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ORIGINAL ARTICLE

Low-level HIV viraemia during antiretroviral therapy: Longitudinal patterns and predictors of viral suppression

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Abstract

Objectives: Our objective was to characterize longitudinal patterns of viraemia and factors associated with viral suppression in people with HIV and low-level viraemia (LLV) during antiretroviral therapy (ART).

Methods: We included people with HIV in the EuResist Integrated Database with LLV following ART initiation after 2005. LLV was defined as two or more consecutive viral load (VL) measurements of 51–199 copies/mL 30–365 days apart after >12 months of ART. Viraemia patterns were analyzed over 24 months. Factors associated with viral suppression at 12 months after LLV episodes were identified using univariable and multivariable logistic regression.

Results: Of 25 113 people with HIV, 2474 (9.9%) had LLV. Among 1387 participants with 24 months of follow-up after LLV, 406 (29%) had persistent suppression, 669 (48%) had transient viraemic episodes, 29 (2%) had persistent LLV, and 283 (20%) had virological failure. Following LLV episodes, the proportion with detectable viraemia declined (p for trend <0.001 and 0.034, in the first and second year, respectively). At 12 months, 68% had undetectable VL, which was associated with suppression before LLV (adjusted odds ratio [aOR] 1.7; 95% confidence interval [CI] 1.2–2.4) and ART modification after LLV (aOR 1.6; 95% CI 1.0–2.4). The following factors were negatively associated with undetectable VL at 12 months: higher VL during LLV (aOR 0.57 per $\log_{10}$ copies/mL; 95% CI 0.37–0.89), injecting drug use (aOR 0.67; 95% CI 0.47–0.96), and regimens with protease inhibitors (aOR 0.65; 95% CI 0.49–0.87) or combined anchor drugs (aOR 0.52; 95% CI 0.32–0.85).

Conclusion: Most people with LLV did not experience sustained viral suppression during 24-month follow-up, supporting the association between LLV and inferior treatment outcome.

KEYWORDS

ART, HIV, low-level viraemia, viral suppression, virological failure

INTRODUCTION

Antiretroviral therapy (ART) leads to viral suppression in most people with HIV. High ART coverage has been achieved in many parts of the world, including Europe, where an estimated 85% of people with HIV received treatment in 2021 [1]. However, there are challenges for long-term virological control, such as insufficient adherence, drug toxicity, and resistance, which may lead to treatment failure. Whereas consecutive viral load (VL) >200 copies/mL during ART is considered virological failure in high-income settings [2–5], a subset of ART recipients also repeatedly show detectable HIV RNA below this threshold, a phenomenon referred to as low-level viraemia (LLV) [6, 7].

LLV (defined as consecutive VLs in the range 50–199 copies/mL) has been reported in 3.5–7.5% of ART recipients in large cohort studies from Europe and North America [8–10]. LLV has been associated with higher pre-ART VL and more advanced immunodeficiency at ART initiation [8, 11] and has been proposed to reflect a larger viral reservoir [11–13]. Release of virions from clonally expanded memory T cells has been demonstrated in some people with LLV <200 copies/mL [14]. On the other hand, LLV can also reflect ongoing viral replication due to suboptimal therapy [15].

Several studies show that LLV is associated with subsequent virological failure [10, 16–19] and adverse clinical events [9]; however, definitions of LLV vary, and the persistence of LLV over time has not been systematically characterized. In this study, we analysed longitudinal patterns of viraemia in people with LLV identified from a European multicentre cohort. We also determined factors associated with achieving viral suppression 12 months after LLV episodes in these individuals.

METHODS

Study setting

We conducted a retrospective study of people with HIV with LLV during ART based on the EuResist Integrated Database (EIDB). The EIDB is a large multinational dataset managed by the EuResist Network with integrated data from different databases, mostly in western Europe [20]. We included data from 2005 to 2021 from the following origin databases: ARCA (Italy), Arevir (Germany), CoRIS and irsiCaixa Foundation (Spain), Karolinska (Sweden), Rega institute (Belgium), Instituto de Higiene e Medicina Tropical (Portugal), and Laboratoire de Rétrovirologie du CRP-Santé (Luxembourg). The EIDB was queried in May 2021, after which we received anonymized data for the investigation.

Definitions and criteria for inclusion

We included people with HIV starting ART after 2005 with VL results available for ≥12 months after therapy initiation. ART was defined as three-drug regimens containing one anchor drug (non-nucleoside/nucleotide reverse transcriptase inhibitor [NNRTI], protease inhibitor [PI], integrase strand transfer inhibitor [INSTI] or entry inhibitor [EI]) or two-drug regimen with dolutegravir and lamivudine. We defined undetectable VL as ≤50 copies/mL. LLV was defined as two or more consecutive VL measurements, 30–365 days apart, of 51–199 copies/mL (also including cases with one of these VLs in the range 200–999 copies/mL) after ≥12 months of therapy. Virological failure was defined as two or more consecutive VLs ≥200 copies/mL more than 30 days apart, or any VL ≥1000 copies/mL, after ≥12 months of therapy.

We excluded people with discordant VL measurements registered on the same date. People with LLV were followed from the date of the repeated VL result, which was considered as the study inclusion date, and were only included once (at their first episode of LLV, if several such episodes occurred during follow-up). Participants without VL data for a period >365 days were considered lost to follow-up from the last registered VL before this period. For analysis of longitudinal viraemia profiles, individuals with <24 months follow-up after study inclusion were excluded.

Statistical analysis

First, to describe longitudinal viraemia patterns in people with LLV, we considered VL results within 24 months after the inclusion date. We categorized the participants into one of four viraemia profiles during this follow-up: persistent viral suppression (only undetectable VLs), persistent low-level viraemia (only VLs in the LLV range), transient viraemic episodes (both detectable and undetectable VLs), or virological failure. We also analysed the persistence of viraemia after LLV as the proportion of all tested participants with detectable viraemia (VL >50 copies/mL) each month after inclusion. We tested for trends in this proportion during the first and second year of follow-up, separately, using the Mann–Kendall test of trend. In addition, to reflect the magnitude of viraemia, we plotted monthly VL percentiles, based on tested individuals, during the 24-month follow-up.

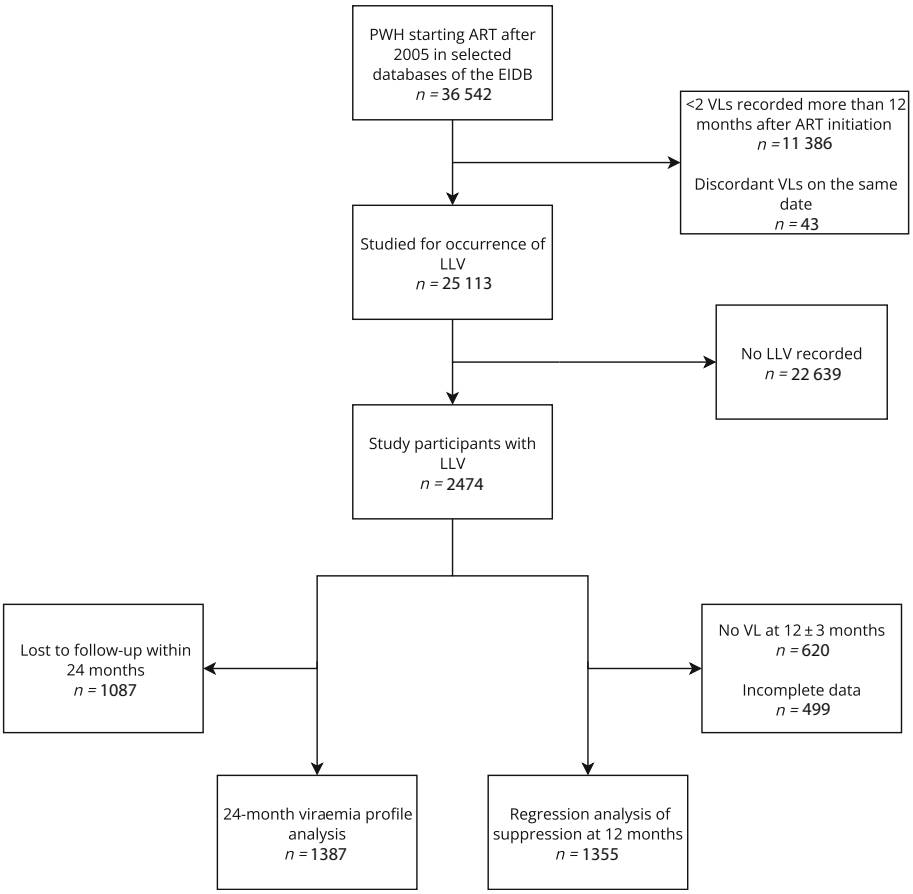

FIGURE 1 Inclusion of study participants and subgroups for specific analyses. ART, antiretroviral therapy; EIDB, EuResist Integrated Database; LLV, low-level viraemia; PWH, people with HIV; VL, viral load.

Second, we analysed factors associated with undetectable VL at 12 months after study inclusion. For this analysis, participants were required to have a registered VL within 3 months of that date. Based on the 12-month VL result, we used univariable and multivariable logistic regression to analyse association with viral suppression for the following factors: age, sex, injecting drug use, viral suppression before LLV (i.e., if the LLV episode reflected viral rebound rather than incomplete response after ART initiation), virological failure before LLV, ART initiation before 2014, pre-ART VL, VL magnitude at the LLV episode, treatment duration, anchor drug of ART regimen at inclusion, and ART modification after LLV. ART modification was defined as a change in non-booster antiretrovirals within 3 months of the inclusion date.

For all continuous variables modelled, we assessed the assumption of linearity to the log odds by graphical method. Based on this, we decided to include pre-ART VL as a binary variable (above/below 100 000 copies/mL) and VL at inclusion after logarithmic transformation. The main regression models were based on complete case analysis, but we also added a sensitivity analysis using missing data categories. We also performed a subanalysis including only participants with LLV strictly in the range 51–199 copies/mL.

RESULTS

Characteristics of study participants

Among 36 542 people with HIV starting ART after 2005, 25 113 had two or more VL measurements ≥12 months after starting ART and were studied for LLV episodes, during a median follow-up time of 5.7 years. In total, 2474 people (9.9%) met the definition of LLV at some point during that period and were included in the study (Figure 1). Of these, 1785 (73%) were male, and the median age at inclusion was 43 years. The median year of ART initiation was 2008. In median, LLV occurred 2.8 years after starting ART and most participants ($n = 2056$, 83%) had one or more undetectable VL before LLV occurred. In addition, 742 (30%) had recorded virological failure before LLV. Most participants ($n = 1556$, 63%) had switched ART regimen at some point before inclusion, and 262 (11%) had ART modification during the first 3 months after inclusion. Compared

TABLE 1 Characteristics of people with low-level viraemia in the EIDB compared with people with no registered low-level viraemia.

Characteristic	LLV $n = 2474$	No LLV $n = 22\,639$
Male sex	1785 (73)	16 605 (76)
Age at ART initiation, years	39 (32–46)	38 (31–46)
Database of origin		
ARCA (Italy)	704 (28)	6072 (27)
CoRIS (Spain)	627 (25)	7242 (32)
irsiCaixa (Spain)	15 (0.60)	228 (1.0)
Arevir (Germany)	431 (17)	3500 (15)
Karolinska (Sweden)	600 (24)	4758 (21)
Rega (Belgium)	45 (1.8)	104 (0.46)
CRP-Santé (Luxembourg)	33 (1.3)	459 (2.0)
IHMT (Portugal)	19 (0.77)	276 (1.2)
Mode of HIV acquisition		
Male-to-male sexual contact	804 (38)	9330 (48)
Heterosexual contact	918 (43)	7682 (39)
Injecting drug use	246 (12)	1742 (9)
Mother–child or blood products	60 (2.8)	172 (0.90)
Other	90 (4.2)	500 (2.6)
Region of origin		
European	1434 (67)	13 829 (72)
African	493 (23)	2951 (15)
The Americas	146 (6.8)	1577 (8.2)
South-East Asian	35 (1.6)	529 (2.8)
Eastern Mediterranean	27 (1.3)	158 (0.82)
Western Pacific	12 (0.56)	155 (0.81)
Subtype of HIV-1		
B	732 (43)	6993 (55)
Non-B	956 (57)	5631 (45)
Pre-ART CD4 count, cells/mm^3	240 (117–362)	312 (192–455)
Pre-ART VL, copies/mL	120 000 (29 000–390 000)	42 000 (8300–150 000)
Pre-ART VL >100 000 copies/mL	1117 (54)	6331 (33)
Transmitted DRMs[a]	288 (23)	2320 (21)
Calendar year of ART initiation	2009 (2007–2011)	2011 (2008–2014)
Starting ART before 2014	2181 (88%)	16 655 (74%)
Anchor drug at ART initiation		
NNRTI	908 (37)	10 806 (48)
PI	1259 (51)	7336 (32)
INSTI	228 (9.2)	4089 (18)
EI/combination	79 (3.2)	401 (1.8)
Follow-up after ART start, years	8.0 (5.0–11)	5.5 (3.2–8.6)
VL frequency, per year	3.1 (2.5–3.9)	2.7 (2.2–3.5)
Characteristics unique for people with LLV		
VL at inclusion, $\log_{10}$ copies/mL	2.0 (1.8–2.2)	
LLV on first ART regimen	918 (37)	

TABLE 1 (Continued)

Characteristic	LLV $n = 2474$	No LLV $n = 22\,639$
Anchor drug at inclusion		
NNRTI	753 (30)	
PI	1172 (47)	
INSTI	387 (16)	
EI/combination	162 (6.6)	
Time on treatment (years)	2.8 (1.7–5.0)	
Undetectable VL before LLV	2056 (83)	
Virological failure before LLV	752 (30)	
DRMs at inclusion[a]	554 (22)	
ART modification following LLV	262 (11)	

Note: Numerals are median (interquartile range) for continuous variables and *n* (%) for categorical variables. Among those with LLV ($n = 2474$), data were missing for the variables sex ($n = 17$), age ($n = 33$), region of origin ($n = 327$), pre-ART VL ($n = 392$), transmission mode ($n = 446$), subtype of HIV-1 ($n = 786$), pre-ART CD4 cell count ($n = 871$), DRMs at inclusion ($n = 901$), and transmitted DRMs ($n = 1203$).

Abbreviations: ART, antiretroviral therapy; DRM, drug-resistance mutation; EI, entry inhibitor; EIDB, EuResist Integrated Database; INSTI, integrase strand transfer inhibitor; LLV, low-level viraemia; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

[a]Presence of non-accessory mutations, as defined in Stanford HIV Drug Resistance Database [34], based on sequencing performed within 10 days of ART initiation (transmitted DRMs) or inclusion (DRMs at inclusion).

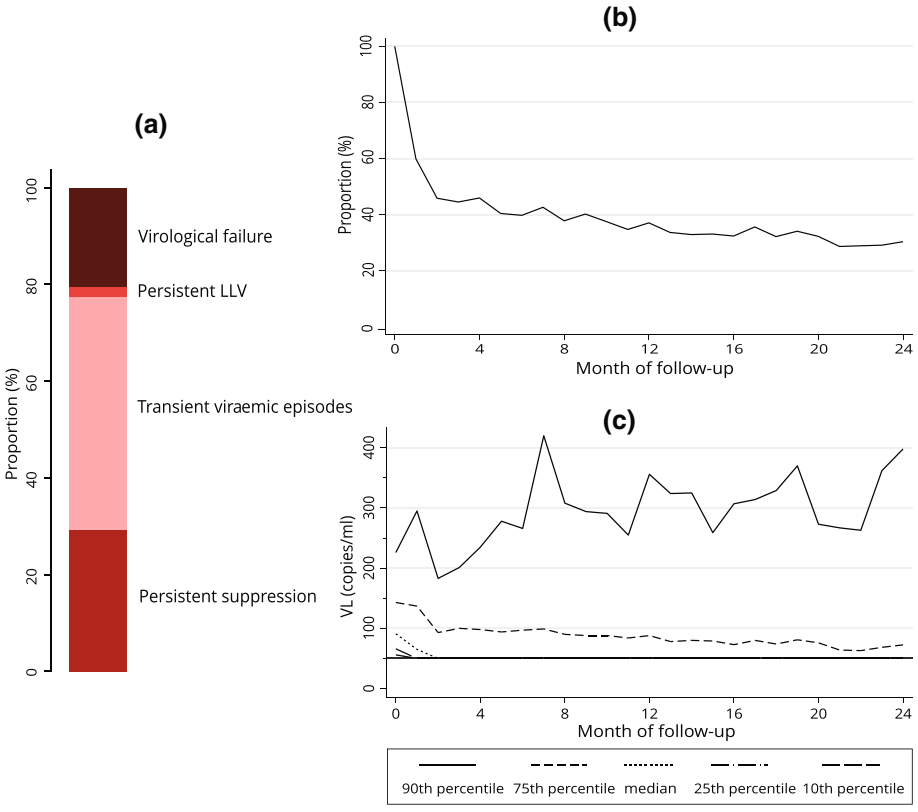

FIGURE 2 Viraemia patterns 24 months after LLV. (a) Proportions of different viraemia profiles during the follow-up period. Only 1387/2474 people with at least 24 months of follow-up were categorized into these profiles. (b) Proportion of tested participants who had recorded viraemia (VL ≥50 copies/mL) each month after inclusion. (c) VL percentiles for tested participants each month after inclusion. Percentiles not shown if ≤50 copies/mL (threshold for undetectable VL per study definition). LLV, low-level viraemia; VL, viral load.

with people without LLV, study participants had higher VL and lower CD4 count before starting ART, and they were more likely to have initiated PI-based or EI/combination-based regimens. They were also more likely to be of African origin and less likely to have acquired HIV through male-to-male sexual contact (Table 1).

Patterns of viraemia 24 months after LLV

Among 2474 participants, 1387 (56%) had follow-up data for ≥24 months and were categorized based on viraemia patterns during the follow-up period (Figure 1). These 1387 participants differed from the overall LLV population in that they started ART at earlier years (median 2008 vs. 2009), with a lower proportion receiving INSTI-based ART (7.9% vs. 16%) (Supplementary Table S1). We found the following distribution of viraemia profiles: persistent viral suppression 406 (29%), transient viraemic episodes 669 (48%), persistent low-level viraemia 29 (2%), and virological failure 283 (20%) (Figure 2a). The median magnitudes of detectable VLs during follow-up was lowest for transient viraemic episodes (89 copies/mL), followed by persistent LLV (113 copies/mL) and virological failure (325 copies/mL). For the subset of 153 (11%) participants who displayed neither undetectable VL nor virological failure before the first LLV episode, the following viraemia profiles were observed: persistent viral suppression 27 (18%), transient viraemic episodes 95 (62%), persistent low-level viraemia 2 (1%), and virological failure 29 (19%).

Furthermore, we analysed the persistence of viraemia for 24 months after the first recorded LLV episode, based on registered VLs for each month of this period. Overall, the proportion of participants with detectable viraemia declined, from 60% to 30% between the first and last month of follow-up (Figure 2b). The declining trend was statistically significant during both the first and the second year after inclusion (p for trend <0.001 and 0.034, respectively). Between the first and last month of this period, the 75th percentile of individual VLs also decreased from 137 to 73 copies/mL (Figure 2c).

Predictors of undetectable VL at 12 months after LLV

For this analysis, 1355/2474 (55%) of the study participants were included (Figure 1). Compared with the overall LLV population, those included in this sub-study differed mainly by initiating ART in earlier calendar years (median 2008 vs. 2009), with a lower frequency of INSTI-based ART (11% vs. 16%) (Supplementary Table S1). At 12 months, 927 (68%) had undetectable VL. In univariable analysis, we found viral suppression before LLV as well as ART regimens based on NNRTI to predict undetectable VL at 12 months, whereas greater VL magnitude during LLV and injecting drug use were predictors of detectable VL at this timepoint. Most of these associations remained statistically significant in multivariable analysis, including viral suppression before LLV (adjusted odds ratio [aOR] 1.7; 95% confidence interval [CI] 1.2–2.4), greater VL magnitude during LLV (aOR 0.57 per $\log_{10}$ copies/mL; 95% CI 0.37–0.89), and injecting drug use (aOR 0.67; 95% CI 0.47–0.96).

However, for ART regimen at inclusion, only PI- and EI/combination-based regimens (and not INSTI-based regimens) remained associated with lower odds of suppression compared with NNRTI-based ART (aOR 0.65; 95% CI 0.49–0.87 and aOR 0.52; 95% CI 0.32–0.85, respectively). Additionally, in multivariable analysis only, ART modification after LLV was associated with undetectable VL at 12 months (aOR 1.6; 95% CI 1.0–2.4) (Table 2).

In a subanalysis of participants with LLV strictly <200 copies/mL at inclusion (excluding 420 participants with one VL in the range 200–999 copies/mL; $n = 935$), ORs were largely similar to those in the main analysis. However, in the adjusted model, associations were no longer statistically significant for the following factors: viral suppression before LLV, injecting drug use, and PI- or EI/combination-based regimens. ART modification after LLV remained associated with undetectable VL at 12 months in the multivariable model (aOR 1.8; 95% CI 1.1–2.9) in this subanalysis (Supplementary Table S2). In sensitivity analysis with missing data categories ($n = 1833$), most results from the main analysis were unchanged; however, the association between injecting drug use and lack of suppression was not statistically significant (Supplementary Table S3).

DISCUSSION

Although most people receiving ART experience sustained viral suppression, it is well recognised that some people have detectable HIV RNA in plasma at low levels, a phenomenon commonly referred to as LLV [6]. LLV was relatively common in our study population, in line with previous data from similar settings [8, 9]. LLV has been associated with adverse virological and clinical outcomes, but the optimal management (as well as the underlying reasons) of LLV remain unclear. In addition, definitions of LLV vary in terms of the range and persistence of viraemia [7]. In this study, based on a large European database of ART recipients, we defined LLV as two or more consecutive VLs 51–199 copies/mL. We observed sustained viral suppression after an LLV episode in only 29% of people with HIV during 24-month follow-up; instead, the majority displayed different patterns of recurrent viraemia. Virological failure occurred in 20% of study participants during the follow-up, consistent with studies showing LLV to be a risk factor for loss of control of viral replication [10, 16–19]. However, persistent LLV was rare in our study population.

TABLE 2 Factors associated with undetectable viral load 12 months after low-level viraemia.

Factor $n = 1355$	Unadjusted model		Adjusted model	
	Odds ratio	95% CI	Odds ratio	95% CI
Male sex	1.1	0.81–1.4	1.1	0.80–1.4
Age (per year)	1.0	0.98–1.0	0.99	0.98–1.0
Injecting drug use	0.65	0.46–0.92	0.67	0.47–0.96
Undetectable VL before LLV	1.9	1.4–2.6	1.7	1.2–2.4
Virological failure before LLV	0.78	0.61–1.0	0.84	0.63–1.1
Pre-ART VL >100 000 copies/mL	0.90	0.71–1.1	0.93	0.73–1.2
VL at inclusion (per $\log_{10}$ copies/mL)	0.58	0.38–0.89	0.57	0.37–0.90
Starting ART before 2014	1.2	0.78–1.9	1.1	0.66–1.9
Time on treatment (per year)	1.0	0.99–1.1	1.0	1.0–1.1
Regimen anchor drug				
NNRTI	1 (ref.)		1 (ref.)	
PI	0.61	0.46–0.80	0.65	0.49–0.87
INSTI	0.65	0.43–0.97	0.67	0.42–1.1
EI/combination	0.48	0.30–0.77	0.52	0.32–0.85
ART modification following LLV	1.5	0.99–2.2	1.6	1.0–2.4[a]

Note: Odds ratios calculated using univariable and multivariable logistic regression, for unadjusted and adjusted model, respectively.
Abbreviations: ART, antiretroviral therapy: CI, confidence interval; EI, entry inhibitor; INSTI, integrase strand transfer inhibitor; LLV, low-level viraemia; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.
[a]Interval does not cross 1.

The degree of viraemia persistence in people with LLV has been shown to have prognostic impact in prior studies, with higher risk of virological failure in people with >25% of VL measurements in the LLV range [10, 17]. Moreover, in a Swedish nationwide register study, association with increased mortality was restricted to individuals with detectable viraemia in >25% of recorded measurements [9]. In our aggregated monthly follow-up after LLV episodes, we observed a general declining trend in the proportion of participants with viraemia, also during the second year, implying that long-term virological control improves after LLV in most people. Since we cannot determine the underlying mechanism behind LLV in this observational study, the reasons for this remain unknown; both enhanced therapeutic inhibition of viral replication (e.g., related to better adherence or therapy switch) [15] and continuous decay of the HIV reservoir during ART may be considered [21].

As mentioned, our study was not designed to analyse mechanisms of LLV and subsequent virological outcomes; however, we did find diverse factors associated with having undetectable VL at 12 months after LLV occurrence. To begin with, this outcome was more common in people who had experienced viral suppression before meeting the criteria for LLV (i.e., rebound viraemia). Based on our study, this is the most common scenario in which LLV occurs (83% of participants). It is also the best characterized, since some studies restrict the definition of LLV to rebound viraemia after previous suppression [8, 16]. It is possible that failure to achieve undetectable VL within 12 months of starting ART represents non-suppressible viraemia, with lower likelihood of a sustained virological response in the short-term.

Intensification of ART has not been shown to impact residual viraemia <50 copies/mL [22, 23]. However, it remains unclear whether therapy modifications can lead to suppression of LLV in the range 50–200 copies/mL. Improved virological outcome was found after ART regimen shift in a randomized trial in Lesotho [24], in which LLV was defined as 100–999 copies/mL. In our population, change of antiretroviral regimen in ART recipients with LLV 50–199 copies/mL was associated with undetectable VL, in contrast to a smaller French study, in which no such association was observed [25]. However, this finding must be interpreted with caution, since ART modifications were not allocated randomly, and indications for switch are unknown. Also, only 11% of participants with LLV had ART modifications, and a majority still achieved undetectable VL at 12 months, which could imply that inadequate regimen is not a main cause of LLV in our setting.

We also identified several factors associated with not experiencing undetectable VL. First, greater viraemia magnitude during LLV was associated with non-suppression at follow-up. Routine VL assays show variability in the LLV range [26]; hence, a higher cut-off level within the range 51–199 copies/mL might be considered to identify people with worse virological outcome. In addition, our main analysis found that individuals with injecting drug use had lower likelihood of achieving viral suppression after LLV, in line with studies showing worse ART outcomes in people who inject drugs [27]. However, this finding was not robust in sensitivity analysis, where missing data were handled through missing data categories. It should also be noted that our data did not distinguish individuals with ongoing injecting drug use at inclusion, which might be an important distinction in terms of odds of suppression [28].

Lastly, the type of ART regimen was associated with viral suppression at 12 months, with lower odds for people receiving PI-based regimens and regimens based on non-conventional combinations of drugs. These associations could be due to channelling bias since selection of PI-based ART may be more common in clinical practice for people with anticipated inferior adherence. However, associations between PI-based regimens and LLV have been reported previously [8, 11], including in a study with randomized regimen allocation [29]; hence, a direct class effect is possible. INSTI-based regimens, which are currently predominant globally [30], and which confer more rapid decline in VL than do other regimens [31], were not associated with different virological outcomes in people with HIV with LLV. However, in our study population, the number of people receiving such regimens was relatively low (11% in the regression model), and further studies are warranted to clarify the impact of INSTI-based ART on viral kinetics in people with LLV.

To our knowledge, this study is the first to describe longitudinal patterns of viraemia in people with LLV, based on a multinational dataset of people with HIV. We acknowledge certain limitations of this study. Detection and classification of viraemia during ART depend on the frequency of VL monitoring [32], and it is plausible that more frequent VL measurements could have resulted in different classification of participants. Additionally, analysis of factors associated with virological outcome at 12 months was based on a single VL measurement to define this outcome; considering the variability in viraemia patterns among people with LLV, it is possible that associations might have been different if several VL measurements during follow-up had been used to define viral suppression. Furthermore, variation in sensitivity of VL assays used for therapy monitoring could result in measurement bias. Although we investigated several factors known to be associated with virological outcomes, we did not have access to certain potentially relevant information such as therapy adherence [33]. However, accurate data on adherence are rarely available in registers. Data on CD4 count and drug-resistance mutations were also missing for many participants and could therefore not be included in this analysis. Finally, changes in ART guidelines during the study period may affect the generalizability of these results to people starting therapy in more recent years.

In conclusion, we found variable patterns of viraemia during longitudinal follow-up of ART recipients with LLV 51–199 copies/mL. Long-term persistence of LLV was rare; however, most people with HIV did not have sustained viral suppression for 2 years after an episode of LLV, supporting the association between LLV and inferior treatment outcome. Our results may help identify which people with HIV have the lowest odds of viral suppression after LLV and who may benefit from intensified follow-up.

AUTHOR CONTRIBUTIONS

S Elén: Data curation, formal analysis, and writing – original draft. P Björkman: Conceptualization, supervision, and writing – review and editing. M Zazzi, M Böhm, E Bernal, and A Sönnerborg: Resources and writing – review and editing. O Elvstam: Conceptualization, data curation, supervision, and writing – review and editing. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

P Björkman has received a grant to his institution from the Swedish Heart-Lung Foundation and from Gilead Sciences, honoraria for acting as speaker and participating in an advisory board from Gilead Sciences, outside the submitted work. M Zazzi has received grants to his institution from Gilead Sciences, MSD, Theratechnologies, and ViiV Healthcare; honoraria for acting as speaker or on advisory boards from Gilead Sciences, GSK, MSD, Theratechnologies, ViiV Healthcare, and Gilead Sciences, unrelated to this research. E Bernal has received grants to his institution from Gilead Sciences, ViiV, MSD, and Janssen and honoraria for acting as speaker or on advisory boards from Gilead Sciences, ViiV, MSD, and Janssen. A Sönnerborg has received grants to his institution from Gilead Sciences, GSK, and ViiV and honoraria for acting as speaker or on advisory boards from Gilead Sciences, GSK, ViiV, AstraZeneca, Merck, and Jansen. O Elvstam has received a grant to his institution from Pfizer and honoraria for acting as speaker from Gilead Sciences, unrelated to this research. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data from the EuResist Integrated Database are available for researchers who meet the criteria for access after application to the steering committee.

ETHICS STATEMENT

This is an observational study of the EuResist Integrated Database, a collection of linked genotypic and clinical information on people living with HIV from several different European centra. Ethical approval for the study was granted by the respective ethical boards of the studied databases. We received anonymized data from the EuResist Integrated Database to conduct our investigation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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