Estimating the Benefit of an HIV-1 Vaccine That Reduces Viral Load Set Point

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Vaccines designed to induce cell-mediated immune responses against human immunodeficiency virus (HIV)–1 are being developed. Such vaccines are unlikely to provide sterilizing immunity but may be associated with reduced viral set points after infection. We modeled the potential impact of a vaccine that reduces viral set point after infection, using natural history data from 311 HIV-1 seroconverters. Log-normal parametric regression models were used to estimate the log median time to events of interest. Relative times were estimated for those with viral load set points of 30,000 copies/mL (reference group) versus those with lower viral set points. The time to key clinical events in the course of HIV-1 disease progression was significantly extended for those with viral set points 0.5–1.25 log10 copies/mL lower than the reference group. By quantifying the anticipated clinical benefits associated with a reduction in viral set point, these findings support the use of virologic end points in HIV-1 vaccine trials.

The goals of current prophylactic HIV-1 candidate vaccines include providing either complete or partial protection from HIV-1 infection. In this context, complete protection refers to preventing establishment of HIV-1 infection, whereas partial protection refers to an attenuation of the course of HIV-1 infection due to suppression of viral replication based primarily on cell-mediated immune responses [1]. To evaluate these 2 potential outcomes for any HIV-1 vaccine candidate, it will be necessary to measure vaccine efficacy through the comparison of rates of HIV-1 acquisition as well as through end points that measure HIV-1 disease progression, such as progression to AIDS, once a person becomes infected. Given the slow progression of HIV-1 infection, with a median time to AIDS of ~9 years [2] and the ethical responsibility to provide treatment to HIV-1-infected vaccine trial participants, there is a need for surrogate end points of disease progression for the evaluation of HIV-1 vaccine candidates. A number of surrogate end points have been suggested, including viral load set points shortly after seroconversion and before initiation of therapy and loss of virologic control [1].

The appropriateness of viral load set point as a surrogate end point in HIV-1 vaccine trials is strongly supported by several large natural history cohort studies that found that plasma viral load measured up to 18 months after seroconversion strongly predicts the risk of disease progression [3, 4]. Specifically, a reduced viral load set point is associated with an attenuated course of HIV-1 infection. Data from clinical trials of antiretroviral therapy (ART) have indicated that even small decreases in viral load during the first 6 months after initiation of treatment in established infection are also associated with lower rates of progression over 1–3 years of follow-up [5]. Changes in viral load are accepted as standard measures of ART efficacy and are implemented in the most widely used clinical practice guidelines [6]. However, it remains to be shown that a reduction in viral load after vaccination will have the same meaning.

A vaccine capable of reducing viral load could provide important clinical benefit through a delay in HIV-1 disease progression, such as the onset of AIDS or need for antiretroviral therapy. However, the long-term benefit that could be obtained from a reduced HIV-1 RNA set point after seroconversion has not been precisely defined. Such information would be of use to policy makers and regulatory authorities in evaluating the potential effectiveness of an HIV-1 vaccine designed to reduce...
viremia. To inform this issue, we employed data from the Multicenter AIDS Cohort Study (MACS), one of the few studies providing long-term natural history data on a population of HIV-1–infected persons. We determined the time to various immunological and clinical outcomes for HIV-1 seroconverters with different levels of pretreatment plasma HIV-1 RNA to illustrate potential clinical benefits from a vaccine that reduces viral load set point.

Methods. MACS is an ongoing observational, prospective cohort study of HIV-1 infection that enrolled 5622 homosexual or bisexual men from 1984–1990 in Baltimore/Washington, Chicago, Los Angeles, and Pittsburgh. Semiannual study visits include physical examination, collection of blood specimens, and administration of questionnaires. HIV seropositivity is defined by Western blot confirmation of positive ELISAs. Methods for ascertainment of clinical AIDS [7], plasma HIV RNA concentration (Amplicor; Roche Diagnostics; assay detection limit of 400 copies/mL) [8], and CD4+ T cell lymphocyte quantification and standardization [9] have been described elsewhere.

We restricted the analysis to participants who were HIV-1 seronegative at enrollment into MACS, who seroconverted during the follow-up period, and who had 1 year or less between their last HIV-1–seronegative and first HIV-1–seropositive visits. In addition, individuals had to have HIV-1 RNA measurements at either 3, 9, or 15 months after seroconversion, defined as the midpoint between the last seronegative and first seropositive visit. Finally, this early HIV-1 RNA measurement was required to precede the initiation of any ART. Of the 568 seroconverters in the cohort, 375 fulfilled the above criteria. Demographic characteristics such as race, median age, and median year of seroconversion did not differ significantly between those who met the inclusion criteria (n = 375) and those who did not (n = 193) (data not shown).

We investigated the relationship between viral load set point and the following outcome variables: (1) time to clinical AIDS (defined as the diagnosis of an opportunistic illness [OI]); (2) time to specific CD4+ T cell counts (<350 cells/mm³ and <200 cells/mm³); (3) time to loss of virologic control (defined as HIV-1 RNA levels >55,000 copies/mL); and (4) time to a clinical indication for initiation of antiretroviral therapy based on US treatment guidelines [6] (defined as HIV-1 RNA level ≥55,000 copies/mL, CD4+ T cell count <350 cells/mm³, or diagnosis of an OI). Because log-normal parametric models appropriately describe the incubation period of AIDS [2], they were used to estimate the log median time and relative times to these outcomes. Relative times were calculated for those with viral load set points of 30,000 copies/mL versus those with lower viral load set points. Relative time was defined as the ratio of times in which the same percentile of persons in the 2 groups (defined by viral set point) will develop the event. Comparison values were computed for those with viral load set points in log₁₀ increments (0.5, 0.75, 1.0, and 1.25 log₁₀) below the reference value of 30,000 copies/mL to simulate potential vaccine effects. On the basis of the established intraperson biologic variability of plasma HIV RNA levels (~0.3 log₁₀) and a low intraassay sample variability (0.12–0.2 log₁₀), a 0.5 log₁₀ copies/mL reduction was chosen to represent the minimal threshold for a biologically relevant change for our analyses [10]. We chose to minimize the potentially confounding effect that combination ART would have on our analyses by censoring data at 31 December 1992. Because monotherapy was not effective in improving survival, this cutoff date was chosen based on when combination therapy became more widely available [11]. Overall follow-up was defined as the time from 9 months after seroconversion until either 31 December 1992, death if before 31 December 1992, or last visit date if before 31 December 1992. For each outcome, follow-up time was the minimum of the overall follow-up time or the time from 9 months after seroconversion to the event of interest. All models were adjusted for age at seroconversion [2].

Results. Intraindividual HIV-1 RNA measurements were similar at 3, 9, and 15 months after seroconversion (median range, 25,495–28,832 copies/mL; geometric means range, 19,815–22,387 copies/mL) (table 1). The median difference in the individual log₁₀ HIV RNA measurements obtained at 9 and 3 months after seroconversion was −0.01 (interquartile range [IQR], −0.38 to 0.35), and, similarly, the median difference between 15 and 9 months was −0.05 (IQR, −0.30 to 0.29). Based on this close similarity over time, we defined the HIV-

### Table 1. Viral RNA and CD4+ T cell count values after seroconversion.

<table>
<thead>
<tr>
<th>Months after seroconversion</th>
<th>HIV-1 RNA</th>
<th>CD4+ T cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects tested</td>
<td>Median (IQR), copies/mL</td>
</tr>
<tr>
<td>≤3</td>
<td>340</td>
<td>28,832 (7887–90,441)</td>
</tr>
<tr>
<td>≤9</td>
<td>311</td>
<td>27,986 (7903–63,861)</td>
</tr>
<tr>
<td>≤15</td>
<td>275</td>
<td>25,495 (9238–58,478)</td>
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</tbody>
</table>

**NOTE.** IQR, interquartile range.

* The SD of the geometric mean represents 10 to the x, where x is the SD of the log₁₀ HIV RNA level.
Table 2. Median and relative time to immunological and clinical events for those with 0.5–1.5-log_{10} reductions in HIV-1 RNA load at 9 months after seroconversion, compared with the reference group (30,000 copies/mL), using log-normal models.

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of subjects free of event at set point; no. of events</th>
<th>Median time to event for the reference group, a years</th>
<th>0.5-log_{10} reduction</th>
<th>Median time to event, years</th>
<th>Relative time (95% CI)</th>
<th>0.75-log_{10} reduction</th>
<th>Median time to event, years</th>
<th>Relative time (95% CI)</th>
<th>1-log_{10} reduction</th>
<th>Median time to event, years</th>
<th>Relative time (95% CI)</th>
<th>1.25-log_{10} reduction</th>
<th>Median time to event, years</th>
<th>Relative time (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS f</td>
<td>310; 93</td>
<td>8.4</td>
<td>11.9</td>
<td>1.4 (1.3–1.6)</td>
<td>14.2</td>
<td>1.7 (1.5–2.0)</td>
<td>16.9</td>
<td>2.0 (1.6–2.5)</td>
<td>20.2</td>
<td>2.4 (1.9–3.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CD4+ T cell count</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>&lt;200 cells/mm³</td>
<td>298; 95</td>
<td>6.1</td>
<td>8.1</td>
<td>1.3 (1.2–1.5)</td>
<td>9.2</td>
<td>1.5 (1.3–1.8)</td>
<td>10.6</td>
<td>1.7 (1.4–2.1)</td>
<td>12.1</td>
<td>2.0 (1.5–2.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;350 cells/mm³</td>
<td>263; 133</td>
<td>3.4</td>
<td>4.5</td>
<td>1.3 (1.2–1.5)</td>
<td>5.2</td>
<td>1.5 (1.3–1.8)</td>
<td>5.9</td>
<td>1.7 (1.4–2.1)</td>
<td>6.8</td>
<td>2.0 (1.6–2.6)</td>
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<tr>
<td>HIV-1 RNA &gt;55,000 copies/mL</td>
<td>149; 59</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8 (1.4–2.2)</td>
<td>5.7</td>
<td>2.4 (1.6–3.4)</td>
<td>7.6</td>
<td>3.1 (1.9–5.0)</td>
<td>10.1</td>
<td>4.1 (2.3–7.5)</td>
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<tr>
<td>Clinical indication for initiation of antiretroviral therapy g</td>
<td>137; 76</td>
<td>1.9</td>
<td>2.7</td>
<td>1.4 (1.2–1.7)</td>
<td>3.3</td>
<td>1.7 (1.3–2.2)</td>
<td>3.9</td>
<td>2.0 (1.5–2.9)</td>
<td>4.7</td>
<td>2.4 (1.6–3.7)</td>
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**NOTE.** Relative time is calculated as the ratio of time to each event for the comparison HIV-1 RNA categories and the reference group category. Clinical models were age adjusted, with age included as a continuous variable in all models. CI, confidence interval.

a HIV-1 RNA load of 30,000 copies/mL.
b HIV-1 RNA load of 9487 copies/mL.
c HIV-1 RNA load of 5335 copies/mL.
d HIV-1 RNA load of 3000 copies/mL.
e HIV-1 RNA load of 1687 copies/mL.
f Defined as diagnosis of an opportunistic illness.
g Defined as HIV-1 RNA level >55,000 copies/mL, CD4+ T cell count <350 cells/mm³, or diagnosis of an opportunistic illness.
1 RNA value at 9 months after seroconversion as the viral set point, and this value was used for all subsequent analyses. This time point was chosen to most closely approximate the HIV-1 RNA measurement at 6 months after seroconversion, which is currently being used as part of a coprimary end point in the first proof-of-concept HIV-1 vaccine efficacy trial to evaluate a cell-mediated immunity-based HIV-1 vaccine candidate. The median follow-up time for the 311 seroconverters before 31 December 1992 was 5.5 years (IQR, 3.1–6.9 years).

Table 2 provides the median times to events and 95% confidence intervals (CIs) of the relative times for viral load set points, compared with the reference value of 30,000 copies/mL. For example, the median time to clinical AIDS from 9 months after seroconversion was 16.9 years for those with viral load set point measurements of 3000 copies/mL, compared with 8.4 years for those with viral load set points of 30,000 copies/mL (relative time [RT], 2.0 [95% CI, 1.6–2.5]). The median time to a viral load set point >55,000 copies/mL was 7.6 years for those with viral load set points of 3000 copies/mL, compared with 2.4 years for those with a viral load set point of 30,000 copies/mL (RT, 3.1 [95% CI, 1.9–5.0]). Reducing the viral load set point by 1 log resulted in approximately a doubling or greater in the time to each event.

Discussion. Several findings from the present study should be highlighted. We found that the event-free times were significantly lengthened for those with viral load set points of 0.5–1.25 log_{10} below the reference value of 30,000 copies/mL. For example, event-free times were lengthened by 70%–300% for those with viral load set points of 1.0 log_{10} below the reference value, including events that occur earlier in HIV-1 disease progression, such as a clinical indication to initiate ART. Comparison values were computed for those with viral load set points in log_{10} increments below the reference value to simulate potential vaccine effects, and these values have clinical relevance. For example, a comparison value of 1.25 log_{10} below the reference value (1687 copies/mL) is clinically significant because it has been shown that 1700 HIV-1 RNA copies/mL is the threshold below which secondary transmission of HIV-1 infection is virtually nonexistent [12]. A value of 0.75 log_{10} below the reference value (5335 copies/mL) is important because it has been suggested that a vaccine that is able to reduce early HIV-1 RNA levels to below ~5000 copies/mL would be considered efficacious [1]. The data presented in table 2 provide a way to quantify the potential clinical benefit of HIV-1 vaccines that reduce viral load set point by calculating the additional years gained before reaching significant immunological or clinical events in the course of HIV disease progression. Thus, these data could be of importance in the planning and interpretation of HIV-1 vaccine trials.

A few issues concerning external validity of the study results should be noted. Our reference of 30,000 copies/mL conforms to the median viral load set points of ~11,000–50,000 copies/mL for men observed by other researchers [3, 4, 13]. The variation could be due to defining set points at later time points than we examined (e.g., >15 months after seroconversion) or inclusion of individuals after initiation of therapy. By definition, viral load set point should precede therapy. Additionally, we found a median time to AIDS of 8.4 years; once one takes into account that the follow-up time was measured from the 9-month postseroconversion time point, our estimate is similar to the 9.6 years estimated by Mellors et al. [3]. Finally, MACS was designed to examine the natural history of HIV-1 infection in men who have sex with men in the United States, and the vast majority of participants are infected with clade B HIV-1. Because the natural history of HIV-1 infection may differ by infecting clade [14] and the distribution of viral load differs in men versus women [15], it will be important to conduct similar analyses in populations infected with nonclade B subtypes and in women.

Although the results from this study strongly suggest that a vaccine that reduces viral load set point by at least 0.5 log_{10} will reduce the risk of disease progression, it should be noted that, in order for clinical effects of this magnitude to occur, the vaccine would need to mimic cell-mediated immune-based responses seen in natural infection. It is possible that vaccine efficacy could wane over time due to the emergence of viral escape mutants [1]. Therefore, although the use of plasma HIV RNA levels has been widely accepted as a surrogate end point in antiretroviral trials [1], its validity for vaccine trials will need to be established as clinical data become available.

To our knowledge, this is the first attempt to estimate the potential clinical and immunological benefit that might be expected from an efficacious HIV-1 vaccine that reduces viral set point. The data demonstrate that short-term virological end points currently being used in proof-of-concept HIV-1 vaccine trials can be linked to meaningful clinical effects. Furthermore, the analyses provide a way to quantify the clinical benefit that might be expected from a vaccine with partial efficacy and could be of use for licensure decisions.

References

5. Katzenstein DA, Hammer SM, Hughes MD, et al. The relation of virologic and immunologic markers to clinical outcomes after nucle-


