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Virologic Failure Following Persistent Low-level Viremia in a Cohort of HIV-Positive Patients: Results From 12 Years of Observation

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Background. The current goal of antiretroviral therapy (ART) is to maintain a suppressed human immunodeficiency virus (HIV) viral load below limits of assay detection. When viral loads remain in low-level viremia (LLV), especially between 50 and 200 copies/mL, the best management and clinical consequences remain unknown. Our objective was to study the long-term impact of persistent LLV on the subsequent risk of virologic failure in a cohort of people living with HIV in Montreal, Canada.

Methods. We compared the cumulative incidence of subsequent virologic failure (defined as an HIV RNA viral load of >1000 copies/mL) in patients receiving ART for at least 12 months by following 4 persistence categories (<50, 50–199, 200–499, and 500–999 copies/mL) for 6, 9, or 12 months, using Kaplan-Meier analysis. The association between subsequent virologic failure and persistence status were estimated using a Cox proportional hazards model.

Results. The cumulative incidence of virologic failure 1 year after having maintained a LLV for 6 months was 22.7% (95% confidence interval [CI], 14.9–33.6) for 50–199 copies/mL, 24.2% (95% CI, 14.5–38.6) for 200–499 copies/mL, and 58.9% (95% CI, 43.1–75.2) for 500–999 copies/mL, compared with 6.6% (95% CI, 5.3–8.2) for an undetectable HIV RNA viral load. Even after adjustment for potential confounders, a persistent LLV of 50–199 copies/mL for 6 months doubled the risk of virologic failure (hazard ratio, 2.22; 95% CI, 1.60–3.09), compared with undetectable viral loads for the same duration. Similar results have been found for persistent LLV of 9 or 12 months.

Conclusions. In this cohort, all categories of persistent LLV between 50 and 999 copies/mL were associated with an increased risk of virologic failure. The results shed new light for the management of patients with LLV, especially with regard to LLV of 50–199 copies/mL.

Keywords. cohort study; HIV; viral load; virological failure; low-level viremia.

The prognosis of people living with human immunodeficiency virus (HIV) has improved consistently in developed countries since the advent of antiretroviral therapy (ART) in 1996. Although it remains virtually impossible to cure HIV infection, ART allows the suppression of plasma HIV viral loads, which permits the restoration of immune function and avoids progression to AIDS and death [1, 2]. Virologic suppression also decreases the ability of HIV to develop antiretroviral (ARV) resistance. The current goal of ART is therefore to achieve and maintain virologic suppression below limits of assay detection, which is generally <20 to <75 copies/mL depending on the assay used [3]. While complete virologic suppression is ideal, it can be challenging in practice. Some patients may maintain persistent low-level viremia (LLV), defined as an HIV viral load of <1000 RNA copies/mL, and the clinical consequences and optimal management of these patients remain unclear, especially for LLV of 50–200 copies/mL. In addition, the exact minimal viral load at which viral replication occurs is unknown [3, 4]. Most experts agree that occasional transient viral loads of <400

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copies/mL (ie, blips) are common and do not reflect viral replication nor predict virologic failure. However, the best management and the potential clinical consequences of persistent LLV, especially between 50–200 copies/mL, remain controversial. The guidelines recently published by the Department of Health and Human Services state that "low-level positive viral load results (typically <200 copies/mL) appear to be more common with some viral load assays than with others. Furthermore, there is no definitive evidence that patients with viral loads quantified as <200 copies/mL using these assays are at increased risk for virologic failure" [3pC7]. The same guidelines therefore define virologic failure an HIV viral load of > 200 copies/mL and admit the absence of consensus regarding the best conduct for persistent LLV between 50–200 copies/mL. Our objective was to study and compare the long-term impact of 3 categories of persistent LLV (50–199, 200–499, and 500–999 copies/mL) on the subsequent risk of virologic failure (>1000 copies/mL) in a cohort of HIV-positive patients.

METHODS

Patient and Data Collection

We used data from an opened cohort of 2416 HIV-infected patients of the Clinique médicale du Quartier Latin in Montreal, Canada. This is an observational cohort started in July 1997, and recruitment and follow-up are ongoing. All participants signed an informed consent form, and the study protocol was approved by the Research Ethics Board of Sainte-Justine Hospital. Data collected included results of laboratory tests, such as measurement of HIV viral load and CD4 cell count, usually repeated every 3 months; sociodemographic information, and a complete history of ART. Data were collected from the time of HIV diagnosis (prospectively for most data and retrospectively for data collected between the time of HIV diagnosis and the start of follow-up at the clinic, when different, or for certain sociodemographic data, such as race, socioeconomic status, and sexual orientation). The majority of laboratory analyses were completed through the regular healthcare system at the Centre Hospitalier de l'Université de Montréal, where the Versant HIV-1 RNA 3.0 Assay (bDNA), with a lower limit of detection of <50 copies/mL, was used from 1999 to 2010, and Abbott Real-Time HIV-1 assay, with a lower limit of detection of <40 copies/mL, was used since 2010.

Statistical Analysis

Participants were included if they had at least 1 viral load measurement and had received any ARV for at least 12 months, to allow enough time to reach treatment potential and confirm the presence or absence of viral load suppression. We also only considered data from 1 July 1999, corresponding to when the viral load assay used was able to quantify HIV loads of < 50 copies/mL. Baseline characteristics were determined at the first HIV-related appointment on or after 1 July 1999.

Kaplan-Meier analysis was used to estimate the cumulative incidence of virologic failure (ie, > 1000 copies/mL), stratified according to 4 different exposure statuses: (1) undetectable viral load (<50 copies/mL), (2) persistent LLV of 50–199 copies/mL, (3) persistent LLV of 200–499 copies/mL, and (4) persistent LLV of 500–999 copies/mL. Durations of persistence were analyzed in 3 different models, one for every duration of LLV of at least 6, 9, and 12 months. Subjects were followed until a virologic failure occurred or, for censored observations, the most recent visit for which a viral load measurement was available. Participants were entered in the survival analysis at the visit following the occurrence of persistence defined as above. The duration of persistence was measured as the time between the first and last viral load measurement during an episode in which all consecutive viral loads remained in a specific LLV category (50–199, 200–499, or 500–999 copies/mL). Analyses of 6-month persistence therefore only included patients whose duration in a specific LLV category was at least 6 months. Patients remaining in a LLV category for 12 months were also included in the 9-month and 6-month analyses of the same LLV category. The undetectable reference category only included patients whose viral load remained undetectable for the selected duration (at least 6, 9, or 12 months) and who never had a LLV for ≥6 months. Patients whose viral load never reached <1000 copies/mL were excluded. The few patients who never had undetectable levels for at least 6 months but also never had a persistent LLV status nor an HIV load > 1000 copies/mL were excluded (ie, patients with recurrent blips, defined as viral load of 50–999 copies/mL preceded or followed by a viral load of < 50 copies/mL). Once a patient reached a higher category of LLV persistence, he remained in this higher category for the analyses. For example, if a patient had LLV of 50–199 copies/mL for 6 months, followed by LLV of 500–999 copies/mL for 6 months before virologic failure, they were categorized in the exposure status of 500–999 copies/mL for 6 months. We used the log-rank test to assess the statistical significance of differences in the incidence of virologic failure between exposure statuses. To determine whether there was a diminution of the risk of virologic failure following a LLV in more recent years, the 3-year cumulative incidence of virologic failure (>1000 copies/mL), by LLV category (6-month persistence status), was stratified for the periods when LLV occurred (1999–2000, 2000–2004, and 2004–2008).

Cox proportional hazards regression modeling was used to measure the association between virologic failure and exposure status. Multivariate modeling was used to control for potential confounders, using the 10% change in estimate method (included variables that changed the hazard ratios [HRs] for the association between LLV and virologic failure by ±10%) among

the following list of variables: age, sex, date of HIV infection diagnosis, race, sexual orientation, monthly income, type of employment, CD4 cell count, injection drug use (IDU), and any ARV use. All analyses were done using Stata, version 11 (StataCorp).

RESULTS

Of 2416 patients, 459 were excluded because they were not exposed to any ARV, 79 were excluded because they were followed for <1 year, and 18 were excluded because they had no viral load measurement. The baseline characteristics of the 1860 participants included in the study are shown in Table 1. The date of HIV diagnosis varied from 1980 to 2012.

Table 1. Baseline Characteristics of Human Immunodeficiency Virus (HIV)–Infected Patients Included in the Study[a]

Characteristic	Value (n = 1860)
Categorical	
Sex	
Male	1744 (93.8)
Female	116 (6.2)
Race	
White	985 (91.8)
Black	31 (2.9)
Other	57 (5.3)
Country of birth	
Canada	951 (88.2)
Other	127 (11.8)
Sexual orientation	
Homosexual	1112 (86.3)
Heterosexual	132 (10.3)
Other	44 (3.4)
Injection drug user[b]	
Yes	521 (28.0)
No/unknown	1339 (72.0)
Monthly income	
≤$1500	203 (20.5)
>$1500	789 (79.5)
Employment	
Full time	523 (55.9)
Other	413 (44.1)
Continuous	
Age, y	40.8 (35.4–46.9)
Follow-up duration, y[c]	7.1 (2.9–11.2)

Data are no. (%) of patients or median value (interquartile range).

[a] Baseline characteristics were determined at the first HIV-related appointment on or after 1 July 1999. Missing data are not listed, and total frequencies may differ slightly from total numbers of patients.

[b] Data are period prevalences (July 1997, March 2012).

[c] Defined as the interval between the first and the last appointment.

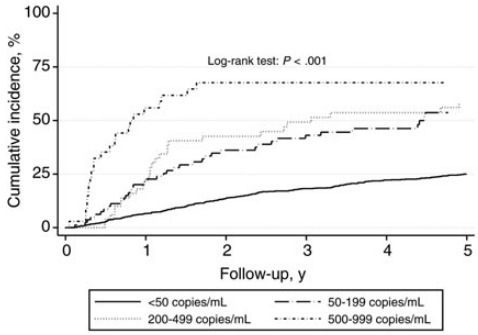
For the 6-month persistence analysis, 1357 patients were included (443 were excluded because they never reached a persistent HIV load status [neither undetectable nor LLV] for at least 6 months, and 60 were excluded because they had only 1 viral load measurement after the persistence period). At entry for survival analysis, the protease inhibitor mostly used was lopinavir, by 17.3% of patients (235/1357); the nonnucleoside reverse transcriptase inhibitor mostly used was efavirenz, by 26.8% (364/1357); and a nucleoside reverse transcriptase inhibitor–only regimen was used by 13.2% (179/1357). These data were similar for the 9- and 12-month analyses, except that the number of excluded patients was higher because it was restricted to patients with longer follow-up durations. The median time between viral load measurements was 97 days (interquartile range [IQR], 84–121 days). The median numbers of viral load measurements per patient were 14 (IQR, 5-27), 13 (IQR, 5-25) and 13 (IQR, 5-24) for the 6-, 9-, and 12-month groups, respectively.

Cumulative Incidence of Virologic Failure, According to Persistent LLV Status

Figure 1 shows the cumulative incidences of subsequent virologic failure (ie, > 1000 copies/mL) over 5 years, following persistence of LLV for 6, 9, or 12 months. Participants with any LLV persistence, including LLV of 50–199 copies/mL, were at higher risk of virologic failure than patients who maintained an undetectable viral load. The 1-year cumulative incidences of virologic failure after persistent LLV of 50–199, 200–499, and 500–999 copies/mL for 6 months were 22.7% (95% confidence interval [CI], 14.9–33.6), 24.2% (95% CI, 14.5–38.6), and 58.9% (95% CI, 43.1–75.2), respectively, compared with 6.6% (95% CI, 5.3–8.2) for patients who maintained an undetectable HIV load (P<.001). Similar results were found for patients who persisted with these viral loads for 9 or 12 months. When looking at the group with persistent LLV of 50–199 copies/mL, the cumulative incidence was significantly higher than that for the undetectable group, regardless of the duration of this persistence. Descriptive data for Kaplan-Meier graphs are shown in Table 2. Of the 41 patients who had virologic failure after a persistent LLV of 50–199 copies/mL for at least 6 months, 56% (23/41) achieved virologic suppression before the LLV episode, and 34% (14/41) had an episode of a complete suppression (<50 copies/mL) between the LLV episode and virologic failure.

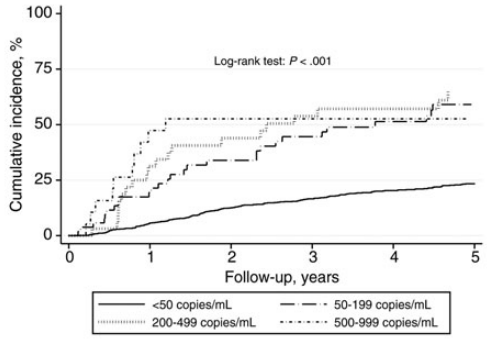
Figure 2 shows the 3-year cumulative incidence of subsequent virologic failure, by 6-month persistence status, stratified according to periods when persistence occurred. Although the graph suggests a tendency toward a decreasing risk for virologic failure after persistent status of 50–199 copies/mL, CIs overlap widely. However, the undetectable category remained at a significantly lower risk of virologic failure at 3 years than all other LLV categories, regardless of the period.

Persistent viral load status defined with a duration of 6 months



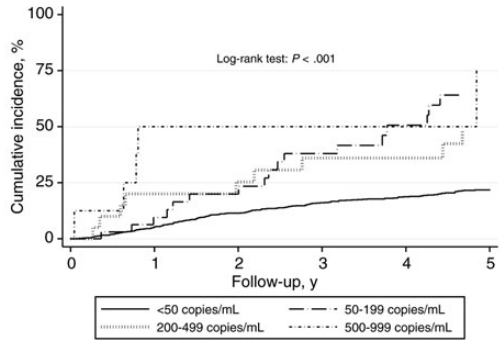
Time	<50 copies/mL, % (95% CI)	50-199 copies/mL, % (95% CI)	200-499 copies/mL, % (95% CI)	500-999 copies/mL, % (95% CI)
After 1 year	6.6 (5.3-8.2)	22.7 (14.9-33.6)	24.2 (14.5-38.6)	58.9 (43.1-75.2)
After 2 year	13.8 (12.0-16.1)	36.1 (26.5-47.9)	42.6 (30.2-57.5)	67.7 (52.0-82.4)
After 5 year	25.1 (22.4-28.1)	53.7 (42.4-65.9)	58.5 (44.9-72.7)	67.7 (52.0-82.4)

Persistent viral load status defined with a duration of 9 months



Time	<50 copies/mL, % (95% CI)	50-199 copies/mL, % (95% CI)	200-499 copies/mL, % (95% CI)	500-999 copies/mL, % (95% CI)
After 1 year	5.7 (4.5-7.2)	21.4 (12.5-35.4)	31.2 (18.2-50.3)	47.4 (28.1-71.3)
After 2 year	12.5 (10.7-14.7)	33.9 (22.6-48.9)	43.9 (28.8-62.6)	52.6 (32.7-75.6)
After 5 year	23.5 (20.8-26.4)	59.1 (45.3-73.4)	64.9 (48.1-81.3)	52.6 (32.7-75.6)

Persistent viral load status defined with a duration of 12 months



Time	<50 copies/mL, % (95% CI)	50-199 copies/mL, % (95% CI)	200-499 copies/mL, % (95% CI)	500-999 copies/mL, % (95% CI)
After 1 year	5.3 (4.1-6.8)	9.5 (3.2-26.7)	20.3 (8.0-44.9)	50.0 (22.5-84.8)
After 2 year	11.4 (9.6-13.5)	23.4 (11.9-43.0)	25.3 (11.4-50.6)	50.0 (22.5-84.8)
After 5 year	21.9 (19.3-24.8)	64.1 (45.7-82.1)	48.8 (28.7-73.4)	75.0 (36.5-98.6)

Figure 1. Cumulative incidence of virological failure (defined as a human immunodeficiency virus [HIV] load of >1000 RNA copies/mL), according to viral load persistence status

Association Between Persistent LLV and Subsequent Virologic Failure

Table 3 shows the results of Cox modeling. After adjustment for confounders, persistent LLV of 50–199 copies/mL or 200–499 copies/mL for at least 6 months doubled the risk of virologic failure (HR, 2.22 [95% CI, 1.60–3.09] and 2.15 [95% CI, 1.46–3.17], respectively), while a persistent viral load of 500–999 copies/mL increased the risk by almost 5 times (HR, 4.85 [95% CI, 3.16–7.45]), compared with patients who maintained an undetectable viral load. Similar effects were seen for LLV persisting for 9 or 12 months.

DISCUSSION

In this study, we estimated the cumulative incidence of virologic failure in patients who experienced persistent LLV for 6–12 months. The Kaplan-Meier curves showed that all LLV categories led to a higher incidence of virologic failure, compared with an undetectable viral load for similar duration. The multivariate regression models also showed that all categories of LLV led to an increased risk of virologic failure, and this risk was similar for all durations of LLV persistence. Although the CIs overlapped more in the longer duration category because the

Table 2. Descriptive Data of Kaplan-Meier Graphs, According to Duration of Human Immunodeficiency Virus (HIV) Load Persistence

	HIV Viral Load, RNA Copies/mL			
Persistence Duration, Variable	<50	50–199	200–499	500–999
≥6 mo[a]				
Patients, no.	1192	81	50	34
Virologic failure, patients, no.	272	41	29	24
Follow-up duration, person-years, no.	5575.7	298.3	223.7	82.7
Incidence[b] (95% CI)	4.9 (4.3–5.5)	13.7 (10.1–18.7)	13.0 (9.0–18.7)	29.0 (19.5–43.3)
≥9 mo				
Patients, no.	1186	53	32	19
Virologic failure, patients, no.	248	30	20	11
Follow-up duration, person-years, no.	5539.4	185.3	121.8	52.1
Incidence[b] (95% CI)	4.7 (4.0–5.1)	16.2 (11.3–23.2)	16.4 (10.6–25.5)	21.1 (11.7–38.1)
≥12 mo				
Patients, no.	1166	34	20	8
Virologic failure, patients, no.	224	19	9	5
Follow-up duration, person-years, no.	5329.0	117.2	103.1	25.7
Incidence[b] (95% CI)	4.2 (3.7–4.8)	16.2 (10.3–25.4)	8.7 (4.5–16.8)	19.5 (8.1–46.7)

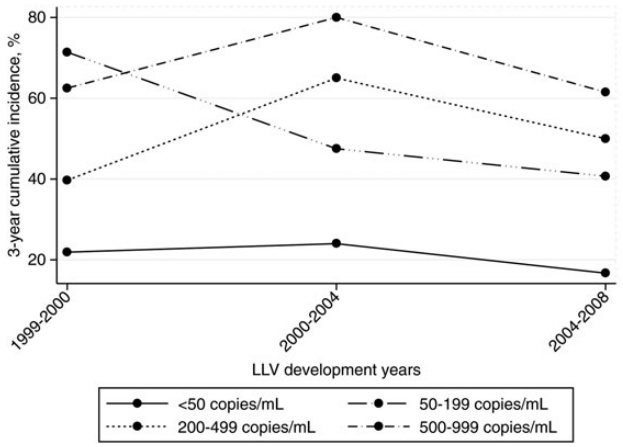
Abbreviation: CI, confidence interval.

[a] Participants without at least 6 months of follow-up (ie, patients with a follow-up duration too short to define a persistence status) or patients without follow-up data after their HIV viral load persistence episode were excluded.

[b] Defined as the cases of virological failure per person-years of follow-up.

number of participants was smaller, the study was powered enough to show statistically significant relative risks in all models. A persistent LLV of 500–999 copies/mL had the highest risk of virologic failure (almost 5 times that of a persistently undetectable HIV load), but both lower categories of persistent LLV, 50–199 and 200–499 copies/mL, doubled the risk of eventual virologic failure, compared with persistently undetectable viral loads for the same durations. These findings suggest that persistent LLV, including a LLV of 50–199 copies/mL, may have clinical consequences.

It is possible that the risk of virologic failure following LLV has been decreasing in recent years because of the use of newer ART, but further studies will be required to investigate this. The 3-year cumulative incidence of virologic failure following LLV that developed during 2000–2004 or 2004–2008 was lower than that following LLV that developed in 1999–2000, but CIs largely



Interval	<50 copies/mL, % (95% CI)	50-199 copies/mL, % (95% CI)	200-499 copies/mL, % (95% CI)	500-999 copies/mL, % (95% CI)
1999-2000	21.9 (17.1-28.0)	71.4 (38.9-95.9)	39.7 (22.2-63.9)	62.5 (32.6-91.3)
2000-2004	24.0 (19.5-29.4)	47.5 (32.3-65.6)	65.0 (44.8-84.3)	80.0 (52.5-96.9)
2004-2008	16.7 (13.1-21.2)	40.7 (25.0-61.4)	50.0 (19.6-88.9)	61.5 (37.2-86.0)

Figure 2. Cumulative incidence of virologic failure (defined as a human immunodeficiency virus load of >1000 RNA copies/mL) over 3 years, according to 6-month viral load persistence status stratified by periods of persistence development. Abbreviation: LLV, low-level viremia.

Table 3. Cox Modeling of Univariate and Multivariate Analyses of the Association Between Persistent Human Immunodeficiency Virus (HIV) Viral Load and Virologic Failure

	Univariate		Multivariate[a]	
Persistence Duration, HIV Load	HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
≥6 mo				
<50 RNA copies/mL	1.00 (reference)		1.00 (reference)	
50–199 RNA copies/mL	2.61 (1.88–3.63)	<.001	2.22 (1.60–3.09)	<.001
200–499 RNA copies/mL	2.92 (1.99–4.28)	<.001	2.15 (1.46–3.17)	<.001
500–999 RNA copies/mL	5.57 (3.67–8.46)	<.001	4.85 (3.16–7.45)	<.001
≥9 mo				
<50 RNA copies/mL	1.00 (reference)		1.00 (reference)	
50–199 RNA copies/mL	3.35 (2.29–4.89)	<.001	2.32 (1.57–3.42)	<.001
200–499 RNA copies/mL	3.73 (2.36–5.88)	<.001	2.18 (1.37–3.47)	.001
500–999 RNA copies/mL	4.11 (2.25–7.53)	<.001	4.70 (2.54–8.71)	<.001
≥12 mo				
<50 RNA copies/mL	1.00 (reference)		1.00 (reference)	
50–199 RNA copies/mL	3.52 (2.20–5.63)	<.001	1.90 (1.16–3.11)	.011
200–499 RNA copies/mL	2.33 (1.20–4.53)	.013	1.60 (.81–3.14)	.174
500–999 RNA copies/mL	4.37 (1.80–10.60)	.001	4.16 (1.68–10.29)	.002

Virologic failure was defined as an HIV viral load of >1000 RNA copies/mL

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Empirical control for confounding was done (see Methods for more details) among the following variables: age, sex, date of HIV infection diagnosis, race, sexual orientation, monthly income, type of employment, CD4 cell count at baseline, injection drug use, and use of antiretroviral therapy. Variables were included in the multivariate models and were kept if they changed the HR by ±10% (inclusion or the confounding variables may be different in each model). In the multivariate model with a 6-month persistence definition, date of HIV infection and use of tenofovir, emtricitabine, and efavirenz were kept; for the model defined with 9-month persistence, date of HIV infection and use of abacavir, emtricitabine, tenofovir, efavirenz, and ritonavir were included; and for the model defined with 12-month persistence, race, date of HIV infection, and use of abacavir, emtricitabine, tenofovir, efavirenz, etravirine, darunavir, ritonavir, and raltegravir were included.

overlapped between periods, and we cannot conclude that there was a significant difference across periods. Furthermore, the risk of virologic failure remained higher for all LLV categories, compared with that for an undetectable HIV load, across all periods.

There is a paucity of data regarding the impact of LLV, especially very LLV (such as 50–199 copies/mL) on the risk of virologic failure. Our results support those of previous studies on the risk of eventual virologic failure with persistent LLV. In a study of 2055 patients achieving viral suppression (defined as an HIV load of <50 copies/mL), Greub et al found that 2 consecutives viral load measurements of 51–500 copies/mL (which occurred in 155 patients) increased the risk of virologic failure of > 500 copies/mL by >5 times (HR, 5.8; 95% CI, 4.26–7.90) [5]. Geretti et al studied 1386 patients receiving their first ART regimen, of whom 85 had persistent LLV (defined as 50–400 copies/mL on ≥2 consecutive measurements) after viral suppression. The risk of virologic failure of > 400 copies/mL for patients with persistent LLV was more than double that for patients whose viral load remained undetectable (HR, 2.29; 95% CI, 1.22–4.29) [6]. Garcia-Gasco et al showed that virologic failure of > 500 copies/mL occurred in 20 of 131 patients (15%)s who had been virologically suppressed previously and who maintained a LLV of 51–500 copies/mL on 2 consecutive measurements [7]. However, these studies used a lower cutoff than we used for the definition of virologic failure (>400–500 copies/mL). The following studies are smaller but used the same definitions of virologic failure as we did (>1000 copies/mL). In a retrospective cohort of 362 patients, Sungkanuparph et al found that patients who achieved virologic suppression and experienced a 3-month persistent LLV (51–1000 copies/mL) had a 3.8 times higher risk (95% CI, 2.2–6.4) of virologic failure than patients with undetectable viral load, with a higher risk associated with LLV of >400 copies/mL [8]. Pham et al reviewed the charts of 149 patients with at least 2 consecutive viral load measurements between 50–1000 copies/mL, of whom 26 did and 123 did not have a change in treatment [9]. No significant difference was found between the groups with regard to the proportion reaching complete virological suppression or virologic failure after 6 months (virologic failure occurred in 7% of patients with no change). The majority continued to have LLV 6 months later. In addition, Karlsson et al showed that 18 patients with persistent LLV had a higher risk of virologic failure than 13 patients with sustained viral suppression [10]. Despite many differences in the study designs and specific methods of these previous studies and our study, all studies conclude that persistent LLV increases the risk of

eventual virologic failure. Our study is the first to investigate the impact of 3 categories of LLV and 3 persistence durations on the risk of virologic failure in such detail.

Our study has strengths and limitations. One of the strengths is the long follow-up period of a cohort with a considerable sample size. Another strength is the stratification of persistent LLV by several categories, which allowed study of the impact of different viral load thresholds. Among the limitations, the cohort was mainly composed of white men having sex with men, making the results generalizable only to this population. Confounding variables may also have biased the results because groups of patients may have differed in unmeasured characteristics, although most important variables associated with virologic failure were considered in the modeling strategy. It would have been interesting to analyze the difference in rates of persistent LLV and in the risk of virologic failure by ART regimen. Our regression models suggest some ARVs (abacavir, tenofovir, efavirenz, and ritonavir) have a protective effect, but the study was neither designed nor sufficiently powered to look into this. Further studies will be required to investigate the specific role of ART. Despite the large sample size, persistent LLV remains a relatively rare occurrence, which explains the wide and overlapping CIs between the 3 categories of persistent LLV. Although a higher risk of failure for all 3 LLV persistence categories, compared with that for undetectable viral load, is clear, the difference between the groups would require a larger sample size that is delineated with more precision. We admit that clinical scenarios can differ widely among patients with a persistent LLV, including whether patients have previously achieved virologic suppression. However, when we restricted the analyses only to patients who achieved virologic suppression before their LLV episode, the association was similar to that in previous studies (HR, 1.52; 95% CI, .99–2.33). Other factors may also influence the results, such as treatment adherence, being naive to ART, and sociodemographic characteristics. However, our study was not powered to stratify by more categories, and we understand that caution and clinical judgment needs to be used in the generalizability of these results. Another limitation is that we did not have information on adherence or interventions taken to improve adherence, and we did not take into account changes in ART regimen during follow-up. Moreover, we did not analyze the cause of virologic failure or its impact on the risk of developing resistance mutations. Some authors have clearly shown the risk of developing resistance mutations during LLV [11]. For example, Delaugerre et al showed that 11 of 37 patients with an episode of LLV of < 500 copies/mL developed at least 1 drug-resistance mutation [11]. Taiwo et al showed that 37% (of 54 patients) developed new resistance mutations during LLV [12]. In patients with an HIV load of 50–400 copies/mL, Nettles et al found that 9 of 21 patients had resistance mutations [13]. McConnell also documented in a cohort of 92 patients that optimizing ART on the basis of genotyping findings during LLV was more successful at achieving an undetectable HIV load than observation and continued receipt of the current regimen [14]. Our cases of virologic failure probably include many situations, including HIV resistance and adherence issues. In 34% of patients (14/41), virologic suppression was achieved between their LLV episode and virologic failure. One possible explanation for this is that a problem with adherence was resolved after an intervention, whereas another is that suppression occurred following an ART-related change/addition, with virologic failure arising because of resistance.

Virologic failure of > 1000 copies/mL is known to have clinical consequences, and our analyses showed that any persistent LLV of > 50 copies/mL increased the risk of such failures. One of the difficulties when managing LLV is that HIV genotyping is mostly accessible and reliable in patients with an HIV load of > 1000 copies/mL but less so at HIV loads of 400–1000 copies/mL [15]. Therefore, in the context of LLV, ART would often need to be adjusted blindly or based on past ART and genotyping history. This is why the option to observe and follow was and remains often considered, with most actions involving adherence counseling. However, the clearly increased risk of virologic failure shown here suggests that, for all persistent LLV of > 50 copies/mL, even at a viral load of <200 copies/mL, it might be beneficial to act more aggressively (eg, by providing adherence counseling; measuring plasmatic ART dosage, if available; consider interactions of medications; performing genotyping; and providing closer monitoring).

In conclusion, our study was intended to better understand the consequences of persistent LLV. Our analyses showed that the risk of subsequent virologic failure of > 1000 copies/mL was higher after persistent LLV, even when is the viral load was as low as 50–199 copies/mL for only 6 months, and the impact appears as soon as a few months after the LLV persistence. For patients with LLV (especially 50–199 copies/mL), the decision to either change ART rapidly or continue observation is a difficult one: the clinician has limited data to support either decision, and both options may have substantial consequences for the patient. We hope that our data contribute to the knowledge required to guide clinical conduct in such situations.

Notes

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Potential conflicts of interest. A. d. P. has served as a consultant on advisory boards for Abbott/Abbvie and Tibotec; has received speaker fees from Abbott/Abbvie, Pfizer, Tibotec, Merck Canada, and Gilead Sciences; and is a member of institutions that have received research funding from

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