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Low Level Viremia and Virologic Failure in Persons with HIV Infection Treated with Antiretroviral Therapy

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Abstract

Background: The clinical management of low level viremia (LLV) remains unclear. The objective of this study was to investigate the association of blips and LLV with virologic failure.

Methods: We enlisted patients who newly enrolled into the HIV Research Network between 2005-2015, had HIV-1 RNA >200 c/mL, and were either ART-naïve or ART-experienced and not on ART. Patients were included who achieved virologic suppression (≤ 50 on two consecutive viral loads) and had ≥ 2 viral loads following suppression. Blips and LLV (≥ 2 consecutive > 51 c/mL) were categorized separately into 3 categories: no blips/LLV, 51-200, 201-500. Cox proportional hazards regression was used to assess association between rates of blips/LLV and virologic failure (two consecutive >500).

Results: The 2795 patients were mostly male (75.4%), black (50.3%), and MSM (52.9%). Median age was 38 years old (IQR 29-48). Most patients (88.8%) were ART-naïve at study entry. Overall, 283 (10.1%) patients experienced virologic failure. A total of 152 (5.4%) patients experienced LLV to 51-200 and 110 (3.9%) patients experienced LLV to 201-500. Both LLV 51-200 (adjusted hazard ratio (aHR) 1.83 [1.10,3.04]) and LLV 201-500 (aHR 4.26 [2.65,6.86]) were associated with virologic failure. In sensitivity analysis excluding ART experienced patients, the association between LLV51-200 and virologic failure was not statistically significant.

Conclusions: LLV between 201-500 was associated with virologic failure, as was LLV between 51-200, particularly among ART experienced patients. Patients with LLV below the current DHHS threshold for virologic failure (persistent viremia ≥ 200) may require more intensive monitoring because of increased risk for virologic failure.

Author Contributions:
Conceptualization, J.G.F., R.D.M.; Methodology, J.G.F., R.D.M.; Formal Analysis, J.G.F. and R.D.M.; Writing-Original Draft Preparation, J.G.F., R.D.M.; Writing-Review & Editing, J.G.F., R.D.M., W.C.M., R.M.R., J.A., C.S., K.A.G., S.A.B.

Background:

Combination antiretroviral therapy (ART) has decreased morbidity and mortality among persons with HIV (PWH)[1]. The Department of Health and Human Services (DHHS) HIV Guidelines recommend ART for all PWH with the goal of virologic suppression to improve clinical outcomes, reduce HIV transmission, and to prevent the development of antiretroviral resistance[2].

After achieving virologic suppression of <50 copies/mL, most patients maintain a residual HIV-1 viremia at very low levels (1-10 copies/mL) [3, 4]. Even though patients have achieved virologic suppression <50 copies/mL, both transient and persistent increases in viral load are frequently seen. Blips, an isolated HIV-1 RNA ≥ 50 copies/mL that is immediately preceded and followed by virologic suppression, have been found in between 10 and 50% of PWH in studies[5]. Low level viremia (LLV), defined as two or more consecutive HIV-1 RNA ≥ 50 copies/mL, has an estimated prevalence of between 5% and 30% [6, 7].

Studies have varied in identifying the origin of blips. Prior studies have found that blips represent random biologic variation around a mean steady state HIV-1 RNA[8], while others have found that blips represent release of virus from the latent reservoir[9]. Several studies have found that blips are related to adherence to ART, while others have not [8, 10, 11]. Still others have identified that laboratory errors may result in false elevations in viral load[12]. However, the clinical significance of blips continues to be debated. While early studies found that blips were not associated with virologic failure [6, 8, 10, 13, 14], others have found that blips were associated with virologic failure [5, 15, 16]. Blips have also been associated with the development of drug resistance in some studies [17, 18], while not in others[8].

The clinical significance of low level viremia remains unclear and is an area of particular clinical interest. Much of the challenge in interpreting the significance of LLV comes from the discrepancies between various studies, including the lack of uniformity in definitions of low level viremia and virologic failure. Using a relatively expansive definition, LLV between 200-1000 copies/mL has consistently been associated with virologic failure, viral evolution, and the emergence of drug resistance [19, 20]. However, questions remain about whether LLV 50-199 copies/mL, a level below the current HHS definition of failure (persistent viremia ≥ 200 copies/mL), is associated with virologic failure. Few studies have restricted the definition of LLV to 50-199 copies/mL[21, 22]. A recent study by the ART-CC group found that LLV 50-199 copies/mL was not associated with virologic failure. In contrast, a retrospective analysis by Laprise et al found that LLV 50-199 copies/mL was associated with virologic failure[22]. Others have found LLV 51-199 to be associated with the emergence of drug resistance[23].

The objectives of this study were to: (1) Evaluate the association of blips between 51-200 copies/mL and 201-500 copies/mL with virologic failure, (2) Evaluate the association of low level viremia between 51-200 copies/mL with virologic failure, and (3) Assess the

association of clinical and demographic characteristics, including frequency of clinical monitoring, with virologic failure.

Methods:

Study Population:

The HIV Research Network (HIVRN) is a consortium of seventeen clinics that provide primary and specialty care to PWH in the United States[24]. Following de-identification, sites collect and send patient data to a central coordinating center, where data are combined into a uniform database. Local institutional review boards (IRBs) approved the collection of data at each site, and the IRB of Johns Hopkins University approved the collection and analysis of these data.

Patients who were engaged in HIV care at any HIVRN site were eligible for inclusion in this study. Patients were eligible for inclusion if they: enrolled in the HIVRN cohort between January 1, 2005 and December 31, 2015; started ART prior to December 31, 2015; had either no prior history of ART or, if they did have a history of ART, a new ART regimen was started at least 90 days after HIVRN enrollment and the patient was not virologically suppressed at enrollment; had a HIV-1 RNA >200 copies/mL at time of ART start; all HIV-1 RNA was measured on virologic assays with 50 copies/mL or less as the lower limit of detection. Patients were included if, after the initiation of ART, they achieved virologic suppression (HIV-1 RNA 50 copies/mL or lower) on two consecutive viral loads and then had a minimum of two additional HIV-1 RNA measurements. For the analysis, the follow-up period started on the date of the first suppressed HIV-1 RNA. Follow-up ended on the date of the last HIV-1 RNA measured. Patients were considered lost to follow-up if there was more than a 366 day gap in time to the next HIV-1 RNA measurement and were censored at the date of the last HIV-1 RNA prior to the gap. All patients were right-censored after 6 years or were censored at virologic failure, transfer away from an HIVRN site, loss to follow-up, last HIV-1 RNA prior to end of study period (December 31st, 2015), or death.

Definitions of outcome and exposure:

The primary outcome was virologic failure. Virologic failure was defined as two consecutive viral loads > 500 copies/ml. Viral suppression was defined as two consecutive HIV-1 RNA ≤ 50 copies/mL.

Blip 51-200 was defined as one isolated viral load between 51-200 copies/mL that was both preceded and followed by HIV-1 RNA ≤ 50 copies/mL. Blip 201-500 was defined as one isolated viral load between 201-500 copies/mL that was both preceded and followed by HIV-1 RNA ≤ 50 copies/mL. LLV 51-200 was defined as two or more consecutive viral loads between 51-200 copies/mL. LLV 201-500 was defined as two or more consecutive viral loads between 201-500 copies/mL or two or more consecutive viral loads with at least one HIV-1 RNA between 51-200 and one between 201-500 copies/mL.

We analyzed several covariates that we hypothesized would be associated with virologic failure. We categorized race as non-Hispanic Black (“Black”), non-Hispanic White (“White”), Hispanic, and other/missing. The racial groups Asian / Pacific Islander and

American Indian comprised too few patients to perform meaningful statistical tests. For purposes of analysis, these groups were combined into the "other" race category. Self-reported primary HIV risk transmission factor was defined as heterosexual contact (HET), men who have sex with men (MSM), persons who inject drugs (PWID), and other/unknown. Patients reporting an HIV risk factor of injection drug use (PWID) in conjunction with another risk factor, e.g. same sex male contact (MSM), were coded as PWID. Age and CD4 were identified at the time of viral load suppression. Age was categorized as <24, 24-39, 40-49, and ≥ 50 years old at time of VL suppression. CD4 count was categorized as < 200 cells/mm^3, 200-499 cells/mm^3, and ≥ 500 cells/mm^3. Antiretroviral therapy category was defined based on the anchor drug at ART start: non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), and integrase strand transfer inhibitor (InSTI). Each patient could have more than one anchor drug. "ART start" was defined as the date of initial ART start for ART-naïve or date of ART restart for ART-experienced and categorized into 2005-2009 and 2010-2015. Number of viral loads obtained after virologic suppression was included as a time-varying variable. Sites were categorized into adult or pediatric.

Statistical Analysis:

Longitudinal follow-up began at the time of first HIV-1 RNA ≤ 50 copies/mL. Kaplan-Meier analyses were done of virologic failure stratified by LLV and stratified by blip categories. For each plot, the highest category of LLV or blip defined the stratum. However, the Kaplan-Meier approach does not allow for LLV and blips as time-varying. Therefore, Cox proportional hazards regression was used to assess the association between blips, LLV and virologic failure, with blips and LLV analyzed as time-varying categorical variables. A patient could experience both blips and LLV over the course of the follow-up period. A patient was moved into the blip 51-200 or blip 201-500 category on the date the blip was measured. A patient was moved into LLV 51-200 or LLV 201-500 category on the first date that a viral load in this category was identified. Once a patient experienced a blip or LLV episode in a higher category, they would remain in the higher category for the duration of follow-up. For example, if a patient who had experienced LLV 51-200 then experienced LLV 201-500, they would move into the LLV 201-500 category.

Also included in the multivariate analyses were sex, age, HIV risk factor, CD4 count and HIV-1 RNA at ART start, date of ART start/restart, regimen at time of viral load suppression, and type of HIVRN site (pediatric vs adult). These variables were time-fixed. Number of viral loads measured was included as time-varying as a surrogate for intensity of follow-up. Proportional hazards were validated based on Schoenfeld residuals and graphical methods. A sensitivity analysis was done excluding patients with blips, and another was done excluding patients with LLV. A sensitivity analysis was done excluding ART naïve patients, and another was done excluding patients with a prior history of ART. All analyses were performed using Stata 15.0 (StataCorp LP, College Station, TX, USA).

Results:

During 2005-2015, 2795 patients were observed during 8423 person years of outpatient care. The median age was 38 years old (Interquartile range 29-48). The study patients were male

(75.4%), black (50.3%), and MSM (52.9%) (Table 1). Most patients enrolled in the cohort and started/restarted ART between 2010-2015 (71.1%). The majority of patients (88.8%) were ART-naïve at study entry. At ART start, most patients had an HIV-1 RNA >10,000 copies/ml (73.8%) and a CD4 > 200 cells/ml (83.9%). The anchor drugs at virologic suppression were NNRTI (48.6%), PI (36.8%) and INSTI (17.1%). Median number of viral loads obtained was 13 (IQR 8-16) during a median follow-up time of 3.8 years.

The majority of patients (64.9%) achieved virologic suppression within 6 months of ART start. Most patients maintained virologic suppression (50.3%) for the duration of the follow-up period. An additional 803 (28.7%) patients experienced either blips or low level viremia, with 88 (3.1%) who experienced both blips and LLV. Of 2795 patients, 283 (10.1%) patients experienced virologic failure at a median of 2.2 years (IQR 1.3-3.6 years)

Overall, 152 (5.4%) patients experienced LLV to 51-200 copies/mL, and 110 (3.9%) patients experienced LLV to 201-500 copies/mL. Kaplan-Meier plots of virologic failure stratified by LLV category and blip category are shown. There was a higher risk of virologic failure for successively higher LLV categories (Figure 1). However, there was not a greater risk of failure with higher blip categories (Figure 2).

Analyzing LLV and blips as time-varying covariates, we found that LLV 51-200 was associated with virologic failure in univariate (Hazard Ratio (HR) 2.01 [1.22,3.30]) and multivariate analysis (aHR 1.83 [1.10,3.04]). LLV 201-500 was also associated with virologic failure in both univariate (HR 3.51 [2.22,5.55]) and multivariate analysis (aHR 4.26 [2.65,6.86]) (Table 2). In sensitivity analysis excluding patients with blips, the associations of LLV 51-200 and LLV 201-500 with virologic failure remained the same. In sensitivity analysis including only ART naïve patients, LLV 51-200 was no longer associated with failure (aHR 1.61 [0.45, 1.11]). In sensitivity analysis including only ART experienced patients, LLV 51-200 remained statistically significantly associated with failure (aHR 3.50 [1.25, 9.81]).

A total of 556 (19.9%) patients experienced blips to 51-200 copies/mL, and 118 (4.2%) patients experienced blips to 201-500 copies/mL. In multivariate analysis, neither blip 201-500 (aHR 1.71 [0.91,3.22]) nor blip 51-200 (aHR 0.68 [0.45,1.03]) were associated with virologic failure (Table 2). In sensitivity analysis excluding patients with LLV, the associations of blip 51-200 remained the same; however, the association between blip 201-500 with virologic failure became significant (aHR 2.12 [1.06,4.21]). In a separate sensitivity analysis including only ART-naïve patients, blips between 201-500 copies/mL remained significantly associated with virologic failure (aHR 1.96 [1.01, 3.83]).

In the multivariate analysis, several other factors were associated with virologic failure. The number of viral loads performed was inversely associated with virologic failure (aHR 0.83 [0.77,0.89]) (Table 2). Compared to NNRTIs, PIs (aHR 1.61 [1.26,2.07]) were associated with increased risk of virologic failure. There was no difference in risk for virologic failure among INSTIs (aHR 1.07 [0.73,1.56]) compared to NNRTIs. Those who were ART experienced at baseline had an increased risk of failure (aHR 1.45 [1.02,2.05]). ART start before 2010 was not associated with an increased risk of failure (aHR 1.22 [0.94,1.59]).

Male sex was associated with an increased risk of failure compared to females (aHR 1.42 [1.01,2.00]). Black race (compared to white race: aHR 1.49 [1.07,2.08]) and PWID (compared to MSM: 1.80 [1.05,3.11]) also had an increased risk of virologic failure. There was an increasing risk of failure for each age category younger than 50 years old. Type of site (pediatric or adult) was not associated with virologic failure (not shown).

Discussion:

This study was designed to determine the associations of LLV and blips with subsequent virologic failure in those who achieved viral suppression on ART. Low level viremia between both 51-200 copies/mL and 201-500 copies/mL was associated with virologic failure as defined by two consecutive viral loads > 500 copies/ml. Also, neither blips between 201-500 copies/mL nor blips between 51-200 copies/mL were significantly associated with virologic failure.

The clinical management of LLV remains challenging, due to concern for viral evolution and emergence of drug resistance. Various definitions of low level viremia, including 50-500 copies/mL [13, 25, 26] and 50-1000 copies/mL [27, 28], have been associated with increased risk of virologic failure and development of resistance associated mutations[7, 19, 23, 29]. Our finding that LLV between 201-500 copies/mL is associated with virologic failure adds to the evidence from prior studies[21, 30], providing further support to current HHS guidelines that define virologic failure as persistent viremia ≥200 copies/mL[2].

As commercial assays become more sensitive, it is increasingly important to understand the significance of lower levels of viremia. Few studies have directly examined the association between LLV 50-199 copies/mL and virologic failure[21, 22, 31]. Our results provide evidence that low level viremia between 51-200 copies/mL may also be associated with virologic failure [31]. Vandenhende et al. demonstrated that LLV 50-199 was associated with virologic failure (two consecutive viral loads ≥ 200 copies/mL) among a cohort of 2,374 PWH. However, similar to our findings, sensitivity analysis showed this finding to be statistically significant only for ART-experienced patients, not ART-naïve patients [31]. Laprise et al. also found that among a cohort of 1,357 PWH, there was an association between LLV50-199 (for at least 6 months) and virologic failure [22]. In contrast to our findings, the ART-CC study of 17,902 PWH found that the LLV 50-199 was only weakly associated with virologic failure [21].

We found that blips were not associated with failure. Our results are consistent with prior research that low amplitude blips (<500 copies/mL) are unlikely to be associated with virologic failure[5, 6, 8, 14]. With over 2500 patients, our study included more patients than most prior studies of blips. Our findings support current guideline recommendations that blips can safely be monitored without need to alter the antiretroviral regimen. However, in sensitivity analysis, we found that blips 201-500 copies/mL were associated with failure among ART naïve patients, suggesting that these patients may benefit from closer monitoring.

We found that ART-experienced patients were at increased risk of virologic failure compared to ART-naïve patients. In our sensitivity analyses excluding ART-naïve patients, there was an association between LLV 51-200 and virologic failure. However, when excluding ART-experienced patients, the direct association between LLV 51-200 copies/mL and virologic failure was no longer significant. One hypothesis is that this difference may be due to underlying resistance mutations. ART experienced patients are more likely than ART naïve patients to harbor resistance mutations, which increases the risk for virologic failure[32]. We were not able to assess other factors that may have contributed to this difference, including adherence. Overall, this suggests that ART experienced patients are at higher risk for virologic failure and may benefit from increased supportive services.

In order to account for the role of clinical monitoring on virologic failure, we modeled the number of viral loads being performed as a time-varying variable to account for the intensity of virologic monitoring. We found an inverse association between the number of viral loads and virologic failure. We speculate that increased monitoring may have allowed for increased patient-physician interaction and opportunity for adherence counseling. This finding suggests that the patient-physician relationship and close clinical monitoring are important to successfully achieving virologic control.

Male sex, black race, injection drug use, and younger age were directly associated with virologic failure, consistent with prior studies. Previous research has found an association between several of these risk factors (younger age, black race, IDU) and adherence, suggesting that adherence may play a role in increased virologic failure in these persons[33, 34]. These demographic and clinical characteristics have also previously been linked to increased hospitalizations[35], frailty[36], mortality[37], and lower virologic suppression [38]. We also found that use of PIs, compared with NNRTIs, was associated with an increased risk of virologic failure. However, because behavioral risk factors for virologic failure often influence choice of ART, we hypothesize that provider preference and perceived risk of failure may result in use of PIs in higher risk patients, which may account for the increased risk of failure associated with PIs. Lastly, CD4 count < 200 cells/mm^3 at time of treatment start was associated with an increased risk of failure.

There are several important limitations to our study. First, we do not have data on ART adherence and thus were not able to assess any effect of adherence on virologic failure. Second, we do not have genotype results on patients who experienced blips or low level viremia and were not able to determine if there was emergence of new resistance mutations. Several studies have found new resistance mutations in the setting of low level viremia, although it is not clear if these mutations result in virologic failure[7, 20, 23]. Third, we were not able to assess ART changes at the time of blip or LLV. Changes in ART may be an unmeasured confounder in the relationship between blips, LLV, and virologic failure. Lastly, the HIVRN represents a sample of high-volume, high quality HIV primary care clinics, which may not be representative of all clinics that care for PWH. The demographic heterogeneity of these clinics also allowed us to determine differences occurring by race, age, HIV transmission risk group and use of ART.

In summary, we demonstrated that LLV between 51-200 and 201-500 copies/mL were strongly associated with virologic failure. These findings provide support for the current DHHS definition of virologic failure as persistent viremia greater than 200 copies/mL. In addition, our findings also suggest that patients with LLV < 200 copies/mL are at increased risk for failure and may benefit from increased clinical monitoring and intervention.

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References:

1. Group, I.S.S., et al., Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med, 2015 373(9): p. 795–807. [PubMed: 26192873]
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf Accessed 6/4/18.
3. Maldarelli F, et al., ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. PLoS Pathog, 2007 3(4): p. e46. [PubMed: 17411338]
4. Palmer S, et al., Low-level viremia persists for at least 7 years in patients on suppressive antiretroviral therapy. Proc Natl Acad Sci U S A, 2008 105(10): p. 3879–84. [PubMed: 18332425]
5. Grennan JT, et al., Magnitude of virologic blips is associated with a higher risk for virologic rebound in HIV-infected individuals: a recurrent events analysis. J Infect Dis, 2012 205(8): p. 1230–8. [PubMed: 22438396]
6. Garcia-Gasco P, et al., Episodes of low-level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome. J Antimicrob Chemother, 2008 61(3): p. 699–704. [PubMed: 18192682]
7. Taiwo B, et al., Antiretroviral drug resistance in HIV-1-infected patients experiencing persistent low-level viremia during first-line therapy. J Infect Dis, 2011 204(4): p. 515–20. [PubMed: 21791652]

8. Nettles RE, et al., Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. JAMA, 2005 293(7): p. 817–29. [PubMed: 15713771]
9. Yukl SA, et al., Differences in HIV burden and immune activation within the gut of HIV-positive patients receiving suppressive antiretroviral therapy. J Infect Dis, 2010 202(10): p. 1553–61. [PubMed: 20939732]
10. Podsadecki TJ, et al., Decreased adherence to antiretroviral therapy observed prior to transient human immunodeficiency virus type 1 viremia. J Infect Dis, 2007 196(12): p. 1773–8. [PubMed: 18190257]
11. Miller LG, et al., No evidence of an association between transient HIV viremia ("Blips") and lower adherence to the antiretroviral medication regimen. J Infect Dis, 2004 189(8): p. 1487–96. [PubMed: 15073687]
12. Stosor V, et al., Transient viremia in HIV-infected patients and use of plasma preparation tubes. Clin Infect Dis, 2005 41(11): p. 1671–4. [PubMed: 16267742]
13. Greub G, et al., Intermittent and sustained low-level HIV viral rebound in patients receiving potent antiretroviral therapy. AIDS, 2002 16(14): p. 1967–9. [PubMed: 12351960]
14. Havlir DV, et al., Prevalence and predictive value of intermittent viremia with combination hiv therapy. JAMA, 2001 286(2): p. 171–9. [PubMed: 11448280]
15. Moore AL, et al., Raised viral load in patients with viral suppression on highly active antiretroviral therapy: transient increase or treatment failure? AIDS, 2002 16(4): p. 615–8. [PubMed: 11873005]
16. Sorstedt E, et al., Viral blips during suppressive antiretroviral treatment are associated with high baseline HIV-1 RNA levels. BMC Infect Dis, 2016 16: p. 305. [PubMed: 27329293]
17. Cohen Stuart JW, et al., Transient relapses ("blips") of plasma HIV RNA levels during HAART are associated with drug resistance. J Acquir Immune Defic Syndr, 2001 28(2): p. 105–13. [PubMed: 11588503]
18. Macias J, et al., Transient rebounds of HIV plasma viremia are associated with the emergence of drug resistance mutations in patients on highly active antiretroviral therapy. J Infect, 2005 51(3): p. 195–200. [PubMed: 16230215]
19. Vardhanabhuti S, et al., Phylogenetic evidence of HIV-1 sequence evolution in subjects with persistent low-level viraemia. Antivir Ther, 2015 20(1): p. 73–6. [PubMed: 24699164]
20. Li JZ, et al., Prevalence and significance of HIV-1 drug resistance mutations among patients on antiretroviral therapy with detectable low-level viremia. Antimicrob Agents Chemother, 2012 56(11): p. 5998–6000. [PubMed: 22890763]
21. Antiretroviral Therapy Cohort, C., et al., Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. AIDS, 2015 29(3): p. 373–83. [PubMed: 25686685]
22. Laprise C, et al., Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. Clin Infect Dis, 2013 57(10): p. 1489–96. [PubMed: 23946221]
23. Delaugerre C, et al., Impact of low-level-viremia on HIV-1 drug-resistance evolution among antiretroviral treated-patients. PLoS One, 2012 7(5): p. e36673. [PubMed: 22590588]
24. Yehia BR, et al., Structures of care in the clinics of the HIV Research Network. AIDS Patient Care STDS, 2008 22(12): p. 1007–13. [PubMed: 19072107]
25. Lo Re V 3rd, et al., Natural history of patients with low-level HIV viremia on antiretroviral therapy. AIDS Patient Care STDS, 2004 18(8): p. 436–42. [PubMed: 15321015]
26. Geretti AM, et al., Determinants of virological failure after successful viral load suppression in first-line highly active antiretroviral therapy. Antivir Ther, 2008 13(7): p. 927–36. [PubMed: 19043927]
27. Sungkanuparph S, et al., Persistent low-level viraemia and virological failure in HIV-1-infected patients treated with highly active antiretroviral therapy. HIV Med, 2006 7(7): p. 437–41. [PubMed: 16925729]
28. Karlsson AC, et al., Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. AIDS, 2004 18(7): p. 981–9. [PubMed: 15096800]
29. Aleman S, et al., Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. AIDS, 2002 16(7): p. 1039–44. [PubMed: 11953470]

30. Boillat-Blanco N, et al., Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. Antivir Ther, 2015 20(2): p. 165–75. [PubMed: 24964403]

31. Vandenhende MA, et al., Risk of virological failure in HIV-1-infected patients experiencing low-level viraemia under active antiretroviral therapy (ANRS C03 cohort study). Antivir Ther, 2015 20(6): p. 655–60. [PubMed: 25735799]

32. Richman DD, et al., The prevalence of antiretroviral drug resistance in the United States. AIDS, 2004 18(10): p. 1393–401. [PubMed: 15199315]

33. Golin CE, et al., A prospective study of predictors of adherence to combination antiretroviral medication. J Gen Intern Med, 2002 17(10): p. 756–65. [PubMed: 12390551]

34. Howard AA, et al., A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. AIDS, 2002 16(16): p. 2175–82. [PubMed: 12409739]

35. Berry SA, et al., Trends in reasons for hospitalization in a multisite United States cohort of persons living with HIV, 2001–2008. J Acquir Immune Defic Syndr, 2012 59(4): p. 368–75. [PubMed: 22240460]

36. Piggott DA, et al., Frailty, HIV infection, and mortality in an aging cohort of injection drug users. PLoS One, 2013 8(1): p. e54910. [PubMed: 23382997]

37. Croxford S, et al., Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. Lancet Public Health, 2017 2(1): p. e35–e46. [PubMed: 29249478]

38. Kahana SY, et al., Rates and correlates of antiretroviral therapy use and virologic suppression among perinatally and behaviorally HIV-infected youth linked to care in the United States. J Acquir Immune Defic Syndr, 2015 68(2): p. 169–77. [PubMed: 25590270]

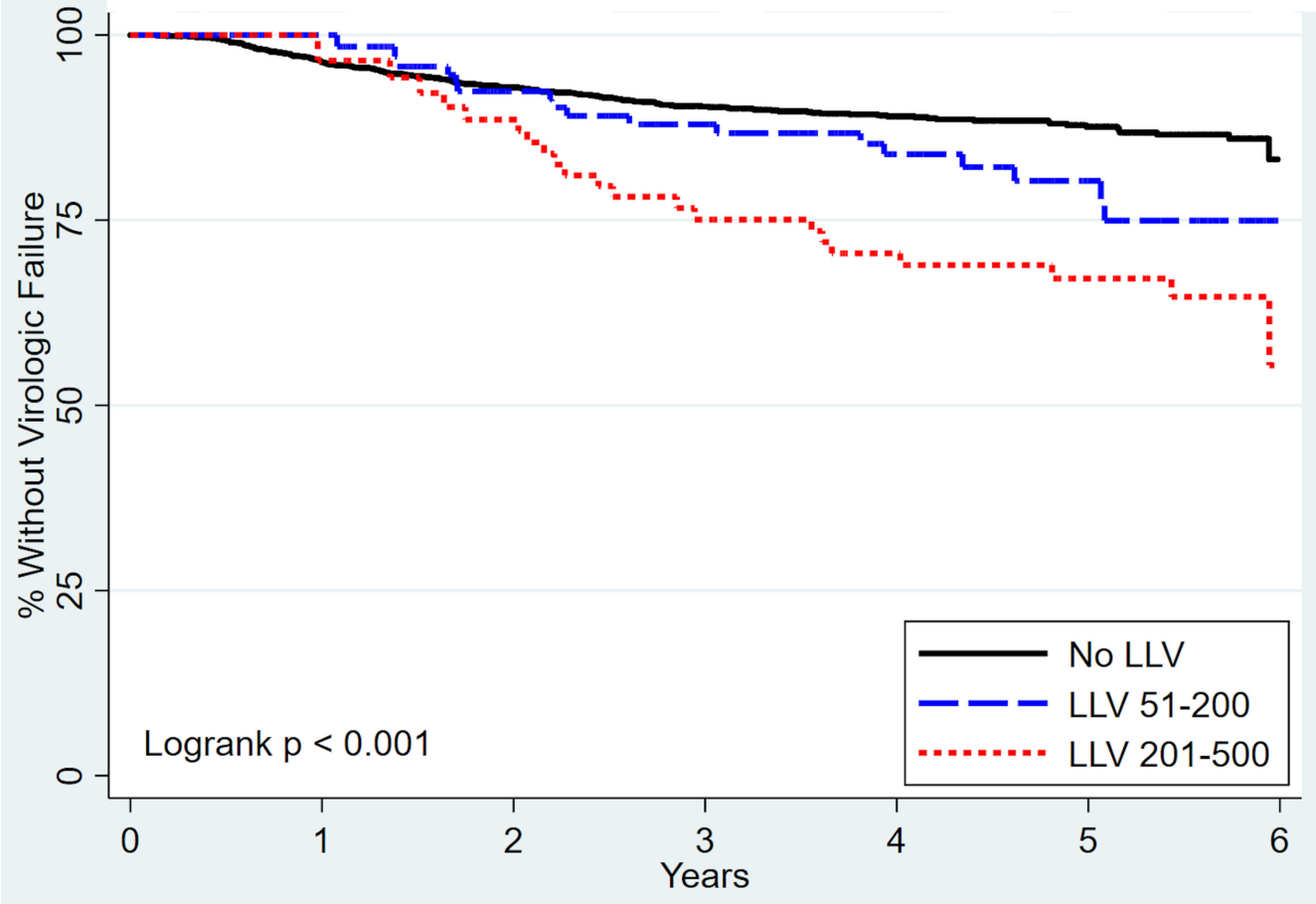

Figure 1:
Failure rates per LLV category

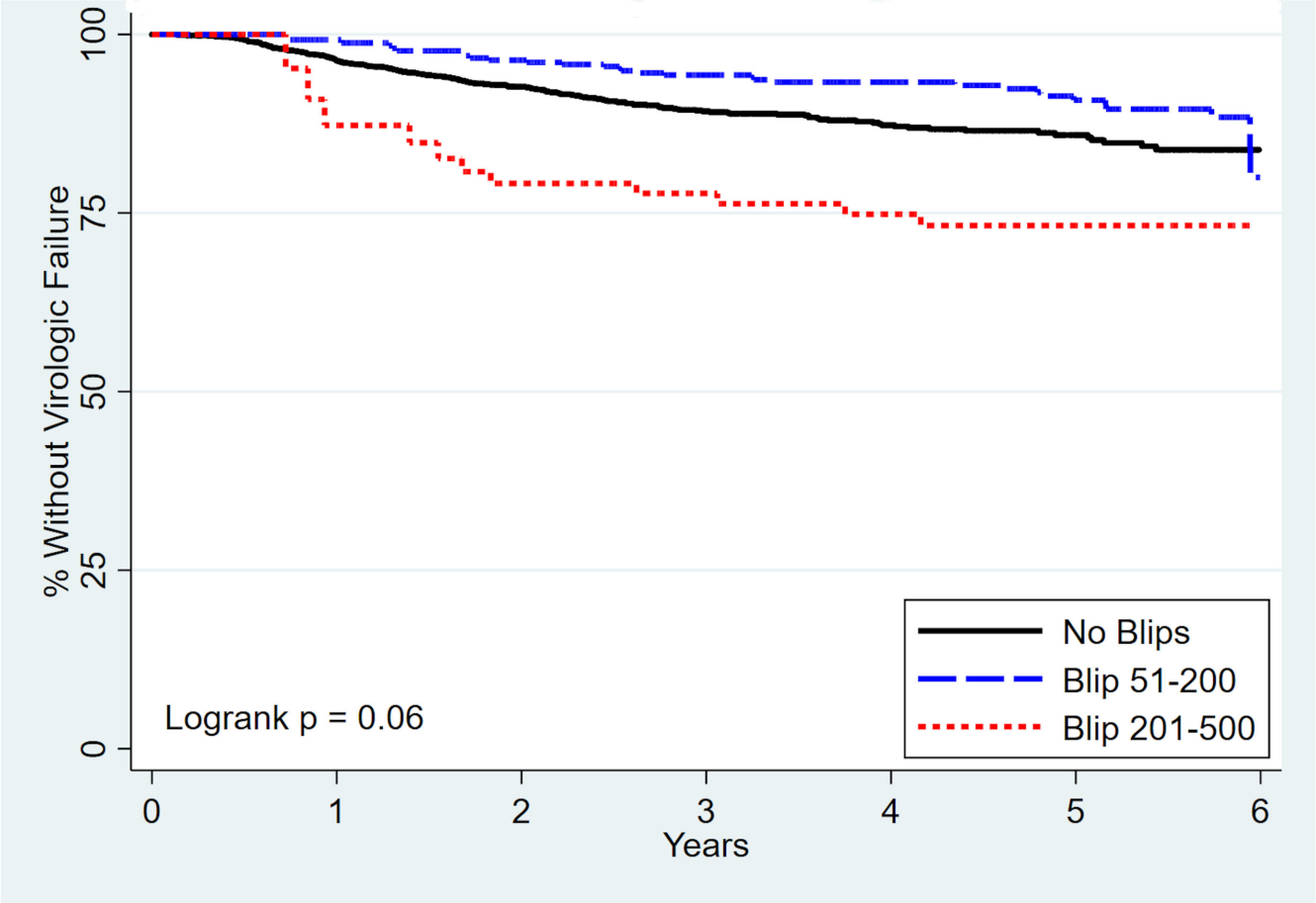

Figure 2:
Failure rates per blip category

Table 1:

Demographic and Clinical Characteristics

Variable	Number (%)
Total	2795
Age (years)	
<24	458 (16.4)
24-39	1157 (41.4)
40-49	697 (24.9)
≥50	483 (17.3)
Sex	
Male	2107 (75.4)
Female	676 (24.2)
Transgender	12 (0.4)
Race/Ethnicity	
White	588 (21.0)
Black	1407 (50.3)
Hispanic	704 (25.2)
Other/Missing	96 (3.4)
HIV Transmission Risk	
MSM	1479 (52.9)
PWID	124 (4.4)
Heterosexual	1067 (38.2)
Other	125 (4.5)
CD4 Count at ART start (cell/ml)[a]	
≥500	1042 (37.3)
200-499	1302 (46.6)
<200	451 (16.1)
HIV-1 RNA at ART start (copies/mL)[a]	
200-1000	180 (6.4)
1001-10K	552 (19.7)
>10K - 100K	1241 (44.4)
>100K	822 (29.4)
Antiretroviral Therapy[b]	
PI	1028 (36.8)
NNRTI	1358 (48.6)
INSTI	477 (17.1)
Year of ART start/restart	
2005-2009	809 (28.9)
2010-2015	1986 (71.1)
History of ART	
ART naïve	2481 (88.8)

Variable	Number (%)
ART experienced	314 (11.2)

[a] CD4 Count and HIV-1 RNA at ART start

[b] ART (anchor drug) at virologic suppression. Anchor drugs are not mutually exclusive. May add up to more that 100%. PI is protease inhibitor. NNRTI is non-nucleoside reverse transcriptase inhibitor. INSTI is integrase inhibitor

Table 2.

Multivariate analysis of factors associated with virologic failure

	HR (95% CI)	aHR (95% CI)
Low Level Viremia (LLV)		
No LLV	1 (Ref.)	1 (Ref.)
LLV 51-200	2.01(1.22,3.30)	1.83(1.10,3.04)
LLV 201-500	3.51(2.22,5.55)	4.26(2.65,6.86)
Blips		
No Blips	1 (Ref.)	1 (Ref.)
Blips 51-200	0.71(0.48,1.06)	0.68(0.45,1.03)
Blips 201-500	1.60(0.86,2.96)	1.71(0.91,3.22)
Age (years)		
<24	1.78(1.19,2.68)	2.98(1.87,4.75)
24-39	1.21(0.84,1.74)	1.72(1.16,2.54)
40-49	1.36(0.93,2.00)	1.61(1.08,2.38)
≥50	1 (Ref.)	1 (Ref.)
Sex		
Female	1 (Ref.)	1 (Ref.)
Male	1.10(0.83,1.45)	1.42(1.01,2.00)
Transgender	2.49(0.78,7.92)	3.60(1.09,11.9)
Race/Ethnicity		
White	1 (Ref.)	1 (Ref.)
Black	1.51 (1.10,2.07)	1.49(1.07,2.08)
Hispanic	0.98(0.67,1.43)	0.91(0.61,1.34)
Other	0.24(0.059,0.99)	0.27(0.066,1.13)
HIV Risk Factor		
MSM	1 (Ref.)	1 (Ref.)
PWID	1.54(0.93,2.55)	1.80(1.05,3.11)
Heterosexual	1.18(0.92,1.50)	1.33(0.97,1.82)
Other	0.95(0.52,1.76)	1.04(0.55,1.95)
CD4 Count (cells/mm^3)[c]		
≥500	1 (Ref.)	1 (Ref.)
200-499	1.20(0.91,1.57)	1.14(0.86,1.50)
<200	1.63(1.17,2.26)	1.60(1.12,2.28)
HIV-1 RNA (copies/mL)[c]		
200-1000	1 (Ref.)	1 (Ref.)
1001-10K	0.48(0.30,0.78)	0.49(0.30,0.80)
>10K-100K	0.59(0.39,0.89)	0.59(0.39,0.90)
>100K	0.77(0.51,1.17)	0.72(0.46,1.11)
Antiretroviral Therapy[d]		
NNRTI	1 (Ref.)	1 (Ref.)

	HR (95% CI)	aHR (95% CI)
PI	1.66(1.31,2.11)	1.61(1.26,2.07)
INSTI	0.94(0.65,1.37)	1.07(0.73,1.56)
ART Start/Restart		
2005-2009	1.42(1.12,1.82)	1.22(0.94,1.59)
2010-2015	1 (Ref.)	1 (Ref.)
History of ART[e]		
ART Naïve	1 (Ref.)	1 (Ref.)
ART Experienced	1.35(0.97,1.87)	1.45(1.02,2.05)
Number of Viral Loads	0.88(0.82,0.94)	0.83(0.77,0.89)

[a] Includes Asian/Pacific Islander, Native American/Alaskan Native, and other/missing/unknown

[b] Includes female-with-female sexual transmission, vertical transmission, blood products, and other/missing/unknown

[c] CD4 Count and HIV-1 RNA at the time of ART start

[d] Antiretroviral therapy documented at time of virologic suppression

[e] Documented at the time of enrollment in the HIVRN cohort