Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

HIV Low-Level Viremia is Not Related to Subsequent Virological Failure Under NNRTI-Based Regimens: A Multicenter Retrospective Study in China

Xinmin Duan[1,2], Xiaojing Song[1], Wei Lyu[1], Yanling Li[1], Jing Tang[3], Wei Cao[1], Yang Han[1], Taisheng Li[1,4]

[1]Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, People's Republic of China; [2]School of Clinical Medicine, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, People's Republic of China; [3]General Office of Biological Products, National Institutes for Food and Drug Control, Beijing, People's Republic of China; [4]State Key Laboratory for Complex, Severe, and Rare Diseases, Peking Union Medical College Hospital, Beijing, People's Republic of China

Correspondence: Yang Han; Taisheng Li, Department of Infectious Diseases, Peking Union Medical College Hospital, No. 1 Shuaifuyuan, Wangfujing, Dongcheng District, Beijing, 100730, People's Republic of China, Email hanyang_pumch@126.com; litsh@263.net

Background: The long-term impact of low-level viremia (LLV), defined as two consecutive viral loads (VL) of <200 copies/mL, on virological failure remains unclear. This study aimed to investigate the association between viremia patterns and virological failure in people living with HIV (PLWH) in China who predominantly received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapies.

Methods: Data from six HIV-infected cohorts in China were analyzed. Adult antiretroviral therapy (ART)-naïve patients were included. Patients were excluded if they received less than 24 weeks of ART, had fewer than two documented VL and CD4+ T cell count, initiated ART during the acute infection stage, or had a follow-up duration of less than 48 weeks. All patients were stratified according to virological suppression (VS), virological blips (VB), or LLV. Cox regression analysis was used to evaluate the association between virological failure and patterns of viremia. Genotypic drug resistance mutations were compared at baseline and during LLV.

Results: Among the 1532 patients, 374 (24.4%) had blips and 166 (10.8%) had LLV. The LLV group had a higher baseline viral load and lower $CD4^+$ T cell count. Approximately 90% of patients received NNRTI-based regimens. In the adjusted Cox regression, neither the blip nor LLV groups demonstrated a significantly increased risk of virological failure compared to the VS group (Blip, adjusted HR = 0.5 [95% CI: 0.2–1.2], $p = 0.116$; LLV, aHR = 0.7 [95% CI: 0.3–1.9], $p = 0.474$). Among the 17 patients who successfully underwent sequencing, three (17.6%) developed new drug resistance mutations, but none experienced virological failure.

Conclusion: Neither blip nor LLV were significantly associated with an increased risk of virological failure in China. Emerging drug resistance mutations in LLV are rare and do not correlate with subsequent virological failures. Further research is needed to understand the clinical significance of these patterns of viremia.

Keywords: HIV, low-level viremia, virological failure, drug resistance mutation

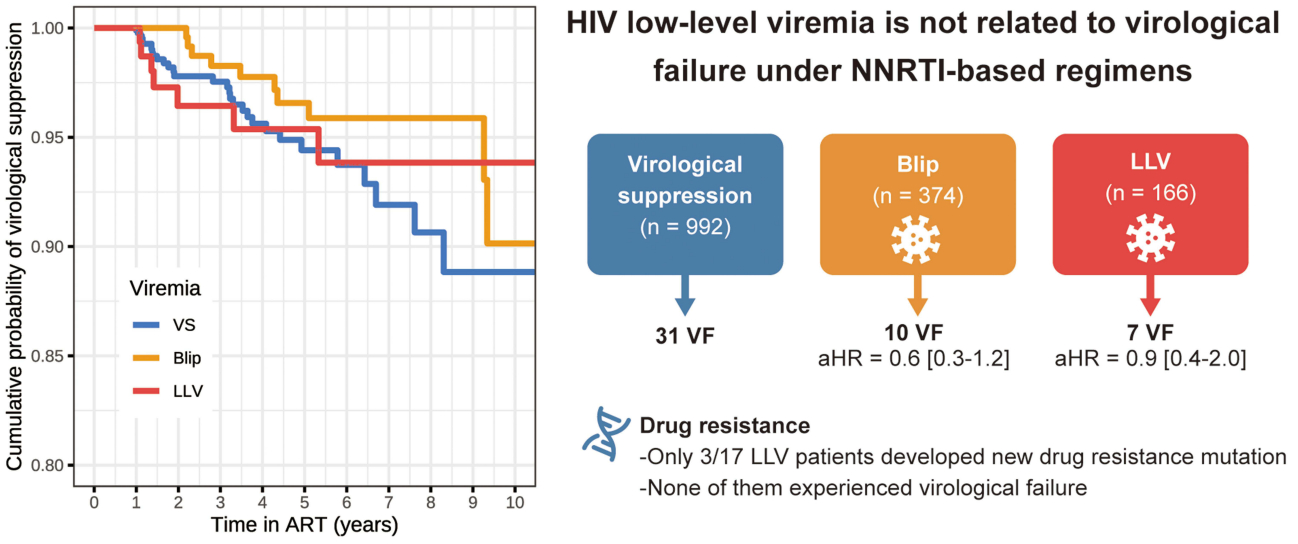
Introduction

The HIV plasma viral load is one of the most important indicators for monitoring responses to antiretroviral therapy (ART).[1–4] After therapy, most patients reach and maintain undetectable viral loads. However, some patients still exhibit persistent and detectable viremia above the lower limit of detection (LLOD) despite the use of potent antiretroviral regimens. This phenomenon is referred to as low-level viremia (LLV). Another type of viremia, characterized by one or more temporary and intermittent increases in the HIV viral load during ART, is known as a blip.

Although the threshold for defining viremia varies between studies owing to different local health policies, numerous studies have confirmed the association between viral loads of 200–1000 copies/mL and clinical progression.[5–7] The

Received: 11 May 2025
Accepted: 14 August 2025
Published: 27 August 2025

Graphical Abstract



updated guidelines define virological failure (VF) as 200 copies/mL or more.[1,2,4] However, the clinical significance of viremia levels of < 200 copies/mL remains controversial. A retrospective analysis of a large European study indicated that both blips and LLV of 50–200 copies/mL during ART are associated with an increased risk of subsequent VF,[8] which aligns with previous evidence[9–15] but contradicts others.[16–19] For example, a Spanish cohort of 5986 patients reported no association between LLV and AIDS events, death, or virological failure.[16] There is also ongoing debate regarding the role of drug resistance mutations (DRMs) in LLV, particularly within the range of the LLOD to 200 copies/mL, where low-level viral replication makes resistance detection challenging.[20] Limited evidence suggests that the rate of DRMs in patients with LLV is comparable to that in virologically suppressed individuals.[8] Moreover, several studies have indicated that the majority of LLV patients do not exhibit resistance mutations to the antiretroviral drugs they are currently receiving, prompting a reevaluation of the relationship between LLV and future virological failure.

Here, we conducted a retrospective analysis of six cohorts of people living with HIV (PLWH) in China, where non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART regimens are predominantly used, to investigate whether blip or LLV is associated with an increased risk of virological and virological failure. Additionally, we retrospectively analyzed drug resistance mutations at baseline and during LLV episodes to assess the role of resistance mutations in the occurrence of LLV.

Methods

Cohorts and Population

This retrospective, multicenter, observational study was based on six HIV cohorts, including five prospective nationwide HIV cohorts from the National Free Antiretroviral Treatment Program of the 13th Five-Year Plan and one clinical HIV cohort of Peking Union Medical College Hospital (PUMCH). Five nationwide HIV cohorts were established from 2008 to 2017 and mainly enrolled adults aged 18 to 65 years who were ART-naïve. All patients received two nucleoside reverse transcriptase inhibitors (NRTIs) + 1NNRTI ART regimen after enrollment and were followed up for a minimum of 2 years with visits scheduled every 24 or 48 weeks, following the cohort design (details in Supplementary Material 1). The PUMCH cohort was an observational cohort that enrolled all outpatients at the HIV center of PUMCH between 2003–2022. Follow-up visits were scheduled every 12–48 weeks based on clinical needs.

We extracted data from the databases of the aforementioned cohorts, including PLWH aged 18–65 years who were ART-naïve at baseline. Patients were excluded if they received less than 24 weeks of ART, had fewer than two documented viral loads and CD4+ T cell count measurements, or initiated ART during the acute infection stage due to the significant difference in VF between immediate and deferred initiation of ART.[21,22] Follow-up began on the date of the first virological suppression or at 48 weeks after ART. Patients were also excluded if their total follow-up duration was less than 48 weeks. Follow-up ended upon virological failure, loss to follow-up for more than four years, or administrative censoring (August 20, 2022).

Definitions

All patients were classified into three groups based on their viremia pattern during follow-up: virological suppression (VS), virological blip (VB), and low-level viremia (LLV). Blips were defined as a single viral load between the LLOD (50 or 20 copies/mL, depending on the local laboratory) and 399 copies/mL, followed by a subsequent viral load below the LLOD. LLV was defined as two or more consecutive viral loads between the LLOD and 200 copies/mL. Persistent viral loads below the LLOD or results reported as "target not detected" were considered virological suppression. Additionally, a single viral load rebound that did not meet the criteria for virological failure was classified as virological suppression if no subsequent measurements were available after administrative censorship. If an individual experienced both blips and LLV during the follow-up, they were classified as having LLV to reflect the highest historical viremia exposure. Virological failure was defined as a single viral load of ≥400 copies/mL or two or more consecutive viral loads between 200 and 399 copies/mL.

HIV-1 Drug Resistance Testing

Cryopreserved plasma samples were thawed and concentrated by ultracentrifugation at 20,000 g for 2h at 4°C. Nucleic acids were extracted from the resulting pellet using a Viral RNA Extraction Kit (Guangzhou Life Technologies, Daan Diagnostics Co., Ltd). Sequences spanning the reverse transcriptase and protease genes were amplified by Sanger sequencing, and the resulting products were analyzed on a 3500XL DX Genetic Analyzer (Applied Biosystems, USA). The experimental procedures were described in detail as previously reported.[20]

HIV-1 drug resistance mutations (DRMs) and resistance profiles were interpreted using the Stanford HIV Drug Resistance Database algorithm (version 9.0). The genotypic sensitivity score (GSS) was calculated for each patient according to the latest interpretation guidelines provided by the Stanford HIV Drug Resistance Database (https://hivdb.stanford.edu/). For each antiretroviral drug, a GSS of 1 was assigned if there was no resistance or only potential low-level resistance. A score of 0.5 was assigned for drugs showing low-level or intermediate resistance and a score of 0 was assigned in cases of high-level resistance. The total GSS for each treatment regimen was obtained by summing the scores of all included drugs.

HIV-1 subtypes and circulating recombinant forms (CRFs) were identified using the COMET tool (http://comet.retrovirology.lu). Phylogenetic analysis was conducted using the MEGA software (version 7.0, USA), and the robustness of the phylogenetic trees was evaluated using bootstrap analysis.

Statistical Analysis

The baseline characteristics of the participants are summarized as means with standard deviations for normally distributed data and as medians with interquartile ranges for non-normally distributed data. Pearson's χ^2-test was used for categorical variables, whereas the Kruskal–Wallis test was used for continuous variables. Survival analyses assessing the risk of virological failure across different viremia categories were conducted using Kaplan-Meier curves and Cox proportional hazards regression models. The adjusted Cox models accounted for potential confounders, including age (years, modeled as a continuous linear variable), sex (male/female), baseline CD4+ T cell count (cells/μL, modeled linearly), and baseline viral load ($\log_{10}$ copies/mL, modeled linearly). Schoenfeld and Martingale residuals were examined to verify the proportional hazards assumption and assess model adequacy. All statistical analyses were performed using R programming language (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).[23]

Results

Baseline Characteristics

Our study database included 2655 participants from five nationwide cohorts and 1394 participants from the PUMCH cohort (Figure 1). Of the 4049 individuals extracted from the database, 1532 (37.8%) met inclusion criteria. Of these, 992 (64.8%), 374 (24.4%), and 166 (10.8%) were categorized into VS, VB, and LLV groups, respectively (Table 1). The majority of participants in all three groups were male, with a median age of 33 years, with no significant differences between the groups. The median baseline CD4+ T cell counts were significantly lower in the VB group (237 cells/μL) and LLV group (218 cells/μL) groups than in the VS group (266 cells/μL; $p < 0.001$). Median baseline viral loads also differed significantly across the three groups: 4.6 $\log_{10}$ copies/mL in the VS group, 4.7 $\log_{10}$ copies/mL in the VB group, and 4.9 $\log_{10}$ copies/mL in the LLV group ($p < 0.001$). Additionally, participants were compared based on whether ART was initiated before or after 2012, as China's National Free Antiretroviral Therapy Program provided only NNRTI-based first-line regimens for PLWH with $CD4^+$ T cell counts < 350 cells/μL prior to 2012. The details regarding the co-infections and initial ART regimens are summarized in Table 1. Most participants had their baseline plasma samples stored for drug resistance testing; however, ART initiation did not necessarily delay the test results.

Association of Virological and Immunological Failure with Viremia

Over a total follow-up period of 5452 person-years, 48 virological failure (VF) events were documented: 31 in the VS group, 10 in the VB (Blip) group, and 7 in the LLV group. The median follow-up duration were 2.3 years. Among participants in the LLV group, the median viral load during the LLV period was 57 copies/mL (interquartile range [IQR]: 38–105), lasting a median of 168 and occurring a median of 591 days after ART initiation. For those in the VB group, the

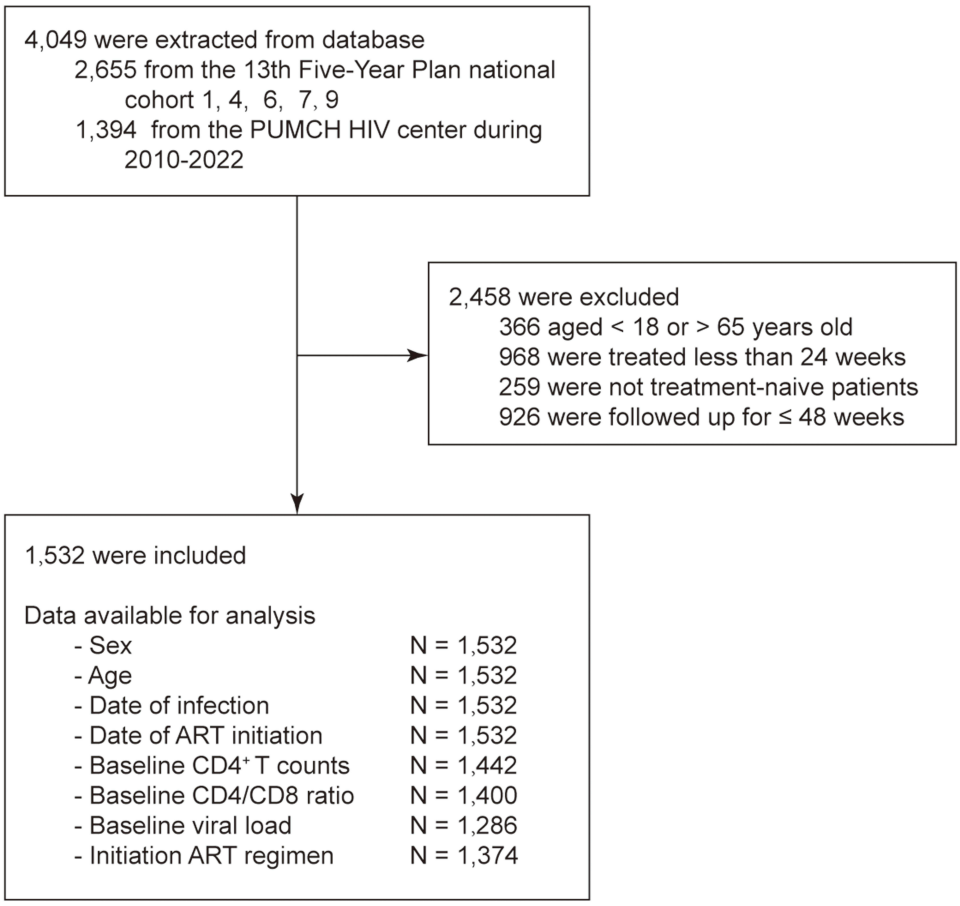


Figure 1 Enrollment flowchart of study population.

Table 1 Clinical Characteristics at Baseline

Groups	VS	VB	LLV	*p*
N	992	374	166	
Gender (%)				
Female	225 (22.7)	52 (13.9)	24 (14.5)	<0.001
Male	767 (77.3)	322 (86.1)	142 (85.5)	
Age (years, median [IQR])	34 [27, 43]	33 [27, 41.75]	34 [28, 45]	0.207
Calendar year of initiation ART (%)				
After 2012	749 (75.5)	275 (73.5)	119 (71.7)	0.497
Before 2012	243 (24.5)	99 (26.5)	47 (28.3)	
Calendar year of infection (%)				
After 2012	631 (63.6)	237 (63.4)	93 (56.0)	0.166
Before 2012	361 (36.4)	137 (36.6)	73 (44.0)	
Route of HIV transmission (%)				
Heterosexual	446 (45.0)	116 (31.0)	57 (34.3)	<0.001
Homosexual	426 (42.9)	214 (57.2)	81 (48.8)	
Blood product	20 (2.0)	12 (3.2)	5 (3.0)	
Other	100 (10.1)	32 (8.6)	23 (13.9)	
Baseline CD4+ T count (cells/ul, median [IQR])	266 [163, 371]	237 [125, 324]	218 [126, 306]	<0.001
Baseline CD4/CD8 ratio (median, [IQR])	0.3 [0.2, 0.4]	0.2 [0.1, 0.4]	0.2 [0.1, 0.3]	<0.001
Baseline viral load (log10 copies/mL, median [IQR])	4.6 [4.2, 5.0]	4.7 [4.4, 5.2]	4.9 [4.5, 5.4]	<0.001
RPR (%)				
Negative	633 (63.8)	214 (57.2)	93 (56.0)	0.067
Positive	186 (18.8)	74 (19.8)	38 (22.9)	
Untested	173 (17.4)	86 (23.0)	35 (21.1)	
HBs-Ag (%)				
Negative	854 (86.1)	323 (86.4)	147 (88.6)	0.785
Positive	107 (10.8)	37 (9.9)	13 (7.8)	
Untested	31 (3.1)	14 (3.7)	6 (3.6)	
HCV-Ab (%)				
Negative	897 (90.4)	342 (91.4)	153 (92.2)	0.588
Positive	63 (6.4)	17 (4.5)	7 (4.2)	
Untested	32 (3.2)	15 (4.0)	6 (3.6)	
Baseline ART regimens (%)				
2NRTI+1NNRTI	812 (91.5)	267 (84.8)	122 (84.1)	<0.001
2NRTI+1PI	17 (1.9)	14 (4.4)	8 (5.5)	
2NRTI+1INSTI	45 (5.1)	18 (5.7)	11 (7.6)	
Other	13 (1.5)	16 (5.1)	4 (2.8)	

Abbreviations: VS, virological suppression; VB, virological blip; LLV, low-level viremia; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; INSTI, integrase inhibitor.

median viral load at the time of blipping was 41 copies/mL [IQR: 27–74 copies/mL], with a median of 498 days after ART initiation.

After adjusting for age and sex, neither the VB group nor the LLV group demonstrated a statistically significant increase in the risk of VF compared to the VS group (Figure 2A; VB, adjusted hazard ratio [aHR] = 0.6, 95% confidence interval [CI]: 0.3–1.2, $p = 0.15$; LLV, aHR = 0.9, 95% CI: 0.4–2.0, $p = 0.760$). This association remained nonsignificant after further adjustment for baseline CD4+ T cell count and baseline viral load (Supplementary Table 1; VB, aHR = 0.5, 95% CI: 0.2–1.2, $p = 0.116$; LLV, aHR = 0.7, 95% CI: 0.3–1.9, $p = 0.474$). After excluding 272 participants with missing baseline data, the number of VF events reduced to 37. Given the potential impact of shorter follow-up intervals on the detection of viremia and VF events, we compared the frequency of follow-up visits among the three groups. The analysis

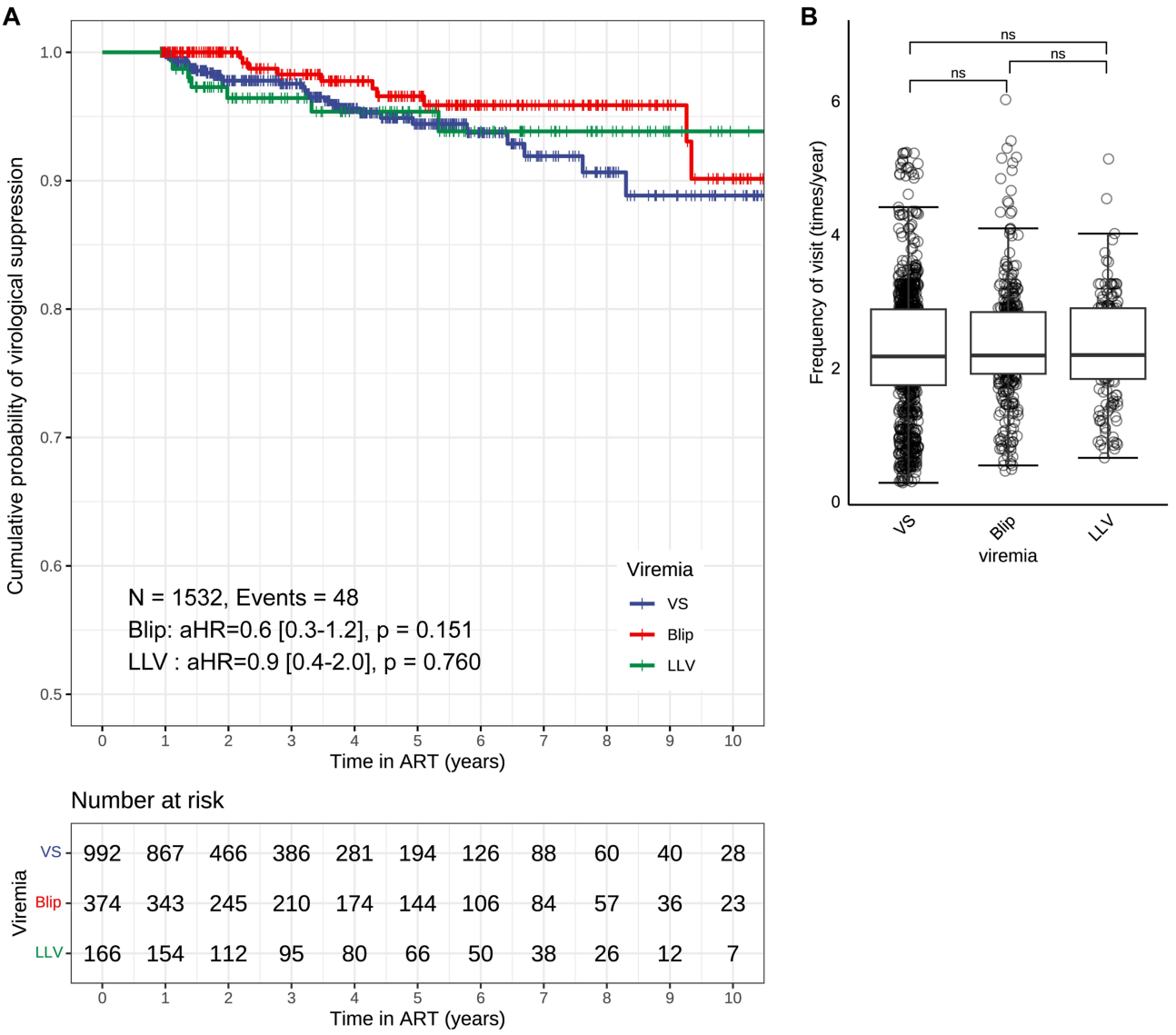


Figure 2 Survival curves of patients in virological failure. (**A**) Survival curves for virological failure defined as one viral load of ≥400 copies/mL or ≥2 consecutive viral loads of 200–399 copies/mL. (**B**) Frequency of visit in VS, blip and LLV groups.
Abbreviations: aHR, adjusted hazard ratio; VS, virological suppression; LLV, low-level viremia.

showed an average annual visit rate of 2.2 visits per patient, with no significant differences between the groups (Figure 2B; $p = 0.436$).

Drug Resistance Mutation in LLV

Among 166 patients with LLV, paired plasma samples from both baseline and LLV episodes were retrieved from 70 individuals from the specimen repository. An ultracentrifugation-based method was used to process plasma collected at both time points. All baseline samples underwent successful PCR amplification and sequencing, whereas only 17 LLV episode specimens yielded detectable DRMs and valid genotypic results, likely due to the low viral load during these episodes. The baseline characteristics of these 17 LLV patients were comparable to those of the remaining LLV cohort (Supplementary Table 2). All patients received an 2NRTIs+1NNRTI initial ART regimen. Among the 17 patients with successful LLV genotyping, 11 (64.7%) were classified as CRF01_AE (Table 2). Notably, three patients (P04, P15, and P17) developed newly emerging DRMs; however, none of them experienced VF. All patients maintained a GSS score of 3 during LLV episodes. By contrast, P11, the only patient who experienced VF, showed no detectable DRMs during LLV.

Table 2 Genotypic Drug Resistance and GSS at Baseline and LLV Episode

Patient ID	Gender	Age (years)	VL (log10 cps/mL)	CD4 (Counts/μL)	VF	Baseline					LLV				
						ART Regimen	RT	PR	GSS	Subtype	ART Regimen	RT	PR	GSS	Subtype
P01	M	41	5.53	230	N	3TC+D4T+NVP	N	N	3	CRF01_AE	3TC+D4T+NVP	N	N	3	CRF01_AE
P02	M	28	5.33	278	N	3TC+D4T+NVP	N	N	3	CRF01_AE	3TC+D4T+NVP	N	N	3	CRF01_AE
P03	M	49	5.06	286	N	3TC+D4T+NVP	N	N	3	CRF07_BC	3TC+AZT+NVP	N	N	3	CRF07_BC
P04	F	36	–	13	N	3TC+D4T+NVP	N	N	3	CRF01_AE	3TC+D4T+NVP	Y181C	N	2	CRF01_AE
P05	M	46	–	194	N	3TC+D4T+NVP	N	N	3	CRF01_AE	3TC+D4T+NVP	N	N	3	CRF01_AE
P06	M	45	–	46	N	3TC+D4T+NVP	V106VI	N	2.5	B	3TC+AZT+NVP	N	N	3	B
P07	M	50	5.26	240	N	3TC+TDF+EFV	N	N	3	B	3TC+TDF+EFV	N	N	3	B
P08	M	32	5.01	214	N	3TC+TDF+EFV	N	N	3	CRF07_BC	3TC+TDF+EFV	N	N	3	B + C
P09	M	29	4.53	191	N	3TC+TDF+EFV	N	N	3	CRF01_AE	3TC+TDF+EFV	N	N	3	CRF01_AE
P10	F	44	4.41	378	N	3TC+TDF+EFV	N	N	3	B	3TC+TDF+EFV	N	N	3	B
P11	M	31	4.65	197	Y	3TC+TDF+EFV	N	N	3	CRF01_AE	3TC+TDF+EFV	N	N	3	CRF01_AE
P12	F	58	5.33	55	N	3TC+AZT+NVP	N	N	3	CRF01_AE	3TC+TDF+LPV/r	N	N	3	CRF01_AE
P13	F	47	5.37	15	N	3TC+AZT+EFV	V75VLM, V106VI	N	2.5	CRF01_AE	3TC+AZT+EFV	N	N	3	CRF01_AE
P14	M	24	4.27	122	N	3TC+TDF+EFV	N	L33F	3	CRF01_AE	3TC+TDF+EFV	N	L33F	3	CRF01_AE
P15	M	25	4.12	216	N	3TC+TDF+EFV	N	N	3	CRF01_AE	3TC+TAF+EFV	N	L100LF	3	CRF01_AE
P16	M	32	4.64	220	N	3TC+TDF+EFV	N	N	3	CRF01_AE	3TC+TDF+EFV	N	N	3	B + C
P17	M	62	4.94	456	N	3TC+D4T+EFV	N	N	3	C	3TC+AZT+EFV¶	N	K103KN	3	CRF07_BC

Notes: ¶ P17 received EFV with a dosage of 400 mg/day. Others received EFV with a dosage of 600mg/day.

Abbreviations: GSS, genotypic sensitivity score; VL, viral load; ART, antiretroviral therapy; RT, reverse transcriptase; PR, protease; VS, virological suppression; VB, virological blip; LLV, low-level viremia; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; INSTI, integrase inhibitor.

https://doi.org/10.2147/IDR.S533871

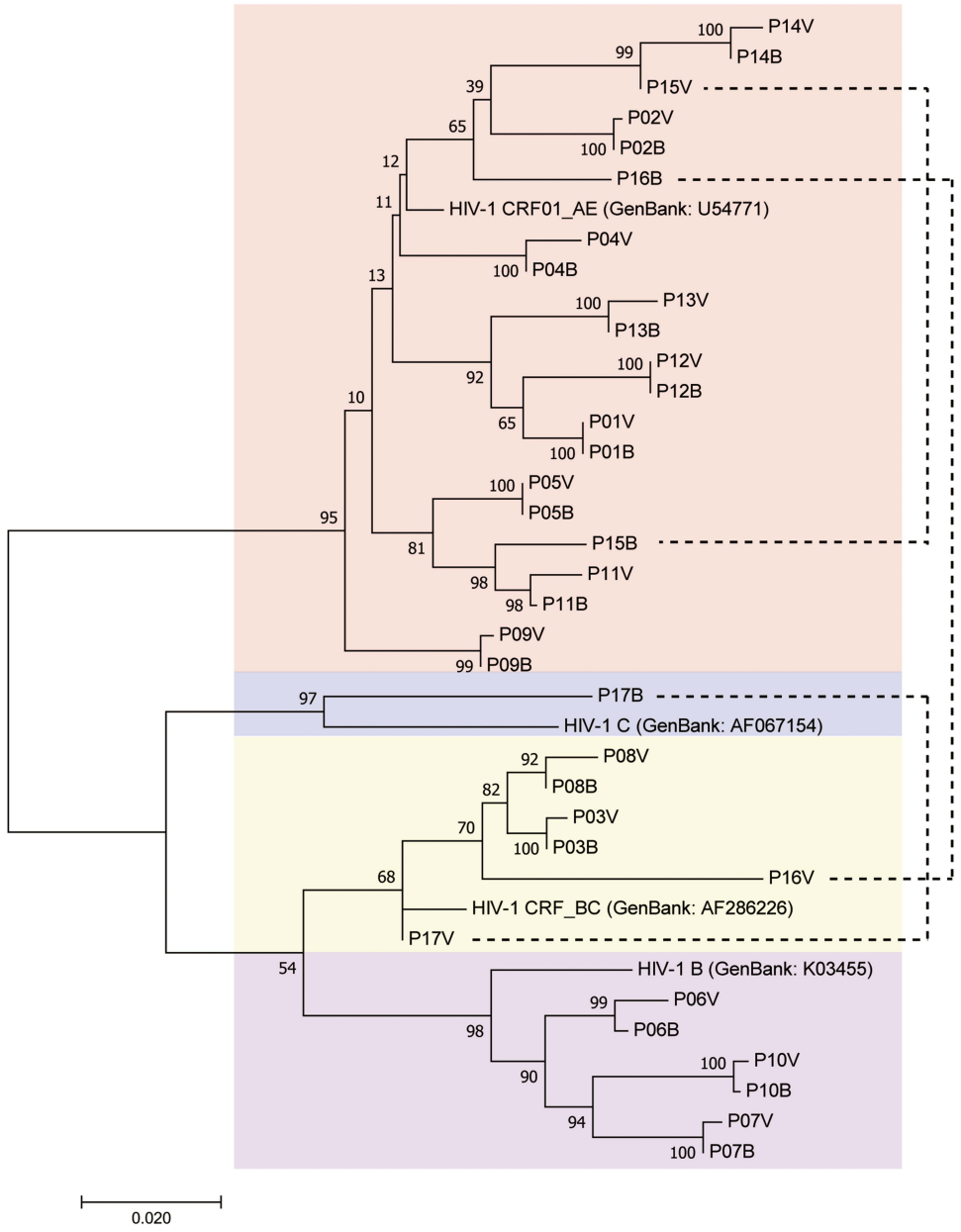


Figure 3 Phylogenetic tree of *pol* sequences. P01B represented *pol* sequence at baseline from patient 01 and P01V represented *pol* sequence at LLV duration from patient 01. The numbers on the line represent genetic distance. The numerical values at the nodes of the phylogenetic tree represent the bootstrap confidence levels following 100 replicates. Four reference sequences were utilized to denote distinct subtypes: CRF01_AE (GenBank: U54771), CRF_BC (GenBank: AF286226), B subtype (GenBank: K03455), and C subtype (GenBank: AF067154). The four color-coded blocks correspond to the subtypes classified based on the *pol* sequences. The dashed lines indicate the three patients with newly emerged drug resistance mutations.

Phylogenetic analysis of 34 sequences from the baseline and LLV episodes revealed close genetic relatedness between the paired sequences in all patients, except for P15, P16, and P17. These results were consistent with the corresponding DRM profiles (Figure 3). Overall, the association between emergent DRMs and VF during LLV remains unclear.

Discussion

In this study, based on data from large-scale, long-term, multicenter cohorts in China, we found no significant association between LLV or blips and increased risk of VF. A retrospective analysis of resistance mutations at the baseline and during LLV episodes in 17 patients revealed no substantial emergence of new DRMs. Moreover, the viral strains in these patients remained susceptible to the ART regimens used during LLV episodes. These findings suggest that in China, a resource-

limited setting where NNRTI-based ART remains the predominant first-line regimen, LLV ranging from the lower limit of detection to 200 copies/mL does not appear to be definitively associated with VF.

Our findings differ from those reported by other centers in developed area,[8–15] some of which included larger sample sizes and longer follow-up periods. However, we believe that our study is the first real-world study in a resource-limited setting, where > 80% of PLHW received NNRTI-based regimens as the initial treatment based on the National Free Antiretroviral Treatment Program. The difference between the initial ART regimens may be attributed to the lack of an association between LLV and VF.

Previous studies have shown that among individuals with baseline viral loads exceeding 5 $\log_{10}$ copies/mL, NNRTI-based regimens take longer to achieve virological suppression and are associated with a higher risk of VF.[24,25] To minimize the misclassification of patients whose VL was still declining as LLV cases, we extended the observation window for LLV onset to 48 weeks after ART initiation rather than 24 weeks. Nevertheless, this adjustment does not fully eliminate a key limitation. Our study found that over 60% of patients with LLV were infected with the CRF01_AE subtype. Several epidemiological studies conducted in China have indicated an association between CRF01_AE and pretreatment resistance to NNRTI-based antiretroviral therapy.[26,27] This suggests that in regions where NNRTI-based regimens are commonly used as first-line treatment, individuals harboring CRF01_AE may experience rapid virological rebound once a secondary resistance mutation develops. Consequently, the transient LLV phase may go undetected under routine monitoring, potentially leading to an underestimation of the true prevalence of LLV.

We observed that patients with blips or LLV in our cohort did not undergo follow-up more frequently than those with sustained virological suppression, which reflects the relatively insufficient frequency of follow-up for patients with LLV. As of 2019, more than 80% of HIV-infected individuals in China had initiated ART with NNRTI-based regimens.[28] For this population, enhancing the frequency of clinical follow-up and reducing the interval between VL monitoring sessions may be particularly beneficial.

It is still controversial whether low-level viremia originates from cyclical viral replication, the release of latent viruses, or intermittent viral escape from sanctuary.[29–38] The emergence of drug-resistant mutations is a potential marker for cyclical viral replication. Despite numerous studies indicating a relationship between LLV and virological failure, ambiguous and inconsistent definitions of LLV have undermined the clarity and interpretability of their findings. Substantial causal evidence between LLV and drug resistance mutations is still lacking,[8,39,40] as echoed in our study. These findings collectively suggest that, although LLV is associated with VF, the emergence of drug-resistant mutations may not be the major driver.

Our findings suggest that maintaining previous ART regimens and intensifying viral load monitoring is currently the best management strategy for LLV, especially in middle- or low-income regions using NNRTI-based ART regimens. Consideration must be given to further drug resistance testing, which is dependent on the baseline viral load of patients, ART regimen employed, and success rate of resistance testing. The necessity of drug resistance testing should be further discussed in regions where drug resistance testing is less accessible and relatively expensive.

This study had some limitations. First, most patients in this study were enrolled from five prospective clinical trials, which limited modifications to ART regimens unless virological failure occurred. Second, our database lacks specific quantitative measures of medication adherence, a known factor associated with the occurrence of LLV. Owing to data limitations, we failed to use all-cause death and AIDS-related events as the direct study outcomes. Finally, not all cohorts were designed to routinely assess drug resistance mutations, except when requested by physicians, regardless of the viremia status. The low success rate of drug resistance mutation detection may have introduced selection bias and limited the representativeness of the findings for the overall LLV population. Notwithstanding these problems, our retrospective study provides a high-quality reference for developing countries to better understand and manage HIV viremia.

Conclusion

This study showed that the occurrence of blips or LLV during routine ART had no clear correlation with virological failure in China, where NNRTI-based ART regimens are mainstream. Emerging drug resistance during LLV is rare and not associated with subsequent virological failure. Maintaining previous ART regimens and intensifying viral load

monitoring are currently the best management strategies for LLV, and further drug resistance testing should be considered based on baseline viral loads and ART regimens.

Abbreviations

ART, antiretroviral therapy; CRF, circulating recombinant forms; DRM, drug resistance mutation; GSS, genotypic sensitivity score; HIV, human immunodeficiency virus; INSTI, integrase inhibitor; LLV, low-level viremia; LLOD, lower limit of detection; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; PUMCH, Peking Union Medical College Hospital; VL, viral loads; VS, virological suppression.

Data Sharing Statement

The datasets analyzed during the current study are not publicly available because the database is still under ongoing analysis, but is available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

All patients provided informed consent. For the five national HIV cohorts, written consent was obtained at enrollment, covering follow-up and future use of anonymized data. In the PUMCH cohort, patients signed a broad informed consent form during outpatient visits, allowing use of blood samples and clinical information for future research. All cohort studies received ethical approval from the PUMCH Ethics Committee at study initiation (Approval Number: JS-1431), as our hospital served as the leading institution for the multicenter research. This retrospective study was also approved by the PUMCH Ethics Committee (Approval Number. I-24PJ2022).

Acknowledgments

During the preparation of this work, the author used ChatGPT-4o to checking manuscript. After using this service, the authors reviewed and edited the content as needed, and took full responsibility for the content of the publication.

Funding

This work was supported by the Special Research Fund for the Central High-level Hospitals of PUMCH (2022-PUMCH -D-008), the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (2021-I2M-1-037), and the National Key Technologies R&D Program for the 13th Five-Year Plan (2017ZX10202101-001).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. *Dep Health Human Services*. 2021.
2. Eropean AIDS Clinical Society. European guidelines for the treatment of people living with HIV (PLWH). 2019.
3. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the international antiviral society-USA panel. *JAMA*. 2020;324(16):1651–1669. doi:10.1001/jama.2020.17025
4. Chinese Center for Disease Control and Prevention. Chinese guidelines for the diagnosis and treatment of HIV/AIDS (2021 Edition). *Infect Dis Immunity*. 2022;2(3):145–167. doi:10.1097/ID9.0000000000000044
5. Hermans LE, Moorhouse M, Carmona S, et al. Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study. *Lancet Infect Dis*. 2018;18(2):188–197. doi:10.1016/S1473-3099(17)30681-3
6. Fleming J, Mathews WC, Rutstein RM, et al. Low-level viremia and virologic failure in persons with HIV infection treated with antiretroviral therapy. *AIDS*. 2019;33(13):2005–2012. doi:10.1097/QAD.0000000000002306
7. Zhang T, Ding H, An M, et al. Factors associated with high-risk low-level viremia leading to virologic failure: 16-year retrospective study of a Chinese antiretroviral therapy cohort. *BMC Infect Dis*. 2020;20(1):147. doi:10.1186/s12879-020-4837-y
8. Elvstam O, Malmborn K, Elén S, et al. Virologic failure following low-level viremia and viral blips during antiretroviral therapy: results from a European multicenter cohort. *Clin Infect Dis*. 2022;76(1):25–31.

9. Elvstam O, Marrone G, Medstrand P, et al. All-cause mortality and serious non-AIDS events in adults with low-level HIV viremia during combination antiretroviral therapy: results from a swedish nationwide observational study. *Clin Infect Dis*. 2020;72:2079–2086.
10. Vandenhende MA, Ingle S, May M, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS*. 2015;29(3):373–383.
11. Navarro J, Caballero E, Curran A, et al. Impact of low-level viraemia on virological failure in HIV-1-infected patients with stable antiretroviral treatment. *Antiviral Ther*. 2016;21(4):345–352. doi:10.3851/IMP3023
12. Joya C, Won SH, Schofield C, et al. Persistent low-level viremia while on antiretroviral therapy is an independent risk factor for virologic failure. *Clin Infect Dis*. 2019;69(12):2145–2152. doi:10.1093/cid/ciz129
13. Lanz C, Meier J, Stöckle M, et al. HIV-1 low-level viremia predicts viral failure in participants on antiretroviral therapy in the Swiss HIV cohort study. *Clin Infect Dis*. 2024;81(1):57–66.
14. Laprise C, de Pokomandy A, Baril J-G, Dufresne S, Trottier H. 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):1489–1496. doi:10.1093/cid/cit529
15. Li Q, Chen M, Zhao H, et al. Persistent low-level viremia is an independent risk factor for virologic failure: a retrospective cohort study in China. *Infect Drug Resist*. 2021;14:4529–4537. doi:10.2147/IDR.S332924
16. Bernal E, Gómez JM, Jarrín I, et al. Low-level viremia is associated with clinical progression in HIV-infected patients receiving antiretroviral treatment. *J Acquired Immune Deficiency Syndromes*. 2018;78(3):329–337. doi:10.1097/QAI.0000000000001678
17. Qin S, Lai J, Zhang H, et al. Predictive factors of viral load high-risk events for virological failure in HIV/AIDS patients receiving long-term antiviral therapy. *BMC Infect Dis*. 2021;21(1):448. doi:10.1186/s12879-021-06162-z
18. Elvstam O, Medstrand P, Yilmaz A, Isberg PE, Gisslén M, Björkman P. Virological failure and all-cause mortality in HIV-positive adults with low-level viremia during antiretroviral treatment. *PLoS One*. 2017;12(7):e0180761. doi:10.1371/journal.pone.0180761
19. Gandhi RT, Deeks SG. Plasma HIV-1 RNA levels during antiretroviral therapy: how low is low enough? *Clin Infect Dis*. 2012;54(5):733–735. doi:10.1093/cid/cir933
20. Li Q, Yu F, Song C, et al. A concentration method for HIV drug resistance testing in low-level viremia samples. *Biomed Res Int*. 2022;2022 (1):2100254. doi:10.1155/2022/2100254
21. Molina JM, Grund B, Gordin F, et al. Which HIV-infected adults with high CD4 T-cell counts benefit most from immediate initiation of antiretroviral therapy? A post-hoc subgroup analysis of the START trial. *Lancet HIV*. 2018;5(4):e172–e180. doi:10.1016/S2352-3018(18)30003-1
22. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373 (9):795–807.
23. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021. Available from: https://www.R-project.org/. Accessed August 22, 2025.
24. Chen S, Han Y, Song XJ, et al. Very high baseline HIV viremia impairs efficacy of non-nucleoside reverse transcriptase inhibitor-based ART: a long-term observation in treatment-naïve patients. *Infect Dis Poverty*. 2020;9(1):75. doi:10.1186/s40249-020-00700-8
25. Burgos J, Moreno-Fornés S, Reyes-Urueña J, et al. Mortality and immunovirological outcomes in patients with advanced HIV disease on their first antiretroviral treatment: differential impact of antiretroviral regimens. *J Antimicrob Chemother*. 2022;78(1):108–116. doi:10.1093/jac/dkac361
26. Wang Z, Zhang M, Zhang R, et al. Diversity of HIV-1 genotypes and high prevalence of pretreatment drug resistance in newly diagnosed HIV-infected patients in Shanghai. *China BMC Infect Dis*. 2019;19(1):313. doi:10.1186/s12879-019-3927-1
27. Xia H, Jin J, Ba H, et al. Genetic diversity and characteristics of drug resistance among treatment-naive people living with HIV in Xi'an, China. *Drug Des Devel Ther*. 2023;17:1485–1494. doi:10.2147/DDDT.S406255
28. Zhao Y, Han MJ, Gan XM, Ma Y, Zhao DC. Characteristics and viral suppression among people living with HIV from the national free antiretroviral therapy programme, 2019. *HIV Med*. 2020;21(11):701–707. doi:10.1111/hiv.13020
29. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science*. 1997;278(5341):1295–1300. doi:10.1126/science.278.5341.1295
30. Pierson T, McArthur J, Siliciano RF. Reservoirs for HIV-1: mechanisms for viral persistence in the presence of antiviral immune responses and antiretroviral therapy. *Ann Rev Immunol*. 2000;18(1):665–708. doi:10.1146/annurev.immunol.18.1.665
31. Perelson AS, Essunger P, Cao Y, et al. Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature*. 1997;387 (6629):188–191. doi:10.1038/387188a0
32. Blankson JN, Persaud D, Siliciano RF. The challenge of viral reservoirs in HIV-1 infection. *Annu Rev Med*. 2002;53(1):557–593. doi:10.1146/annurev.med.53.082901.104024
33. Murray AJ, Kwon KJ, Farber DL, Siliciano RF. The latent reservoir for HIV-1: how immunologic memory and clonal expansion contribute to HIV-1 persistence. *J Immunol*. 2016;197(2):407–417. doi:10.4049/jimmunol.1600343
34. Lorenzo-Redondo R, Fryer HR, Bedford T, et al. Persistent HIV-1 replication maintains the tissue reservoir during therapy. *Nature*. 2016;530 (7588):51–56. doi:10.1038/nature16933
35. Bailey JR, Sedaghat AR, Kieffer T, et al. Residual human immunodeficiency virus type 1 viremia in some patients on antiretroviral therapy is dominated by a small number of invariant clones rarely found in circulating CD4+ T cells. *J Virol*. 2006;80(13):6441–6457. doi:10.1128/JVI.00591-06
36. Kearney MF, Spindler J, Shao W, et al. Lack of detectable HIV-1 molecular evolution during suppressive antiretroviral therapy. *PLoS Pathog*. 2014;10(3):e1004010. doi:10.1371/journal.ppat.1004010
37. Anderson JA, Archin NM, Ince W, et al. Clonal sequences recovered from plasma from patients with residual HIV-1 viremia and on intensified antiretroviral therapy are identical to replicating viral RNAs recovered from circulating resting CD4+ T cells. *J Virol*. 2011;85(10):5220–5223. doi:10.1128/JVI.00284-11
38. Vancoillie L, Hebberecht L, Dauwe K, et al. Longitudinal sequencing of HIV-1 infected patients with low-level viremia for years while on ART shows no indications for genetic evolution of the virus. *Virology*. 2017;510:185–193. doi:10.1016/j.virol.2017.07.010
39. Kao SW, Liu ZH, Wu TS, et al. Prevalence of drug resistance mutations in HIV-infected individuals with low-level viraemia under combination antiretroviral therapy: an observational study in a tertiary hospital in Northern Taiwan, 2017-19. *J Antimicrob Chemother*. 2021;76(3):722–728. doi:10.1093/jac/dkaa510
40. Mackie NE, Phillips AN, Kaye S, Booth C, Geretti AM. Antiretroviral drug resistance in HIV-1-infected patients with low-level viremia. *J Infect Dis*. 2010;201(9):1303–1307. doi:10.1086/651618