Annals of Epidemiology 38 (2019) 22–27

Contents lists available at ScienceDirect

Annals of Epidemiology

Original article

Bias in the estimation of cumulative viremia in cohort studies of HIV-infected individuals

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ARTICLE INFO

Article history:
Received 28 January 2019
Accepted 16 August 2019
Available online 23 August 2019

Keywords:
cumulative viral load
HIV
viral load
cumulative exposure
viral copy years

ABSTRACT

Purpose: The use of cumulative measures of exposure to raised HIV viral load (viremia copy-years) is increasingly common in HIV prevention and treatment epidemiology due to the association of long-term elevated viral load with more rapid progression to disease. We sought to estimate the magnitude and direction of bias in a cumulative measure of viremia caused by different frequency of sampling and duration of follow-up.
Methods: We simulated longitudinal viral load measures and reanalyzed cohort study data sets with longitudinal viral load measurements under different sampling strategies to estimate cumulative viremia.
Results: In both simulated and observed data, estimates of cumulative viremia by the trapezoidal rule show systematic upward bias when there are fewer sampling time points and/or increased duration between sampling time points, compared with estimation of full time series. Absolute values of cumulative viremia vary appreciably by the patterns of viral load over time, even after adjustment for total duration of follow-up.
Conclusions: Sampling bias due to differential frequency of sampling appears extensive and of meaningful magnitude in measures of cumulative viremia. Cumulative measures of viremia should be used only in studies with sufficient frequency of viral load measures and always as relative measures.

Introduction

Cumulative measures of exposure are widely used in different areas of epidemiologic research in the estimation of the effects associated with exposures over time [1]. In infectious disease epidemiology, cumulative viral load (cVL), or viremia copy-years, has been proposed as an estimate of the cumulative exposure to raised HIV-RNA viral load (VL) in individuals infected with HIV. This cumulative exposure measure has high biological plausibility: raised VL is the primary marker of both disease control and infection transmission risk [2], and long durations with elevated VL are associated with more rapid progression to disease (AIDS) and mortality. In individuals receiving antiretroviral therapy (ART), raised VL is associated with treatment failure and poor long-term treatment outcomes [3]. Cumulative exposure to raised VL has been hypothesized as a potential risk factor, or predictor of poor outcomes [4–6].

cVL appears to have been developed independently by Zoufaly et al. [7] and Cole et al. [8] to associate VL measures with outcomes related to the development of AIDS. Subsequently, variants of cVL appeared in use across a variety of studies, where the measure was often intended as a potential risk factor to predict outcomes such as all-cause mortality [4–6,9,10]. The empirical evidence for cVL as a useful prognostic factor for long-term outcomes is mixed. Although there is a biological argument to be made that the cumulative exposure to raised VL [11,12] could be predictive of health outcomes, the empirical measurement of cumulative exposure by cVL has failed to demonstrate consistent associations. For example, Cates et al [13] conclude that cVL burden before pregnancy is not informative in a study of risk of pregnancy loss among HIV-infected women, but current VL appears highly predictive. In a follow-up efficacy study comparing the antiretroviral drugs efavirenz and boosted lopinavir, cautious optimism was expressed toward the use of cVL as a prognostic factor [14]. Kukoyi et al [15] found that a $\log_{10}$ copies/mL/year measure to evaluate morbidity outcomes in a pediatric cohort was predictive, but the VL measure is included in analyses as a discrete variable, with just three levels. Kowalkowski et al [16] also found associations in subanalyses between a measure

The authors have no competing interests to declare.

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https://doi.org/10.1016/j.annepidem.2019.08.008
1047-2797/

of cVL and non-AIDS–defining malignancies, utilizing a complex series of data imputation on 7-day follow-up windows. Taken together, it remains unclear if cVL has greater utility than current or most recent VL.

Common concerns related to cumulative measures of exposure in epidemiology include time-based dependence of exposure and the method of measurement (direct or indirect) [7]. cVL may be defined as the area under the plasma VL curve and has been calculated using copies/mL or $\log_{10}$ copies/mL. However, the phrase "under the curve" is not precise, as VL is not continuously measured over time, but sampled at discrete time points, and therefore the true individual trajectory is unknown and the area must be approximated using integral approximation methods. Some of the mixed empirical results in estimating the association of cVL to health outcomes may be due to the inconsistencies in estimation. Most analyses estimate cumulative viremia or viral copy-years using the trapezoidal rule, which sums the areas between two successive points joined by linear interpolation [17]. Although it has been established that this method is scale dependent [18], no research has examined the impact of sampling frequency bias. Here we estimate the bias due to changes in sampling frequency when estimating cVL by the trapezoidal rule. We utilize two empirical and one simulated data set, each with repeated VL measures, to estimate the magnitude and direction of the bias in the estimation of cVL and make recommendations for improved usage.

Methods

Data sources

We used three different data sources to examine how sampling time points affect cVL estimation: an intensively monitored cohort of women initiating ART [11], a simulated data set of longitudinal HIV VL trajectories developed for a monitoring study [19,20], and a random sample of routine VL data collected by the South African National Health Laboratory Services [21]. The two empirical data sets were selected to reflect different types of data collection, either under intensive health research and follow-up or under routine care and with different expected longitudinal VL trajectories drawing from different populations. The inclusion of simulated data provides an opportunity to evaluate estimation of cVL at different sampling frequencies against a known "truth."

The cohort study has VL measures of 518 women initiating ART during pregnancy and followed up to approximately 18 months postpartum. This is a frequently measured cohort with a median of 7 VL measures during the follow-up, which is much more frequent than most routine clinical settings. The routine monitoring sample includes $n = 29{,}519$ individuals, who were not virally suppressed for the entire duration of follow-up and had a minimum of 5 VL measures from the National Health Laboratory Services data set. The sample is extracted from routine laboratory data comprising individuals in ART programs in the Western Cape, South Africa. This routinely collected monitoring data have either 6 or 12 months between VL measures, on average, following South African treatment guidelines [22].

The simulated data set is contributed from a model of longitudinal VL trajectories for 80 weeks on a weekly time step [20]. The data are simulated to mimic trajectories and conditions of patients initiating ART during pregnancy and contains a simulated sample of 10,000 individuals. Briefly, simulation model parameters for this analysis were 100% of women initiating ART during pregnancy at a mean gestational age of 21 week and 5% in the "nonadherent" class, and 30% in the partially adherent class.

This study is an analysis of secondary data that were originally collected by studies carried out under ethics approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (865/2016; 329/2014; 451/2012).

Estimation of cVL

Log_{10} VL measures are used throughout in the calculation of cVL. cVL is calculated for each time series using the trapezoidal rule which uses a linear approximation between successive points (Equation 1 and Fig. 1). VL measures below 50 copies per mL are set to zero to avoid an increase in cVL while below the limit of detection. In addition to estimating cVL over the given time frame (between first and last VL observations, regardless of total duration of observation), we calculate a standardized cVL that adjusts for individual follow-up time (Equation 2). Median (interquartile) range of the individual estimates of cVL is reported.

$$cVL = \frac{t_n - t_0}{n}\left[\frac{VL(t_0) + VL(t_n)}{2} \sum_{k=1}^{n-1} VL\left(t_0 + k\frac{t_n - t_0}{n}\right)\right] \quad (1)$$

$$cVL_{FU} = cVL(J) \,/\, t_n \quad (2)$$

Subsampling

We calculate cVL based on subsets of the available data and compare these estimates to the cVL_{REF}, which uses every data point in the full time series. We use two different subsampling strategies: (1) random subsample to a set number of VL measures ($n = 2$–5),

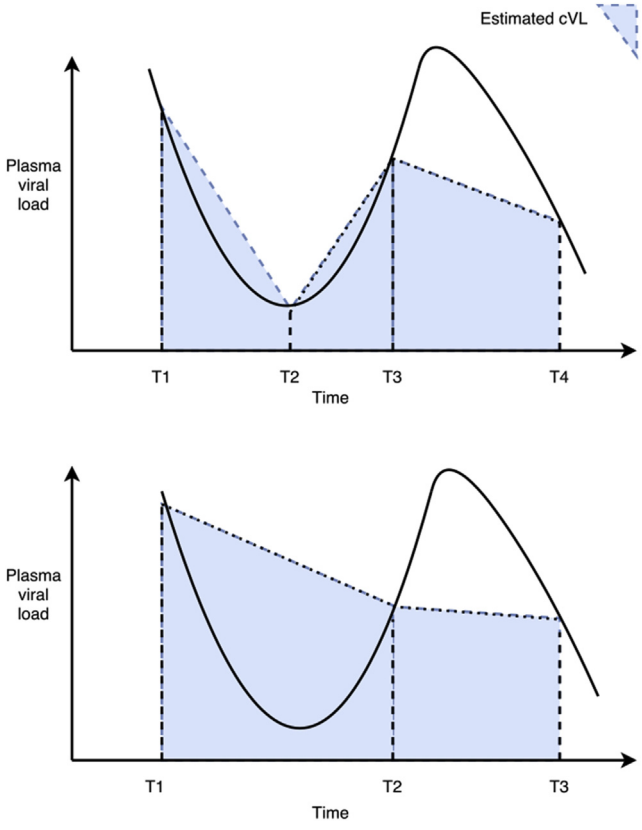

Fig. 1. Schematic of plasma VL versus time for one profile under two different monitoring schemes. Profile A (top) has been measured at 4 time points and profile B (bottom) at only three time points. In each profile, the resulting estimated cVL is represented by the shaded region.

Table 1
Summary characteristics of data sets used for estimation of cVL

Characteristic	Simulated data, $n = 10{,}000$	Cohort, $n = 518$	Routine laboratory, $n = 29{,}519$
VL measures (N)	601,070	3519	253,503
Proportion VL < 50	0.17	0.66	0.39
Proportion VL 50–1000	0.67	0.16	0.188
Proportion VL > 1000	0.16	0.19	0.43
VL measures available per individual median (Q1, Q3)	61 (55, 65)	7 (5, 9)	7 (6, 9)
Follow-up duration per individual (y) median (Q1, Q3)	1.2 (1.0, 1.2)	1.1 (0.6, 1.4)	3.8 (2.7, 5.2)
Follow-up duration per individual (wk) median (Q1, Q3)	60.0 (54.0, 64.0)	59.6 (33.6, 71.6)	199.7 (142.4, 271.7)
Median time between observations per individual median (Q1, Q3) (wk)	1.0 (1.0,1.0)	7.1 (4.9, 13.0)	19.8 (4.0, 33.7)
Total person-years	11,367	548	117,279

ensuring that the first and last VL measures per individual are always retained to ensure consistency with total follow-up time and (2) sampling based on average interval between VL measures, retaining the first and last VL measures per individual.

Analyses

Proportion of VL measures below 50 copies/mL, between 50 and 1000 copies/mL, and above 1000 copies/mL are calculated for each data set. Median and interquartile ranges (IQRs) are used to summarize the number of observations per individual, the duration of follow-up (years, weeks), and the time between consecutive observations. Duration of follow-up is calculated as days between the last and first observation in the data set and converted to appropriate units. Median (IQR) for estimated cVL is provided, as well as the percent change compared with cVL_{REF}. This estimate reflects both the viremia and duration of follow-up of individuals in the respective data sets. A follow-up standardized measure is also calculated and reported with the same measures to reduce the dependence on the individual's total duration of follow-up. This measure is analogous to the viral copy-year. The cVL_{FU} is calculated using all available VL measures and then individually standardized for total follow-up time. Cohort VL trajectories were visualized using linear and generalized additive model smoothing with a natural b-spline.

Results

Characteristics of the three data sets can be found in Table 1. The data sources vary over indicators including the median number of VL measures available per individual, the median time between VL measures, and the total duration of follow-up. The median duration between VL measures varies from a low of one week (simulated data) to a high of five months (routine laboratory data). The median VL measures available per person is 7 (IQR: 5–9), 7 (IQR: 6–9), and 21 (IQR: 15–26) in the cohort, routine monitoring, and in the simulated data sets, respectively. The duration of follow-up is the longest in the routine data, at a median of 3.8 years (IQR: 2.7–5.2 years) and shortest in the cohort data at 1.1 years (IQR: 0.6, 1.4 years).

The cVL_{REF} is calculated using all available VL measures in each data set and represents the most accurate possible measure of cVL (Table 2). The median cVL measure is 0.49 $\log_{10}$ copies/mL years (IQR: 0.20–0.97 $\log_{10}$ copies/mL years) using the cohort data, 7.39 $\log_{10}$ copies/mL years (IQR: 4.55–11.41 $\log_{10}$ copies/mL years) in the routine monitoring laboratory data, and 2.08 $\log_{10}$ copies/mL years (IQR: 1.84–2.72 $\log_{10}$ copies/mL years) in the simulated data. The median standardized cVL measure in the cohort is 0.50 $\log_{10}$ copies/mL year (IQR: 0.23–1.34 $\log_{10}$ copies/mL year), in the routine laboratory data 2.10 $\log_{10}$ copies/mL year (IQR: 1.29–3.12 $\log_{10}$ copies/mL year), and in the simulated data 2.09 $\log_{10}$ copies/mL year (IQR: 1.57–2.24 $\log_{10}$ copies/mL year).

Large differences in estimated cVL are found between cVL_{REF} compared with random subsamples with reduced numbers of observations (Table 2). There is a significant and meaningful bias toward overestimation, ranging from +50% to +344% change compared with cVL reference in the cohort, and a +16% to +44% change from reference in the simulated data. The routine monitoring data demonstrate a different pattern of bias of small but consistent overestimation of between +3% and +4% from reference cVL. Use of the follow-up standardized reference measure reduces the extent of the bias in the cohort and simulation data,

Table 2
Estimated cVL using complete time series per individual (bold) and using different random subsamples of observations

Characteristic	Simulated data	Cohort	Routine laboratory
Reference cVL (cVL_{REF})	**2.08 (1.84, 2.72)**	**0.49 (0.20, 0.97)**	**7.39 (4.55, 11.41)**
cVL_2 subsample: $n = 2$ VL/person (first and last observations)	2.99 (2.44, 3.71)	2.17 (0.93, 3.18)	7.52 (3.98, 11.82)
Percent change from cVL_{REF}	+44%	+344%	+2%
cVL_3 subsample: $n = 3$ VL/person	2.62 (2.08, 3.24)	1.05 (0.53, 1.93)	7.69 (4.35, 11.94)
Percent change from cVL_{REF}	+26%	+115%	+4%
cVL_4 subsample: $n = 4$ VL/person	2.48 (1.98, 3.06)	0.79 (0.42, 1.53)	7.58 (4.43, 11.90)
Percent change from cVL_{REF}	+19%	+62%	+3%
cVL_5 subsample: $n = 5$ VL/person	2.41 (1.94, 2.95)	0.73 (0.37, 1.42)	7.52 (4.46, 11.82)
Percent change from cVL_{REF}	+16%	+50%	+2%
Standardized reference cVL ($cVL_{FUD} = cVL_{REF}$/FUD_y)	**2.09 (1.57, 2.24)**	**0.50 (0.23, 1.34)**	**2.1 (1.29, 3.12)**
cVL_2 subsample: $n = 2$ VL/person (first and last observations)	2.65 (2.19, 3.22)	2 (1.54, 2.50)	2.21 (1.27, 3.14)
Percent change from cVL_{FUD}	+27%	+301%	+5%
cVL_3 subsample: $n = 3$ VL/person	2.34 (1.86, 2.84)	1.24 (0.59, 1.74)	2.21 (1.35, 3.21)
Percent change from cVL_{FUD}	+12%	+149%	+5%
cVL_4 subsample: $n = 4$ VL/person	2.24 (1.78, 2.65)	0.79 (0.37, 1.50)	2.18 (1.33, 3.21)
Percent change from cVL_{FUD}	+7%	+59%	+4%
cVL_5 subsample: $n = 5$ VL/person	2.20 (1.72, 2.55)	0.59 (0.30, 1.26)	2.15 (1.32, 3.19)
Percent change from cVL_{FUD}	+5%	+18%	+2%

Estimates given as median (IQR) of individual cVL calculations and as relative percent change between median cVL levels. Values given as median (Q1, Q3) unless specified.

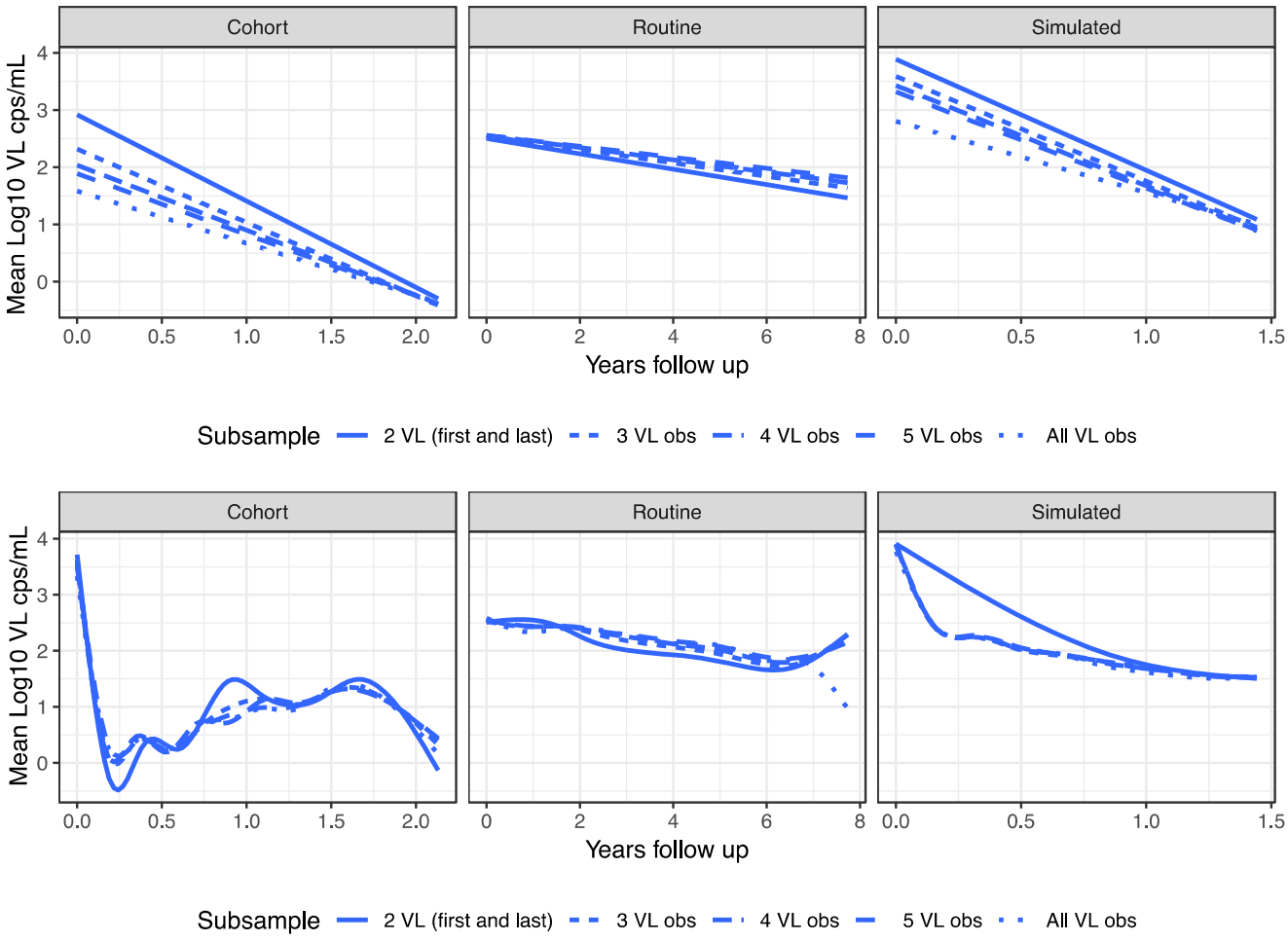

Fig. 2. Smoothed sample trajectories for each data set under subsampling. Top panel is linear fit and bottom panel fit by generalized additive models (GAMs) using all VL measures available in each of the available (subsampled) data sets.

where it ranges from +18% to +301% (cohort) and +5% to +27% (simulation). In the routine laboratory data, the change from reference remained consistently positive and ranged from +2% to +5%. In general, the different subsamples give estimates further away from the reference measure as the number of subsamples decreases (Table 2).

Figure 2 shows smoothed trajectories for subsamples, under linear and generalized additive model smoothing, to aid in understanding the mean data trends under each of the subsampling strategies. Specifically, we see that both the linear and spline fits show the 2 VL subsample superior to the fits of all other samples, including the complete data case in the cohort and simulated data, but this is reversed in the routine laboratory data.

When evaluating the subsamples where sampling was based on increasing the mean duration between VL measures, there was an increasing positive bias in the estimation of cVL, from +7% to +20% as the duration between samples increases from 4 weeks to 24 weeks. The empirical cohort data demonstrate the same trend, but with much larger bias, ranging from +36% at 4 weeks minimum duration to +335% at 24 weeks minimum duration between samples. It is important to note that the sample size reduces as the duration between samples increases in the cohort data. Estimation of the follow-up time standardized version of cVL for the same subsets indicates a similar tendency but with a slightly smaller magnitude of bias compared with the nonstandardized estimates, ranging to only +9% in the simulated data to +299% in the cohort data (Table 3).

Discussion

Estimating the true cumulative exposure by approximating the area under a curve using repeat measures of a biomarker such as VL on time scales that are routine in clinical care (weeks to months) is subject to a number of sources of bias. As the “true” shape of the trajectory between measurements is unknown, approximation of cVL has typically been by a crude method of geometric approximation known as the trapezoidal rule. In most empirical work with repeated measures of VL, the sparsity of VL measures over time ensures that accurate approximation of the true trajectory is unlikely. Even within a single study, unless VL measures occur with the same timing and frequency for every individual, the measure of cVL may be more reflective of sampling frequency bias than any underlying biological mechanism: cVL for individuals with fewer, or more widely spaced measures will be inaccurate and biased upward compared with individuals with more, or more frequent, VL measures. This analysis also demonstrates that estimates of cVL depend, at least in part, on the overall proportion of individuals with well-controlled VL, hence the number of measurements less than the limit of detection and the behavior of the trajectories—for example the relative proportion of individuals initiating versus continuing ART.

Estimation of cVL via the trapezoidal rule has the potential for significant bias and inaccuracy depending on the frequency of VL measures and underlying stochastic process. In populations with

Table 3
Estimated cVL using complete time series per individual (bold) and using different frequencies of observations for subsamples

Characteristic	Simulated data		Cohort data	
	cVL_{REF}	cVL_{FUD}	cVL_{REF}	cVL_{FUD}
Reference cVL (all samples)	**2.08 (1.84, 2.72)**	**2.09 (1.57, 2.24)**	**0.49 (0.20, 0.97)**	**0.50 (0.23, 1.34)**
4 wk between samples	2.25 (1.8, 2.74)	2.07 (1.64, 2.31)	0.67 (0.37, 1.12)	0.73 (0.36, 1.52)
Percent change from cVL_{REF}	+8%	−1%	+36%	+46%
8 wk between samples	2.23 (1.83, 2.75)	2.07 (1.61, 2.34)	0.79 (0.48, 1.55)	1.07 (0.47, 1.83)
Percent change from cVL_{REF}	+7%	+0%	+62%	+115%
12 wk between samples	2.31 (1.91, 2.82)	2.14 (1.65, 2.4)	0.98 (0.58, 1.93)	1.26 (0.63, 1.95)
Percent change from cVL_{REF}	+11%	+2%	+100%	+154%
24 wk between samples	2.5 (1.99, 3.02)	2.27 (1.75, 2.61)	2.12 (0.92, 3.09)	1.99 (1.53, 2.48)
Percent change from cVL_{REF}	+20%	+9%	+335%	+299%

Estimates given as median (IQR) of individual cVL calculations and as relative percent change between median cVL levels. Values given as median (Q1, Q3) unless specified.

moderate to high rates of partial or nonadherence, long periods between observations may result in inaccuracy with respect to estimation of the time an individual spends with elevated VL. Similarly, different frequencies of observation have a clear impact on estimated cumulative viremia and tend to, if anything, overestimate the exposure. Cumulative VL may be a useful indicator for relative exposure within studies if individuals have been subject to similar frequency and timing of VL measures. Comparison of cVL between data sets or studies is best undertaken with a great deal of caution, as variation in observation frequency or timing invalidates comparison of the relative measure. There are examples where it may be feasible to compare cVL across studies or cohorts, for example, comparing routine laboratory VL data that have been collected under the same monitoring guidelines across districts within a country. While relative measures of exposure, for example, pack-years in smoking exposure, are routinely compared across studies, it is necessary to do so with an assumption that the underlying exposure is not changing substantially over time, although this is rarely stated.

Limitations in this analysis include not accounting for the variation in the upper limit of quantification, which may vary by assay and would have a clear additional impact on estimation of cVL. As a rule, measures of cVL using assays with higher upper limits will result in higher estimates of cVL, and this effect would typically be on a log order magnitude. There are other sources of variation; in particular, in observational data, the number of VL measures an individual has over a period may be a reflection of access and engagement to care.

Some approaches to reducing the impact of sampling bias have been applied. Mugavero et al. [4] use inverse weights to adjust for sampling frequency, resulting in a positive association between cVL and mortality outcomes. However, this approach is only applicable in the case where a reasonable approach to estimation of the inverse weights is possible. Other integral estimation methods are available, for example, composite Simpson's rule [17] which uses a third-order polynomial to interpolate between successive points and is known to be more accurate than trapezoidal estimation [17], but requires evenly spaced time points which are uncommon in most cohort studies. Another approach may be to avoid attempts at cumulative viremia exposures altogether in favor of simpler measures which may be more directly interpretable [23,24]. Finally, we note that the use of the term cumulative viremia or viral copy-years is nonprecise, as different researchers have utilized slightly different definitions, in terms of using copies/mL versus $\log_{10}$ copies/mL, different methods of handling of VL measures less than the limit of detection, and different methods of follow-up duration standardization. The key point here is that without standardization of the estimate, and without an explicit process for managing sampling frequency and other sources of obvious bias, the measures of cumulative exposure to raised HIV VL cannot be presumed consistent and are unlikely to be comparable across studies.

In summary, cVL exposure estimates should be used with caution as they will tend to overestimate the true exposure to raised viremia and should not be used as an absolute measure of comparison between studies or cohorts with different frequencies of VL monitoring. Utilization of cVL as a relative measure within a well characterized and consistently observed cohort may provide useful relative estimates of differential exposure to raised VL over time.

Acknowledgments

The authors thank the MCH-ART study and South African National Health Laboratory Service project for contribution of anonymized data utilized in this analysis, as well as the anonymous reviewers for helpful suggestions to improve the manuscript.

The work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health [R21HD093463]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. T.G. and B.R. were supported by the Medical Research Council of South Africa in terms of the National Health Scholars Programme from funds provided for this purpose by the National Department of Health/Public Health Enhancement Fund; South African Department of Science and Technology/National Research Foundation (DST-NRF), Centre of Excellence in Epidemiological Modeling and Analysis (SACEMA), Stellenbosch University, Stellenbosch.

Authors' contributions: M.L. and L.M. conceived of the study idea. M.L., L.M., E.J.A., and N-Y.H. contributed to the acquisition of the data. M.L. and T.G. developed the simulation model. M.L., B.R., and T.G. carried out the analysis and interpretation of the results. M.L. and T.G. wrote the first draft. All authors reviewed and critically revised the draft and approved the final version to be submitted.

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