Viremia Copy-Years as a Predictive Marker of All-Cause Mortality in HIV-1–Infected Patients Initiating a Protease Inhibitor–Containing Antiretroviral Treatment

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Background: Viremia copy-years (VCY) has been reported as a short-term predictor of mortality. We evaluated the association of this parameter with 10-year outcome within the APROCO-COPILOTE cohort.

Methods: Prospective data from 1281 HIV-1–infected patients who started a first protease inhibitor–containing regimen in 1997–1999 were analyzed. Patients with baseline plasma viral load (pVL) > 500 copies per milliliter and at least 2 pVL measures from the eighth month of follow-up were selected. VCY was calculated individually over the follow-up as the area under the pVL curve. Multivariate Cox models analyzed the relation between all-cause mortality and the following variables: age, sex, geographical origin, transmission group, HIV infection duration, ART-naive, pVL at baseline, time-dependent CD4 count, and VCY.

Results: Nine hundred seventy-nine patients were followed up for a median of 10 years (interquartile range: 5–11.5). At baseline, median (interquartile range) values for duration of HIV infection, pVL, and CD4 cell count were 43 (4–95) months, 4.6 (3.9–5.2) $\log_{10}$ copies per milliliter, and 278 (125–416) cells per cubic millimeter, respectively. At censoring date, 77 patients (8%) had died. VCY >1.4 $\log_{10}$ copies × yrs/mL was an independent predictor of death (hazard ratio: 2.0; 95% confidence interval: 1.2 to 3.5), which was no longer the case after adjustment for the latest pVL value [risk ratio (RR): 1.2 for 1 additional $\log_{10}$ copies per milliliter; 95% confidence interval: 1.1 to 1.4].

Conclusions: VCY was associated with mortality in HIV-infected patients under combined antiretroviral therapy but did not overweigh the predictive value of the latest pVL. VCY might be more useful as a marker of persistent viral replication than for routine clinical care.

Key Words: viremia copy-years, HIV, mortality, protease inhibitor

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INTRODUCTION

The goal of combined antiretroviral therapy (cART) is to achieve and maintain plasma viral load (pVL) of HIV below detectable levels.[1,2] However, some patients do not achieve complete virologic suppression throughout the duration of follow-up. They experience viral failures that are more or less frequent and can last for a short or long time with sometimes high levels of pVL. It would be interesting to assess whether cumulative replication over time has an impact on mortality, AIDS, or non-AIDS events, which cannot be performed through cross-sectional measures of pVL. Recently, Cole et al[3] proposed to estimate the cumulative exposure to detectable HIV replication through the calculation of a new parameter, viremia copy-years (VCY). VCY is defined as the area under a patient's longitudinal viral load curve and thus combines both the level of viral replication and the duration of this replication. This new parameter was identified by Mugavero et al[4] as a predictor of mortality in a cohort of HIV-naive patients who had a median time of follow-up of 2.7 years [interquartile range (IQR): 1.6–4.6 years].

The aim of this study was to re-assess the relationship between VCY and mortality in a large cohort of HIV-infected (naive and pretreated) patients and to examine whether VCY

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can be confirmed as a prognosis factor and thus could be interesting in routine clinical practice.

PATIENTS AND METHODS

ANRS CO8 APROCO-COPILOTE Cohort

Data from the APROCO-COPILOTE cohort were used for the study. This prospective, multicenter, French cohort of HIV-1–infected patients has been presented previously in length.[5–7] Briefly, from May 1997 through June 1999, HIV-1–infected patients who started a first protease inhibitor (PI)-containing antiretroviral regimen in the 47 participating clinical sites were invited to participate in the cohort and followed up until February 2010. All patients included in the APROCO-COPILOTE cohort provided written informed consent and the protocol was approved by the "Comité de Protection des Personnes se prêtant à la Recherche Biomédicale" of the Cochin Hospital (Paris).

Standardized clinical and biological data, including measurements of CD4 cell counts and pVL levels, were collected at baseline, after 1 and 4 months of cART, and every 4 months thereafter. All pVL were measured prospectively by assays routinely available in each center, with lower limits of detection of (LLOD) HIV-1 RNA that decreased over time from 500 to 20 copies per milliliter, with the improvement of quantification techniques.

Patients' Selection

Patients who contributed to this analysis were those who had a pVL ≥500 copies per milliliter at baseline, pVL measured at the eighth month from baseline (M08), and at least 1 pVL measure afterward.

Definition and Calculation of Viremia Copy-Years

VCY was defined as the area under the individual curve of pVL, with the assumption of linearity (trapezoidal integration) between 2 successive pVL measures, and expressed in copies × years per milliliter (c × yr/mL).

For the description of the distribution of VCY, calculation was performed on the whole set of available pVLs until the end of follow-up for each patient. However, during the model processing with time-dependent VCY as a covariate, we used current value of VCY driven from pVLs available from M08 to time to death for each death. When VCY was calculated as a time-dependent covariable in proportional hazards models (see below), if no pVL was available at the exact time of calculation, then pVL was estimated by linear interpolation between the closest measures available before and after this time. This definition of VCY was considered our reference and noted VCY_{REF}.

All pVL values equal to or below the limit of assay detection were set to zero to preclude a mechanical increase of VCY with increasing duration of follow-up even without detectable pVL. In addition, for VCY calculation, we used viral load values from M08 because we thought that from that date, patients must have an undetectable viral load.

Censoring date was defined as either the date of death or the date of the last clinical follow-up visit.

Prognostic Value of VCY_{REF}

We searched for the determinants of all-cause death occurring from M08 in a 2-step process using proportional hazards models. The potential mortality determinants that were considered were 2-fold: (1) baseline variables, which included age, sex, geographical origin (Africa vs. others), presumed HIV transmission group (men having sex with men, heterosexual, intravenous drug use), duration of HIV infection (since first positive HIV serology), history of an AIDS-classifying event, ART-naive, duration of previous ART, CD4 cell count, and pVL and (2) time-dependent variables, which included CD4 cell count and VCY_{REF}.

As a first step, we selected variables with a *P*-value below 20% after univariate analysis, and we chose the best coding for VCY_{REF} based on the Akaike information criterion (AIC). In a second step, we performed a multivariate analysis with backward selection at the alpha level 5%, and VCY_{REF} was forced into the model.

Sensitivity Analyses

We then performed sensitivity analyses using different formulas for the calculation of VCY: VCY_{NAIVE} (for ARV-naive patients only), VCY/FUD (VCY_{REF} divided by the corresponding follow-up duration, FUD), VCY_{1YR} and VCY_{5YR} (VCY calculated over 1-year and 5-year period).

Comparison of the Prognostic Impact of VCY With that of the Latest pVL

As the most recent pVL measure has been reported to be an independent predictor of death,[8] we also used the final model on mortality with VCY_{REF} to assess the predictive value of VCY as compared with that of the latest pVL available. We added the time-dependent latest pVL into the model and measured the remaining prognostic value of VCY_{REF}.

Statistical analyses were performed with the SAS software (SAS, version 9.2; SAS Institute, Cary, NC).

RESULTS

Table 1 summarizes the main baseline characteristics of the 979 patients who met selection criteria among the 1281 enrolled in the cohort. The reasons why 302 patients did not fulfill selection criteria were as follows: pVL below 500 copies per milliliter or missing at baseline (n = 98), no pVL at M08 or later (n = 204). Of the 979 patients analyzed, 765 (78%) were male patients and 468 (48%) were ART-naive. Median duration of known HIV infection was 43 months (IQR: 4–95 months), median pVL was 4.6 $\log_{10}$ copies per milliliter (IQR: 3.9–5.2 copies/mL), and median CD4 cell count was 278 cells per cubic millimeter (IQR: 125–416 cells/mm^3). The median time of follow-up was 10 years (IQR: 5–12 years) and contributed to a total follow-up of 8112 person-years. Seventy-seven patients (8%) had died, 30 (6%) of 468 patients and 47 (9%) of 511 patients in the ARV-naive population and in the ARV-experienced population, respectively ($P = 0.1$). The overall mortality rate was 1.1 for 100 patient-years. Main causes of death were non-AIDS related (n = 59, 77%). The

TABLE 1. Baseline Characteristics of 979 HIV-1–Infected Patients Initiating PI-Containing Therapy Included in the Analyses (APROCO-COPILOTE ANRS CO8 Cohort, 1997–2009)

Baseline Characteristics	Patients (N = 979)
Age (yrs), median (IQR)	37 (32–43)
Female sex, n (%)	214 (22)
Transmission group, N (%)	
MSM	395 (40)
Heterosexual	323 (33)
IVDU	160 (16)
Geographical origin, n (%)	
France	678 (69)
Africa	119 (12)
Other	63 (6)
ART-naive, n (%)	468 (48)
CDC-group C, n (%)	206 (21)
Duration of HIV infection (mo), median (IQR)	43 (4–95)
pVL (log_{10} copies/mL), median (IQR)	4.6 (3.9–5.2)
CD4 cell count (cells/mm^3), median (IQR)	278 (125–416)
VCY_{REF} (log_{10} c × yr/mL), median (IQR)	4.8 (1.3–13.5)

MSM, men who have sex with men; IVDU, intravenous drug use.

distribution of deaths was quite stable during the follow-up except for an increase in the fourth year (Fig. 1).

At M08, the median of pVL value was 2.3 log_{10} copies per milliliter (IQR: 1.9–2.7 log_{10} copies/mL); at the last visit, the median pVL value had decreased to 1.7 log_{10} copies per milliliter (IQR: 1.6–2.3 log_{10} copies/mL). The pVL values' proportion relative to the LLOD showed that 64% of pVLs were under the LLOD at M08 and 68% at the last visit. In the subgroup of patients who died, the median of the last pVL values at the last visit was somewhat higher and more often detectable (2.3 log_{10} copies/mL, 46% of pVL measures under the LLOD, respectively). The median time between the last pVL measure and death was 3 months (IQR: 2–7 months). The median number of pVL measures below LLOD and above LLOD used in the model for calculating VCY was 12 (IQR: 4–23) and 5 (IQR: 2–11), respectively.

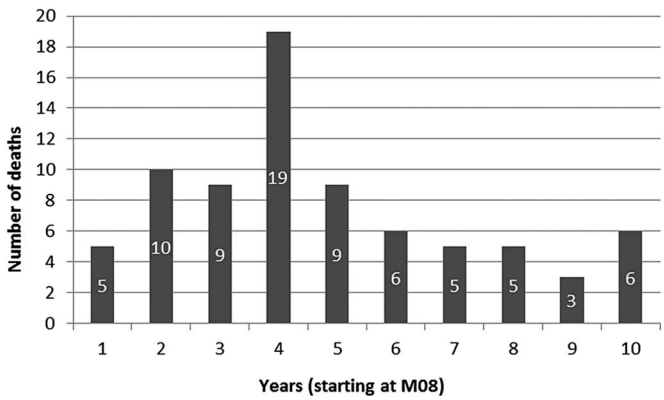

FIGURE 1. Annual deaths over whole follow-up in the study population.

On the whole follow-up, median VCY was 4.8 (IQR: 1.3–13.5) log_{10} c × yr/mL in the whole population, 2.7 (IQR: 1.0–1.1) log_{10} c × yr/mL in the ART-naive population and 7.8 (IQR: 2.4–16.6) log_{10} c × yr/mL in the ARV-experienced population.

After the univariate analysis, the best coding for VCY_{REF} was dichotomized (cut off at 1.4 log_{10} c × yr/mL based on AIC). This value was retained in the multivariate analysis where VCY_{REF} >1.4 log_{10} c × yr/mL was an independent predictor of mortality [hazard ratio (HR): 2.0; 95% confidence interval (CI): 1.2 (1.2) to 3.5], in addition to age and time-updated CD4 count. VCY/FUD was also predictive of death (HR: 1.8; 95% CI: 1.1 to 3.0 for a VCY/FUD >2.8 log_{10} copies/mL—cutoff based on AIC) (Table 2).

In the ART-naive population, with a cutoff value at 1.4 log_{10} c × yr/mL, VCY_{NAIVE} was not predictive of death (HR: 1.3; 95% CI: 0.6 to 2.8), whereas being older than 36 years was (HR: 2.8; 95% CI: 1.2 to 6.6). VCY_{5YR} was predictive of death (HR: 2.4; 95% CI: 1.1 to 5.3), whereas VCY_{1YR} was not (HR: 2.3; 95% CI: 0.8 to 1.2).

Finally, after adjustment to the latest pVL available, VCY did not remain associated with mortality, whereas the latest pVL did (RR: 1.2 for 1 additional log_{10} copies/mL; 95% CI: 1.1 to 1.4) (Table 3).

DISCUSSION

In this large cohort of patients treated by cART and followed up over a long period, the overall median VCY was lower than that calculated by Mugavero et al[4] (4.8 log_{10} c × yr/mL and 5.3 log_{10} c × yr/mL, respectively). We found that higher VCY was associated with all-cause 10-year mortality among HIV patients starting a PI regimen; this association did remain even after adjustment for duration of follow-up. However, it was neither evidenced in the ART-naive population nor over a short follow-up period (1-year window). Moreover, the most recent pVL was a better predictor of death than VCY.

There are 2 main differences between the study design by Mugavero et al[4] and that of our study. The first difference is the duration of the follow-up, which was much longer in our study (median of 2.7 years in that of Mugavero et al[4] vs. 10 years in ours). The second one is the management of the LLOD of the viral load assays. In 10 years, many different assays were used with progressively lowered LLOD with time. We decided to set to zero all pVL values equal or below the limit of detection of the assays, whereas Mugavero et al[4] chose to set each value below the limit of assay detection to half the limit of detection, the consequence of which was the mathematical increase of VCY over time in patients with undetectable pVL. However, both strategies for calculating VCY could be criticized because the significance of undetectable viral load is not straightforward: many patients with undetectable viral load still have persistent viral replication. Indeed, despite suppressive ARV treatment, viral RNA can be detected in peripheral blood plasma using ultrasensitive assays to a LLOD of 5 copies per milliliter.[9] So the method of calculation used by Mugavero et al[4] probably led to overestimating VCY value while that of ours led to minimizing it.

TABLE 2. Predictors of All-Cause Mortality in the Whole Study Population (N = 979) With 77 Deaths

	Model With VCY_{REF}				Model With VCY/FUD			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
Variables	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Sex (female vs. male)	0.9	0.5 to 1.6	—	—	1	0.6 to 1.7	—	—
Age at baseline ≥36 vs. < 36 yrs	2.2	1.3 to 3.6	2.5	1.5 to 4.3	2.2	1.3 to 3.6	2.5	1.5 to 4.2
Men who have sex with men	0.6	0.4 to 1.1	0.6	0.4 to 1.1	0.6	0.4 to 1.1	0.6	0.4 to 1.1
IVDU	1.9	1.1 to 3.3	—	—	1.9	1.1 to 3.3	—	—
Geographical origin (Africa vs. others)	1.6	0.9 to 2.9	—	—	1.7	1.0 to 3.1	—	—
ARV-naive at baseline	0.7	0.5 to 1.1	—	—	0.7	0.4 to 1.1	—	—
History of AIDS-defining event at baseline	1.3	0.8 to 2.1	—	—	1.3	0.8 to 2.2	—	—
Duration of HIV infection (≥44 mo)	1.1	0.7 to 1.7	—	—	1.1	0.7 to 1.7	—	—
Baseline CD4 cell count <350 cells/mm^3	1.8	1.0 to 2.9	—	—	1.8	1.0 to 2.9	—	—
CD4, time-dependent (per 100 cells/mm^3)	0.8	0.7 to 0.9	0.8	0.7 to 0.9	0.8	0.7 to 0.9	0.8	0.7 to 0.9
Baseline pVL ≥5 $\log_{10}$ copies/mL	1.6	1.0 to 2.5	—	—	1.6	1.0 to 2.5	—	—
VCY, time dependent (per 1 $\log_{10}$ c × yr/mL)	1.0	1.0 to 1.1	—	—	1.4	1.2 to 1.6	—	—
VCY_{REF}, time-dependent >1.4 $\log_{10}$ c × yr/mL	2.1	1.2 to 3.7	2.0	1.2 to 3.5	—	—	—	—
VCY/FUD, time-dependent >2.8 $\log_{10}$ copies/mL	—	—	—	—	2.1	1.3 to 3.4	1.8	1.1 to 3.0

IVDU, intravenous drug use; VCY_{REF}, viremia copy-years calculated for the whole follow-up; VCY/FUD, VCY_{REF} divided by the corresponding follow-up duration.

In our study, the association between VCY and mortality was not very consistent across groups and duration of follow-up. In the subgroup of ART-naive patients, we found no association between VCY and mortality. However, ART-naive patients suffered from a more advanced disease (baseline median CD4 cell count: 186 cells/mm^3, IQR: 65–367 cells/mm^3)[10] and thereby were at higher risk to develop AIDS-related events. A possible explanation could be that the first PI-containing regimen, more effective in wild-type virus than in resistant virus,[11] has induced a rapid and sustained initial treatment response and thus prevented us to highlight a relationship between VCY and prognosis. Besides, the small number of ART-naive patients could have precluded to evidence the prognosis effect of VCY.

These differences in the prognostic value of VCY across groups may be linked to difficulties we met to calculate VCY (the main one was the changes of the thresholds of quantification techniques of pVL over time). Consequently, in a pragmatic approach, we have then limited our investigations to comparisons between prognostic value of VCY and others parameters already accepted as predictors.

TABLE 3. Predictors of All-Cause Mortality: Comparison of VCY_{REF} With Other Predictors of Death

	Multivariate Analysis		
Variables	**RR**	**95% CI**	**AIC**
Age at baseline ≥36 vs. <36 yrs	2.7	1.6 to 4.6	—
Men who have sex with men vs. others	0.6	0.4 to 1.1	—
CD4, time-dependent (per 100 cells/mm^3)	0.8	0.8 to 0.9	—
VCY_{REF} > 1.4 $\log_{10}$ c × yr/mL	1.3	0.7 to 2.5	957.4
pVL at 8 months from baseline ($\log_{10}$ copies/mL)	1.0	0.9 to 1.2	960.5
Latest pVL, time-dependent ($\log_{10}$ copies/mL)	1.2	1.1 to 1.4	950.4

RR, risk ratio.

Thus, the prognostic value of VCY disappeared when the latest pVL measure was entered into the model. Because calculating VCY is delicate and because it has not provided an important prognostic value, VCY cannot replace, in our opinion, latest pVL measures in clinical practice. However, VCY reflects the cumulative exposure to long-time HIV replication and in this sense, it seems more accurate in an etiopathogenic approach to determine the long-term impact of HIV replication on all-cause mortality or on HIV-related morbidity. VCY could therefore be used as a marker of viral replication in concurrence with other markers that reflect immune activation or microbial translocation in HIV infection.[12–14] Indeed, HIV infection is responsible for a chronic inflammation that persists in successfully ART-treated HIV-infected individuals and that may promote comorbidities such as atherosclerosis or pathologies linked with aging and so-called "inflammaging," such as bone demineralization, cancer, and immune senescence.[13,15] There are many contributors to chronic inflammation, among which persistent replication is probably one of the most important.[7,16] Because VCY reflects both pVL and duration of persistent detectable pVL, it could be a novel marker linked to low-level chronic inflammation and could explain at least part of non-AIDS morbidity. This possible association between VCY and non-AIDS morbidity should be tested and further analysis should evaluate the association between VCY and markers of HIV-induced inflammation, such as plasma activation markers, coagulation biomarkers, and endothelial activation markers.[14,17,18]

CONCLUSIONS

Although VCY was a predictor of death once ART had been initiated, its predictive value did not outweigh that of the latest pVL. Thus, VCY should not become a parameter in routine clinical practice especially because it is difficult to calculate and interpret. However, VCY can help approach

cumulative HIV burden over time and its clinical impact. In this sense, our findings confirm that plasma HIV viral load should remain undetectable at any time in patients receiving ART.

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APPENDIX

The ANRS CO8 APROCO-COPILOTE Study Group is composed of the following:

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Clinical Centers (Investigators)

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