk_0^{*EP}(v|s_1, x)$ is estimated consistently

5. $risk_0^*(\tau, v|x)$ is estimated consistently

With the principal strata proportions $p^{*EAS} \equiv P(T(1^*) > \tau, T(0^*) > \tau)$ and $p^{*EP} \equiv P(T(1^*) > \tau, T(0^*) \leq \tau)$, No-early-harm* has the following implications:

$$\begin{aligned} p^{*EAS} &= P(T(0^*) > \tau), \qquad VE^{d^*}(\tau) = -p^{*EP}, \\ P(T(0^*) > \tau | T(1^*) > \tau) &= \left[1 - VE^{d^*}(\tau)/P(T(0^*) > \tau)\right]^{-1}. \end{aligned}$$

Using these identities, straightforward calculation yields

$$\begin{aligned} VE^{d*}(t) &= VE^{d*EAS}(t)p^{*EAS} + VE^{d*EP}(t)p^{*EP} \\ &= VE^{d*EAS}(t)P(T(0^*) > \tau) - VE^{d*}(\tau)VE^{d*EP}(t) \text{ for } t \in (\tau, \tau_1] \quad (8) \end{aligned}$$

where

$$\begin{aligned} VE^{d*EAS}(t) &\equiv P(T(1^*) \leq t | T(1^*) > \tau, T(0^*) > \tau) - P(T(0^*) \leq t | T(1^*) > \tau, T(0^*) > \tau) \\ VE^{d*EP}(t) &\equiv P(T(1^*) \leq t | T(1^*) > \tau, T(0^*) \leq \tau) - P(T(0^*) \leq t | T(1^*) > \tau, T(0^*) \leq \tau). \end{aligned}$$

Algebra then yields, for $t \in (\tau, \tau_1]$,

$$\begin{aligned} VE^{d*EAS}(t) &= -\int\int\int \phi(t, v|s_1, x) VE(t, v|s_1, x) \\ &\quad \times mrisk_0^*(t, v|s_1, x) dv dF^*(s_1|x) dH^*(x), \quad (9) \\ VE^{d*EP}(t) &= -\int\int\int \phi^{EP}(t, v|s_1, x) VE^{EP}(t, v|s_1, x) \\ &\quad \times mrisk_0^{*EP}(v|s_1, x) dv dF^{*EP}(s_1|x) dH^{*EP}(x), \quad (10) \\ VE^{d*}(\tau) &\equiv -\int\int \phi(\tau, v|x) VE(\tau, v|x) risk_0^*(\tau, v|x) dv dH^*(x). \quad (11) \end{aligned}$$

The principal effects "general immuno-bridging transport formula" for additive-difference $VE^{d*}(t)$ is defined by (8) with terms (9)–(11) substituted into (8).

In the main article, the No-early-VE assumption implied the second term of (8), $VE^{d*}(\tau)VE^{d*EP}(t)$, was zero, but now under No-early-harm it may be non-zero. It is generally useful to evaluate the plausible magnitude of this term compared to the first

term $VE^{d*EAS}(t)P(T(0^*) > \tau)$, as it may be negligible if $p^{*EAS} = P(T(0^*) > \tau)$ is much larger than $p^{*EP} = -VE^{d*}(\tau)$, which can easily be checked given that p^{*EAS} and p^{*EP} can be estimated by empirical fractions under the No-early-harm assumption. If the second term is deemed potentially non-negligible, then retaining it and using the full formula (8) requires specifying the two extra $\phi(\cdot)$ bridging functions in (10) and (11), where now the perfect bridging assumption is expressed as $\phi(\cdot) = \phi^{EP}(\cdot) = \phi(\cdot) = 1$. The following additional terms also need to be estimated: $VE^{EP}(t, v|s_1, x)$, $mrisk_0^{*EP}(v|s_1, x)$, $F^{*EP}(s_1|x)$, $H^{*EP}(x)$, $VE(\tau, v|x)$, $risk_0^*(\tau, v|x)$, and $H^*(x)$.

We now consider how to estimate the extra terms in the formula that exist when relaxing No-early-VE. Under No-early-VE, $F^*(s_1|x)$ and $H^*(x)$ could be directly estimated from the Phase I/II trial via the identities $F^*(s_1|x) = F^{*1}(s_1|x) \equiv P(S(1^*) \leq s_1|T(1^*) > \tau, x)$ and $H^*(x) = H^{*1}(x) \equiv P(X^* \leq x|T(1^*) > \tau)$. Under the weaker assumption No-early-harm*, however,

$$F^*(s_1|x) = [1 - \theta(\tau, x)]\, F^{*1}(s_1|x) + \theta(\tau, x) F^{*EP}(s_1|x), \tag{12}$$

where $\theta(\tau, x) \equiv VE^{d*}(\tau, x)/P(T(0^*) > \tau|x)$ may differ from zero. Thus estimation of $F^*(s_1|x)$ requires a sensitivity analysis to deal with the partial non-identifiability of $F^{*EP}(s_1|x)$. One approach to a sensitivity analysis specifies a pattern mixture model linking the conditional distributions of $S(1^*)$ in the EAS and EP subgroups that is indexed by a fixed sensitivity parameter, and repeats the analysis for a range of values of the sensitivity parameter [e.g., as done in Jemiai et al. (2007)]. Such a sensitivity analysis would require estimating $VE^{d*}(\tau, x)/P(T(0^*) > \tau|x)$. If the placebo group in the Phase I/II trial is small then there may be few data points for direct estimation of either $VE^{d*}(\tau, x)$ or $P(T(0^*) > \tau|x)$, again highlighting the major advantage in settings where No-early-VE can be reasonably assumed.

Under No-early-harm*, $H^*(x) = P(X^* \leq x|T(0^*) > \tau)$ and $dH^{*EP}(x) = [VE^{d*}(\tau, x)/$

$VE^{d*}(\tau)]dH^*(x)$, such that $H^*(x)$ and $H^{*EP}(x)$ can be estimated by estimating $P(X^* \leq x|T(0^*) > \tau)$ and $VE^{d*}(\tau, x)/VE^{d*}(\tau)$ directly from the Phase I/II trial. If the placebo group in the Phase I/II trial is small, then the approximation $P(X^* \leq x|T(0^*) > \tau) \approx P(X^* \leq x|T(1^*) > \tau)$ may be considered to improve precision for estimating $P(X^* \leq x|T(0^*) > \tau)$, which should be reasonable in rare event trials.

If No-early-VE is relaxed to No-early-harm, then it is also necessary to estimate $VE^{EP}(t, v|s_1, x)$. Given non-identifiability of the early-protected subgroup and the fact that this subgroup will typically be small, in general it is challenging to estimate $VE^{EP}(t, v|s_1, x)$ with adequate precision. One practical approach assumes $VE^{EP}(t, v|s_1, x) =$
$VE(t, v|s_1, x)$ in order to estimate $VE^{EP}(t, v|s_1, x)$ with $\widehat{VE}(t, v|s_1, x)$. This approach could be augmented with a sensitivity analysis, for example by defining a sensitivity parameter $\nu \equiv VE(t, v|s_1, x)/VE^{EP}(t, v|s_1, x)$ and repeating the analysis with ν varying around the default setting $v = 1$. The sensitivity analysis approach should account for any modeling assumptions employed for estimating $VE(t, v|s_1, x)$.

References

Aalen, O. and Johansen, S. (1978). An empirical transition matrix for non-homogeneous markov chains based on censored observations. *Scandinavian Journal of Statistics* **5**, 141–150.

Gilbert, P. and Hudgens, M. (2008). Evaluating candidate principal surrogate endpoints. *Biometrics* **64**, 1146–1154.

Gray, G. E., Moodie, Z., Metch, B., Gilbert, P. B., Bekker, L.-G., Churchyard, G., Nchabeleng, M., Mlisana, K., Laher, F., Roux, S. and Corey, L. (2014). Recombinant adenovirus type 5 HIV gag/pol/nef vaccine in South Africa: unblinded, long-term

follow-up of the phase 2b HVTN 503/Phambili study. *The Lancet Infectious Diseases* **14**, 388–396.

Haynes, B., Gilbert, P., McElrath, M. and et al. (2012). Immune correlates analysis of the ALVAC-AIDSVAX HIV-1 vaccine efficacy trial. *New England Journal of Medicine* **366**, 1275–1286.

Jemiai, Y., Rotnitzky, A., Shepherd, B. and Gilbert, P. (2007). Semiparametric estimation of treatment effects given base-line covariates on an outcome measured after a post-randomization event occurs. *Journal of the Royal Statistical Society, Series B* **69**, 879–902.

Lassauniere, R. and Tiemessen, C. (2014). Fc-gamma receptor variability in the South African population– Will this impact on HVTN097 and vaccine efficacy? HIV R4P Conference. Cape Town, South Africa, 2014. Abstract P37.05.

Li, S., Gilbert, P., Tomaras, G. and et al. (2014). Association of FCGR2C polymorphisms with vaccine efficacy and correlates of HIV-1 infection risk in the RV144 trial. *Journal of Clinical Investigation* **124**, 3879–3890. *Contributed equally.

Liao, H.-X., Bonsignori, M., Alam, S. and et al. (2013). Vaccine induction of antibodies against a structurally heterogeneous site of immune pressure within HIV-1 envelope protein variable regions 1 and 2. *Immunity* **38**, 176–186.

Lunn, M. and McNeil, D. (1995). Applying Cox regression to competing risks. *Biometrics* **51**, 524–532.

Pearl, J. (2001). *Direct and Indirect Effects.* Morgan Kaufmann, San Francisco.

Pearl, J. (2009). *Causality: Models, Reasoning, and Inference, Second Edition.* Cambridge University Press, London.

Robins, J. and Greenland, S. (1992). Identifiability and exchangeability of direct and indirect effects. *Epidemiology* **3**, 143–155.

Rolland*, M., Edlefsen*, P., Larsen, B. and et al. (2012). Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. *Nature* **490**, 417–420.

*Contributed equally.

Zolla-Pazner, S., DeCamp, A., Gilbert, P. and et al. (2014). Vaccine-induced IgG antibodies to V1V2 regions of multiple HIV-1 subtypes correlate with decreased risk of HIV-1 infection. *PLoS One* **9**, e87572.