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

Olof Elvstam[1], Gaetano Marrone[2], Patrik Medstrand[1], Carl Johan Treutiger[3], Anders Sönnerborg[4,5], Magnus Gisslén[6,7], Per Björkman[1,8]

1. Department of Translational Medicine, Lund University, Malmö
2. Department of Infectious Diseases and Clinical Virology, Karolinska University Hospital, Stockholm
3. Department of Infectious Diseases/Venhälsan, South General Hospital, Stockholm
4. Department of Infectious Diseases, Karolinska University Hospital, Stockholm
5. Division of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institute, Stockholm
6. Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg
7. Department of Infectious Diseases, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg
8. Department of Infectious Diseases, Skåne University Hospital, Malmö

Corresponding author: Olof Elvstam, Clinical infection medicine, Department of Translational Medicine, Lund University, Ruth Lundskogs gata 3, plan 6, 214 28, Malmö, Sweden; E-mail: olof.elvstam@med.lu.se; Telephone: +46-70-5776503.

Summary: In retrospective analysis of the Swedish HIV cohort, low-level viremia 50–999 copies/mL was independently associated with increased mortality. Participants with HIV RNA 200–999 copies/mL had increased risk of serious non-AIDS events compared with those with virologic suppression.

Abstract

Background

The impact of low levels of HIV RNA (low-level viremia; LLV) during combination antiretroviral therapy (cART) on clinical outcomes is unclear. We explored the associations between LLV and all-cause mortality, AIDS, and serious non-AIDS events (SNAE).

Methods

We grouped individuals starting cART 1996–2017 (identified from the Swedish InfCare HIV register) as virologic suppression (VS; <50 copies/mL), LLV (repeated viral load 50–999 copies/mL), and non-suppressed viremia (NSV; ≥1000 copies/mL). Separately, LLV was subdivided into 50–199 and 200–999 copies/mL (reflecting different definitions of virologic failure). Proportional-hazard models (including sex, age, pre-ART CD4 count and viral load, country of birth, injection drug use, treatment experience and interruptions, and an interaction term between viremia and time) were fitted for the study outcomes.

Results

6,956 participants were followed for a median of 5.7 years. At the end of follow-up, 60% were categorized as VS, 9% as LLV, and 31% as NSV. Compared with VS, LLV was associated with increased mortality (adjusted hazard ratio [aHR] 2.2, 95% confidence interval [CI] 1.3–3.6). This association was also observed for LLV 50–199 copies/mL (aHR 2.2, 95% CI 1.3–3.8), but was not statistically significant for LLV 200–999 copies/mL (aHR 2.1, 95% CI 0.96–4.7). LLV 50–999 copies/mL was not linked to increased risk of AIDS or SNAE, but in subanalysis, LLV 200–999 copies/mL was associated with SNAE (aHR 2.0, 95% CI 1.2–3.6).

Conclusions

In this population-based cohort, LLV during cART was associated with adverse clinical outcomes.

Keywords: HIV, Low-level viremia, Mortality, Serious non-AIDS events, Antiretroviral therapy

Introduction

Although survival continues to improve for people living with human immunodeficiency virus (HIV) who receive combination antiretroviral therapy (cART), their overall mortality remains elevated compared with the general population [1]. With reduced incidence of acquired immunodeficiency syndrome (AIDS), non-communicable diseases represent an increasing proportion of deaths among people living with HIV (PLHIV), in whom several non-communicable diseases are more prevalent than in the general population [2]. The reasons for this increased risk are complex and not fully characterized. Three separate mechanisms can be considered: higher rates of conventional risk factors (such as smoking) [3], antiretroviral drug toxicity [4], and HIV-related chronic immune activation and inflammation [5].

Persistent suppression of viral replication to undetectable levels is achieved in most persons receiving cART. However, in 3–10% of cART recipients, low levels of HIV RNA remain detectable, a phenomenon commonly referred to as low-level viremia (LLV) [6] . Whereas high levels of HIV RNA are strongly associated with death, AIDS, and serious non-AIDS events (SNAE) [7], the impact of LLV on clinical outcomes is debated [8-13]. Most studies demonstrate an increased risk of subsequent virologic failure associated with viral load (VL) ≥200 copies/mL [8, 9]. This is currently the definition of virologic failure in high-income countries [14], whereas repeated VL measurements ≥1000 copies/mL defines failure in WHO guidelines [15]. For LLV 50–199 copies/mL the risk of virologic failure is less apparent [8, 16] and increased risk of adverse clinical events has hitherto not been reported.

We aimed to determine the associations between LLV (defined as 50–999 copies/mL, and subdivided into 50–199 and 200–999 copies/mL) and all-cause mortality, AIDS-defining conditions, and SNAE among adults receiving cART.

Methods

Study population

Participants were identified from the InfCare HIV register, a nationwide observational cohort including >99.9% of PLHIV in Sweden [17]. For this study, individuals who started cART (complete list as supplementary material) January 1996 or later were included if they were ≥15 years old when starting cART, had a personal identity number, and had ≥2 VL results available ≥6 months after cART initiation. The data from InfCare HIV were last updated in June 2017. All data were pseudo-anonymized prior to analysis.

Outcome definitions

Data on overall mortality and causes of death were based on the Swedish Cause of death register, which includes date and cause of death for all deceased persons in Sweden, coded according to the International Classification of Diseases (ICD).

The following conditions were considered as SNAE: cardiovascular diseases, venous thromboembolic disease, pulmonary arterial hypertension, chronic kidney disease, decompensated liver disease, and non-AIDS defining malignancies. Codes for AIDS-defining conditions and SNAE were searched in the Patient register, which covers all in-patient care in Sweden. In addition, the Cause of death register was used to identify SNAE and AIDS that may

have caused death without prior hospitalization. A complete list of ICD codes used for classification is provided as supplementary material.

Study design

Participants were followed from start of cART until reaching the respective clinical outcomes with administrative censoring June 14, 2017. Individuals without VL data for >12 months were considered lost to follow-up. All participants were categorized by their longitudinal viremia profiles ≥6 months after starting cART, using the following definitions: 1) virologic suppression (VS), defined as VL <50 copies/mL (including cases with one or several episodes of a single VL 50–999 copies/mL if preceded and followed by VL <50 copies/mL); 2) LLV 50–999 copies/mL, defined as ≥2 consecutive VLs 50–999 copies/mL, at least 1 month apart; 3) non-suppressed viremia (NSV), defined as ≥1 VL ≥1000 copies/mL. In a separate analysis, LLV was subdivided into LLV 50–199 copies/mL (≥2 consecutive VLs 50–199 copies/mL at least 1 month apart) and LLV 200–999 copies/mL (≥2 consecutive VLs 50–999 copies/mL with ≥1 VL 200–999 copies/mL). The cut-off 50 copies/mL was chosen to account for VL assays used during the first part of the study period. Results obtained with VL assays reported as <500 copies/mL were considered as VS.

Statistical analysis

The study size was determined by the number of cases in Sweden during the study period. Median and interquartile range (IQR) were used to summarize numerical values, frequencies and percentage to summarize categorical variables. Patient characteristics were compared using Pearson's χ^2 and Kruskal-Wallis tests for categorical and continuous variables, respectively.

We fitted three separate Cox proportional-hazard models to determine the associations between viremia category and all-cause mortality, first AIDS-defining condition, and first-ever SNAE. A time-updated measure of viremia was used, so that participants were reclassified if they developed viremia during follow-up. Reclassification was only done to higher viremia strata. The proportional hazard assumption was checked graphically and by Schoenfeldt residuals. Since the proportional hazard assumption was violated for NSV in the model for all-cause mortality (but not in the model for SNAE), we included an interaction term between viremia category and time. In multivariable analysis, the following variables were included to adjust for potential confounders: sex, age (defined as age at outcome event), CD4 count and VL before initiation of any ART, birth in Sweden, injection drug use, exposure to antiretroviral drugs prior to cART, and documented treatment interruptions during follow-up. Since treatment recommendations have changed during the study period and more potent antiretroviral agents have become available, a sensitivity analysis was performed restricted to participants starting cART after January 2005. To test the robustness of the model, we also modelled age using restricted cubic splines. To rule out that a possible effect of viremia on the risk of adverse outcome was dependent on type of cART regimen, we conducted a subanalysis restricted to participants not changing treatment during follow-up, including type of regimen (protease inhibitors [PI] yes/no, non-NRTI [NNRTI] yes/no, integrase strand transfer inhibitors [INSTI] yes/no, and abacavir yes/no) as covariates. In order to assess the importance of viremia persistence among participants with LLV 50–199 copies/mL, we performed a subanalysis separating persons with <25% versus >25% VL measurements >50 copies/mL. Cumulative viral burden was calculated as viremia copy-years using the trapezoidal rule [18].

Missing data were handled using a 'complete-case' approach and the number of missing values is reported for each step of the analysis. Statistical analyses were performed using Stata SE 15 (StataCorp, TX, USA). The study was approved by the Lund regional ethics committee, Sweden (2017/1023). Data linkage was performed by Statistics Sweden and the National Board of Health and Welfare.

Results

Patient characteristics

Of 10,855 PLHIV in the InfCare HIV cohort, 3,899 (36%) were excluded (Fig. 1). The 6,956 included participants had lower overall mortality compared with the entire cohort (7% versus 22%, respectively), and most excluded individuals were diagnosed earlier than included participants (median year of diagnosis 1994 versus 2005).

Demographic and clinical data for participants stratified by their final viremia category are presented in Table 1. The majority were male (63%) with a median age at cART initiation of 37 years. Individuals with LLV during cART had higher median VL before receiving any ART than persons with VS (P<0.001). Compared with other viremia profiles during cART, participants with VS were more likely to be included at a later time-point (P<0.001) and were less likely to initiate cART with PI-based regimens (P<0.001). Furthermore, exposure to antiretroviral drugs prior to cART was lower among individuals with VS compared with those with LLV (P<0.001).

Viremia profiles during cART

During follow-up, 953 participants (14%) met the criteria for LLV 50–999 copies/mL; 521 belonged to the LLV 50–199 copies/mL category at some time point and 508 to LLV 200–999 copies/mL. The following distribution of viremia categories was found at the end of follow-up: 60% VS, 9% LLV 50–999 copies/mL (5% LLV 50–199 and 4% LLV 200–999 copies/mL), and 31% NSV (Fig. 2). Of 5,169 individuals with VS, 1,808 (35%) had ≥1 isolated VL 50–999 copies/mL. The median interval between VL results was 120 days (interquartile range [IQR] 78–175), and participants had a median of 15 (IQR 6–29) VLs during follow-up. Of 143,347 VLs included in the final analysis, 1,094 measurements of undetectable VL (0.8%) in 668 individuals were performed with assays having a lower detection limit of 500 copies/mL.

Counted from 6 months after starting cART, participants with LLV had a median cumulative exposure to viremia, measured as viremia copy-years, of 2.2 (IQR 1.9–2.5) $\log_{10}$ copy×year/mL for LLV 50–199 copies/mL and 2.5 (IQR 2.2–2.8) $\log_{10}$ copy×year/mL for LLV 200–999 copies/mL (Table 1).

All-cause mortality and viremia profiles during cART

During 49,986 person-years of follow-up (median 5.7, maximum 20.7 years), 459 deaths were registered. HIV/AIDS was the most frequently stated cause of death (31%), followed by cardiovascular disease and non-AIDS malignancy (Table 2).

In unadjusted analysis including an interaction term between viremia category and time, participants with LLV had significantly higher mortality compared with those with VS, crude

hazard ratio (HR) for LLV 50–999 copies/mL 2.6 (95% confidence interval [CI] 1.8–3.7). Adjustment for potential confounders resulted in slightly decreased HR for LLV, although with retained statistical significance (Table 3). When analyzing the LLV groups separately, LLV 50–199 copies/mL had an adjusted HR (aHR) of 2.2 (95% CI 1.3–3.8) and LLV 200–999 copies/mL of 2.1 (95% CI 0.96–4.7) (Table 4). The interaction term between viremia category and time had an aHR of 0.86 (95% CI 0.76–0.98), suggesting a decreasing influence of viremia category with increasing follow-up time (Table S1). LLV was also associated with increased all-cause mortality in participants starting cART after January 2005 (*n*=3,186), aHR 3.2 (95% CI 1.5–6.7) for LLV 50–999 copies/mL compared with VS (Table S2). Adjusting for type of cART regimen did not change the impact of LLV on all-cause mortality in a subanalysis of participants not switching treatment (*n*=3,207); likewise, neither PI, NNRTI, INSTI, or abacavir was associated with increased all-cause mortality (Table S3). In a subanalysis of participants in the LLV 50–199 category with regard to proportions of VL measurements ≥50 copies/mL (<25% vs. ≥25%), only those with ≥25% detectable VL had significantly increased mortality, aHR 3.3 (95% CI 1.8–6.4). Besides viremia profiles, the following were significantly associated with all-cause mortality: higher age, male sex, higher pre-ART CD4 cell counts, injection drug use, and treatment interruptions (Table S1).

Incident AIDS and viremia profiles during cART

Ninety-four participants developed at least one AIDS-defining condition during follow-up. Compared with individuals with VS, persons with NSV had increased risk of AIDS, aHR 23.9 (95% CI 6.3–90.1), while this risk was not elevated for participants with LLV (Table 3).

Incident serious non-AIDS events and viremia profiles during cART

In total, 684 participants experienced at least one SNAE during 47,247 person-years of follow-up (median 5.5, maximum 20.7 years). NSV, but not LLV 50–999 copies/mL, was associated with a higher risk of SNAE, aHR 2.8 (95% CI 1.6–5.2) (Table 3). Separate analysis of the two LLV categories showed that only LLV 200–999 copies/mL was associated with SNAE, aHR 2.0 (95% CI 1.2–3.6) (Table 4). This relationship was similar in a sensitivity analysis restricted to participants starting cART after January 2005 (*n*=3,145) (Table S2). Type of cART was not associated with SNAE, and in a subanalysis of individuals without cART regimen switch during follow-up (*n*=3,168), the relationship between LLV 200–999 copies/mL and SNAE was independent of regimen type (Table S3). The most common type of SNAE was cardiovascular disease (*n*=357), followed by non-AIDS malignancy (*n*=197) (Table S4).

Discussion

In this nationwide Swedish cohort, LLV 50–999 copies/mL during cART was independently associated with increased all-cause mortality. Furthermore, persons with LLV in the higher stratum (200–999 copies/mL) had higher risk of SNAE, whereas LLV was not linked to AIDS-defining conditions.

Several factors could explain the discordant results previously reported on associations between LLV and mortality [8-13, 19, 20], such as study design, population characteristics, and duration of follow-up. Furthermore, varying criteria for virologic treatment failure has resulted in different definitions of LLV. Since our study is based on a cohort with follow-up since 1996, we chose to define LLV using an upper limit of 1000 copies/mL (which is also in agreement with

WHO guidelines [15]). To account for the lower threshold of virologic failure currently used in high-income countries, we performed subanalyses for LLV 50–199 and 200–999 copies/mL. Interestingly, the reported association with mortality was statistically significant also for LLV <200 copies/mL. In a separate subanalysis, the association with mortality was restricted to participants with ≥25% of VL ≥50 copies/mL, supporting the existence of a relationship between persistent LLV and mortality.

Our finding of increased mortality for persons with LLV is in agreement with a Spanish study that observed a higher risk for the composite endpoint all-cause mortality/AIDS for persons with LLV 200–499 copies/mL [10]. In contrast, the Antiretroviral Therapy Cohort Collaboration study did not observe higher risk of death for either LLV 50–199 or 200–499 copies/mL [8], similar to three smaller studies [12, 13, 20]. Compared with all prior studies, our cohort had longer follow-up, increasing the chance of detecting a difference in mortality. The proportion of participants meeting criteria for LLV was comparatively high (7.5% versus 3.5% [8] and 4.0% [10] for LLV 50–199 copies/mL). Since our participants were identified from a nationwide cohort, selection bias is likely to be low.

The impact of viremia could also be estimated by measuring cumulative exposure defined as viremia copy-years [18]. This variable has been associated with both elevated mortality [21] and SNAE [22]. Different methods have been used to calculate cumulative viremia. While most studies have used the linear scale, Sempa *et al.* suggested that the logarithmic scale is more predictive [23]. To our knowledge, only one study has focused specifically on LLV and mortality using viremia copy-years, with no association observed [20]. An important caveat of the copy-

year variable is the high dependence on timing and frequency of sampling; consequently, levels of viremia copy-years can usually not be compared between studies [24]. For these reasons, and since our aim was to explore the effects of LLV specifically, we chose a time-updated classification based on different cut-offs used for definition of virologic failure (1000 and 200 copies/mL) instead of copy-years to assess viremia exposure.

Previous studies have not found associations between LLV and SNAE [10, 11]. Compared with these, we used a wider definition of SNAE, including venous thromboembolic disease and pulmonary arterial hypertension, conditions for which HIV is a known risk factor [25, 26]. Like the analysis of mortality, the longer follow-up period in our study could increase the chance of revealing an association between LLV and SNAE.

LLV during ART can be due to separate mechanisms: release of viral particles from latently infected cells and active replication [27]. Interestingly, different profiles of inflammatory cytokines have been associated with two distinct HIV *env* sequence patterns, monotypic and diverse LLV [28]. Biological pathways might therefore explain an association between LLV and adverse clinical outcomes. For example, the role of chronic inflammation in the pathogenesis of atherosclerosis may be of particular importance in PLHIV [5]. Based on trials of structured treatment interruptions, HIV replication has been associated with inflammation as well as increased risk of SNAE and death [7, 29]. Moreover, several studies have found higher levels of blood biomarkers reflecting cellular immune activation [30], inflammation, innate immunity, coagulation, and cardiovascular risk [31-33] in ART recipients with LLV compared with those with undetectable viremia.

The potential relation between non-AIDS morbidity and antiretroviral drugs has been extensively studied. Specifically, an increased risk of cardiovascular events has been reported for regimens including PIs and for recent exposure to abacavir [4]. Due to the long follow-up in our cohort, many participants changed regimens, and the specific impact of certain drugs on long-term outcomes is therefore difficult to elucidate. Nonetheless, in a subanalysis of participants not switching treatment, the effects of LLV on the risk of mortality and SNAE were independent of cART regimen.

If individuals with LLV have increased long-term risk of adverse clinical outcomes, could ART modification abrogate this? Several studies have indicated that residual viremia measured with ultra-sensitive assays is not affected by treatment intensification [34, 35]. In persons with LLV, however, resistance-guided treatment modification has led to better virologic control [36, 37], but whether this also results in improved clinical outcomes is unknown. In our cohort, relatively low proportions of participants with detectable viremia switched regimens, both for LLV and NSV. This was due to either subsequent loss to follow-up or resuppression without regimen modification (data not shown).

Our study has certain limitations. Firstly, the classification of viremia is based on VL measurements from clinical care, with median interval between samples of 120 days; thus, shorter episodes of LLV might have been missed. A substantial proportion (35%) of participants categorized as VS had isolated elevated VL results. Whereas these probably represent blips, some of these could be transient episodes of LLV. Secondly, residual confounding could occur if

unmeasured factors are associated with both LLV and the study outcomes. We have controlled for potential confounders but lack information on some factors associated with death and morbidity in PLHIV, such as smoking and socio-economic background [3, 38]. Still, to our knowledge, these conditions have not been linked to LLV. Thirdly, data originating from the initial years of our study may have limited relevance in relation to currently recommended regimens. Nevertheless, our findings are robust in sensitivity analysis restricted to participants starting cART 2005 and later. Lastly, ICD classification has been reported to overestimate HIV as underlying cause of death among PLHIV [39], which explains why the number of HIV-related deaths exceeds the number of AIDS diagnoses.

In conclusion, we observed increased mortality for participants with LLV 50–999 copies/mL during cART, which was also found in the subset of persons with LLV 50–199 copies/mL. In addition, individuals with LLV 200–999 copies/mL had an elevated risk of SNAE compared with those with virologic suppression. These findings add to mounting evidence that LLV is associated with worse clinical outcomes.

Notes

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Potential conflicts of interest

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Table 1. Characteristics of study participants identified from the Swedish InfCare HIV cohort. Participants are grouped by the last viremia category they belonged to during follow-up.

	Overall	Virologic suppression	LLV 50–199 copies/mL	LLV 200–999 copies/mL	Non-suppressed viremia	
	n=6,956	*n*=4,177 (60%)	*n*=339 (5%)	*n*=258 (4%)	*n*=2,182 (31%)	*P*-value[a]
Males	4,396 (63%)	2,649 (63%)	244 (72%)	179 (69%)	1,324 (61%)	<0.001
Age at start of cART (years)	37 (31–45)	38 (31–46)	39 (33–47)	39 (33–49)	36 (31–44)	<0.001
Median year of HIV diagnosis	2005	2008	2006	2003	1996	<0.001
Median year of start of cART	2007	2010	2007	2005	1999	<0.001

Country of birth					<0.001
Sweden	2,643 (38%)	1,482 (35%)	151 (45%)	106 (41%)	904 (41%)
Outside Sweden	4,152 (60%)	2,582 (62%)	182 (54%)	149 (58%)	1239 (57%)
Unknown	5 (0%)	1 (0%)	0	0	4 (0%)
Country of birth missing	156 (2%)	112 (3%)	6 (2%)	3 (1%)	35 (2%)
Transmission group					<0.001
Heterosexual	3,566 (51%)	2,189 (52%)	153 (45%)	133 (52%)	1,091 (50%)
Homo-/bisexual	2,332 (34%)	1,417 (34%)	129 (38%)	83 (32%)	703 (32%)
Injection drug use	396 (6%)	156 (4%)	20 (6%)	15 (6%)	205 (9%)
Other[b]	531 (8%)	310 (7%)	33 (10%)	26 (10%)	162 (7%)

Transmission group missing	131 (2%)	105 (3%)	4 (1%)	1 (0%)	21 (1%)	
VL before ART initiation[c] (copies/mL)	73,000 (18,050–242,000) [28% missing]	58,400 (15,150–196,000) [21% missing]	230,000 (66,000–750,000) [21% missing]	194,500 (55,600–541,000) [31% missing]	80,000 (20,900–246,000) [43% missing]	<0.001
CD4 cell count before ART initiation[c] (cells/mm^3)	240 (140–360) [18% missing]	252 (146–370) [17% missing]	189 (90–290) [13% missing]	200 (90–280) [17% missing]	240 (150–350) [19% missing]	<0.001
Ever HCV positive	651 (9%)	308 (7%)	38 (11%)	28 (11%)	277 (13%)	<0.001
HCV status missing	975 (14%)	589 (14%)	42 (12%)	35 (14%)	309 (14%)	
Ever HBsAg positive	243 (3%)	137 (3%)	11 (3%)	10 (4%)	85 (4%)	0.78

HBV status missing	3,695 (53%)	2,220 (53%)	174 (51%)	144 (56%)	1,157 (53%)	
Type of first cART regimen						
Including PI	4,040 (58%)	1,874 (45%)	220 (65%)	169 (66%)	1,777 (81%)	<0.001
Including NNRTI	2,475 (36%)	1,874 (45%)	102 (30%)	84 (33%)	415 (19%)	<0.001
Including INSTI	588 (8%)	523 (13%)	26 (8%)	12 (5%)	27 (1%)	<0.001
Including abacavir	1,414 (20%)	1,097 (26%)	58 (17%)	44 (17%)	215 (10%)	<0.001
Switched treatment during follow-up	2,368 (34%)	600 (14%)	87 (26%)	75 (29%)	1,606 (74%)	<0.001
Treatment experienced at start of cART	1,331 (19%)	337 (8%)	63 (19%)	63 (24%)	868 (40%)	<0.001

Total viremia copy-years from start to end of follow-up (log_{10} copy×y/mL)	2.4 (1.6–4.0)	1.6 (1.1–2.1)	2.2 (1.9–2.5)	2.5 (2.2–2.8)	4.4 (3.6–5.1)	<0.001

Values are *n* (%) or median (interquartile range).

[a] *P*-values are the results of Kruskal-Wallis tests for continuous variables and Pearson's χ^2 tests for categorical variables.

[b] Including blood products, mother-to-child, and unknown.

[c] Refers to any antiretroviral treatment before start of cART.

Abbreviations: LLV, low-level viremia; cART, combination antiretroviral therapy; WHO, World Health Organization; VL, viral load; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor.

Table 2. Cause of death by viremia category at time of death.

	Overall *n*=459	Virologic suppression *n*=142 (31%)	LLV 50–199 copies/mL *n*=31 (7%)	LLV 200–999 copies/mL *n*=16 (3%)	Non-suppressed viremia *n*=270 (59%)
Underlying cause of death					
HIV/AIDS	144 (31%)	39 (27%)	2 (6%)	5 (31%)	98 (36%)
Cardiovascular death	84 (18%)	32 (23%)	8 (26%)	3 (19%)	41 (15%)
Non-AIDS malignancy	84 (18%)	25 (18%)	7 (23%)	1 (6%)	51 (19%)
Violent/accidental death	63 (14%)	19 (13%)	7 (23%)	3 (19%)	34 (13%)
Other conditions[a]	59 (13%)	15 (11%)	4 (13%)	3 (19%)	37 (14%)
Unknown	15 (3%)	7 (5%)	3 (10%)	0	5 (2%)
Cause of death missing	10 (2%)	5 (4%)	0	1 (6%)	4 (1%)

Results are presented as *n* (%).

Abbreviations: LLV, low-level viremia.

[a] Liver diseases (*n*=15), pulmonary diseases (*n*=12), non-AIDS infections (*n*=12), gastro-intestinal diseases (*n*=6), neurological conditions (*n*=5), diabetes mellitus (*n*=4), rheumatological conditions (*n*=2), urological conditions (*n*=1), hyperlipidemia (*n*=1), and bipolar disorder (*n*=1).

Table 3. Cox regression models for all-cause mortality, AIDS, and serious non-AIDS events by viremia category.

	Unadjusted model	Unadjusted model with time-interaction	Fully adjusted model[a]
	n=6,956	*n*=6,956	*n*=4,541
All-cause mortality			
Virologic suppression	1 (Ref.)	1 (Ref.)	1 (Ref.)
LLV 50–999 copies/mL	1.7 (1.2–2.4)	2.6 (1.8–3.7)	2.2 (1.3–3.6)
Non-suppressed viremia	2.5 (2.0–3.1)	6.6 (4.2–10.6)	7.7 (3.8–15.6)
AIDS	*n*=6,823	*n*=6,823	*n*=4,440
Virologic suppression	1 (Ref.)	1 (Ref.)	1 (Ref.)
LLV 50–999 copies/mL	0.45 (0.11–1.9)	0.84 (0.19–3.7)	no event
Non-suppressed viremia	4.6 (2.9–7.3)	20.1 (8.3–48.6)	23.9 (6.3–90.1)
Serious non-AIDS events	*n*=6,884	*n*=6,884	*n*=4,486
Virologic suppression	1 (Ref.)	1 (Ref.)	1 (Ref.)
LLV 50–999 copies/mL	1.2 (0.92–1.6)	1.6 (1.2–2.2)	1.2 (0.78–1.8)

Non-suppressed viremia	1.5 (1.3–1.8)	2.9 (1.9–4.3)	2.8 (1.6–5.2)

Values are hazard ratio with 95% confidence interval.

Abbreviations: LLV, low-level viremia; VL, viral load; ART, antiretroviral therapy.

[a] Adjusted for age, sex, CD4 count and VL before start of ART, injection drug use, born in Sweden, treatment experience, and treatment interruptions. Including an interaction term between viremia category and time.

Table 4. Cox regression models for all-cause mortality and serious non-AIDS events by viremia category. LLV subdivided into 50–199 copies/mL and 200–999 copies/mL.

	Unadjusted model	Unadjusted model with time-interaction	Fully adjusted model[a]
	n=6,956	*n*=6,956	*n*=4,541
All-cause mortality			
Virologic suppression	1 (Ref.)	1 (Ref.)	1 (Ref.)
LLV 50–199 copies/mL	2.3 (1.5–3.3)	2.9 (1.9–4.3)	2.2 (1.3–3.8)
LLV 200–999 copies/mL	1.2 (0.68–2.0)	2.0 (1.1–3.7)	2.1 (0.96–4.7)
Non-suppressed viremia	2.5 (2.0–3.1)	6.3 (3.9–10.1)	7.7 (3.7–15.8)
Serious non-AIDS events	*n*=6,884	*n*=6,884	*n*=4,486
Virologic suppression	1 (Ref.)	1 (Ref.)	1 (Ref.)
LLV 50–199 copies/mL	1.1 (0.76–1.6)	1.3 (0.91–2.0)	0.86 (0.50–1.5)
LLV 200–999 copies/mL	1.3 (0.92–1.9)	2.0 (1.3–3.1)	2.0 (1.2–3.6)
Non-suppressed viremia	1.5 (1.3–1.8)	3.1 (2.1–4.7)	3.3 (1.8–6.0)

Values are hazard ratio with 95% confidence interval.

Abbreviations: LLV, low-level viremia; VL, viral load; ART, antiretroviral therapy.

[a] Adjusted for age, sex, CD4 count and VL before start of ART, injection drug use, born in Sweden, treatment experience, and treatment interruptions. Including an interaction term between viremia category and time.

Figure legends

Figure 1. Exclusion flow diagram. The number of deaths in the group included in the final analysis only counts those that died during follow-up (no loss to follow-up).

Abbreviations: PLHIV, people living with HIV; VL, viral load; cART, combination antiretroviral therapy.

Figure 2. Flow of patients through viremia categories during follow-up. The percentages represent the proportion of participants that were reclassified to the respective category. Reclassification was only possible to higher viremia strata.

Abbreviations: LLV, low-level viremia.

Figure 1

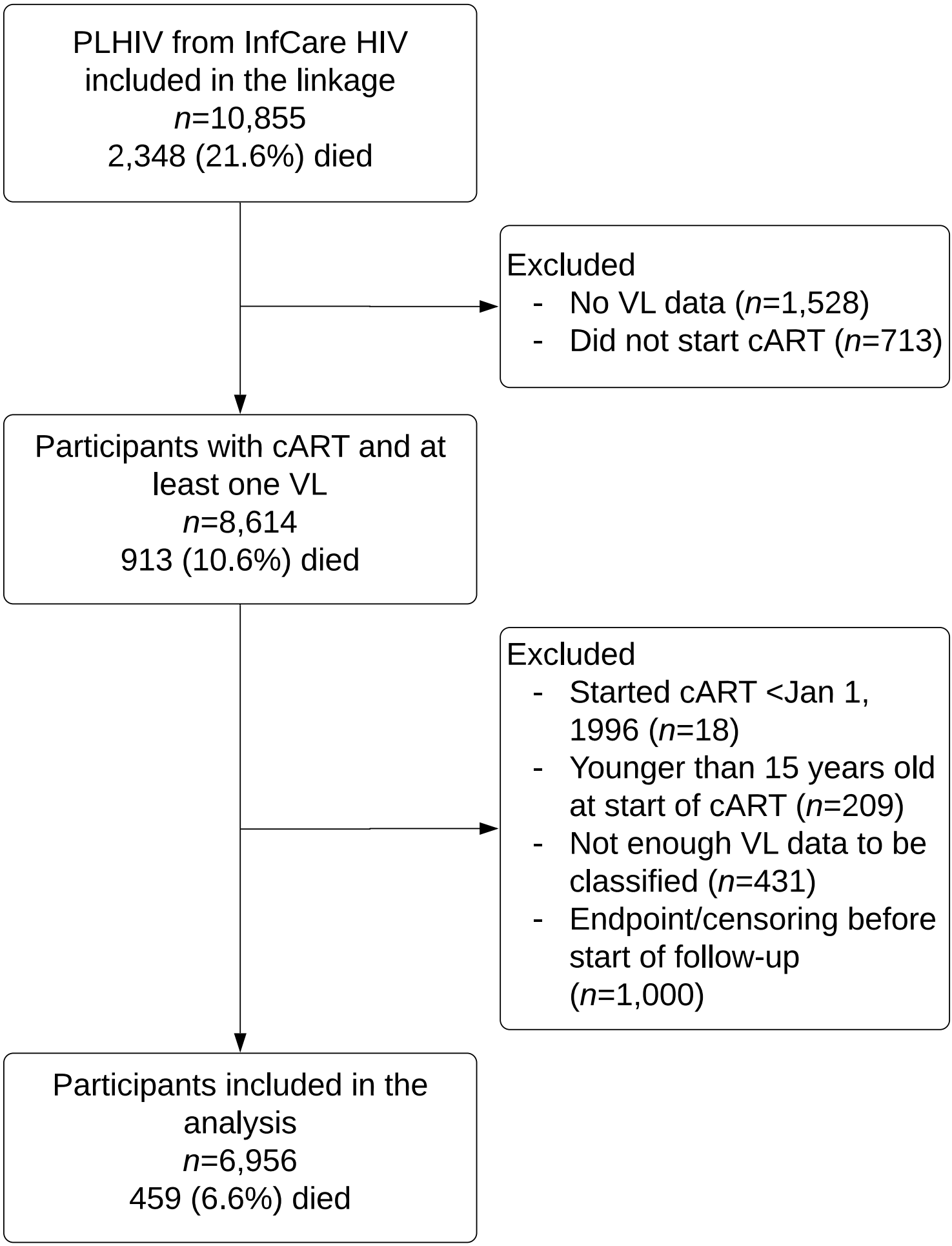

Figure 2