

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

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ABSTRACT

Background: Vaccines designed to induce cell-mediated immune responses against HIV-1 are being developed. Such vaccines may not provide sterilizing immunity but are likely to be associated with reduced viral set points after infection. Using data collected from a cohort study on the natural history of HIV-1 infection, we modeled the potential impact of a vaccine which would reduce viral set point after infection.

Methods: Data from the Multicenter AIDS Cohort Study, an on-going, prospective cohort study of HIV infection in homosexual or bisexual men initiated in 1984, were used to model the natural history of HIV-1 based upon viral set point, defined as the viral load value 9 months post seroconversion. We evaluated the clinical course of 311 seroconverters before December 31, 1992 in order to avoid any confounding effect of combination antiretroviral therapy. Lognormal parametric regression models were used to estimate the log median time and relative time (RT) to events of interest such as a CD4 T-cell count <350 cells/mm³ and loss of virological control (defined as HIV-1 RNA ≥55,000 copies/mL). Relative times were estimated for those with viral load setpoints of 30,000 copies/mL (reference group) vs. those with lower viral set point measurements. Relative time is defined as the ratio of times that the same percentile of persons in the 2 groups (defined by viral set point) will develop the event. A relative time > 1 represents the extension of time and < 1 means that the time is contracted.

Results: The median time to a CD4 T-cell count <350 cells/mm³ was 3.4 years for those with initial viral load measurements of 30,000 copies/mL compared to 5.9 years for those with an initial HIV-1 RNA measurement of 3,000 copies/mL (RT: 1.7; 95% CI: 1.4, 2.1). The median times to HIV-1 RNA ≥ 55,000 copies/mL were 2.4 and 7.6 years for those with initial viral load measurements of 30,000 and 3,000 copies/mL, respectively (RT: 3.1; 95% CI: 1.9, 5.0). All event-free times were significantly longer for those with initial HIV-1 RNA measurements 0.5-1.25 log₁₀ copies/mL lower than the reference group. Compared to those with an HIV RNA of 30,000 copies/mL at set point, an HIV RNA of 10,471 (4.02 log₁₀) would be required to significantly reduce the hazard of progressing to a clinical indication to initiate antiretroviral therapy within 3 years by 25%.

Conclusions: The time to key clinical events in the course of HIV-1 disease progression was significantly extended for those with initial HIV-1 RNA 0.5-1.25 log₁₀ copies/mL lower than the reference group. For those with an initial viral load measurement of 3,000 vs. 30,000 copies/mL, the relative time to clinical events examined was approximately double or higher than that for the reference group, including those events that occur earlier in disease progression. Moreover, a viral set point of no more than approximately 10,000 copies/mL is necessary to achieve a significant reduction in the hazard of progressing to a clinical indication to initiate antiretroviral therapy within 3 years. By quantifying the anticipated clinical benefits associated with a reduction in viral set point, these findings provide support for the use of virologic endpoints in HIV-1 vaccine trials.

BACKGROUND

- Candidate vaccines designed to induce cell-mediated immune responses against human immunodeficiency virus-1 (HIV-1) are currently being developed.
- These vaccines are expected to provide either “complete” or “partial protection” from HIV-1 infection.
 - “Complete protection” refers to preventing establishment of HIV-1 infection.
 - “Partial protection” refers to an attenuation of the course of HIV-1 infection due to suppression of viral replication.
- Vaccines which provide “partial protection” are likely to be associated with reduced viral set points after infection.
- Plasma viral load measured up to 18 months after seroconversion strongly predicts the risk of disease progression.
- Therefore, a vaccine capable of reducing viral load set point could provide important clinical benefit such as delaying the onset of AIDS or the need for antiretroviral therapy.
- Using data collected from a cohort study on the natural history of HIV-1 infection, we modeled the potential impact of a vaccine which would reduce viral set point after infection.

METHODS

STUDY POPULATION

- Multicenter AIDS Cohort Study (MACS)
 - On-going (initiated in 1984), prospective cohort study of HIV infection in men who have sex with men
 - 5622 participants enrolled before 2001
 - 4 sites in Baltimore/Washington, Chicago, Los Angeles and Pittsburgh
 - Participants were either HIV-1 seronegative or HIV-1 seropositive but without a clinical AIDS diagnosis at enrollment
 - Participants seen every 6 months
 - Study visits include the following:
 - Behavioral and medical history
 - Physical Exam
 - Blood collection

LABORATORY MEASUREMENTS

- HIV-1 RNA copies/mL was measured retrospectively on stored samples using reverse-transcription polymerase chain reaction with an assay quantification limit of 400 copies/mL.
- Viral load values of <400 copies/mL were imputed as 300 copies/mL for all analyses.
- CD4+ T-cell counts were measured prospectively at each visit using standardized flow cytometric procedures.

INCLUSION CRITERIA FOR ANALYSES

- HIV-1 seronegative at enrollment into the MACS and seroconverted during the follow-up period
- One year or less between their last HIV-1 seronegative (LN) and first HIV-1 seropositive (FP) visits
- HIV-1 RNA measurement available at 3, 9 or 15 months post-seroconversion (seroconversion dates were calculated as the midpoint between the LN and FP visits)
- Early HIV-1 RNA measurement was required to precede the initiation of any antiretroviral therapy

DATA ANALYSIS

- Early HIV-1 RNA measurements were examined to determine if there were in any trends in viral load soon after seroconversion. Based on the stability of HIV-1 RNA across the three time points following seroconversion (3, 9, and 15 months post seroconversion) examined, the 9 month post seroconversion viral load value was used for all subsequent analyses.
- Lognormal parametric regression models were used to investigate the relationship between viral load set point and time to the following outcome variables:
 - Clinical AIDS (defined as an opportunistic illness)
 - CD4+ T-cell count level (<350 cells/mm³, <200 cells/mm³)
 - Loss of virological control (HIV-1 RNA ≥55,000 copies/mL)
 - Clinical indication for initiation of antiretroviral therapy (HIV-1 RNA ≥55,000 copies/mL or CD4+ T-cell count <350 cells/mm³ or diagnosis of an OI)
- Relative times to events of interest were estimated for those with viral load set points of 30,000 copies/mL (reference group) vs. those with lower viral set points.

RESULTS

TABLE 1. VIRAL RNA AND CD4+ T-CELL COUNT MEASUREMENTS FOLLOWING SEROCONVERSION

Months post seroconversion PSC)	HIV-1 RNA (copies/mL)			CD4+ T-cell count (cells/mm ³)		
	n	Median (IQR)	Geometric mean (SD)*	n	Median (IQR)	Mean (SD)
~3 months PSC	340	28,832 (7,887, 90,441)	22,387 (6.8)	324	738 (548, 944)	780 (332.6)
~9 months PSC	311	27,986 (7,903, 63,861)	19,815 (5.9)	298	639 (460, 847)	681 (291.1)
~15 months PSC	275	25,495 (9,238, 58,478)	20,797 (4.9)	271	587 (450, 792)	643 (289.4)

* The standard deviation of the geometric mean represents 10 to the x, where x is the standard deviation of the log₁₀ HIV RNA

TABLE 3. MEDIAN AND RELATIVE TIME (RT)* TO IMMUNOLOGICAL AND CLINICAL EVENTS FOR COHORT PARTICIPANTS WITH HIV-1 RNA OF 30,000 COPIES/ML COMPARED WITH A 0.50, 0.75, AND A 1 LOG REDUCTION IN HIV-1 RNA AT 9 MONTHS POST-SEROCONVERSION, USING LOG-NORMAL MODELS (N=311)

Event	No. free of event at set point, No. of, events	Median time to event (years) Reference group HIV-1 RNA=30,000	0.50-log reduction: HIV-1 RNA = 9,487		0.75-log reduction: HIV-1 RNA = 5,335		1-log reduction: HIV-1 RNA = 3,000		1.25-log reduction: HIV-1 RNA = 1,687	
			Median Time to event (years)	Relative time (95% CI)	Median Time to event (years)	Relative time (95% CI)	Median Time to event (years)	Relative time (95% CI)	Median Time to event (years)	Relative time (95% CI)
AIDS (defined as diagnosis of an OI)	(310, 93)	8.4	11.9	1.4 (1.3, 1.6)	14.2	1.7 (1.5, 2.0)	16.9	2.0 (1.6, 2.5)	20.2	2.4 (1.9, 3.2)
CD4+ T-cell count < 200 cells/mm ³	(298, 95)	6.1	8.1	1.3 (1.2, 1.5)	9.2	1.5 (1.3, 1.8)	10.6	1.7 (1.4, 2.1)	12.1	2.0 (1.5, 2.6)
CD4+ T-cell count < 350 cells/mm ³	(263, 133)	3.4	4.5	1.3 (1.2, 1.5)	5.2	1.5 (1.3, 1.8)	5.9	1.7 (1.4, 2.1)	6.8	2.0 (1.6, 2.6)
HIV-1 RNA > 55,000 copies/mL	(149, 59)	2.4	4.3	1.8 (1.4, 2.2)	5.7	2.4 (1.6, 3.4)	7.6	3.1 (1.9, 5.0)	10.1	4.1 (2.3, 7.5)
Clinical indication for initiation of antiretroviral therapy**	(137, 76)	1.9	2.7	1.4 (1.2, 1.7)	3.3	1.7 (1.3, 2.2)	3.9	2.0 (1.5, 2.9)	4.7	2.4 (1.6, 3.7)

*Relative time is calculated as the ratio of time to each event for the comparison HIV-1 RNA categories (9487, 5335, 3000, 1687 copies/mL) and reference group category of 30,000 copies/mL.
** Clinical indication for initiation of antiretroviral therapy defined as HIV-1 RNA > 55,000 copies/mL or CD4+ T-cell count < 350 cells/mm³ or OI

DISCUSSION

- HIV-1 RNA measurements were relatively similar at 3, 9, and 15 months after seroconversion (range of geometric means: 19,815-22,387 copies/mL).
- Compared with a viral set point of 30,000 copies/mL, a viral set point of 3,000 copies/mL was associated with an additional 2.5 years before CD4 count fell to 350 cells/mm³ - a common threshold for initiating antiretroviral therapy.
- The median time to HIV-1 RNA ≥ 55,000 copies/mL, commonly defined as the loss of virological control, was three times longer for those with viral load set points of 3,000 compared to those with viral load set points of 30,000 copies/mL.
- Compared to those with an HIV RNA of 30,000 copies/mL at set point, an HIV RNA of 10,471 copies/mL (4.02 log₁₀) would be required to significantly reduce the hazard of progressing to a clinical indication to initiate antiretroviral therapy within 3 years by 25%.
- It should be mentioned that the analysis assumes that a reduction in viral load set point after vaccination would mimic CMI-based responses seen in natural infection.

LIMITATIONS

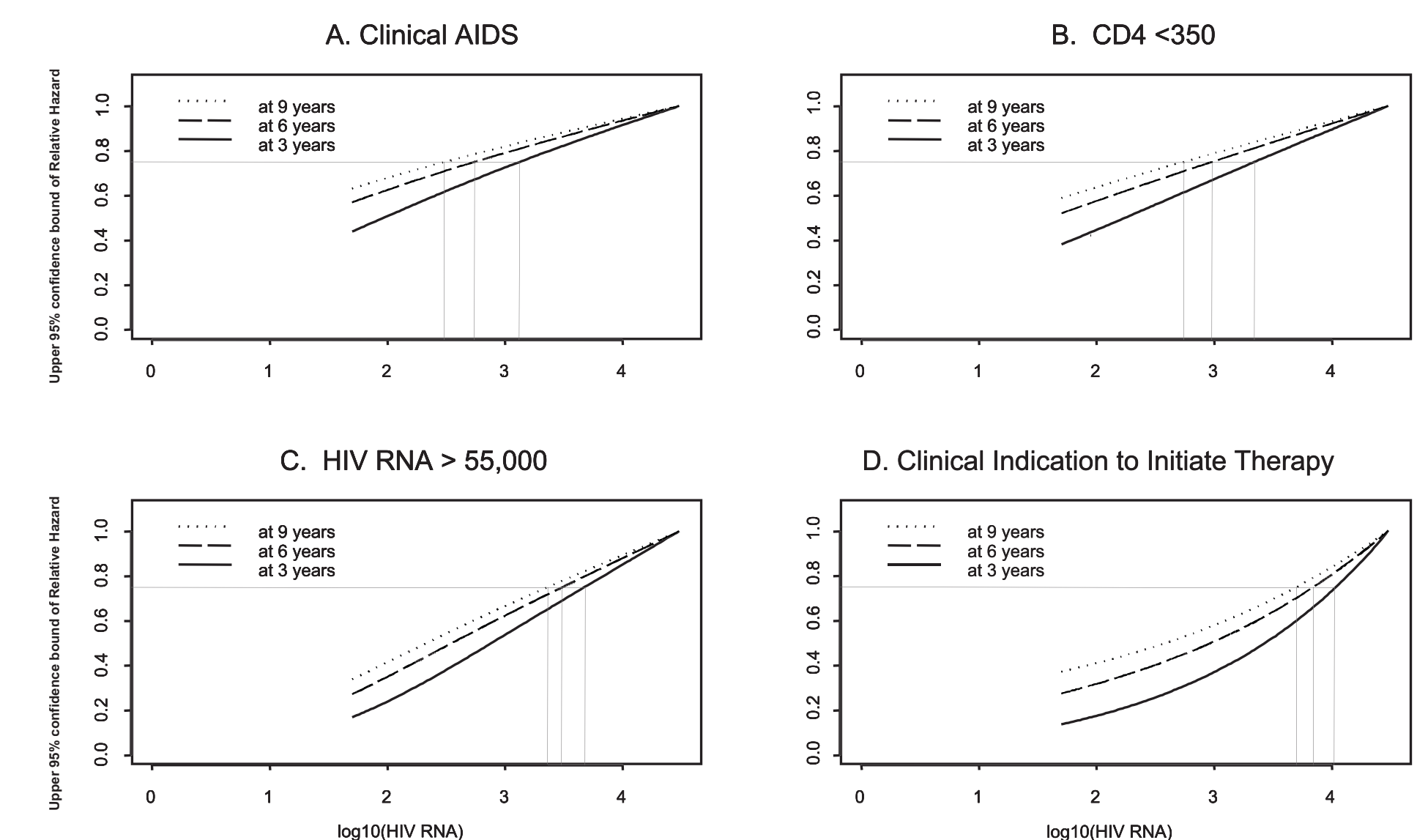
- The MACS does not include women.
 - Additional analyses should be conducted to determine if relative times to events of interest are similar in men and women
- The MACS participants are predominantly infected with clade B HIV-1.
 - Since the natural history of HIV-1 infection may differ by infecting clade, it will be important to conduct similar analyses in populations infected with non-clade B subtypes.
- A number of studies have shown the association between specific HLA alleles and disease resistance or progression.
 - Future analyses of the effect of viral load set point on time to events in HIV disease progression could account for individual HLA types.

TABLE 2. DEMOGRAPHIC STATISTICS FOR 311 SEROCONVERTERS WITH HIV RNA AVAILABLE AT 9 MONTHS POST-SEROCONVERSION

Median year of seroconversion	1986 (IQR*: 1985-1989)
Median age at seroconversion	34 (IQR*: 29-38)
Race	n (%)
White, non Hispanic	269 (86.5)
White, Hispanic	19 (6.1)
Black, non-Hispanic	22 (7.1)
Other	1 (0.3)
Median Follow-up time (years)	5.5 (IQR*: 3.1-6.9)

* IQR = Interquartile range

FIGURE 1. UPPER BOUND OF THE 95% CONFIDENCE INTERVAL OF RELATIVE HAZARDS OF CLINICAL EVENTS IN THE COURSE OF HIV-1 DISEASE PROGRESSION ACCORDING TO LOG₁₀ (HIV-1 RNA) RELATIVE TO 4.48 LOG₁₀ (30,000 COPIES/ML)



* The vertical lines show the HIV RNA (copies/mL) that is required at set point to significantly (p<0.05) reduce the hazard of each outcome by 25% at 3, 6, and 9 years relative to individuals with a viral load set point of 30,000 copies/mL. For any HIV RNA measurements above this value, the 95% confidence limits would include one, and thus would not be significant at the 0.05 level.

CONCLUSIONS

- The time to key clinical events in the course of HIV-1 disease progression was significantly extended for those with initial HIV-1 RNA 0.5-1.25 log₁₀ copies/mL lower than the reference group.
- For those with an initial viral load measurement of 3,000 vs. 30,000 copies/mL, the relative time to study endpoints was approximately double or higher.
 - This also applies to those events which occur earlier in HIV disease progression, such as a CD4 cell count below 350 cells/mm³.
- A viral set point of no more than approximately 10,000 copies/mL is associated with a significant reduction in the hazard of progressing to a standard indication to initiate antiretroviral therapy within 3 years.
- This analysis, based upon natural history data, provides a context for understanding the expected long term clinical value of a reduction in viral set point.
- These findings may be useful in predicting the clinical benefit of HIV-1 vaccines that are currently in clinical trials.

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