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Systematic review on cumulative HIV viraemia among people living with HIV receiving antiretroviral treatment and its association with mortality and morbidity

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Background: We performed a systematic review to generate evidence on the association between cumulative human immunodeficiency virus (HIV) viraemia and health outcomes.

Methods: Quantitative studies reporting on HIV cumulative viraemia (CV) and its association with health outcomes among people living with HIV (PLHIV) on antiretroviral treatment (ART) were included. We searched MEDLINE via PubMed, Embase, Scopus and Web of Science and conference abstracts from 1 January 2008 to 1 August 2022.

Results: The systematic review included 26 studies. The association between CV and mortality depended on the study population, methods used to calculate CV and its level. Higher CV was not consistently associated with greater risk of acquire immunodeficiency syndrome–defining clinical conditions. However, four studies present a strong relationship between CV and cardiovascular disease. The risk was not confirmed in relation of increased hazards of stroke. Studies that assessed the effect of CV on the risk of cancer reported a positive association between CV and malignancy, although the effect may differ for different types of cancer.

Conclusions: CV is associated with adverse health outcomes in PLHIV on ART, especially at higher levels. However, its role in clinical and programmatic monitoring and management of PLHIV on ART is yet to be established.

Keywords: cumulative viraemia, HIV viraemia, viral load, viraemia copy-years.

Introduction

Virological suppression is the best measure of treatment success during human immunodeficiency virus (HIV) infection. Multiple studies have demonstrated the prognostic value of plasma HIV RNA levels or HIV viral load (VL) for mortality, disease progression,[1–6] HIV transmission,[7–9] and immune system activation. The latter may lead to chronic non-communicable health conditions.[2,10–13]

Most programs use a cross-sectional approach when studying virological outcomes, usually relying on the most recent VL.[14] However, VL suppression might not be stable, and cross-sectional approaches do not show how long a patient had a suppressed VL. During HIV treatment, people living with HIV (PLHIV) may transition between suppressed and unsuppressed viraemia. By overlooking these transitions, a cross-sectional approach might misrepresent the level of suppression in HIV cohorts.[15,16] Overestimated VL suppression may result in missed opportunities to improve individual health and result in ongoing HIV transmission in a given context.

In the last two decades, the association between longitudinal measurements of viraemia and health outcomes has emerged

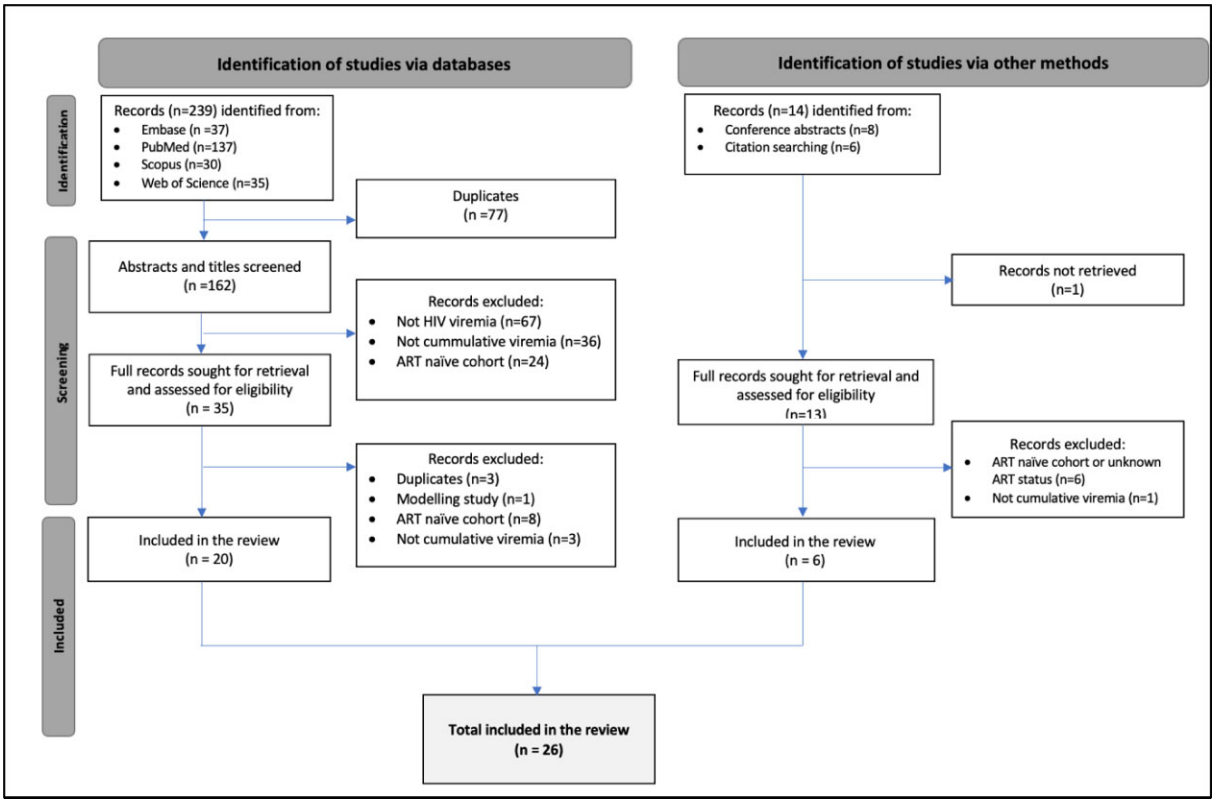

Figure 1. Study inclusion diagram. Citation searching records identified as references of the studies identified via databases and included in the systematic review.

as an area of interest. In 2009 and 2010, Zoufaly et al.[17] and Cole et al.[18] introduced the concept of 'HIV cumulative viremia (CV)', defined by a person's cumulative exposure to unsuppressed VL. No previous review has systematically summarized evidence on different indicators of CV and their association with mortality and morbidity in HIV cohorts. Therefore, we carried out a systematic review to define indicators of CV and the strength of the association with various health outcomes.

Methods

Eligibility

We included quantitative studies reporting HIV CV and its association with health outcomes among PLHIV on antiretroviral treatment (ART). Studies reporting HIV CV among ART-naïve PLHIV, or those that did not clearly specify if viraemia measured before ART initiation contributed to their calculation of the CV, were excluded from the review.

Search strategy and selection criteria

The systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement updated in 2020[19,20] and it was registered in the International Prospective Register of Systematic Reviews database (CRD42021283891). We searched MEDLINE via PubMed, Embase, Scopus and Web of Science from 1 January 2008 to 1 August 2022 using a search strategy (Supplement 1) that combined terms for HIV infection, viraemia, ART and health outcomes, without age or geographic restrictions. The language was restricted to English. An automatic PubMed alert with the same terms was used until 1 August 2022. We also hand-screened references of all included full-text articles. We searched conference abstracts from the International AIDS Society, Conferences on Retroviruses and Opportunistic Infections and International Conference on AIDS and Sexually Transmitted Infections in Africa from 2008 onwards to identify studies not yet published as full-text articles. After reports were identified, they were uploaded to Rayyan, a browser-based tool for support of the literature review.[21] Two authors (AM and LL) independently screened titles and abstracts. They read full articles and assessed selected articles for risk of bias with the Newcastle–Ottawa tool for observational studies.[22] Disagreements about inclusion were resolved by discussion and arbitration with a third researcher (TD).

Data analysis

Two reviewers (AM and LL) extracted data independently in accordance with a predefined data extraction sheet. Outcomes of interest were CV and any health outcomes related to PLHIV on ART. We also extracted data about study settings, population,

methods used to calculate CV, time when viraemia was estimated and the periodicity of VL testing. Due to the heterogeneity among included studies regarding study population, definitions of CV and studied outcomes, we did not conduct a meta-analysis. We have summarized study characteristics, definitions of CV and the measure of CV, as well as the association between CV and various health outcomes in tables. When data were not available, we indicated N/A.

Results

Search and screening results

The database searches, after deduplication, yielded 162 records that underwent title and abstract screening. A total of 35 full-text articles were assessed for eligibility and 20 were included in the analysis. Manual searches of the references of included articles and screening of conference abstracts resulted in another 13 records, of which 6 were included, resulting in 26 records being included in the analysis (Figure 1).

Included studies

Among the 26 included studies, 1 was a randomized clinical trial and 25 were observational cohort studies (Table 1). A total of 13 studies were conducted in the USA, 7 in Europe, 2 in Latin America, 2 in sub-Saharan Africa, 1 in Australia and 1 in South-east Asia. The size of the study population ranged from 140 to 112 243 participants. Participants received ART in combinations recommended by the guidelines used during the respective study periods. Follow-up time on ART was reported by 21 studies and ranged from a median 1 to 10 y. The periodicity of VL monitoring varied from one VL test every 2 y (median 2.0 [interquartile range {IQR} 2.0–8.0])[23] to one every 4 months (average 3.1 VL tests per participant per year).[24]

Risk of bias

Included studies were considered to have a low risk of bias (Supplement 2). The quality assessment showed a good to fair result despite some concerns about the representativeness of study populations,[16,23,25–29] rates of lost to follow-up in observational cohorts[24,26–28,30–42] and duration of follow-up, which may have been too short to reliably measure outcomes of interest in selected studies.[33,34,38–40]

Cumulative viraemia

Cumulative viraemia was defined as the proportion of the follow-up time on ART under or over a certain VL threshold[16,17,26,27,29,35–37,43] or both[16,17,26,27,36,37] or as viraemia copy-years (VCY; or a variation of this definition), which estimates the area under a patient's VL curve[23,24,28,32,33,35,38–42,44–46] (Table 1). The method was first presented by Cole et al. in 2010.[18] Some studies obtained a logarithmic value of CV (log_{10} copy-years/ml) by summing the area under the VL curve and then taking the logarithm, or by summing the area under the logarithmic VL curve.[17,38,42,45]

Most studies calculated CV 4–12 months after ART initiation, allowing the first evaluation of virological suppression.[16,27–29,32,33,35,37–39,41,42,45] Various approaches were used to deal with values below the lower limit of detection (LLD): those were either considered equal to the LLD,[36,38,40] half the LLD[35,39,46] or set to zero.[17,29,32,37,41,42,45]

Studies that used the proportion of time under or over a given VL threshold defined this VL threshold either as the LLD (20–500 copies/ml)[16,17,26,27,29,36,37] or as 1500 copies/ml when transmission risk was studied.[43]

The lowest CV was reported by Elvstam et al.[45] (median 0.22 [IQR 0.0–2.4] log_{10} copy-years/ml for 5.5 y on ART) and the highest was reported by Chirouze et al.[32] (median 7.8 [IQR 2.4–16.6] log_{10} copy-years/ml for a median 10 y on ART). In the latter study, CV was lower (median 2.7 log_{10} copy-years/ml during the same observation period) in participants who were ART naïve at the start of the study.

Studies showed higher CV in patients who were on ART for a longer period. Wright et al.[30] showed a mean VCY of 2.31 (95% confidence interval [CI] 2.26 to 2.36) at 1 y of ART and a mean of 4.3 (95% CI 4.22 to 4.39) VCY at 10 y of ART. Wang et al.[16] reported 2.2 (IQR 1.5–4.1) and 3.1 (IQR 1.8–4.3) log_{10} copy-years/ml at 2 and 3 y of ART, respectively.

Lima et al.[38] reported lower CV for those on an efavirenz-based regimen (median 1.56 [IQR 1.46–1.68] log_{10} copy-years/ml from baseline) compared with those on a boosted lopinavir-based regimen (median 1.75 [IQR 1.51–1.92] log_{10} copy-years/ml from baseline). Pascom et al.[40] reported that CV was significantly lower with a dolutegravir-based regimen as compared with lopinavir/ritonavir- or efavirenz-based regimens (mean 689.5 [standard deviation {SD} 269.6] log_{10} copy-days/ml for dolutegravir vs 728.0 [SD 306.8] log_{10} copy-days/ml for efavirenz and 743.9 [SD 312.2] log_{10} copy-days/ml for atazanavir).

Association between cumulative viraemia and mortality

Eleven studies looked at the association between CV and mortality among PLHIV on ART (Table 2). Mugavero et al.[39] showed a 44% increase in mortality risk by CV (adjusted hazard ratio [aHR] 1.44 per log_{10} copy-years/ml [95% CI 1.07 to 1.94]), independent of the last VL and CD4 cell count values. Salinas et al.[28] categorized CV compared with <1000 copy-years/ml. CV of 1000–14 999 copy-years/ml (aHR 1.36 [95% CI 1.16 to 1.59]), 15 000–99 999 copy-years/ml (aHR 1.89 [95% CI 1.61 to 2.21]) and ≥100 000 copy-years/ml (aHR 4.09 [95% CI 1.61 to 2.21]) were associated with mortality. Similarly, Wright et al.[30] demonstrated that VCY $>10^5$ copy-years/ml predicted mortality (HR 1.52 [95% CI 1.09 to 2.13], p=0.01) independent of the last VL and CD4 cell count values, but failed to confirm the same when CV was included as a continuous variable in the model (aHR 1.14 [95% CI 0.94 to 1.38], p=0.19). Sempa et al.[42] studied VL accumulated on a linear scale (cVL1) or logarithmic scale (cVL2). The latter (but not the former) predicted mortality up to 12 weeks af-

Table 1. Characteristics of the studies reporting cumulative viremia (N=26)

Author, country	Study period	Study design	Study population	Sample size (n)	Duration of follow-up on ART	Frequency of VL monitoring	Measure of cumulative viraemia	Cumulative viraemia
Cates et al., USA[35]	1998–2013	Prospective observational cohort	Pregnant women initiated ART prior conception and with minimum two VL results	149	N/A	Semi-annually	VCY[a] from ART initiation and excluding the first viral load result	Median 4.4 (IQR 3.8–4.9) log_{10} copy-years/ml
Chirouze et al., France[32]	1997–1999	Prospective observational cohort	PLHIV on protease inhibitor treatment with baseline plasma VL >500 copies/ml and at least two VL tests	979	Median 10 y (IQR 5.0–12.0)	Median number of VL tests: 12 (IQR 4.0–23.0) if below LLD 5 (IQR 2.0–11.0) if above LLD	VCY from 8 months of follow-up	Median log_{10} copy-years/ml: overall 4.8 (IQR 1.3–13.5), 2.7 (IQR 1.0–1.1) in the ART-naïve population, 7.8 (IQR 2.4–16.6) in the ART-experienced population
Falasca et al., Italy[31]	2011–2015	Retrospective observational cohort	PLHIV on ART with at least six VL tests during 54 months of follow-up	850	54 months	Mean number of VL tests: 7.5 (SD 1.4)	VCY	Median log_{10} copy-years/ml: 1.3 (IQR 0.9–1.7) if pre-study viraemia suppressed, 1.7 (IQR 1.7–2.2) if pre-study viremia <37 copies/ml, 2.5 (IQR 1.9–3.3) if pre-study viraemia 37– 200 copies/ml
Kukoyi et al., Ghana[23]	2009–2013	Prospective observational cohort	Age 0–13 y with minimum of two VL tests	140	Mean 4.3 y (SD 2.4)	Median number of VL tests: 2.0 (IQR 2.0–8.0)	VCY	36% with <2 log_{10} copy-years/ml, 19.2% with 2– 4 log_{10} copy-years/ml, 44.3% with >4 log_{10} copy-years/ml
Mugavero et al., USA[39]	2000–2008	Prospective observational cohort	PLHIV initiated on ART with a minimum of two VL tests	2027	Median 2.7 y (IQR 1.6–4.6)	Median number of VL tests 8.0 (IQR 4.0–15.0)	VCY from 24 weeks of ART	Median log_{10} copy-years/ml: 5.3 (IQR 4.9–6.3)
Pascom et al., Brazil[40]	2014–2017	Retrospective observational cohort	PLHIV age >12 y initiated on ART with at least two VL tests	112 243	1 y	2 VL tests minimum	VC days in 1 y	Mean log_{10} copy-days/mL: 722.4 (SD 301.5) overall, 689.5 (SD 269.6) for DTG regimen, 728.0 (SD 306.8) for EFV regimen, 743.9 (SD 312.2) for ATV/r regimen
Quiros-Roldan et al., Italy[41]	1998–2012	Retrospective observational cohort	PLHIV starting ART during the study period with a minimum of three VL tests	3271	Median 4.1 y	Median number of VL tests: 4.5	Overall VCY (VCY-o) from start of ART until the end of follow-up Early VCY (VCY-e) in the first 8 months Late VCY (VCY-l) after at least 8 months of ART; categorical variable: VCY/FUD (VCY REF divided by the corresponding follow-up duration, FUD)	Median log_{10} copy-years/ml: 6.16 (IQR 5.58–6.71) VCY-o, 6.15 (IQR 5.57–6.71) VCY-e, 1.47 (IQR 0–3.72) VCY-l/FUD
Salinas et al., USA[28]	1996–2012	Prospective observational cohort	PLHIV started on ART	8168	N/A	N/A	VCY from 180 d after ART initiation	N/A

Table 1. (Continued)

Author, country	Study period	Study design	Study population	Sample size (n)	Duration of follow-up on ART	Frequency of VL monitoring	Measure of cumulative viraemia	Cumulative viraemia
Sempa et al., Uganda[42]	2004–2014	Prospective observational cohort	PLHIV started on ART	489	Median 8.3 y (IQR 2.3–8.8)	Semi-annually	Cumulative VL from 24 weeks of ART accumulated on a linear scale (cVL1) and logarithmic scale (cVL2)	N/A
Wright et al., Australia[30]	1996–2004	Prospective observational cohort	PLHIV on ART >24 months	2073	N/A	N/A	VCY from 6 months of ART	Mean log_{10} copy-years/ml: 2.31 (95% CI 2.26 to 2.36) at 1 y ART, 3.27 (95% CI 3.21 to 3.33) at 3 y ART, 3.71 (95% CI 3.65 to 3.78) at 5 y ART, 4.31 (95% CI 4.22 to 4.39) at 10 y ART Mean copy-years/ml: 204 (95% CI 182 to 229) at 1 y ART, 1862 (95% CI 1622 to 2138) at 3 y ART, 5129 (95% CI 4467 to 6026) at 5 y ART, 19 953 (95% CI 16 596 to 24 547) at 10 y ART
Cozzi-Lepri et al., Italy[44]	N/A	Retrospective observational cohort	PLHIV who initiated ART	5512	N/A	N/A	VCY from ART initiation	Median log_{10} copies/ml: 5.27 (IQR 2.69–11.19)
Coburn et al., USA[34]	1997–2016	Retrospective observational cohort	Women >25 y of age on ART	5279	Median 5 y (IQR 2–9)	N/A	VCY from ART initiation	Median copy-years/ml: 17 306 (IQR 1419–101 338)
Lima et al., Mexico[38]	2005–2007	Clinical trial	PLHIV >18 y of age initiated on ART efavirenz or lopinavir\r	189	48 wks	5 VL tests	VCY from ART initiation and after 6 months of ART	Median log_{10} copy-years/ml on EFV regimen: 1.56 (IQR 1.46–1.68) from baseline, 0.26 (IQR 0.26–0.30) from 6 months Median log_{10} copy-years/ml on Lop/r regimen: 1.75 (IQR 1.51–1.92) from baseline, 0.28 (IQR 0.26–0.32) from 6 months
Marconi et al, USA[24]	2008–2011	Retrospective observational cohort	PLHIV	1949	Mean 5.6 y (SD 3.98)	Mean VL tests per participant per year: 3.1	VC months	Median log_{10} copy-months/ml: 16.3 (IQR 7.14–24.94)

Table 1. (Continued)

Author, country	Study period	Study design	Study population	Sample size (n)	Duration of follow-up on ART	Frequency of VL monitoring	Measure of cumulative viraemia	Cumulative viraemia
Delaney et al., USA[33]	1996–2006	Prospective observational cohort	PLHIV starting ART	11 324	Median 4.4 y	N/A	Cumulative viral load (log_2 transformation) from 6 months after enrolment	Mean million copy-days/ml: 36.1 (SD 140)
Elvstam et al., (Sweden)[45]	1996–2017	Prospective observational cohort	PLHIV on ART	6562	Median 5.5 y	N/A	VCY from the date of the first VL ≥12 months after initiation of ART by viraemia category: overall, virologic suppression <50 copies/ml, LLV of 50–199 copies/ml, LLV of 200–999 copies/ml, high-level viraemia ≥1000 copies/ml	Median log_{10} copy-years/ml: overall 0.22 (IQR 0–2.40), virologic suppression 0 (IQR 0–0.11), LLV of 50–199 copies/ml 1.11 (IQR 0.50–1.72), LLV of 200–999 copies/ml 1.98 (IQR 1.14–3.16), high viraemia 6.39 (IQR 2.69–13.75)
Harding et al., (USA)[46]	2006–2014	Prospective observational cohort	PLHIV on ART	15 974	N/A	Average 12 VL measurements	VC days	Median million copy-days/ml: 1.1 (IQR 0.047–3092)
Kowalkowski et al., USA[26]	1985–2010	Retrospective observational cohort	Male PLHIV ever receiving ART	31 576	Mean 9.0 y (SD 5.0)	Mean number of VL tests: 3.2 (SD 3.1)	VCY % of time being undetectable	Mean copy-years/ml: 212 743 (SD 467 984) Mean proportion of time being undetectable: 49% (SD 34)
Laut et al., EuroSida[a,37]	2011–2015	Prospective observational cohort	PLHIV with minimum three VL test results	11 860	Median 4.5 y (IQR 3.2–5.9)	Semi-annually	VCY after 4 months of ART, consecutive months with VL ≥50 copies/ml, % of time on ART spent fully suppressed	N/A
Wang et al., USA[16]	1995–2004	Prospective observational cohort	MSM PLHIV starting ART	841	10 y follow-up	Semi-annually	VCY during various periods after ART initiation, % participants being supressed	Median log_{10} copy-years/ml: overall 4.3 (IQR 3.6–4.9), 2.2 (IQR 1.5–4.1) in the recent 2 y, 3.1 (IQR 1.8–4.3) in the recent 3 y % of participants supressed: 61% in the recent 2 y, 55% in the recent 3 y, 33% during the whole study period
Pallela et al., USA[27]	1995–2017	Prospective observational cohort	PLHIV on ART at least 6 months and with minimum two VL test results	1645	N/A	Median number of VL tests: 14 (IQR 7.0–24)	VCY from 6 months after ART initiation, % time with VL >50 copies/ml, % time with VL <200 copies/ml	Median log_{10} copy-years/ml: 3.0 (IQR 2.3–4.2) Median of person-years with VL >50 copies/ml: 25.5% Median of person-years with VL >200 copies/ml: 9.7%

Table 1. (Continued)

Author, country	Study period	Study design	Study population	Sample size (n)	Duration of follow-up on ART	Frequency of VL monitoring	Measure of cumulative viraemia	Cumulative viraemia
Zoufaly et al., Germany[17]	1999–2006	Prospective observational cohort	PLHIV on ART with minimum two VL test results and no lymphoma on baseline	6022	Median days of ART duration: lymphoma group 754 (IQR 327–1847), non-lymphoma group 1520 (IQR 730.5–2645)	Mean number of VL tests: 3.97 (SD 2.17)	VCY % of all VL >500 copies/ml	N/A
Hughes et al., USA[36]	2012–2014	Prospective observational cohort	PLHIV on ART with minimum two VL test results	650	2 y	Median number of VL tests: 5.0	VCY, person time spent unsuppressed (<200 copies/ml), p erson time spent transmissible (<1500 copies/ml)	Median log_{10} copy-years/ml: 2 y 2.2 (IQR 1.96–2.0), median time unsuppressed 9.2% (IQR 7.2–11.1), median time transmissible 6.2% (IQR 4.7–7.7)
Chiao et al., USA[25]	1985–2009	Retrospective observational cohort	Male veterans on ART	28 806	166 362 person-years of follow-up	Median number of VL tests: 17.0	% time being supressed <500 copies/ml	Proportion of observation time being supressed: ≤20%: 22.3%, 21–40%: 11.0%, 41–60%: 12.3%, 61–80%: 15.1%, ≥ 80%: 39.2%
Lesko et al., USA[43]	2010–2015	Retrospective observational cohort	PLHIV engaged in HIV care and on ART	3021	Median 5.7 y (IQR 3.9–5.7) observation time	Median number of VL tests: 10 (IQR 5–15)	% follow-up time with VL >1500 copies/ml after ART initiation	12.5% person-years in care with >1500 copies/ml, 12.6% person-years in care with >1500 copies/ml when time spent lost to clinic assumed <1500 copies/ml, 27.2% person-years in care with >1500 copies/ml when time spent lost to clinic assumed >1500 copies/ml
Mesic et al., (Myanmar)[29]	2014–2018	Retrospective observational cohort	PLHIV on ART	1352	Median 54.5 months (IQR 44.6–65.1)	Median number of VL tests: 4 (IQR 2–6)	% of follow-time with VL >200 copies/ml from the second VL (minimum 6 months after ART initiation)	Proportion of participants being unsuppressed (>200 copies/ml): never: 60.3%, 1–19% of follow-up time: 12.7%, 20–49% of follow-up time: 15.8%, 50–79% of follow-up time: 5.9%, ≥80% of follow-up time: 5.3%

[a]VCY: viremia copy-years is a measure of cumulative HIV burden that estimates the area under a patient's longitudinal VL curve. The method was first presented by Cole et al.[18] in 2010. The trapezoidal rule is used to approximate the integral representing the area under each patient's longitudinal VL curve. VL burden for time interval between two consecutive VL values is calculated by multiplying the mean of the two VL values by the time interval. The copy-years/ml for each segment of a patient's VL curve are then summed to calculate viraemia copy-years—the number of copies of HIV RNA per millilitre of plasma over time. Studies report a logarithmic value of cumulative viraemia obtained by either summing the area under the VL curve and then taking the logarithm or, more rarely, by summing the area under the log VL curve.
cVL: cumulative viral load; N/A: data not available in the full-text article; SD: standard deviation; VCY: viraemia copy-years.

Table 2. Association between cumulative viraemia and mortality (n=11)

Author, country	Outcome	Main exposure variable	Effect estimate
Chirouze et al., France[32]	All-cause 10-y mortality	VCY REF >1.4 log_{10} copy-years/ml VCY/FUD (VCY REF divided by the corresponding follow-up duration, FUD) >2.8 log_{10} copy-years/ml VCY at year 1 VCY at year 5	Whole study population: 2.0 (95% CI 1.2 to 3.5) HR for VCY >1.4 log_{10} copy-years/ml, 1.8 (95% CI 1.1 to 3.0) HR for VCY/FUD >2.8 log_{10} copy-years/ml, 1.2 (95% CI 1.1 to 1.4) RR for each log_{10} copy-years/ml increase and when adjusted for the last VL ART-naïve study population: 1.3 (95% CI 0.6 to 2.8) HR for VCY >1.4 log_{10} copy-years/ml, 2.4 (95% CI 1.1 to 5.3) HR for VCY (log_{10} copy-years/ml) at 5 y, 2.3 (95% CI 0.8 to 1.2) HR for VCY (log_{10} copy-years/ml) at 1 y
Mugavero et al., USA[39]	All-cause mortality	VCY log_{10} copy-years/ml as a continuous variable	1.65 (95% CI 1.32 to 2.06, p<0.001) aHR for each log_{10} copy-years/ml increase 1.44 (95% CI 1.07 to 1.94, p=0.02) aHR for each log_{10} copy-years/ml increase, adjusted for cross-sectional VL and time updated CD4
Quiros-Roldan et al., Italy[41]	Mortality after at least 8 months on ART	Overall VCY (VCY-o) from start of ART until the end of follow-up; continuous variable or dichotomized at median (<6.16 and ≥6.16 log_{10} copy-years/ml Early VCY (VCY-e) in the first 8 months; continuous variable or dichotomized at median (<6.15 and ≥6.15 log_{10} copy-years/ml Late VCY (VCY-l) after 8 months of ART; categorical variable: • VCY-l suppressed (VL values equal to or below the limit of detection of 50 copies/ml after 8 months of ART and maintained during all the follow-up) • VCY-l low level (<3 log_{10} copy-years/ml) • VCY-l ≥3 log_{10} copy-years/ml VCY/FUD (VCY REF divided by the corresponding follow-up duration, FUD); categorical variable: • VCY-l/FUD suppressed (VL values equal to or below the limit of detection of 50 copies/ml after 8 months of ART and maintained during all the follow-up) • VCY-l/FUD low level (<2.3 log_{10} copies/ml) • VCY-l/FUD ≥2.3 log_{10} copies/ml per year of follow-up	VCY-o: 1.40 (95% CI 1.03 to 1.90, p=0.033) HR for VCY-o >6.16 log_{10} copy-years/ml, 1.48 (95% CI 1.23 to 1.79, p<0.001) HR for each log_{10} copy-years/ml increase VCY-e: 1.39 (95% CI 1.11 to 2.01, p=0.036) HR for VCY-e >6.15 log_{10} copy-years/ml, 1.47 (95% CI 1.22 to 1.78, p<0.001) HR for each log_{10} copy-years/ml increase VCY-l: 0.86 (95% CI 0.56 to 1.31, p=0.447) HR for VCY-l low level log_{10} copy-years/ml, 1.68 (95% CI 1.16 to 2.44, p=0.006) HR for VCY-l ≥3 log_{10} copy-years/ml VCY-l/FUD: 0.78 (95% CI 0.54 to 1.12, p=0.182) HR for VCY-l/FUD low level, 19.5 (95% CI 11.10 to 34.26, p<0.001) HR for VCY-l/FUD ≥2.3 log_{10} copies/ml

Table 2. (Continued)

Author, country	Outcome	Main exposure variable	Effect estimate
Salinas et al., USA[28]	Mortality	VCY copy-years/ml categorized as <1000, 1000–14 999, 15 000–99 999, ≥100 000	Compared with <1000 copy-years/ml: 1.36 (95% CI 1.16 to 1.59) aHR for 1000–14 999 copy-years/ml, 1.89 (95% CI 1.61 to 2.21) aHR for 15 000–99 999 copy-years/ml, 4.09 (95% CI 1.61 to 2.21) aHR for ≥100 000 copy-years/ml
Sempa et al., Uganda[42]	Mortality 12 and 24 weeks after the last VL	cVL1: calculated by summing the area under the VL curve and then taking the logarithm cVL2: calculated by summing the area under the log VL curve	Predicting 0–12 weeks ahead: 0.97 (95% CI 0.65 to 1.44) aHR for each $\log_{10}$ copy-years/ml increase (cVL1), 1.63 (95% CI 1.02 to 2.60) aHR for each $\log_{10}$ copy-years/ml increase (cVL2) Predicting 0–24 weeks ahead: 0.98 (95% CI 0.80 to 1.22) aHR for each $\log_{10}$ copy-years/ml increase (cVL1), 0.50 (95% CI 0.17 to 1.4) aHR for each $\log_{10}$ copy-years/ml increase (cVL2)
Wright et al., Australia[30]	Mortality	VCY $\log_{10}$ copy-years/ml as continuous variable, VCY $\log_{10}$ copy-years/ml as categorical variable (10^5 copy-years)	1.14 (95% CI 0.94 to 1.38, p=0.19) aHR for each $\log_{10}$ copy-years/ml increase 1.52 (95% CI 1.09 to 2.13, p=0.0) aHR for high VCY (10^5 copy-years)
Laut et al., EuroSida[a,37]	Mortality	VCY copy-years/ml as categorical variable, consecutive number of months with VL ≥50 copies/ml as categorical variable, % of time on ART fully supressed as categorical variable	Poor discriminative ability to predict mortality after 5 yon ART: p=0.77 for VCY, p=0.15 for consecutive months with VL ≥50 copies/ml, p=0.33 for percentage of time on ART spent fully suppressed Note: p-values refer to the discriminative ability of VCY compared with the current VL reference

Table 2. (Continued)

Author, country	Outcome	Main exposure variable	Effect estimate
Wang et al., USA[16]	Mortality	VCY $\log_{10}$ copy-years/ml as continuous variable derived from VLs assessed during different time periods (the most recent 1–10 y and initial 1–10 y following ART initiation)	All participants: −4 (95% CI −36 to 27) adjusted % change in survival time for overall VCY, −1 (95% CI −33 to 30) adjusted % change in survival time for VCY in first 10 y, −21 (95% CI −37 to −6) adjusted % change in survival time for VCY in most recent 3 y Baseline CD4 count <200 cells/μl: −21 (95% CI −36 to −5) adjusted % change in survival time for VCY in most recent 3 y, −12 (95% CI −37 to 12) adjusted % change in survival time for VCY in most recent 10 y Baseline CD4 count ≥200 cells/μl: −24 (−47 to −7) adjusted % change in survival time for VCY in most recent 3 y, −31 (95% CI −57 to −5) adjusted % change in survival time for VCY in most recent 10 y
Pallela et al., USA[27]	Mortality	VCY $\log_{10}$ copy-years/ml as a continuous variable, % of person-years with VL >200 copies/ml, % person-years with VL >50 copies/ml	1.69 (95% CI 1.46 to 1.97) HR for each $\log_{10}$ copy-years/ml increase, 1.22 (95% CI 1.16 to 1.28) HR for 10% increment (% person-years with VL >200 copies/ml), 1.20 (95% CI 1.14 to 1.27) HR for mortality per 10% increment (% person-years with VL >50 copies/ml)
Cozzi-Lepri et al., Italy[44]	AIDS or death due to any cause Severe non-AIDS (SNAE) or death due to any cause	VCY $\log_{10}$ copy-years/ml as continuous variable Shape of the VCY area under curve assessed: • Cohorts with spikes and dips shape • Cohorts with stable VL trajectories	0.77 (95% CI 0.60 to 0.98) aHR and 1.20 (95% CI 1.13 to 1.27, p<0.001) aHR for AIDS/death in cohorts with spikes and dips and those with more stable VL trajectories 0.75 (95% CI 0.60 to 0.94) aHR and 1.10 (95% 1.04 to 1.16, p=0.013) aHR for SNAE/death in cohorts with spikes and dips and those with more stable VL trajectories
Mesic et al., Myanmar[29]	Mortality	% of time being unsuppressed as a categorical variable: never (0%), 1–19%, 20–49%, 50–79%, ≥80%	When compared to participants who were never unsuppressed: 0.60 (95% CI 0.23 to 1.58, p=0.30) aHR for participants with 1–19% of unsuppressed time, 0.88 (95% CI 0.38 to 2.04, p=0.78) aHR for participants with 20–49% of unsuppressed time, 2.92 (95% CI 1.21 to 7.10, p=0.02) aHR for participants with 50–79% of unsuppressed time, 2.71 (95% CI 1.22 to 6.01, p=0.01) aHR for participants with ≥80% of unsuppressed time

aHR: adjusted hazard ratio; aRR: adjusted relative risk; cVL: cumulative viral load; HR: hazard ratio; RR: relative risk; SNAE: severe non-AIDS event; VCY: viraemia copy-years.

ter the last VL result (aHR 1.63 [95% CI 1.02 to 2.60] vs 0.97 [95% CI 0.65 to 1.44], p<0.05 for each log_{10} copy-years/ml increase).

The effect of CV on mortality depended on its level. A study from Myanmar reported that among PLHIV with viraemic time of 50–79% or >80%, mortality hazard was almost threefold higher compared with those who were not viraemic during their follow-up time (aHR 2.92 [95% CI 1.21 to 7.10], p=0.02; aHR 2.71 [95% CI 1.22 to 6.01], p=0.01, respectively).[29] In the same study, mortality hazard was not increased in participants with a viraemic time <50% of their follow-up. Similarly, Quiros-Roldan et al.[41] demonstrated that among participants who maintained levels of CV <3 log_{10} copy-years/ml or <2.3 log_{10} copy-years/ml of VCY, the risk of death was similar to that of participants with permanently suppressed VL. However, they reported that the risk of mortality doubled among participants with >15% of VL results of >500 copies/ml compared with those without.

One study demonstrated that the association between CV and mortality depended on the ART status of the population. Chirouze et al.[32] reported that CV was associated with 10-y mortality (aHR 2.0 [95% CI 1.2 to 3.5] for VCY >1.4 log_{10} copy-years/ml) among their entire study population. This association was not shown in ART-naïve participants (aHR 1.3 [95% CI 0.6 to 2.8] for VCY >1.4 log_{10} copy-years/ml).

Three studies compared the prognostic value of CV with cross-sectional measures. Pallela et al.[27] studied multiple viraemia exposure measures and showed that all measures individually and in combination predicted mortality. However, the most predictive model used a combination of the most recent VL and time spent with VL >200 copies/ml (aHR 1.15 [95% CI 1.07 to 1.23]). In their EuroSida cohort study, Laut et al.[37] reported a poor discriminative ability of VCY (p=0.77), consecutive months with VL ≥50 copies/ml (p=0.15) and percentage of time on ART spent fully suppressed (p=0.33) when compared with current VL as a reference to predict mortality after 5 y on ART. Wang et al.[16] concluded that VCY calculated during the three most recent years on ART better predicted mortality than VCY for the entire period on ART or cross-sectional VL measures.

Association between cumulative viraemia and morbidity

We identified 14 studies that assessed the relationship between CV and different morbidities (Table 3). Higher CV was not consistently associated with the incidence of opportunistic infections. Marconi et al.[24] and Laut et al.[37] demonstrated an increased risk of AIDS-defining clinical conditions in participants with higher CV; however, Sempa et al.[42] and Kukoyi et al.[23] failed to identify an association between CV and the incidence of studied opportunistic infections. Nonetheless, Kukoyi et al.[23] reported that those with CV >4 log_{10} copy-years/ml had more frequent outpatient encounters compared with participants with <4 log_{10} copy-years/ml (p=0.03).

CV was investigated as a predictor of non-communicable diseases. Three studies[28,33,45] confirmed a strong relationship between CV and acute myocardial infarction (AMI). This was particularly strong for type-2 AMI, showing that CV increasing from the 25th to the 75th percentile was associated with a hazard that was more than double (aHR 2.31 [95% CI 1.59 to 3.35]).[33] Elvstam et al.[45] reported an association between CV and cardiovascular disease (CVD) (adjusted subhazard ratio [aSHR] 1.03 [95% CI 1.01 to 1.05]). When analysed as viraemia categories, participants with high-level viraemia (>1000 copies/ml) had a higher hazard of CVD compared with those who had virological suppression (aSHR 1.45 [95% CI 1.03 to 2.05]), and low-level viraemia (LLV; unsuppressed <1000 copies/ml) was not associated with a risk of CVD. In contrast, a study from the USA showed that CV was not associated with an increased hazard of stroke.[46]

Studies that assessed the effect of CV on the risk of cancer reported a positive association between CV and malignancy, although the effect may differ for different types of cancer. In the study by Zoufaly et al.,[17] CV was associated with the incidence of AIDS-related lymphoma (aHR 1.67 [95% CI 1.27 to 2.20], p<0.001). The strongest association was for Burkitt-type lymphoma (aHR 3.45 [95% CI 1.52 to 7.85], p<0.003), but there was no association between CV and central nervous system lymphoma (aHR 1.00 [95% CI 0.39 to 2.57], p=1.00). Another study reported a lower hazard of carcinoma (aHR 0.55 [95% CI 0.40 to 0.77], p=0.0004) among participants with detectable viraemia during <20% of their follow-up time when compared with those with a detectable viraemia during >80% of their follow-up time.[25] Kowalkowski et al.[26] investigated the relationship between CV and non-AIDS-defining malignancies. A positive association was found for Hodgkin lymphoma (aHR 1.22 [95% CI 1.06 to 1.40], p=0.005) and squamous cell anal carcinoma (aHR 1.36 [95% CI 1.21 to 1.52], p<0.001), but not for hepatocellular carcinoma (aHR1.02 [95% CI 0.93 to 1.13], p=0.67). In contrast, Coburn et al.[34] could not demonstrate an association between CV and an increased risk of breast cancer (aHR 0.91 [95% CI 0.63 to 1.32] per log_{10} increase in the current VCY).

Discussion

This systematic review summarized findings from 26 studies that investigated cumulative HIV viraemia among PLHIV on ART and its association with morbidity and mortality. The prognostic effect of CV on health outcomes depended on the statistical methods used, study populations and when it was measured.

Several studies reported a firm and independent association between CV and all-cause mortality.[16,28,30,39,44] This finding is consistent with the landmark study by Cole et al.,[18] which is not included in the review as it measured VCY from the time of HIV seroconversion. However, the study was the first to report a cumulative indicator providing prognostic information beyond cross-sectional measures of viraemia.[18] HIV replication is related to chronic inflammation and immune reactivation, both causing clinical deterioration and mortality.[47,48] In the randomized clinical trial Strategic Management of Antiretroviral Therapy (SMART), an increased risk of death and other adverse outcomes in PLHIV—who received ART intermittently—persisted even after ART was reintroduced.[49] In this trial, investigators reported increased levels of inflammatory biomarkers (interleukin-6 and D-dimers) in the experimental arm, known to be associated with all-cause mortality.[12] Starting ART in PLHIV with a CD4 cell count >500 cells/μl was proven to have benefits over delaying ART until the CD4 cell count is <350 cells/μl.[50] While a high viraemia burden predicted mortality, this was not always the case for PLHIV with a lower CV burden when compared with those who were continuously suppressed.[29,41] Increased inflammatory markers are not

Table 3. Association between cumulative viraemia and morbidity (n=14)

Author, country	Outcome	Main exposure variable	Effect estimate
Cates et al., USA [35]	Miscarriage or still birth	VCY log_{10} copy-years/ml as continuous variable	0.80 (95% CI 0.69 to 0.92) aRR for each log_{10} copy-years/ml increase, 0.10 (95% CI 0.14 to 0.05) risk difference for each log_{10} copy-years/ml increase
Falasca et al., Italy[31]	Virological failure	VCY log_{10} copy-years/ml as continuous variable	1.01 (95% CI 1.01 to 1.02, p<0.001) HR for each log_{10} copy-years/ml increase
Kukoyi et al., Ghana[23]	Frequency of hospital admissions, opportunistic infections and outpatient sick visits	VCY log_{10} copy-years/ml categorized as <2 log_{10} copy-years/ml, 2–4 log_{10} copy-years/ml, >4 log_{10} copy-years/ml	Participants with >4 log_{10} copy-years/ml had increased outpatient encounters compared with participants with <log_{10} copy-years/ml (85.5% [53/62] vs 70.5% [55/78], p=0.03). There was no association between VCY and the frequency of opportunistic infections or hospital admissions (data not shared).
Salinas et al., USA[28]	Acute myocardial infraction	Log_{10} copy-years/ml categorized as <1000, 1000–14 999, 15 000–99 999, ≥100 000	Compared with <1000 copy-years/ml: 1.61 (95% CI 1.06 to 2.44) aHR for 1000–14 999 copy-years/ml, 1.67 (95% CI 1.07 to 2.61) aHR for 15 000–99 999 copy-years/ml, 2.02 (95% CI 1.30 to 3.14) aHR for ≥100 000 copy-years/ml
Sempa et al., Uganda[42]	Opportunistic infections	cVL1: calculated by summing the area under the VL curve and then taking the logarithm	Predicting 0–12 wks ahead: 0.97 (95% CI 0.86 to 1.09) aHR for each log_{10} copy-years/ml increase (cVL1), 0.78 (95% CI 0.52 to 1.15) aHR for each log_{10} copy-years/ml increase (cVL2)
		cVL2: calculated by summing the area under the log VL curve	Predicting 0–24 wks ahead: 1.00 (95% CI 0.91 to 1.10) aHR for each log_{10} copy-years/ml increase (cVL1), 1.00 (95% CI 0.68 to 1.48) aHR for each log_{10} copy-years/ml increase (cVL2)

Table 3. (Continued)

Author, country	Outcome	Main exposure variable	Effect estimate
Coburn et al., USA[34]	Breast cancer	Log_{10} VCY as a continuous variable VCY on ART was lagged 1–5 y to account for cancer latency	0.91 (95% CI 0.63 to 1.32) aHR for each log_{10} copy-years/ml increase in the current VCY, 0.78 (95% CI 0.55 to 1.10) aHR for each log_{10} copy-years/ml increase when VCY lagged 1–5 y on ART
Marconi et al, USA[24]	AIDS events and CD4 recovery	VC months dichotomized based on the median	2.38 (95% CI 1.56 to 3.62, p<0.001) RR for AIDS when CV greater than the median, 1.96 (95% CI 1.24 to 3.13, p=0.004) RR for AIDS when CV greater than the median and when VL suppression achieved at 6 months, 2.33 (95% CI 1.44 to 3.80, p=0.001) RR for AIDS when CV greater than the median and when VL suppression achieved at 12 months 1.78 (SE 24.11, p=0.941) coefficient for overall CD4 gain in association with CV, 52.19 (SE 10.87, p<0.001) coefficient for CD4 gain after 2 y of ART in association with CV
Delaney et al., USA[33]	MI type 1 (atheroembolic) and type 2 (vasospasm induced)	Log_2 VCY as a continuous variable Distribution of cumulative VL at 5 y was used	Doubling of CV: 1.06 (95% CI 1.02 to 1.10) aHR for both types of MI, 1.02 (95% CI 0.97 to 1.08) aHR for MI type 1, 1.10 (95% CI 1.06 to 1.15) aHR for MI type 2 Increase of CV from 25th to 75th percentile: 1.65 (95% CI 1.22 to 2.23) aHR for both types of MI, 1.22 (95% CI 0.78 to 1.91) aHR for MI type 1, 2.31 (95% CI 1.59 to 3.35) aHR for MI type 2
Elvstam et al., Sweden[45]	CVD (MI, stroke, heart failure)	VCY log_{10} copy-years/ml as continuous variable for overall, virologic suppression <50 copies/ml, LLV of 50–199 copies/ml, LLV of 200–999 copies/ml, high-level viraemia ≥1000 copies/ml	Overall: 1.03 (95% CI 1.01 to 1.05) for each log_{10} copy-years/ml increase When compared with those with virologic suppression (<50 copies/ml): 0.95 (95% CI 0.45 to 2.01) for LLV 50–199 copies/ml for each log_{10} copy-years/ml increase, 1.11 (95% CI 0.53 to 2.35) for LLV 200–999 copies/ml for each log_{10} copy-years/ml increase, 1.45 (95% CI 1.03 to 2.05) for high-level ≥1000 copies/ml viraemia for each log_{10} copy-years/ml increase

Table 3. (Continued)

Author, country	Outcome	Main exposure variable	Effect estimate
Harding et al., USA[46]	Stroke	VCY as copy-days/ml	Compared with participants with CV in 25th percentile: 0.91 (95% CI 0.45 to 1.9) HR for participants with CV in 75th percentile for any stroke, 0.97 (95% CI 0.46 to 2.1) HR for participants with CV in 75th percentile for ischaemic stroke
Kowalkowski et al., USA[26]	Non-AIDS-defining malignancy	VCY $\log_{10}$ copy-years/ml as a continuous variable, % of time undetectable as a categorical variable: <20%, 20–39%, 40–59%, 60–79% and ≥80%	1.22 (95% CI 1.06 to 1.40, p=−0.005) aHR for HL for each $\log_{10}$ copy-years/ml increase, 1.36 (95% CI 1.21 to 1.52, p<0.001) aHR for SCCA for each $\log_{10}$ copy-years/ml increase, 1.02 (95% CI 0.93 to 1.13, p=0.67) aHR for HCC for each $\log_{10}$ copy-years/ml increase Compared with participants with <20% time undetectable VL: 0.62 (95% CI 0.37 to 1.02, p=0.06) aHR for HL in participants with undetectable HIV VL ≥80% of time, 0.64 (95% CI 0.44 to 0.93, p=0.02) aHR for SCCA in participants with undetectable HIV VL ≥80% of time, 1.39 (95% CI 0.98 to 1.99, p=0.07) aHR for HCC in participants with undetectable HIV VL ≥80% of time
Laut et al., EuroSida[a,37]	Failure and HIV resistance, AIDS/non-AIDS clinical events	VCY copy-years/ml as a categorical variable, consecutive number of months with VL ≥50 copies/ml as a categorical variable, % of time on ART fully supressed as a categorical variable	Poor discriminative ability to predict clinical events after 5 y on ART VCY: p=0.33 for any AIDS/non-AIDS clinical event, p<0.01 for resistance, p=0.42 for triple class failure Consecutive months with VL ≥50 copies/ml: p=0.01 for any AIDS/non-AIDS clinical event, p=0.17 for resistance, p=0.65 for triple class failure Percentage of time on ART spent fully suppressed: p=0.22 for any AIDS/non-AIDS clinical event, p<0.02 for resistance, p=0.65 for triple class failure Note: p-values refer to the discriminative ability of VCY compared with the current VL reference

Table 3. (Continued)

Author, country	Outcome	Main exposure variable	Effect estimate
Zoufaly et al., Germany[17]	Incidence of AIDS lymphoma	VCY log_{10} as a continuous variable	All lymphomas: 1.67 (95% CI 1.27 to 2.20, p<0.001) aHR per 2000 d log_{10} copies/ml (reference group 0 d log_{10} copies/ml), 1.81 (95% CI 1.32 to 2.49, p<0.001) aHR CV in the past 3 y Burkitt NHL: 3.45 (95% CI 1.52 to 7.85, p<0.003) aHR per 2000 days log_{10} copies/ml (reference group 0 d log_{10} copies/ml) Non-Burkitt high-grade B cell NHL: 2.02 (95% CI 1.37 to 2.98, p<0.001) aHR per 2000 d log_{10} copies/ml (reference group 0 d log_{10} copies/ml) Primary CNS lymphoma: 1.00 (95% CI 0.39 to 2.57, p=1.00) aHR per 2000 d log_{10} copies/ml (reference group 0 d log_{10} copies/ml)
Chiao et al., USA[25]	Incidence of SCAC	% undetectable VL	Compared with participants with ≤20% of undetectable VL: 0.85 (95% CI 0.59 to 1.22, p=0.371) aHR for SCAC among participants with 21–40% undetectable VL, 0.86 (95% CI 0.59 to 1.23, p=0.389) aHR for SCAC among participants with 41–60% undetectable VL, 0.56 (95% CI 0.37 to 0.83, p=0.004) aHR for SCAC among participants with 61–80% undetectable VL, 0.55 (95% CI 0.40 to 0.77, p=0.0004) aHR for SCAC among participants with >80% undetectable VL

aHR: adjusted hazard ratio; aRR: adjusted relative risk; CNS: central nervous system; CV: cumulative viraemia; cVL: cumulative viral load; HCC: hepatocellular carcinoma; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; SCCA: squamous cell anal carcinoma; SE: standard error; VCY: viraemia copy-years.

always observed in patients with LLV,[51,52] which might partially explain the lack of increased risk of mortality[41] and morbidity in this subgroup.[45]

The prognostic value of CV depended on when it was measured. The impact of timing was demonstrated by Wang et al.,[16] who reported a greater mortality prognostic value of VCY calculated on the recent 3 y than that of the overall VCY or cross-sectional VL. The lack of prognostic value of distant viraemia could be partially explained by ART reversing the risk of opportunistic infections[53] or immune activation.[54]

Higher CV was associated with AIDS[24,37,44] and virological failure,[31] but not the overall incidence of opportunistic infections.[23,42] The type of participants and methods used to calculate CV varied among those studies, limiting their comparison. With increasing life expectancy among PLHIV, age-related morbidity such as from CVDs[55,56] or malignancies[57] is now prevalent in HIV cohorts. HIV replication is an important factor of chronic inflammation,[58] influencing atherosclerosis[59] and oncogenesis.[60] We found that CV strongly predicted AMI and CVD,[28,33,45] especially when the viraemia burden is high. It has been known that HIV viraemia contributes to the risk of stroke through HIV-associated and traditional stroke risk factors.[61] However, a study from the USA reported that increased hazards of stroke were not associated with CV; rather, they were predicted by baseline and time-updated VLs,[46] suggesting that acute VL increases might cause inflammatory responses, which in turn result in a higher risk of stroke. Those immune responses might be reversed by effective ART and subsequent viral suppression, reducing the risk of morbidity.[62] CV was reported as an independent risk factor for Burkitt lymphoma, Hodgkin lymphoma and squamous cell anal cancer, but not central nervous system–related lymphoma or breast or hepatocellular carcinoma,[17,25,26,34] emphasizing the complexity of oncogenesis and the yet not fully understood role of HIV replication in it.

Pallela et al.[27] found that longitudinal and cross-sectional viraemia measured individually and in combination predicted mortality very well, while others reported poor discriminative ability of CV indicators to predict mortality or morbidity when compared with the cross-sectional VL reference.[32,37] Cross-sectional VL is a simple indicator that should remain the basis for monitoring the effectiveness of ART and adherence in an individual, but it can fail to predict certain morbidity. Despite the challenges, the main advantage of CV is that it represents the overall viraemia status of a patient and as such is a good tool to simultaneously evaluate the individual and public health benefit of ART. Not all levels of CV are associated with mortality. However, unsuppressed VL may result in transmission, thus is a risk for public health. As demonstrated by Hughes et al.,[36] a cohort in the USA spent on average almost 1 month per year at a transmittable VL (>1500 copies/ml).

Reviewed studies applied different methods to measure CV, and as Sempa et al.[42] argue, this has an impact on its predictive value. In their study, CV predicted mortality up to 12 weeks from the last VL only when calculated on a logarithmic scale. Most of the studies included in this review measured CV by first summing VL values on a linear scale, followed by log transformation of the cumulative measure, which according to Sempa et al.[42] is a method prone to confounding and does not reflect the log-linear nature of the relationship between CV and clinical events. Furthermore, when using a limited number of VL tests, often spread over time, assumptions are made about the VL status between the two measurements. As demonstrated by Lesosky et al.,[63] CV for PLHIV with more time between VL measures tends to be biased upwards. They demonstrated that sampling frequency bias led to inaccuracy, which could especially affect study populations with longer exposure to ART and more frequent periods with reduced treatment adherence. In recent decades, technologies to measure VL have improved, demonstrating better sensitivity for viraemia detection. Therefore, the LLD of viraemia in included studies varied from 20 copies/ml to 500 copies/ml. Studies described various imputing strategies regarding the LLD, some setting the value to zero, while others included any VL value in the calculation of CV.

Our review was systematic and it used a replicable search strategy. It also has several limitations. Most of the studies were conducted in well-resourced settings with a high frequency of VL monitoring. This may not reflect the reality of countries with limited resources with a high HIV burden. Most of the studies included in the review were observational, which reduces their capacity to demonstrate causality and we cannot exclude residual confounding. The duration of follow-up may have been insufficient to demonstrate the long-term impact of viraemia on health outcomes. Our review was unable to answer if CV is better than cross-sectional indicators in measuring the risk of unfavourable treatment outcomes. Furthermore, we were unable to assess whether to a certain extent level-to-level viraemia could be tolerated, and from which level onwards does the risk of mortality increase. From a practical point of view, estimating the level of CV burden in HIV cohorts can facilitate identification of patients who would benefit from differentiated care models, such as those who need frequent clinical visits with VL monitoring and enhanced adherence support. CV could also facilitate the selection of patients who need screening for comorbidities, such as CVD and malignancy. However, without a standardized methodology to estimate CV, the comparison of its burden or its effect on health outcomes among different HIV cohorts remains challenging. Further research into a standardized methodology of cumulative HIV viraemia is needed.

Conclusions

Cross-sectional measures of viraemia play an important role during the monitoring of treatment response but may fail to predict some health outcomes, including morbidity caused by long-term inflammation. CV is associated with adverse health outcomes in PLHIV on ART, especially at higher levels. However, the role of CV in clinical and programmatic management is yet to be established and may increase as cohorts grow older.

Supplementary data

Supplementary data are available at *International Health* online.

Authors' contributions: AM, TD and LL conceptualized and designed the study. AM and LL developed and performed the search and extracted the data. AM drafted the original manuscript. All authors contributed to the data analysis and data interpretation, made major contributions to manuscript writing and approved the final version of the manuscript.

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