Short-Term Clinical Outcomes Among Treatment-Experienced HIV-Positive Patients with Early Low Level Viremia

Chun Chao, Ph.D.,¹ Beth Tang, M.A.,¹ William Towner, M.D.,²
Michael J. Silverberg, Ph.D.,³ Leo Hurley, M.S.,³ and Michael Horberg, M.D.⁴

Dear Editor:

Empirical evidence suggests that some HIV-infected patients are unable to achieve and/or maintain undetectable levels of plasma viremia with combination antiretroviral therapy (cART), whether it is due to pharmacokinetic reasons such as poor drug absorption, viral resistance, or poor adherence.¹ In patients with incomplete viral suppression, cART regimen switching can be considered. However, the choice of antiretroviral medication ultimately becomes limited and often requires complex regimens with potentially greater pill burden or adverse effects. Failure to achieve maximal viral suppression thus poses challenges to the clinical management of HIV-infected patients, particularly among those who have been previously treated with multiple antiretrovirals.

While current treatment guidelines advocate maximal viral suppression and early regimen switch in the event undetectable HIV RNA level cannot be achieved,² the recommendation is based on adverse clinical consequences of higher level of HIV viremia. Little distinction is noted between failing with low level viremia (LLV) or advanced virologic failure in current treatment guidelines, perhaps due to our limited understanding concerning the immunologic and clinical consequences of failing with LLV, particularly in treatment experienced patients. A recent review found mixed evidence supporting switching cART regimens for patients failing with LLV.³ However, this conclusion was mostly based on risk of future virologic failure and accumulation of mutations but not on clinical outcomes, due to limited source studies.

In a cohort of 4847 treatment-experienced HIV-infected persons who started their second or greater cART regimen between 2001 and 2008 at Kaiser Permanente (KP) California, we investigated the immunologic and clinical outcomes within 12 months after failing with LLV. Kaiser Permanente California is a large managed care organization in California, serving over 6.6 million racial/ethnically and socioeconomically diverse members who are broadly representative of the California population. KP California health plans have maintained active HIV patient registries. HIV-infected patients included in these HIV registries were initially identified using electronic medical records, and confirmed as cases by chart review and/or consulting with clinical staff. The study

cohort was 90% male, 56% white, and 65% men who have sex with men. Mean age was 48 years. The cohort on average received a total of 2.3 cART regimen.

We defined an "index" regimen to examine the effect of LLV on clinical outcomes in this population. The index regimen was defined as the earliest cART regimen for the person that met the following criteria: (1) it is the second or greater cART regimen; (2) there was at least 6 months of health plan membership prior to the start of the regimen for assessing clinical history; (3) the person remained on the regimen for at least 6 months, i.e., the stabilization period, without switching to another regimen; and (4) there was an HIV RNA measurement to allow assessment of LLV status on the index regimen. A total of 3447 HIV-infected persons for whom an eligible index regimen could be identified were included in the study.

We used HIV RNA measured at the end of the 6 months stabilization period (± 2 months) to determine the person's viral control status on the index regimen. Persons with HIV RNA less than 75 copies per milliliter (i.e., assay detectable limit at KP) were considered achieving maximal viral suppression ($n=2608$). Persons with HIV RNA level between 75 and 5000 copies per milliliter were considered to have LLV ($n=420$). Persons with HIV RNA greater than 5000 copies per milliliter were considered advanced treatment failure ($n=419$) and were excluded from further analyses, since clinical consequences of advanced virologic failure have been previously established. We assessed the following outcomes within 12 months after achieving maximal viral suppression or failing with LLV: (1) AIDS-defining illness (excluding the CD4 < 200 per microliter criterion); (2) death; and (3) CD4 cell count trajectory. All data were collected from KP's HIV registries and electronic medical records.

There were 260 patients with new diagnoses of AIDS-defining illness (47 from LLV and 213 from the maximal viral suppression group) and 42 deaths (13 from LLV and 29 from the maximal suppression group) during the 12-month follow up period (Table 1). Compared with those who achieved maximal viral suppression, those who failed with LLV did not have accelerated progression to AIDS-defining illness: hazard ratio (HR)_{LLV} from multivariable Cox model = 0.82, 95% confidence interval: 0.57–1.18. However, failing with LLV was

¹Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California.

²Los Angeles Medical Center, Kaiser Permanente Southern California, Los Angeles, California.

³Division of Research, Kaiser Permanente Northern California, Oakland, California.

⁴Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic States, Rockville, Maryland.

TABLE 1. CLINICAL OUTCOMES DURING THE 12-MONTH FOLLOW-UP BY LLV STATUS

	HIV RNA status at end of stabilization period				Multivariable analysis ^a LLV vs. maximal viral suppression	
	All (n=3028)	LLV (n=420)	Maximal viral suppression (n=2608)	p Value	Hazard ratio (95% confidence interval)	p Value
Clinical AIDS diagnosis	260 (8.6%)	47 (11.2%)	213 (8.2%)	0.05	0.82 (0.57–1.18) ^b	0.29
Death	42 (1.4%)	13 (3.1%)	29 (1.1%)	0.01	2.36 (1.11–5.02) ^c	0.03
AIDS/death	289 (9.5%)	56 (13.3%)	233 (8.9%)	0.01	0.94 (0.67–1.31) ^d	0.71

^aAll multivariable models adjusted for age, gender, race/ethnicity, HIV transmission risk group, cART class, calendar time, and covariates that showed an univariate association with the outcome of interest at $p < 0.10$ (see below for each outcome).

^bModel also adjusted for Medicare/Medicaid status, HIV genotype resistance test, prior AIDS diagnosis, virologic failure at previous cART regimen, CD4 cell count measured during the stabilization period, regimen count of the index regimen, cART adherence during the stabilization period, comorbidity history including known hepatitis B infection, prior cancer (non-AIDS-defining) diagnosis, and coronary heart disease, and health service utilization including office visits, emergency department visit and hospitalization during the 12 months prior to the beginning of the follow-up period for outcomes.

^cModel also adjusted for all covariates listed in footnote^b, as well as years of antiretroviral agent use and known hepatitis C infection.

^dModel also adjusted for Medicare status, prior AIDS diagnosis, viral failure at previous regimen, CD4 cell count measured during the stabilization period, regimen count of the index regimen, cART adherence during the stabilization period, years of antiretroviral agent use, years of known HIV infection, comorbidity history including known hepatitis C infection and coronary heart disease, and health service utilization including office visits, emergency department visit and hospitalization during the 12 months prior to the beginning of the follow-up period for outcomes.

LLV, low level viremia; cART, combination antiretroviral therapy.

significantly associated with risk of death alone: HR_{LLV} = 2.36 (1.11–5.02). Most of these deaths were found to be HIV-related upon examination of cause of death. These findings suggest that patients failing with LLV were more likely to succumb to the disease when they developed AIDS. Given the lack of known biologic mechanism of how LLV could affect case fatality, these findings indicate a poorer underlying health status of those failing with LLV, despite the adjustment of important potential confounders (Table 1).

CD4 cell count was consistently lower in the LLV group at all-time points compared with that in those who achieved maximal viral suppression. The average number of CD4 measurement during the 12 months was 4.7 per person in the LLV group and 4.0 per person in the maximal viral suppression

group. No meaningful increase in mean CD4 cell count from end of the stabilization period to 6 and 12 months of follow up was observed for the LLV group: mean CD4 cell count was 377 per microliter (standard deviation: 250), 377 per microliter (249), and 358 per microliter (232), respectively, nor for those who achieved maximal viral suppression: mean CD4 cell count was 481 per microliter (264), 482 per microliter (265), and 508 per microliter (259), respectively. We found comparable distributions of individual slope in CD4 cell count over time across the two groups (see Fig. 1 for box plot). Similar findings were obtained from the multivariable mixed-effects model.

In the literature to date, inconsistent findings have been reported concerning the role of LLV in clinical outcomes.

FIG. 1. Box plot individual slope of CD4 cell count over the 12-month follow-up period by low level viremia (LLV) status at the end of the stabilization period.

Differences across studies may be due to variation in length of follow-up, study population, and the definition of LLV. A large cohort study of mostly antiretroviral-experienced subjects enrolled from clinical settings did not find patients with LLV (defined as HIV RNA level between 400–20,000 copies per milliliter) at increased risk of progression to AIDS or death compared to those with HIV RNA level of less than 400 copies per milliliter, after up to 4.3 years of follow-up.⁴ An Italian cohort of antiretroviral-naïve patients also found that risk of clinical progression was not significantly increased for more time spent on LLV (HIV RNA between 501–10,000 copies per milliliter) in comparison to time spent on HIV RNA level less than 500 copies per milliliter.⁵ However, among those who newly initiated cART, the Multicenter AIDS Cohort Study reported HIV RNA level prognostic of AIDS development among those with higher CD4 cell count (i.e., >250 per microliter as opposed to ≤250 per microliter).⁶ In the present study, we did not find evidence for effect modification by CD4 cell count, using 200 or 350 per microliter as the cutoff.

Regarding immunologic outcomes, the Multicenter AIDS Cohort Study also reported that HIV RNA less than 5000 copies per milliliter was predictive of a subsequent rise in CD4 cell count.⁶ Brigido and colleagues⁷ similarly found significant gain in CD4 cells among those with LLV in an open cohort in Brazil. However, both of these studies included cART-naïve patients, and had a much longer follow time. These differences between studies may be the reasons for the seeming contrary findings between these and our studies.

Few clinical studies have directly investigated the effects of different management approaches for patients with LLV. A small clinical trial conducted by Tenorio and colleagues examined the effect of delayed regimen switch for patients with low to moderate viremia (200–9999 copies per milliliter).⁸ They found that delayed switch had no profound impact on the immune parameters in a course of 1 year and suggested that in the absence of fully suppressive regimen, strategies aimed at maintaining viral loads below 10,000 copies per milliliter should be considered. However, given much more suppressive and better tolerated regimens nowadays, there is increasing intolerance for less than maximally suppressive regimens. More clinical studies with well-defined HIV patient population in terms of treatment history and immunological parameters with long-term follow-up are needed to inform the best clinical management strategies of LLV.

A limitation of our study was the lack of standardized follow-up visits for obtaining CD4 cell count and HIV RNA measurements, due to the observational nature of this study. Also, 19% of initially identified treatment-experienced subjects were excluded due to lack of an eligible index regimen. The excluded subjects were slightly younger and with less comorbidities, but reasonably similar to those included regarding HIV disease history. On the other hand, the present study is based on a well-defined treatment-experienced population in a managed care organization, which is likely generalizable to patients in other health care settings. We found that antiretroviral experienced patients failing with LLV are at increased risk of death, despite comparable rates of AIDS diagnoses when compared with those who achieved

maximal viral suppression. These findings suggest that those failing with LLV likely have poorer underlying health status, and are susceptible to deterioration from AIDS-defining illness. More intensive monitoring, prevention and care plan may thus be needed for these patients. These findings should provide additional insight for clinicians when determining the best course of clinical management for such patients.

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Author Disclosure Statement

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Address correspondence to:

Chun Chao, Ph.D.

Department of Research and Evaluation
Kaiser Permanente Southern California
100 S Los Robles Ave, 2nd floor,
Pasadena, CA 91101

E-mail: chun.r.chao@kp.org