Copy-Years Viremia as a Measure of Cumulative Human Immunodeficiency Virus Viral Burden


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Plasma human immunodeficiency virus type 1 (HIV-1) viral load is a valuable tool for HIV research and clinical care but is often used in a noncumulative manner. The authors developed copy-years viremia as a measure of cumulative plasma HIV-1 viral load exposure among 297 HIV seroconverters from the Multicenter AIDS Cohort Study (1984–1996). Men were followed from seroconversion to incident acquired immunodeficiency syndrome (AIDS), death, or the beginning of the combination antiretroviral therapy era (January 1, 1996); the median duration of follow-up was 4.6 years (interquartile range (IQR), 2.7–6.5). The median viral load and level of copy-years viremia over 2,281 semiannual follow-up assessments were 29,628 copies/mL (IQR, 8,547–80,210) and 63,659 copies/mL (IQR, 15,935–180,341). A total of 127 men developed AIDS or died, and 170 survived AIDS-free and were censored on January 1, 1996, or lost to follow-up. Rank correlations between copy-years viremia and other measures of viral load were 0.56–0.87. Each log10 increase in copy-years viremia was associated with a 1.70-fold increased hazard (95% confidence interval: 0.94, 3.07) of AIDS or death, independently of infection duration, age, race, CD4 cell count, set-point, peak viral load, or most recent viral load. Copy-years viremia, a novel measure of cumulative viral burden, may provide prognostic information beyond traditional single measures of viremia.

acquired immunodeficiency syndrome; HIV; HIV infections; viral load; viremia

Abbreviations: AIC, Akaike's information criterion; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study.

Plasma level of human immunodeficiency virus type 1 (HIV-1) RNA (henceforth called viral load) is a valuable tool for the provision of clinical care to persons with HIV infection and the conduct of HIV research (1, 2). Viral load levels are used, in conjunction with CD4 cell counts, symptoms, comorbid conditions, and acquired immunodeficiency syndrome (AIDS)-defining illnesses, in decisions about antiretroviral therapy initiation, response, and modification (1). HIV research also relies heavily on viral load levels for evaluating the comparative efficacy and effectiveness of competing therapy regimens and estimating the prognosis of HIV-infected persons (1, 2).

Although viral load is generally obtained serially in clinical care and research, noncumulative values are commonly used in analysis—for instance, the peak, last pretherapy, or most recent value. Moreover, 1 or 2 values are typically used to guide treatment decisions (3). While these approaches have demonstrated prognostic value in relation to clinical outcomes, they fail to capture a person’s cumulative exposure to HIV-1 replication over time. Measures that reflect cumulative viral replication may become increasingly important as HIV-infected persons live longer and experience non-AIDS-defining clinical conditions to a greater extent (4, 5). Many of these non-AIDS-defining conditions may be related to systemic inflammation and immune activation caused or perpetuated by ongoing replication of HIV-1 (6).

Therefore, we developed a measure of cumulative viral load exposure, which we term “copy-years viremia.” Here
we evaluate copy-years viremia and other common viral load measures as independent prognostic markers for incident AIDS-defining illness or mortality during the period prior to the advent of effective combination antiretroviral therapy.

MATERIALS AND METHODS

Study population

The Multicenter AIDS Cohort Study (MACS) examines the natural and treated histories of HIV infection. Beginning in 1984, 6,972 homosexual and bisexual men in 4 US cities (Baltimore, Maryland; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California) were enrolled in the study (7). Participants completed semiannual physical examinations and questionnaires that included information on medication and treatments and provided blood for laboratory measurements. For seronegative men, positive enzyme-linked immunosorbent assays with confirmatory Western blots were used to determine HIV-1 seropositivity. Participants provided written informed consent, and investigators obtained institutional review board approval from participating institutions.

We explored the calculation of copy-years viremia, its association with other measures of viral load, and its association with incident primary AIDS-defining illness or death during the natural history period of HIV in public-use MACS data release 11, which covers the period between the beginning of the study in 1984 and 1998. We restricted this analysis to the 297 men who seroconverted after study entry and before January 1, 1996, with a seroconversion window of less than 2 years and more than 1 measured viral load. The initial visit was conducted a median of 0.25 years (interquartile range (IQR), 0.23–0.28) after estimated seroconversion.

Ascertainment of AIDS or death

The outcomes of interest were a first diagnosis of clinical AIDS and death from any cause. Because the data were restricted to the time period before the introduction of effective anti-HIV therapies, the majority of deaths were probably AIDS-related (5). The 1993 Centers for Disease Control and Prevention clinical conditions criteria were used to define clinical AIDS (8). Participants were not considered to have clinical AIDS if they had only a CD4 cell count less than 200 cells/mm³ or a CD4 cell percentage less than 14, with no clinical AIDS-defining condition. Diagnoses of any AIDS-defining condition after the first diagnosis (9) were not considered to be outcomes.

A description of outcomes ascertainment has been published elsewhere (7). Briefly, physician or hospital records were used to confirm reported clinical AIDS cases. Deaths were ascertained using active and passive searches of death records and the National Death Index. Dates in the public use data are given by month and year, so we randomly selected the day of the month for each date to avoid ties. Men were censored at dropout (i.e., no measured viral load for more than 2 years) or were administratively censored on January 1, 1996, to preclude the influence of effective combination antiretroviral therapy. The first protease inhibitor (i.e., saquinavir mesylate) was approved by the Food and Drug Administration on December 6, 1995.

Assessment of HIV-1 viral load and CD4 cell count

Plasma was collected from participants in 10-mL Vacutainer tubes (Becton, Dickinson & Company, Franklin Lakes, New Jersey) containing heparin or potassium ethylenediaminetetraacetic acid and was stored at −70°C until testing. The average interval between collection of blood and freezing of plasma samples is estimated to have been 6 hours, but times were not always recorded (10). Plasma HIV-1 RNA levels were measured in laboratories participating in the National Institute of Allergy and Infectious Diseases Virology Quality Assurance Laboratory proficiency testing program. Viral loads were quantified by HIV-1 RNA extracted from 1-mL plasma samples using the standard Amplicor HIV-1 monitor test (Roche Molecular Systems, Branchburg, New Jersey). The coefficient of variation was approximately 12%. The lower detection limit was 400 copies/mL. Seventy-six (3%) of 2,281 viral load assessments were below the lower detection limit and were replaced with values equal to one-half of the detection limit.

T-lymphocyte subsets were determined by immunofluorescence using flow cytometry in laboratories participating in the National Institute of Allergy and Infectious Diseases Quality Assurance Program. Specifically, T-cell subsets were measured in purified peripheral blood mononuclear cells or ethylenediaminetetraacetic acid-anticoagulated whole blood by staining with fluorescent dye-conjugated monoclonal antibodies that were specific for CD4 lymphocytes (Becton, Dickinson, Mountain View, California) (10). Thirty-three (1%) of 2,281 CD4 cell counts were missing and were replaced with the observed median value of 513 cells/mm³. Simple deterministic substitution of such a small percentage of undetectable viral loads and missing CD4 cell counts is appropriate (11).

Statistical analysis

A plasma HIV-1 RNA viral load copy-year is a quantification of viremia. For example, 10,000 copy-years equals having 10,000 copies of the virus every day for 1 year or 1,000 copies of the virus every day for 10 years. We propose copy-years viremia as a way of measuring the amount of exposure a person has had to the virus over a period of time, akin to pack-years of smoking (12).

In theory, copy-years is defined as the number of copies of HIV-1 RNA per mL per year circulating in plasma and integrated over the number of years from seroconversion, or

\[
K(T) = \int_0^T V(t) dt, \]

where \(K(T)\) is copy-years, \(V(t)\) is a measure of viral load continuously monitored over the period 0 to \(T\), and \(T\) is the time from seroconversion over which copy-years are integrated. Copy-years viremia has a range of \([0, \infty)\) and is
expressed in units of number of copies \times \text{years per mL} of plasma.

In practice, copy-years viremia is measured for participants \(i = 1 \rightarrow N\) using a discrete number \(j = 1 \rightarrow J_i\) of viral load assessments at times \(t_{ij}\) after seroconversion. The number of visits \(J_i\), as well as the timing of visits \(t_{ij}\), may vary by participant. Therefore, we approximate the integral \(K(T)\) with a time-weighted sum using the trapezoidal rule (13), as

\[
\kappa_i(J_i) = \sum_{j=1}^{J_i} [t_{ij} - t_{i(j-1)}] \times [V_i(j) + V_i(j-1)]/2,
\]

where \(V_i(j)\) is the viral load measured at assessment \(j\) for participant \(i\), \(t_{i0}\) is the date of HIV seroconversion, and \(V_i(0)\) is 0. For example, let us say that we see a participant at visits 1–5 at years (from seroconversion) 0.28, 0.78, 1.28, 1.62, and 2.53, respectively, with viral load assessments of 11,306, 70,737, 53,255, 121,787, and 87,651 copies/mL, respectively. Copy-years viremia is calculated using the above equation (and here rounded to the nearest integer) as 1,583, 22,094, 53,092, 82,849, and 178,143 copies \times \text{years/mL}, respectively.

In addition to copy-years, we use the set-point, approximated by the average of the first 2 postseroconversion viral loads \(V_i(1)\) and \(V_i(2)\), on average measured at \([t_{i(1)} + t_{i(2)}]/2\) years after seroconversion. The median time from seroconversion to the measured set-point was 0.50 years (IQR, 0.48–0.55). The peak viral load for participant \(i\) at follow-up visit \(j\) was defined as the maximum of \(\{V_i(1), \ldots, V_i(j)\}\) for \(j \in J_i\). The most recent viral load was defined as \(V_i(j)\), during time interval \([t_{ij}, t_{i(j+1)}]\). We assessed the associations among these viral load measures using Spearman rank correlation coefficients; a similar pattern of results was found using Pearson correlation coefficients for raw or \(\log_{10}\)-transformed viral load measures (data not shown).

We estimated Cox proportional hazards models (14) for the time from seroconversion to AIDS or death (i.e., infection duration),

\[
\lambda_T(t) = \lambda_0(t) \times \exp\left\{ \beta_1 g[V_i(t)] + \sum_{p=2}^{10} \beta_p Z_{ip} \right\},
\]

where the function of viral load \(g[\cdot]\) may be the \(\log_{10}\) copy-years, the set-point, the peak, or the most recent value. The covariate vector \(Z_i\) consists of an indicator of Caucasian race, years of age at seroconversion (and 3 basis functions for a 5-knot restricted cubic spline with knots placed at the 5th, 25th, 50th, 75th, and 95th percentiles of the marginal age distribution), and most recent CD4 cell count (and 3 basis functions for a similar spline).

Associations are quantified using the hazard ratio, and precision is quantified using 95% confidence intervals based on a Wald approximation. We explored possible departures from linearity between a \(\log_{10}\)-transformed measure of viral load and incident AIDS or death using a combined Wald test of the nonlinear terms from a restricted cubic spline as described above (15), as well as categorizing viral load by quartiles. We assessed the proportional hazards assumption using a product term between a measure of viral load and time.

In addition to fitting separate models with each individual measure of viral load, we fit all 15 possible models with various combinations of the 4 viral load measures. These 15 models are compared against each other using Akaike’s information criterion (AIC) (16). The AIC is defined as 

\[
-2 \log \text{likelihood} + 2p,
\]

where \(p\) is the number of parameters in the model. A lower AIC is taken as having a better fit to the data. We also constructed a measure of variable importance based on AIC weights (17). The AIC weight for model \(j = 1 \rightarrow 15\) was defined as

\[
\exp(-\Delta_j/2)/\sum_{k=1}^{15} \exp(-\Delta_k/2),
\]

where \(\Delta_j = \text{AIC}_j - \text{minimum} \{\text{AIC}_k\}\) and \(k\) also indexes the 15 models explored. Variable importance was defined by the sum of the AIC weights for models in which that variable appeared, with a possible range from 0 to 100. SAS, version 9.3, was used for all analyses (SAS Institute Inc., Cary, North Carolina).

RESULTS

A description of the 297 men at seroconversion and the 1,446 person-years of follow-up are provided in Table 1.

Table 1. Characteristics\(^a\) of 297 Male Human Immunodeficiency Virus Type 1 Seroconverters Seen at 2,281 Study Visits Over the Course of 1,446 Person-Years, Multicenter AIDS Cohort Study, 1984–1996

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seroconversion</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>34 (29–40)</td>
<td>37 (31–42)</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>84 (249)</td>
<td>88 (2,006)</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>701 (513–916)</td>
<td>513 (350–725)</td>
</tr>
<tr>
<td>Recent viral load</td>
<td>24,729 (7,928–93,395)</td>
<td>29,628 (8,547–80,210)</td>
</tr>
<tr>
<td>Viral set-point</td>
<td>32,920 (12,000–78,673)</td>
<td>NA</td>
</tr>
<tr>
<td>Peak viral load</td>
<td>24,729 (7,928–93,395)</td>
<td>68,737 (24,573–154,108)</td>
</tr>
<tr>
<td>Copy-years viremia</td>
<td>3,307 (1,031–11,753)</td>
<td>63,659 (15,935–180,341)</td>
</tr>
</tbody>
</table>

Abbreviations: AIDS, acquired immunodeficiency syndrome; NA, not applicable.

\(^a\) Data presented are median values and interquartile ranges unless noted otherwise.

\(^b\) A total of 33 (1%) missing CD4 cell counts were replaced with the median value of 513 cells/mm\(^3\).

\(^c\) A total of 76 (3%) undetectable viral loads were replaced with a value equal to one-half of the detection limit.

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The median age at seroconversion was 34 years (IQR, 29–40), and 48 of the 297 men were nonwhite. At the first assessment postseroconversion, the median CD4 cell count and viral load were 701 cells/mm³ (IQR, 513–916) and 24,729 copies/mL (IQR, 7,928–93,395), respectively.

During follow-up, 101 (34%) of the 297 men were diagnosed with an AIDS-defining clinical condition, and 26 (9%) died without contracting AIDS; 80 (27%) were administratively censored on January 1, 1996, and 90 (30%) were lost to follow-up. Men were followed for a median of 4.6 years (IQR, 2.7–6.5) or 7 visits (IQR, 5–10) after seroconversion. The numbers of men under follow-up and at risk of AIDS or death 2.7, 4.6, and 6.5 years after seroconversion were 222, 147, and 79, respectively. The median amount of time between visits was 0.5 years (IQR, 0.42–0.67). The median viral load during follow-up was 29,628 copies/mL (IQR, 8,547–80,210), calculated over 2,281 measurements in the 297 men. The median level of copy-years viremia was 63,659 copies × years/mL (IQR, 15,935–180,341).

A rank correlation matrix for the various measures of viral load is provided in Table 2. In summary, copy-years viremia was correlated positively with other measures of viremia, but not to an extent that would preclude independent contributions from more than one measure. The rank correlation between measurements of copy-years viremia calculated approximately one-half year apart at any visit \( j \) and \( j - 1 \) was 0.95.

The infection duration-, age-, race-, and CD4-adjusted associations of various individual measures of viremia with incident AIDS or death are given in Table 3. When modeled separately, an increase of 1 log₁₀ in each measure of viral load was associated with a more rapid time to AIDS or death. The association with AIDS or death was weakest (albeit elevated) for a log₁₀ unit difference in viral set-point, intermediate for recent viral load, and strongest for peak viral load and copy-years viremia. The AIC values were ordered similarly (Table 3). Associations did not depart strongly from linearity between log₁₀-transformed measures of viral load and incident AIDS or death (for recent viral load, set-point, and copy-years, \( P = 0.1179, P = 0.3547, \) and \( P = 0.1470, \) respectively) but did for peak viral load \( (P = 0.0204) \). Further examination of peak viral load quartiles suggested that the detrimental effect was concentrated in the upper quartile (for uppermost quartile vs. lower 3 quartiles, hazard ratio = 3.91, 95% confidence interval: 1.64, 9.30). Associations of peak viral load and copy-years viremia with incident AIDS or death appeared proportional over infection duration \( (P = 0.2943 \) and \( P = 0.7881, \) respectively). However, associations of recent viral load and viral load set-point appeared to diminish with time from seroconversion \( (P = 0.0616 \) and \( P = 0.0055, \) respectively).

Figure 1 shows copy-years viremia by duration of infection for the 127 participants with incident AIDS or death (part A) and the 170 participants who did not develop AIDS or die during follow-up (part B). This figure illustrates the 3-fold increased hazard ratio from the separate model in Table 3, where, on average, men with impending outcomes

### Table 2. Spearman Rank Correlation Matrix for Various Measures of Viral Load Among 297 Male Human Immunodeficiency Virus Type 1 Seroconverters Seen at 2,281 Study Visits Over the Course of 1,446 Person-Years, Multicenter AIDS Cohort Study, 1984–1996

<table>
<thead>
<tr>
<th>Measure</th>
<th>Recent viral load, copies/mL</th>
<th>Viral set-point, copies/mL</th>
<th>Peak viral load, copies/mL</th>
<th>Copy-years viremia, copies × years/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent viral load, copies/mL</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral set-point, copies/mL</td>
<td>0.58</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak viral load, copies/mL</td>
<td>0.78</td>
<td>0.77</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Copy-years viremia, copies × years/mL</td>
<td>0.63</td>
<td>0.56</td>
<td>0.87</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviation: AIDS, acquired immunodeficiency syndrome.

### Table 3. Hazard Ratios for AIDS or Death (127 Cases) According to Various Measures of Viral Load Among 297 Male Human Immunodeficiency Virus Type 1 Seroconverters Seen at 2,281 Study Visits Over the Course of 1,446 Person-Years, Multicenter AIDS Cohort Study, 1984–1996

| Measure                  | Hazard Ratio 95% Confidence Interval P Value Akaike’s Information Criterion |
|--------------------------|------------------|------------------|------------------|------------------|
| Separate viral load measures |                      |                      |                      |                      |
| Recent viral load, log₁₀ copies/mL | 2.00            | 1.43             | 2.79             | 4.8 × 10⁻⁵       | 1,020.8                |
| Viral set-point, log₁₀ copies/mL | 1.41            | 1.02             | 1.95             | 0.0359           | 1,035.4                |
| Peak viral load, log₁₀ copies/mL | 2.82            | 1.81             | 4.39             | 4.6 × 10⁻⁶       | 1,017.3                |
| Copy-years viremia, log₁₀ (copies × years/mL) | 3.11           | 1.92             | 5.03             | 4.0 × 10⁻⁶       | 1,015.4                |
| Combined viral load measures |                      |                      |                      |                      | 1,016.1                |
| Recent viral load, log₁₀ copies/mL | 1.43            | 0.93             | 2.21             | 0.1064           |                      |
| Viral set-point, log₁₀ copies/mL | 0.88            | 0.61             | 1.27             | 0.4922           |                      |
| Peak viral load, log₁₀ copies/mL | 1.45            | 0.63             | 3.33             | 0.3874           |                      |
| Copy-years viremia, log₁₀ (copies × years/mL) | 1.70           | 0.94             | 3.07             | 0.0798           |                      |

Abbreviation: AIDS, acquired immunodeficiency syndrome.

a Adjusted for duration of infection (as the time scale), an indicator of Caucasian race, and restricted cubic splines for age at seroconversion and recent CD4 cell count.

b A lower value reflects a better fit (see text).

c Lagged by 1 visit.
had an increase in copy-years viremia while an increase was not as apparent for men who remained free of the outcome during follow-up. Figure 2 illustrates the most recent viral load by duration of infection for the same groups. In Figure 2, the association between increased recent viral load and incident AIDS or death is not as clear as for cumulative copy-years viremia in Figure 1.

All measures of viral load had weakened associations with incident AIDS or death when combined in the same model (Table 3). Copy-years viremia maintained the strongest association with incident AIDS or death. By AIC, the combined model fitted about as well as either peak viral load or copy-years viremia alone. When we explored all 15 possible combinations of the 4 measures of viral load, the 3 best-fitting models were: 1) recent viral load and copy-years viremia ($AIC = 1,013.0$); 2) recent viral load, peak viral load, and copy-years viremia ($AIC = 1,014.6$); and 3) recent viral load, viral set-point, and copy-years viremia ($AIC = 1,014.8$). Copy-years viremia had the highest variable importance, measured at 87.8, with recent viral load having the next highest at 71.1, peak viral load at 45.0, and viral set-point at 28.7. In general, beyond copy-years viremia, fit was not improved greatly by simultaneous use of multiple measures of viral load.

DISCUSSION

Copy-years viremia, a novel measure of cumulative viral burden, maintained an elevated but imprecise association with incident AIDS or death, independently of measured covariates and other common measures of viremia. Next to copy-years viremia, peak viral load had the strongest association with incident AIDS or death, as would be expected given the relatively high correlation between peak viral load and copy-years viremia. The association of peak viral load with events was nonlinear: Only the highest quartile of peak viral load was strongly associated with AIDS or death. That these alternative viral load measures appeared to have more prognostic value than viral load set-point may both have clinical importance and aid in the understanding of HIV pathogenesis. For instance, peak viral load may represent the pathogenic potential of HIV infection in a given individual.

HIV-1 RNA viral load is a main determinant of progressive HIV immunodeficiency (18–20). Mellors et al. affirmed that “[t]he prognostic strength of HIV-1 RNA is consistent with a central role of viral replication, manifest as viremia, in AIDS pathogenesis” (21, p. 2350). Indeed, viral load in an untreated or inadequately treated patient is a surrogate for the number of infected cells in the body that are actively replicating HIV (22). Our results suggest that copy-years viremia may more accurately reflect the burden of infection.

Although this was recently disputed (23), the central role of viral load in predicting HIV disease progression in the absence of antiretroviral therapy is well established (24). In the post-1996 era of HIV disease treatment, measures of viral load must be responsive to the effects of therapies in order to be useful (25). Therefore, there may be a role for a cumulative measure of viral burden such as copy-years viremia to complement existing cross-sectional measures.
even in the setting of effective combination antiretroviral therapy. For example, clinicians may want to consider cumulative and peak viral load when contemplating initiation of therapy.

Independently of our work, Zoufaly et al. (26) recently demonstrated an association between a similar measure of cumulative viral load and AIDS-related lymphoma in patients treated with combination antiretroviral therapy. Intermittent viremia during antiretroviral therapy may have prognostic value when cumulated over the course of years of treatment. Furthermore, we speculate that the higher mortality recently reported among patients with CD4 counts exceeding recommended treatment thresholds (3) who delayed therapy initiation (27) may relate, in part, to cumulative viral load burden, as could be measured by copy-years viremia.

Our approach was to quantify the population-averaged association of various measures of viral load with incident AIDS or death. Alternatively, one may characterize the subject-specific associations using a proportional hazards model with random effects for participants. The distinction is analogous to that in longitudinal data analysis (28). For example, using similar data, Lyles et al. (29) showed that changes in individual viral load levels (i.e., higher levels closer to AIDS) and slopes (i.e., larger positive slopes closer to AIDS) were associated with shorter times to AIDS.

The determination of how to use serial measurements of viral load, or any biomarker, should depend primarily upon the causally relevant empirical induction period for the outcome of interest (30). The induction period is the time from the causal action to disease onset. For example, if a threshold of the biomarker must occur in concert with pathology, then a single measure of the peak value over time may be most appropriate. Moreover, if the threshold must be met within a specific time window, then a single measure of set-point may be most appropriate. Alternatively, if an acute, short-lived blip of the biomarker occurs prior to an increased hazard of the outcome, then the single most recent measurement may be most appropriate. Finally, if a long-term, cumulative elevation of the biomarker occurs prior to an increased hazard of the outcome, then a cumulative measure of viral burden, such as copy-years, may be most appropriate.

In recent years, shifts in HIV epidemiology in developed countries have further underscored the potential role of copy-years viremia as a measure of cumulative HIV burden. Life expectancy has increased consistently and dramatically, and mortality rates have declined significantly among HIV-infected patients in industrialized nations since 1996, owing to the widespread use of combination antiretroviral therapy (31, 32). Concurrent with this reduction in overall mortality, shifts in cause of death have been observed, with reductions in AIDS-related deaths relative to non-AIDS-related deaths (e.g., cardiovascular disease, malignancy). Patients in developed countries are living for decades with HIV infection and experiencing morbidity and mortality from non-AIDS-defining clinical conditions (5, 31, 33–37). Many of these non-AIDS conditions are associated with systemic inflammation and immune system activation, which may result from exposure to ongoing, uncontrolled, intermittently controlled, or low-level viral replication that occurs over a long period of time (38). Therefore, the development of a novel measure capturing cumulative HIV viral load exposure is biologically sound and particularly germane.

As evidence accumulates regarding the role of viremia in relation to non-AIDS clinical events (e.g., myocardial infarction, malignancy) (6, 39), a role for copy-years viremia as a surrogate marker of such events seems probable. In the meantime, the association of copy-years viremia and peak viral load with markers of inflammation and immune activation should be explored in detail. In addition, there may be a role for clinical application of copy-years viremia in both AIDS and non-AIDS disease-specific prediction rules for HIV-infected persons. For example, other investigators have evaluated coronary heart disease event risk models among HIV-infected patients (40, 41), but these efforts have not incorporated plasma HIV viral load. Because cross-sectional viral load has been associated with inflammatory biomarkers that are linked to coronary heart disease events (6), cumulative HIV burden as measured by copy-years viremia may have important prognostic capacity in an HIV-disease-associated coronary heart disease event clinical prediction rule, especially over decades of therapy.

There are limitations to this work. First, viral load assessments were relatively infrequent (every 6 months). This infrequency in assessment may have induced information bias. For example, important dips and spikes in viral load are more likely to have been missed than would be the case with a more frequent viral load assessment plan. In future work, investigators might explore the impact of differing viral load monitoring schemes on the estimation of copy-years viremia. Second, we report on a single, first application of the use of copy-years viremia. More empirical comparisons are warranted, and we plan to undertake such work. Third, copy-years viremia is ideally quantified from the outset of infection, as we were able to do here with the MACS cohort; however, this will be impossible in many clinical settings, where patients are first seen more deeply into the course of HIV infection. In such settings, it may be fruitful to measure copy-years viremia from a natural landmark such as HIV diagnosis or initiation of combination antiretroviral therapy. On a related note, we directly account for infection duration as the time scale in the Cox model and indirectly account for infection duration in the calculation of copy-years viremia. This approach does not yield overadjustment (42) for infection duration, as long as there remain participants with heterogeneous copy-years viremia at similar infection durations. Finally, the moderate correlation observed between the viral load measures precluded our ability to precisely estimate the adjusted hazard ratios; similar analyses should be employed in a larger set of seroconverters, such as the CASCADE collaboration (43).

This work had several strengths: copy-years viremia’s being a novel measure of cumulative viral burden; the analyses’ being conducted in a well-characterized cohort of seroconverters; the use of centralized, high-quality longitudinal measurements of viral load; and rigorous follow-up with confirmation of AIDS or death. We conclude that copy-years viremia demonstrated an elevated association...
with incident AIDS or death after adjustment for other measures of viremia and is a promising additional measure of long-term viral burden.

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