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Viral load monitoring and antiretroviral treatment outcomes in a pediatric HIV cohort in Ghana

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Abstract

Background: HIV-infected children in sub-Saharan Africa may be at a high risk of staying on a failing first-line regimen and developing drug-resistance HIV variants due to lack of routine viral load monitoring. We investigated whether cumulative viral load, measured as viremia copy-years (VCY) could predict morbidity in a setting where viral load is not routinely monitored.

Methods: This was a single-center prospective observational longitudinal study of HIV-infected children initiating antiretroviral therapy (ART) at the Pediatric HIV/AIDS Care program at Korle-Bu Teaching Hospital in Accra, Ghana. The main outcome was morbidity measured as frequency of hospitalizations, opportunistic infections, and outpatient sick visits. The main explanatory variable was viral load measured as VCY.

Results: The study included 140 children who initiated ART between September 2009 and May 2013 and had at least 2 viral load measurements. There were 184 hospitalizations, with pneumonia being the most common cause (22.8 %). A total of 102 opportunistic infections was documented, with tuberculosis being the most common opportunistic infection (68 %). A total of 823 outpatient sick visits was documented, with upper respiratory infections (14.2 %) being the most common cause. Forty-four percent of our study participants had >4 $\log_{10}$ VCY. Children in this sub-cohort had a higher frequency of sick visits compared with those with <4 $\log_{10}$ VCY ($p = 0.03$). Only 6.5 % of children with >4 $\log_{10}$ VCY had been identified as treatment failure using WHO clinical and immunological treatment failure criteria.

Conclusions: High level of cumulative viral load may translate to virological failure and subsequent increased all-cause morbidity. Our finding of potential utility of VCY in pediatrics warrants further investigations. VCY may be a good alternate to routine viral load measurement as its determination may be less frequent and could be personalized to save cost.

Keywords: Pediatric HIV, Cumulative viral load, viral copy years, Morbidity, Resource-limited setting

Background

The advent of antiretroviral therapy (ART) has reduced HIV-associated morbidity and mortality in HIV-infected individuals. The benefits of ART have been substantial in sub-Saharan Africa, home to over 90 % of children living with HIV/AIDS [1]. Unfortunately, with the unprecedented scale-up of ART in resource-limited countries and the success of prevention of mother to child transmission (PMTCT) of HIV, pediatric HIV ART coverage still lags behind that of adults. At the end of December 2013, only 23 % of the 3.2 million children estimated to be living with HIV were receiving ART [2]. The World Health Organization (WHO) recently revised its recommendation on when to start ART in children; ART should be initiated among all children (<10 years of age) and adolescents (10 to 19 years) living with HIV, regardless of WHO clinical stage or CD4 cell count [3]. Based on this new recommendation, ART coverage in children living with HIV will increase sharply in the next couple of years.

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Increase in ART coverage will exacerbate the existing challenges with laboratory monitoring of ART in resource-limited countries. In resource-rich countries, ART is monitored routinely with laboratory measures such as blood chemistry, HIV viral load, and CD4 count for early detection of medication side-effects and drug-resistant viruses [4, 5]. The WHO recommendation for ART monitoring has evolved over time from CD4 monitoring every six months and viral load testing only when the capacity exists [6] to viral load being recommended as the preferred monitoring approach to diagnose and confirm treatment failure [3]. However, if viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure [3]. This compromise is due to the fact that routine laboratory monitoring is not feasible in most resource-limited countries due to cost, lack of technical expertise, and lack of infrastructure [7]. Several studies from sub-Saharan Africa have reiterated the need for universal access to viral load monitoring of ART as clinical and immunologic monitoring of treatment failure are not sensitive enough [8–12]. We recently reported that the rate of virological treatment failure after at least 24 weeks on first-line regimen was 16.7 % in our pediatric HIV cohort in Ghana [13]. The virological treatment failure rate in HIV-infected children receiving ART in sub-Saharan ranges from 13 % to 44 % [14–16].

In many resource-limited settings, clinicians rely on clinical and immunologic criteria to identify children failing first-line therapy. These criteria have low sensitivity and positive predictive value of detecting virological failure [11, 17]. Thus without viral load monitoring of ART, HIV-infected children in sub-Saharan Africa may be at increased risk of staying on a failing first-line regimen and developing drug-resistant HIV variants [18–20]. Viral load is therefore an essential complementary test to CD4 cell count [21] in monitoring treatment. The question, therefore, is not whether to do viral load testing in resource-limited countries but what is the most cost-effective way of monitoring viral load. Routine viral load monitoring (every 3–4 months) in resource-rich countries over 20 years was found to have limited additional health benefit considering the cost [22]. Taken together, there is a need to explore different cost-effective viral load measures such as less frequent, targeted, viral load measurements (based on clinical and immune response to ART) and cumulative viral load.

Given the grave consequences of virological treatment failure both at the individual and population level, we designed an exploratory prospective observational study of HIV-infected children receiving care at Korle-Bu Teaching Hospital in Accra, Ghana, to study biomarkers for monitoring ART in children [13, 23]. The main objectives of the current study were: (1) to evaluate the association between cross-sectional viral load and frequency of morbidity while on ART; and (2) to explore whether cumulative viral load, measured as viremia copy-years (VCY) [24], could predict morbidity in a setting where viral load is not routinely monitored.

Methods

Study population
This was a single-center prospective observational longitudinal study of HIV-infected children initiating ART at the Pediatric HIV/AIDS Care program at Korle-Bu Teaching Hospital in Accra, Ghana, from September 2009 to May 2013. Korle-Bu Teaching Hospital (KBTH) is the largest tertiary hospital in Ghana. The Pediatric HIV/AIDS Care program provides comprehensive HIV/AIDS care to over 1100 children. All study participants were on their first-line regimen. The first-line regimen available at the clinic is non-nucleoside analog (NNRTI)-based ART consisting of zidovudine (AZT), lamivudine (3TC), plus either nevirapine (NVP) or efavirenz (EFV).

The rationale, organization, and recruitment of the subjects for the cohort study have been previously described [13]. In brief, we enrolled children aged 0 to 13 years whose biological parents or guardians agreed to participate in a longitudinal study. Written consents from parents or guardians and assents from children were obtained before enrollment in the study. The participants were seen and examined at the pediatric HIV clinic every 4–6 months in accordance with local standard-of-care. At enrollment and subsequent follow-up visits, blood samples were collected for determination of CD4 cell count/percentage, HIV viral load, and complete blood count. The study was reviewed and approved by the Ethics and Protocol Review Committees of University of Ghana Medical School and Yale University School of Medicine.

Study variables
Outcome variables
The main outcome measure was morbidity; measured as frequency of hospitalizations, opportunistic infections, and outpatient sick visits.

Explanatory variables
The main explanatory variable was viremia copy-years (VCY). VCY was defined as the number of copies of HIV RNA/ml/year [24]. Other variables included, gender, age, caregiver type, parental HIV status, history of AIDS defining illness, duration of ART, and WHO clinical staging of HIV infection.

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Other study measures

CD4 cell count and HIV viral load measurements

CD4 absolute cell count and percentage were quantified by a dual-platform flow cytometry technology using a FACS-Count system (Becton-Dickinson, Franklin Lakes, NJ, USA) at the clinical laboratory at Korle-Bu Teaching Hospital (KBTH) according to manufacturer's instructions. HIV viral load was measured using the COBAS® AmpliPrep and the COBAS® TaqMan® 48 Analyzer (Roche Diagnostic Systems, NJ, USA) for automated sample preparation and amplification and detection, respectively. The limit of HIV-1 RNA detection was 20 copies/mL. The laboratory participates in an external quality assurance testing program by the South African Public Health Reference Laboratory.

Definitions

WHO clinical treatment failure

WHO defines clinical failure as a new or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective ART [25].

WHO immunological treatment failure

WHO defines immunological failure as a CD4 count of <200 cells/mm^3 or CD4 < 10 % for children under 5; and a CD4 count of <100 cells/ mm^3 for children above five years of age [25].

WHO virological treatment failure

WHO defines virological treatment failure as plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months of ART, with adherence support [25].

Statistical analysis

Descriptive measures were used to summarize the data. Continuous variables were summarized using mean and standard deviation (SD); categorical variables were summarized using frequency and percent (%). Morbidity was measured using frequency of hospitalizations, opportunistic infections, and outpatient encounters. VCY was calculated as described above. A $\log_{10}$ transformation of each viral load measurement was performed and the area under the curve (AUC) was calculated. Participants were stratified into 3 categories: those with <2$\log_{10}$ VCY (low VCY), 2–4 $\log_{10}$ VCY (intermediate VCY) and >4$\log_{10}$ VCY (high VCY). Wilcoxon Rank Sum test and Fisher's exact tests were used to compare continuous and categorical variables, respectively, among the groups. Regression analyses using logistic regression models were used to estimate the odds of having low, intermediate or high VCY. Two-sided *p*-values are reported for all the statistical tests

used in the analysis. Analyses were performed using SAS 9.3 (Cary, NC).

Results

Characteristics of study participants

We included 140 children who initiated ART between September 2009 and May 2013 with at least 2 viral load measurements. There were no loss to follow up during the study period. Table 1 summarizes the demographic characteristics of the study group. Of the 140 children, 56 (40 %) were female and 84 (60 %) were male. The primary caregiver for the children in this study was predominantly the biological mother (62 %) but varied considerably and included aunt (10 %), uncle (4 %), father (9 %), grandmother (13 %), and stepmother (2 %).

Morbidity among study participants

Morbidity was measured as frequency of hospital admissions, opportunistic infections, and outpatient sick visits. There were a total of 184 hospital admissions, with pneumonia – clinical and radiological diagnosis - being the most common cause (22.8 %). A total of 102 events of opportunistic infections was documented, with TB being the most common (68 %). A total of 823 outpatient

Table 1 Demographic characteristics of study participants

Characteristics	Frequency
	N = 140(%)
Age group (years)	
≤5	18 (12.85)
6–12	95 (67.86)
13–17	27 (19.29)
Gender	
Male	84 (60 %)
Female	56 (40 %)
HIV status of mother	
Positive	93 (66.43)
Negative	4 (2.86)
Unknown	43 (30.71)
HIV status of father	
Positive	34 (24.29)
Negative	17 (12.14)
Unknown	89 (63.57)
Caregiver	
Aunt	14(10.00)
Father	12 (8.57)
Grandmother	18 (12.85)
Mother	87 (62.14)
Stepmother	3 (2.14)
Uncle	6 (4.28)

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sick visits was documented within the group, with upper respiratory infections (14.2 %). Figure 1 illustrates the five most common diagnoses for each of the morbidity measures.

Association between viral load and morbidity

The mean follow up time was 4.3 years (SD ± 2.4). The median number of viral load measurements was 2 with a range of 2 to 8 measurements. We did not have uniform number of viral load measurements among study participants due to periodic shortages of reagents and technical difficulties with the viral load machine. We assessed whether there was any correlation between the number of viral load measurements and the outcome measures of interest (i.e., frequency of hospitalizations, opportunistic infections, and outpatient sick visits). There was no significant correlation between number of viral load measurements and any of the outcome measures. We then analyzed the temporal relationship between viral load and the outcome measures (Fig. 2). As illustrated in the time plots, the number of viral loads increased steadily with time for each participant.
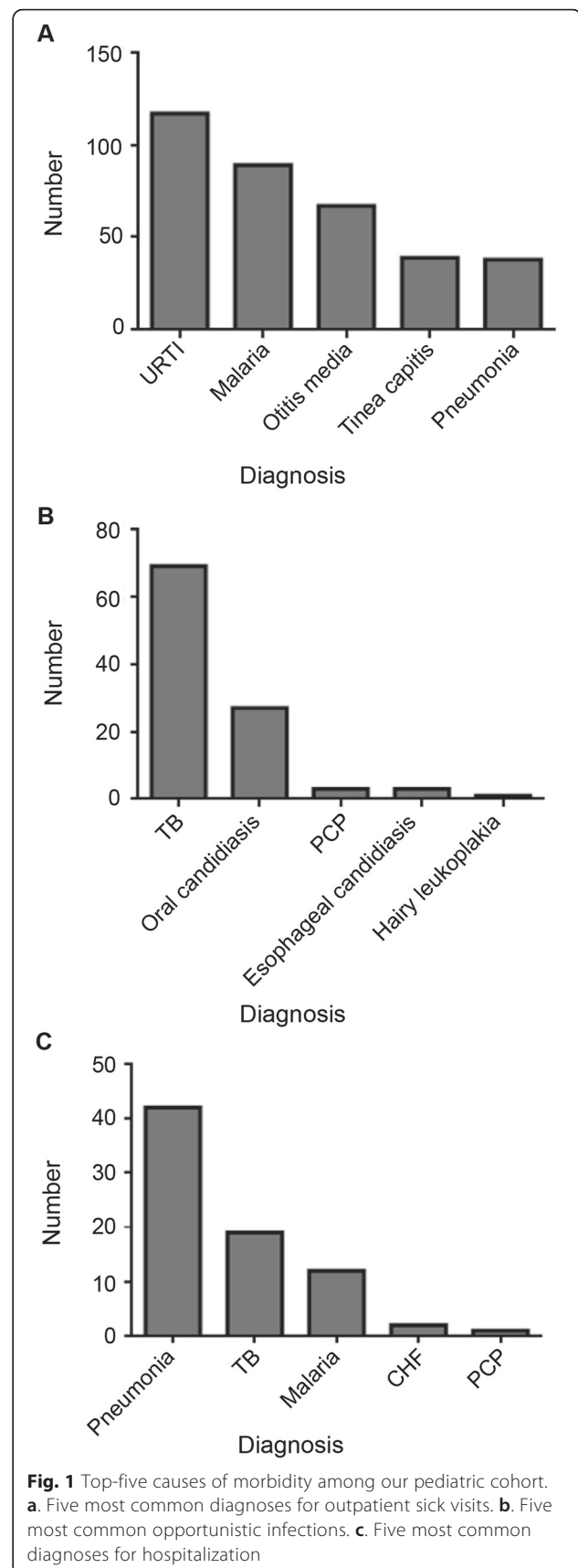
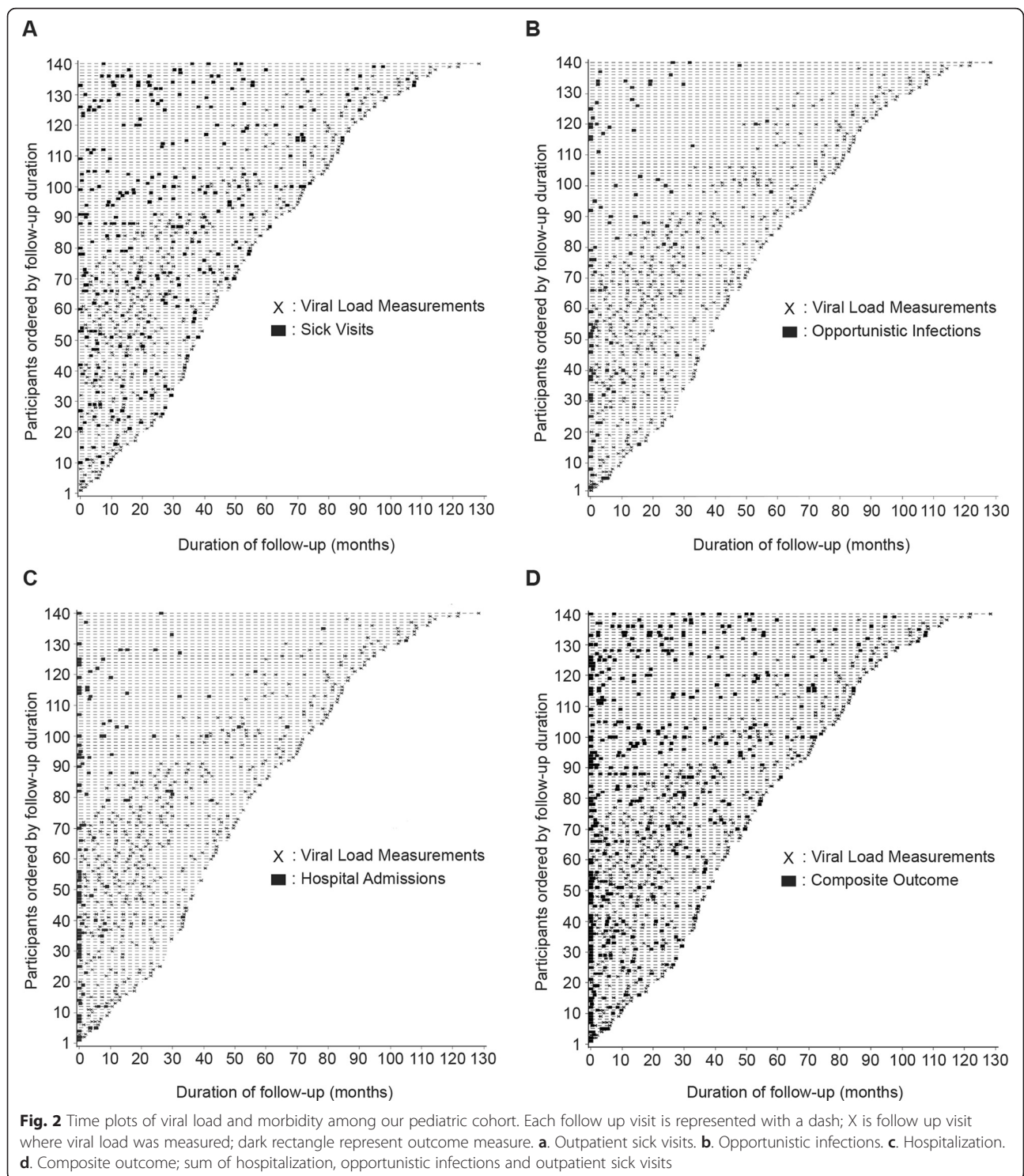## Viremia copy-year as predictor of morbidity

We investigated if any of the demographic characteristics of the study participants could predict cumulative viral load, measured as $\log_{10}$ VCY. Table 2 illustrates demographic characteristics of the study participants stratified into three groups based on $\log_{10}$ VCY; participants with <2 $\log_{10}$ VCY ($N = 51$), 2 to 4 $\log_{10}$ VCY ($N = 27$), and > 4 $\log_{10}$ VCY ($N = 62$). There was no statistically significant association between any of the demographic characteristics and VCY. Moreover, WHO clinical stage of a participant could not predict the level of VCY.

We investigated whether VCY was associated with outcome measures of interest and other HIV disease characteristics. Table 3 illustrates the bivariate analyses of disease characteristics of the study group stratified by VCY. There was no statistically significant difference in the number of years of follow-up among the 3 groups. We did not find any significant association between VCY and the number of opportunistic infections, or hospital admissions. However, the group with >4 $\log_{10}$ VCY had statistically significant outpatient sick visits compared with the other 2 groups ($p = 0.03$). Of note, only 6.5 % (4 of 58) in the group with >4 $\log_{10}$ VCY had been identified as treatment failure using WHO clinical and immunological definitions of treatment failure. There was no significant association between VCY and number of years of follow up.

Discussion

Forty-four percent of our study participants (62 of 140) had >4 $\log_{10}$ VCY. Interestingly, only 6.5 % of the

Fig. 1 Top-five causes of morbidity among our pediatric cohort. **a**. Five most common diagnoses for outpatient sick visits. **b**. Five most common opportunistic infections. **c**. Five most common diagnoses for hospitalization

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Fig. 2 Time plots of viral load and morbidity among our pediatric cohort. Each follow up visit is represented with a dash; X is follow up visit where viral load was measured; dark rectangle represent outcome measure. **a**. Outpatient sick visits. **b**. Opportunistic infections. **c**. Hospitalization. **d**. Composite outcome; sum of hospitalization, opportunistic infections and outpatient sick visits

participants with >4 $\log_{10}$ VCY were identified as meeting the WHO criteria for clinical and immunological treatment failures [25]. Moreover, participants with >4 $\log_{10}$ VCY had statistically significant increased outpatient encounters compared with participants with <4 $\log_{10}$ VCY. We found poor sensitivity of clinical and

immunologic assessments in determining treatment failure, consistent with other pediatric studies from sub-Saharan Africa [8, 10, 11]. Taken together, our study validates the need for viral load monitoring as part of pediatric HIV care in resource-limited setting. Although implementation of viral load monitoring will continue to

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Table 2 Baseline demographic characteristics of study participants stratified by Log10 copy-years/mL

Characteristics	Less than 2 AUVLC (Log10 copy-years/mL) (N = 51)	Between 2 and 4 AUVLC (Log10 copy-years/mL) (N = 27)	Greater than 4 AUVLC (Log10 copy-years/mL) (N = 62)	P value[*]
Age	4.6 (2.9, 51)[a]	4.1 (3.0, 27)	5.4 (3.1, 62)	0.1327
HIV status of father				0.4012
Yes	14 (73.7)[b]	1 (33.3)	19 (65.5)	
No	5 (26.3)	2 (66.7)	10 (34.5)	
HIV status of mother				0.5237
Yes	36 (97.3)	18 (100.0)	39 (92.9)	
No	1 (2.7)	0 (0.0)	3 (7.1)	
Gender				0.2792
Female	16 (31.4)	13 (48.1)	27 (43.5)	
Male	35 (68.6)	14 (51.9)	35 (56.5)	
Care Giver				0.4816
Aunt	4 (7.8)	2 (7.4)	8 (12.9)	
Father	3 (5.9)	5 (18.5)	4 (6.5)	
Grandmother	4 (7.8)	3 (11.1)	11 (17.7)	
Mother	36 (70.6)	17 (63.0)	34 (54.8)	
Stepmother	1 (2.0)	0 (0.0)	2 (3.2)	
Uncle	3 (5.9)	0 (0.0)	3 (4.8)	
WHO clinical Stage				0.9904
Stage I	6 (21.4)	2 (13.3)	6 (14.6)	
Stage II	6 (21.4)	4 (26.7)	9 (22.0)	
Stage III	10 (35.7)	6 (40.0)	17 (41.5)	
Stage IV	6 (21.4)	3 (20.0)	9 (22.0)	

[*]The *p* value was generated using Wilcoxon Rank Sum test and Fisher's Exact test for continuous and categorical variables, respectively
[a]Mean (STD, N) for continuous variables
[b]Number, N(%)for categorical variables

be constrained by budgetary and technical constraints in a resource-limited setting, there is an urgent need for innovative and cost-effective algorithms to include viral load monitoring for accurate and timely diagnosis of treatment failure.

We did not find statistically significant associations between cumulative viremia and frequency of opportunistic infections or hospitalizations during the study period. However, persistent viremia may have deleterious consequences with time. Interestingly, there are reports of an association between transient viremia and virological failure [26–28], depletion of CD4+ T-cells [29], and emergence of HIV drug resistant viruses [30, 31]. The hallmark of HIV infection is progressive depletion of CD4 T-cells leading to development of opportunistic infections (OIs), AIDS, and death [32]. HIV viral load has been found in several studies to be the main determinant of HIV disease progression [4, 33–35]. In a resource-limited setting, the two immediate deleterious effects of persistent viremia will be virological treatment failure and evolution of HIV drug resistant variants. Since the reported sensitivity of clinical/immunological monitoring in detecting treatment

failure is low, 29 %-33 % [36], many of these children will continue to be on failing first-line regimens. Several studies have shown that delayed detection of virological failure to first-line therapy often leads to development of drug resistance, jeopardizing potential second-line treatments [11, 37, 38].

There is a paucity of data on the use of VCY, a measure of cumulative viremia, in monitoring ART in HIV-infected children. Two earlier pediatric studies found no association between cumulative viremia and virological failure or drug resistance [39, 40]. However, two recent studies reported findings consistent with our findings [41, 42]. Thorvaldsson et al. reported that for every 10-fold increase in viremia copy-years, there was about 8.5-fold increase in the risk of morbidity and mortality among a cohort of perinatally HIV-infected children in New Haven, CT, USA [41]. Rossouw et al. found that cumulative viremia in children on protease inhibitor (PI)-based ART was associated with development of PI resistant mutations [42]. In HIV-infected adults, there are several reports of significant association between VCY and morbidity and mortality [10–14]. Cole et al. reported that each $\log_{10}$

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Table 3 HIV disease characteristics of study participants stratified by Log10 copy-years/mL

Characteristics	Less than 2 AUVLC (Log10 copy-years/mL) (N = 51)	Between 2 and 4 AUVLC (Log10 copy-years/mL) (N = 27)	Greater than 4 AUVLC (Log10 copy-years/mL) (N = 62)	P value*
Overall Follow up time (in years)	4.6 (3.2, 51)[a]	4.6 (2.8, 27)	4.3 (1.7, 62)	0.96
AUVLC[b] (copy-years/mL)	52839.09 (200451.75, 51)	334006.10 (963952.93, 27)	142793.89 (360264.57, 62)	
Number of opportunistic infections	0.7 (0.8, 51)	0.7 (0.6, 27)	0.8 (0.8, 62)	0.78
Number of outpatient sick visits	1.8 (2.1, 51)	2.3 (1.9, 27)	2.6 (2.3, 62)	0.08
Number of hospitalizations	0.9 (0.8, 51)	0.9 (1.1, 27)	0.8 (1.1, 62)	0.44
Number of composite events	3.6 (2.8, 140)	3.2 (2.5, 51)	3.7 (2.3, 27)	0.33
Clinical/Immunological Treatment Failure				0.49
Yes	2 (4.2)[c]	0 (0.0)	4 (6.5)	
No	46 (95.8)	26 (100.0)	58 (93.5)	
Opportunistic infections				0.90
Yes	27 (52.9)	16 (59.3)	35 (56.5)	
No	24 (47.1)	11 (40.7)	27 (43.5)	
Outpatient sick visits				0.03
Yes	33 (64.7)	22 (81.5)	53 (85.5)	
No	18 (35.3)	5 (18.5)	9 (14.5)	
Hospitalization				0.13
Yes	34 (66.7)	14 (51.9)	30 (48.4)	
No	17 (33.3)	13 (48.1)	32 (51.6)	
Composite Events[d]				0.39
Yes	47 (92.2)	27 (100.0)	57 (91.9)	
No	4 (7.8)	0 (0.0)	5 (8.1)	

*The p value was generated using Wilcoxon Rank Sum test and Fisher's Exact test for continuous and categorical variables, respectively
[a]Mean (STD, N) for continuous variables
[b]AUVLC, area under viral load curve
[c]Number, N(%)for categorical variables
[d]Composite events, sum of hospitalization, opportunistic infections and outpatient sick visits

increase in VCY was associated with 1.70-fold increased hazard of AIDS or death among HIV seroconvertors, independent of duration of infection, age, race, CD4 cell count, viral load set-point, peak viral load, or most recent vial load [24]. The authors concluded that VCY is a better prognostic indicator of HIV disease progression than traditional single measures of viremia. Reports from other cohorts have reiterated that VCY is a better predictor of HIV all-cause mortality [43–45]. Taken together, viral load monitoring irrespective of the approach taken is critical for any HIV program. Therefore, the WHO in 2013 recommended viral load monitoring as the preferred approach in evaluating treatment failure [25].

The rationale for the new recommendation is to: (1) provide an early and more accurate detection of treatment failure and guide appropriate switch from first to second-line drugs to reduce the accumulation of drug-resistance mutations; and (2) help to differentiate between treatment failure and non-adherence [46]. However, there are several challenges involved in implementing these recommendations in resource-limited settings including costs of the test, costs of second-line drug regimens, accessibility to

centers who offer the tests, and lack of laboratory infrastructure [47, 48]. For example, during our study period, we faced several occasions where there were no reagents to run viral load, breakdown of the equipment, technical problems, or power outages. These obstacles led to re-scheduling patients for blood draws for viral load, and most patients subsequently failed to attend the rescheduled appointments due to lack of time or transportation. Despite the myriad of constraints in performing routine viral load monitoring in resource-limited settings, there is a need for countries to invest in innovative and cost-effective monitoring of HIV treatment. VCY may be a good alternate to routine viral load measurement or part of clinical/immunological criteria to improve sensitivity of detecting treatment failure. It also appears to be a good surrogate for persistent viremia, a determinant of HIV disease progression and non-AIDS-associated clinical events. To adopt VCY as part of treatment monitoring, there will be a need for studies to establish the "set-point" for VCY and how often to determine VCY. It may be possible to have multiple viral loads during the first year on therapy to determine one's VCY "set-point" and thereafter the

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frequency could be personalized. Less frequent viral load determination might be cost-saving in the long-term.

Even though our study is one of the first studies to investigate the utility of VCY in monitoring ART in HIV-infected children, it has several limitations. First, this is a single tertiary center study and, therefore, one has to be cautious in generalization of our findings to all HIV care centers in resource-limited settings. Also, the small sample size limits the generalization of our findings. Moreover, viral load was not ascertained at regular interval so we could not adjust for transient viremia in the analysis. Due to periodic shortage of reagents or technical problems, viral load measurements were not available at each clinic visit or on scheduled dates. Since the viral loads were not uniformly missing at random among study participants we could not use any statistical test to account for data missing at random. Furthermore, data on adherence was not uniformly available in participants' medical records so we could not model adherence in our analyses. Most of these limitations reflect the realities of carrying out observational cohort studies in a resource-limited setting. Our findings suggest potential utility of VCY in pediatrics, and this warrants further investigations in resource-limited settings.

Conclusions

In conclusion, an unexpectedly high proportion of our study participants had increased cumulative viral load. This may translate to virological failure on their first-line regimen and subsequent increased all-cause morbidity. Our finding supports the current WHO recommendation of viral load monitoring as the preferred method for monitoring ART in resource-limited countries. HIV treatment programs in resource-limited countries should come up with innovative and cost-effective algorithms including viral load measurement for accurate and timely diagnosis of treatment failure. VCY may be a good alternate to routine viral load measurement as its determination may be less frequent and could be personalized and therefore a potential cost-saving approach.

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