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Results of Early Virologic Monitoring May Facilitate Differentiated Care Monitoring Strategies for Clients on ART, Rakai, Uganda

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Background. Viral load (VL) monitoring is standard of care in HIV-infected persons initiated on antiretroviral therapy (ART). We evaluated the predictive value of VL measurements at 6 and 12 months after initiation of firstline ART to estimate the future risk of virologic failure (VF).

Methods. HIV-infected persons with VL measurements at 6 and 12 months post-ART initiation and at least 2 additional VL measurements thereafter were assessed for risk of future VF, defined per World Health Organization guidelines. VL at 6 or 12 months post-ART was categorized into <400, 400–1000, 1001–2000, and >2000 copies/mL. Cox proportional hazard models were used to compare VF incidence associated with 6-month, 12-month, and a composite of 6- and 12-month VL prediction indicators.

Results. Overall, 1863 HIV-infected adults had a 6- and 12-month VL measurement, and 1588 had at least 2 additional VLs thereafter for predicting future VF. The majority (67%) were female (median age: females 33 years and males 37 years). At 12 months post-ART, 90% had VL<400 copies/mL (cumulative incidence of VF at 1.5%), 3% had 400–1000 copies/mL (VF 12%), 2% had 1001–2000 copies/mL (VF 22%), and 5% had >2000 copies/mL (VF 71%). The predictive value of the 12-month VL measurement was comparable to the composite of both the 6- and 12-month VL measurements and better than the 6-month VL measurement.

Conclusions. At 12 months after ART initiation, 90% of patients were virally suppressed with a low likelihood of future VF. VL measurement at 12 months post–ART initiation predicts risk of VF and could inform differentiated virologic monitoring strategies.

Keywords. antiretroviral therapy; HIV/AIDS; differentiated care; viral load monitoring; viral suppression.

Globally, 36.7 million are infected with HIV, and an additional 1.8 million new HIV infections occur annually. The number of HIV-infected persons on antiretroviral therapy (ART) has increased from 7 million in 2010 to 21 million in 2017 [1]. In East and Southern Africa, there are 19 million HIV-infected persons, and ART coverage increased from 4 million to 10 million between 2010 and 2016 [2]. The numbers on ART are expected to increase with the World Health Organization's (WHO's) recommendations to "test and treat all" HIV-infected persons and UNAIDS' 90:90:90 targets (90% of HIV-infected persons to know their status, 90% of those to be on ART, and 90% of those on treatment to be virologically suppressed by 2020) [3–5].

HIV-infected persons have variable disease progression, ART treatment responses, and adherence profiles [6, 7]. Among those on ART, differences are reported in time to viral suppression, risk of virologic failure (VF), adherence, and drug tolerance [8, 9]. These differences in patient response to treatment suggest the possibility of more individualized patient care, which is the cornerstone of differentiated care delivery [3].

To effectively and efficiently manage the increasing number of HIV-infected individuals on ART, patient-based differentiated service delivery models based on individual patients' clinical and immunologic/virologic status are encouraged [3, 10]. The WHO recommends patient-centered care that allows lower frequency of ART refills, longer intervals between clinic visits, and community-based ART distribution for stable, virologically suppressed patients [3].

Regular virologic monitoring is recommended for all persons on ART at 6 and 12 months after ART initiation, and then annually [3, 11]. If coupled with timely switching to second-line ART to prevent prolonged periods of undetected viremia in patients

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failing treatment, virologic monitoring may reduce the risk of acquired drug resistance [12]. However, routine viral load (VL) monitoring programs face challenges of inadequate coverage, delays in sample collection, testing, and return of VL results; high cost; and low quality of VL testing [13–16]. Such challenges are likely to increase with scale-up of VL testing and ART use. Strategic approaches that would base VL testing frequency on the client's likelihood of VF could inform differentiated virologic monitoring strategies that could reduce the number of VL tests for clients at low risk of VF and focus resources on the clients most at risk of VF.

We evaluated the predictive value of VL testing at 6 and 12 months after initiation of firstline ART to identify HIV+ patients at risk of future VF in an ART treatment cohort.

METHODS

Analysis Design and Setting

We conducted a retrospective analysis of HIV-infected adults aged 18 years or older initiated on ART in the Rakai Health Sciences Program (RHSP) clinical cohort in south-central Uganda between June 2004 and June 2011. Since 2004, RHSP, with funding from the President's Emergency Plan for AIDS Relief (PEPFAR), has provided free ART using a community-based decentralized service delivery model. Firstline ART regimens consisted of 2 nucleoside reverse transcriptase inhibitors (NRTIs; zidovudine or stavudine and lamivudine) and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI; nevirapine or efavirenz). After ART initiation, participants were seen weekly for the first month, then biweekly for 2 months, and then monthly thereafter, with adherence and HIV risk reduction promotion activities at all visits and with CD4 and VL monitoring every 6 months. HIV-1 viral load testing was performed on-site in the RHSP laboratory using the Roche Amplicor 1.5 Monitor assay (Roche Diagnostics, IL, USA) from June 2005 to September 2010, and it could detect up to 400 copies/mL; thereafter, VL testing was done using the Abbott real-time m2000 assay (Abbott Laboratories, IL), which detected up to 40 copies/mL.

We identified the study population as HIV-infected patients who were aged 18 years or older at the time of ART initiation and had been on ART for more than 12 months, with VL measurements at 6 and 12 months, and further, we identified another subpopulation of patients with at least 2 additional VL measurements beyond the 12-month VL time point. We used the study population to measure the incidence of the first event of VF after ART initiation in the study population and used the subpopulation to measure the predictive value of the 6-month and 12-month VL measurements for the occurrence of future VF after 12 months of ART initiation. The outcome was VF, defined by current WHO guidelines as 12 months on ART with 2 consecutive VLs greater than 1000 copies/mL detected within a time interval not exceeding 12 months [3, 17]. Suppressed VL was defined as a VL <400 copies/mL.

Statistical Analysis

Person-time of observation was computed from the date of ART initiation to the time of the second (confirmatory) VL >1000 copies/mL if VF occurred or to initiation of second-line ART if switching to second-line occurred before meeting the VF criteria, or it was censored at the last available clinic visit if lost to follow-up or at time of death, or administratively censored on June 1, 2012, the end of the study. The incidence of VF was estimated as the first occurrence of VF after 12 months on ART, starting with the 12-month VL measurement. Prediction of VF beyond 12 months of ART initiation was measured as the first occurrence of VF measured using VL results starting with the 18-month VL measurement. We assessed the association between baseline characteristics and VL at 12 months using Pearson's chi^2 test and estimated the cumulative incidence of VF using the Nelson-Aalen cumulative hazard function. To identify the best predictor of future VF beyond 12 months of ART, we compared 3 potential VL prediction indicators, 6-month VL measurement or 12-month VL measurement, or a composite indicator of the 6- and 12-month VL measurements, stratefied into 4 categories: category 1: 6-month VL <400 copies/mL and 12-month VL <400 copies/mL; category 2: 6-month VL ≥400 copies/mL and 12-month VL <400 copies/mL; category 3: 6-month VL <400 copies/mL and 12-month VL ≥400 copies/mL; and category 4: 6-month VL ≥400 copies/mL and 12-month VL ≥400 copies/mL. For each prediction indicator, patients were stratified into the following categories: <400, 400–1000, 1001–2000, and >2000 copies/mL. Potential confounding variables included gender, age, CD4, and WHO stage at ART initiation firstline regimen (efavirenz vs nevirapine-based), location of ART treatment clinic (peripheral or centrally located), and year of ART initiation (2004–2007 vs 2008–2011). We generated 2 models for each prediction indicator, a univariate model and a multivariate model, in which the association of the predicting indicator was adjusted for potential confounding variables that were found to be significantly associated with incidence of VF at a global P value ≤.15 in the univariate analyses. We used Cox proportional hazards models to estimate unadjusted hazard ratios (uHRs) and adjusted hazard ratios (adjHRs). Harrell's C-statistic was used to estimate the predictive power (discrimination) of models stratifying patients by their risk of incident VF [18, 19]. The best predicting model was chosen by the predictive performance (C-statistics) using the Somers' D approach for censored data [20] and the calibration using the Akaike Information Criterion (AIC) score. Analysis was performed using STATA 14.0 (STATA Inc, TX).

Ethical Statement

Retrospective use of routinely collected de-identified clinical data was approved by the Uganda Virus Research Institute, Research Ethics Committee, The Institutional Review Board of Johns Hopkins University School of Medicine, and the Uganda National Council for Science and Technology.

Individual consent was obtained for treatment but not for the research analysis.

RESULTS

We identified 1863 HIV patients aged 18 years with 6- and 12-month VL measurements who were eligible for describing incidence of VF in the study population and a subpopulation of 1588 (85%) that had at least 2 additional VL measurements beyond the 12-month VL measurement and so were eligible for the prediction of subsequent VF beyond 12 months of ART initiation. The median observation time from time of ART initiation (interquartile range [IQR]) was 3.7 (2.7–5.5) years. Sixty-seven percent were females with a median age at ART initiation of 33 years, compared with a median age of 37 years in males. The majority (95%) had a CD4 count ≤250 cells/uL at time of ART initiation, and 66% were initiated on nevirapine-based

Table 1. Baseline Characteristics and Virologic Outcomes of HIV Patients on ART Among HIV-Infected Patients

Characteristics	Study Population, No. (%)	Prediction Analysis Subpopulation, No. (%)
Population	1863 (100)	1588 (100)
Baseline characteristics		
Gender		
Female	1240 (67)	1047 (66)
Male	623 (33)	541 (34)
Age, y		
18–24	121 (6)	93 (6)
25–34	829 (44)	688 (43)
35+	913 (49)	807 (51)
Year of ART initiation		
2004–2007	1025 (55)	1001 (63)
2008–2011	838 (45)	587 (37)
Type of ART treatment clinic		
Central clinic	387 (21)	344 (22)
Peripheral clinic	1476 (79)	1244 (78)
WHO stage		
1	644 (35)	517 (33)
2	703 (38)	602 (38)
3	382 (21)	349 (22)
4	134 (7)	120 (8)
CD4 count at ART initiation, cells/uL		
≥251	84 (5)	63 (4)
100–250	1303 (70)	1086 (68)
≤99	474 (25)	437 (28)
Firstline ART		
EFV-based regimen	635 (34)	607 (38)
NVP-based regimen	1222 (66)	976 (62)
Virologic measurements		
Viral load at 6 mo of ART, copies/mL		
<400	1402 (88)	1402 (88)
401–1000	66 (4)	66 (4)
1001–2000	40 (3)	40 (3)
>2000	80 (5)	80 (5)
Viral load at 12 mo of ART, copies/mL		
<400	1680 (90)	1435 (90)
401–1000	55 (3)	52 (3)
1001–2000	31 (2)	30 (2)
>2000	97 (5)	71 (4)
Viral load at 6 and 12 mo of ART, copies/mL		
6VL < 400 & 12VL < 400	1532 (82)	1293 (81)
6VL ≥ 400 & 12VL < 400	148 (8)	142 (9)
6VL < 400 & 12VL ≥ 400	118 (6)	109 (7)
6VL ≥ 400 & 12VL ≥ 400	65 (3)	44 (3)

Abbreviations: 6VL, viral load at 6 months of ART initiation; 12VL, viral load at 12 months of ART initiation; ART, antiretroviral therapy; EFV, efavirenz; NVP, nevirapine; pys, person years; VF, virological failure; WHO, World Health Organization.

regimens (Table 1). Twelve-month VL measurement was <400 copies/mL in 1680 (90%) patients, 401–100 copies/mL in 55 (3%) patients, 1001–2000 copies/mL in 31 (2%) patients, and >2000 copies/mL in 97 (5%) patients (Table 1). Year of ART initiation, WHO stage, firstline ART regimen type, and CD4 at ART initiation were significantly associated with the detectability of 12-month VL outcome, whereas gender and age were not significantly associated (Supplementary Table 1). Overall, 91% of the total person-time was from patients with 12-month VL<400 copies/mL, and they contributed 29% of VF, whereas only 5% observation time was from patients with 12-month VL >2000 copies/mL, but they contributed 58% of VF (Figure 1).

Incidence of Virologic Failure After ART Initiation

A total of 7042 person-years was measured, and 93 VFs were observed in the study population for describing the incidence of VF. The median time to VF (IQR) was 1.46 (1.4–2.3) years after ART initiation. The overall cumulative incidence of VF at 5 years was 5%, and the cumulative incidence rates of VF at 3 years of follow-up for different levels of 12-month VL were 1.5%, 12%, 22%, and 71% for VL <400 copies/mL, 400–1000 copies/mL, 1001–2000 copies/mL, and >2000 copies/mL, respectively, and remained almost unchanged at 5 years (Figure 2).

The number of VL measurements needed to detect 1 VF ranged from 398 VLs among patients with a 12-month VL <400 copies/mL, 71 VLs with 12-month VL 400–1000 copies/mL, 43 VLs with 12-month VL 1001–2000 copies/mL, to 10 VLs for patients with 12-month VL >2000 copies/mL ($P < .001$) (Table 2).

Predictors of Virologic Failure Beyond 12 Months of ART

A total of 6580 person-years were measured, and 62 incident VFs were observed beyond 12 months of ART initiation in the subpopulation used for predicting VF beyond 12 months of ART. All 3 VL prediction indicators had a strong independent association with incidence of subsequent VF beyond 12 months of ART initiation, and age and gender were found to be potential confounders at $P < .15$ (Table 3).

We measured the C-statistic and AIC value for each prediction model and found that models for the 6-month VL prediction indicator were inferior to those of the 12-month VL prediction indicator; however, there was no significant difference in the predictive value comparing the 12-month VL and the composite 6- and 12-month prediction VL indicators. However, the composite prediction indicator had lower AIC values (Table 4).

The adjusted hazard ratios associated with the 12-month VL prediction indicator when compared with the <400 copies/mL category as reference were 6.46 (95% confidence interval [CI], 2.7–15.7) for VLs of 400–1000 copies/mL, 7.71 (95% CI, 2.7–22.1) for VLs of 1001–2000 copies/mL, and 25.81 (95% CI, 14.8–44.9) for VLs greater than 2000 copies/mL. Males had an adjHR of 1.90 (95% CI, 1.1–3.2), and age of 35 years or older had a marginally significantly lower risk of VF compared with younger HIV patient categories (Table 5).

DISCUSSION

Out study found that VL results at 12 months post-ART initiation performed well in predicting patients at high likelihood of subsequent VF and outperformed VL measurements at 6 months post-ART, whereas a composite indicator of both the 6- and 12-month VL measurements had no added predictive value. Therefore, the VL result at 12 months after ART initiation performed best in this setting to stratify patients by their

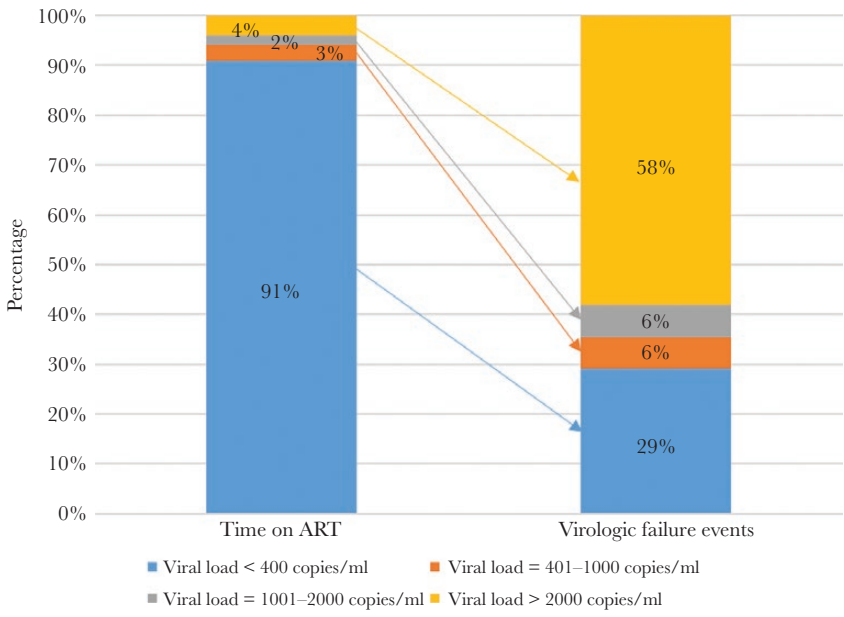

Figure 1. Distribution of cumulative time on ART initiation and their corresponding cumulative virologic failure events, stratified by 12-month viral load, among HIV-infected patients.

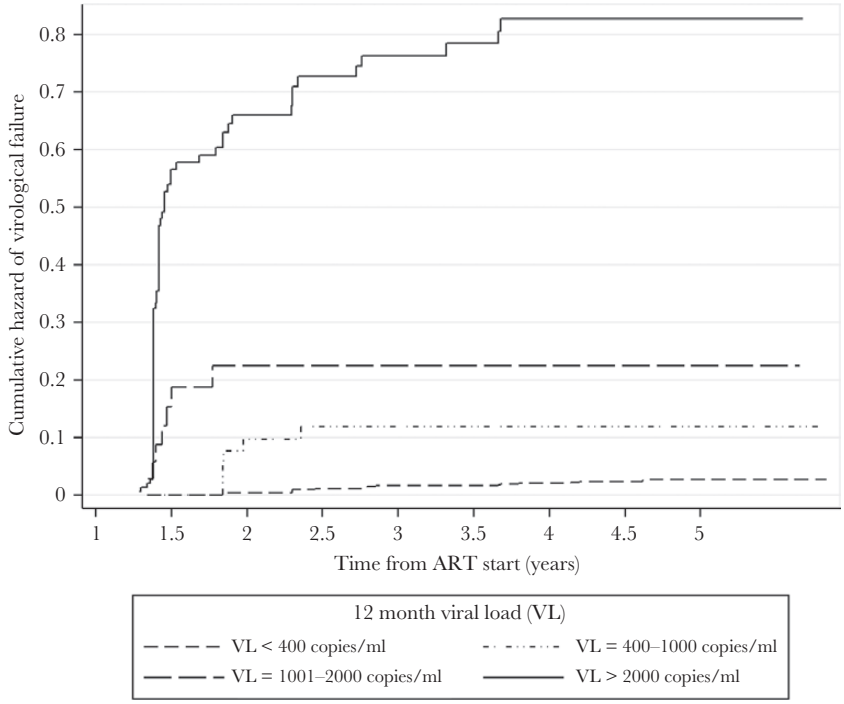

Figure 2. Cumulative incidence of virologic failure after 12 months of ART initiation, by 12-month viral load among HIV-infected patients.

risk of subsequent VF. Ninety percent of patients had a VL <400 copies/mL at 12 months post-ART and had low rates of subsequent VF (~1.5%), suggesting that less frequent long-term viral monitoring could be possible in this low-risk subgroup. However, the 10% of patients with a VL ≥400 copies/mL were at high risk of subsequent VF and may benefit from more frequent long-term VL monitoring. These findings are consistent with other studies that suggest that viral load monitoring at 12 months could facilitate differentiated care by identifying patients at risk for virologic failure [21, 22]. The number of VL measurements required under the current WHO guidelines based on the 12-month VL measurement has low information value in patients with a 12-month VL <400 copies/mL because of the low yield of VFs per VL conducted. Prospective studies incorporating differentiated VL monitoring models are an important programmatic priority.

Incorporating results of early VL monitoring provides a unique opportunity to offer individualized differentiated care to patients in our setting. Identifying patients who are at both high and low risk of VF allows providers to prioritize monitoring and adherence counseling resources to those patients most in need and potentially reduce the monitoring burden both on the patient and provider for patients who have a proven track record of adherence, as shown by early viral load suppression. Although beyond the scope of this manuscript, future strategies that prioritize frequent visits and lab monitoring to those most at risk of VF may ultimately improve efficiency of care delivery in our setting. These strategies could also offer less frequent visits with providers and potentially more flexible dispensing options, ultimately improving quality of care among patients with proven adherence to ART. These types of strategies would need to be carefully monitored for any untoward effects such as

Table 2. Viral Loads Performed and Virological Failures Observed Since ART Initiation

			Performed VLs			
					Average per VL	
12-mo VL Category, Copies/mL	No. of Patient Person-Years	No. of Incident VLs	Total	Average per Patient Person-Year, No.	No.	*P*
Overall	7042.1	93	12 007	1.71	129.1	
0–399	6394.7	27	10 768	1.68	398.8	<.001
400–1000	228.8	6	427	1.87	71.2	
1001–2000	129.8	6	263	2.03	43.8	
≥2001	288.8	54	549	1.90	10.2	

Abbreviations: ART, antiretroviral therapy; VF, virological failure; VL, viral load.

Table 3. Univariate Analysis for Predictors of Subsequent Virologic Failure After 12 Months on ART Among HIV-Infected Patients

		Univariate Analysis	
Characteristics	VF/100 pys (95% CI)[a]	Hazard Ratio (95% CI)	*P*
Predicting virologic measurements			
Viral load at 6 mo of ART, copies/mL			
<400	0.6 (0.4–0.8)	Ref	<.001
401–1000	1.0 (0.3–3.2)	1.89 (0.6–6.2)	
1001–2000	1.6 (0.5–4.9)	3.02 (0.9–9.9)	
>2000	6.7 (4.5–10.1)	13.05 (7.7–22.2)	
Viral load at 12 mo of ART, copies/mL			
<400	0.5 (0.3–0.7)	Ref	<.001
401–1000	2.7 (1.2–6.0)	6.14 (2.5–14.9)	
1001–2000	2.9 (1.1–7.7)	6.97 (2.4–19.9)	
>2000	9.1 (6.2–13.5)	21.60 (12.5–37.2)	
Viral load at 6 and 12 mo of ART, copies/mL			
6VL < 400 & 12VL < 400	0.4 (0.2–0.6)	Ref	<.001
6VL ≥ 400 & 12VL < 400	1.1 (0.5–2.2)	3.01 (1.3–7.1)	
6VL < 400 & 12VL ≥ 400	2.7 (1.6–4.7)	7.64 (3.8–15.4)	
6VL ≥ 400 & 12VL ≥ 400	13.8 (9.1–20.9)	41.05 (22.4–75.3)	
Demographic and confounding factors			
Gender			
Female	0.8 (0.6–1.1)	Ref	.115
Male	1.2 (0.8–1.8)	1.50 (0.9–2.5)	
Age, y			
18–24	1.2 (0.4–3.1)	Ref	.021
25–34	1.3 (1.0–1.8)	1.21 (0.4–3.4)	
35+	0.6 (0.4–0.9)	0.57 (0.2–1.7)	
Year of ART Initiation			
2004–2007	0.9 (0.6–1.2)	Ref	.897
2008–2011	1.1 (0.7–1.7)	1.04 (0.6–1.8)	
WHO stage			
1	0.6 (0.4–1.1)	Ref	.266
2	1.1 (0.8–1.6)	1.81 (0.9–3.5)	
3	1.1 (0.7–1.8)	1.88 (0.9–3.9)	
4	0.7 (0.3–2.0)	1.25 (0.4–3.8)	
CD4 at ART initiation, cells/uL			
≥251	0.9 (0.2–3.4)	Ref	.271
100–250	0.8 (0.6–1.1)	1.01 (0.2–4.2)	
≤99	1.2 (0.8–1.9)	1.54 (0.4–6.5)	
Firstline ART			
EFV-based regimen	0.9 (0.6–1.3)	Ref	.560
NVP-based regimen	1.0 (0.7–1.4)	1.17 (0.7–2.0)	

Abbreviations: 6VL, viral load at 6 months of ART initiation; 12VL, viral load at 12 months of ART initiation; ART, antiretroviral therapy; EFV, efavirenz; NVP, nevirapine; pys, person years; VF, virological failure; WHO, World Health Organization.

[a]VF after 12 months of ART initiation.

Table 4. Performance of Prediction Model of Subsequent Virologic Failure After 2 Months of ART Among HIV-Infected Patients

Model	C-Statistic	AIC
A: 6-mo VL only	0.69	838.2
B: 6-mo VL + age + gender	0.74	829.6
D: 12-mo VL only	0.76	803.3
E: 12-mo VL + age + gender	0.82	789.0
G: 6- and 12-mo viral load only	0.79	786.1
H: 6- and 12-mo VL + age + gender	0.84	774.6

Other confounders include year of ART initiation, World Health Organization stage, CD4 at ART initiation, firstline ART regimen.

Abbreviations: AIC, Akaike Information Criterion; ART, antiretroviral therapy; VL, viral load.

Table 5. Prediction Models of Subsequent Virologic Failure After 12 Months of ART Among HIV-Infected Patients

Characteristics	Multivariate Analysis	
	Model E	Model H
Predicting Virologic Measurements	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Viral load at 12 mo of ART, copies/mL		
<400	Ref	-
401–1000	6.46 (2.7–15.7)	-
1001–2000	7.71 (2.7–22.1)	-
>2000	25.81 (14.8–44.9)	-
Viral load at 6 and 12 mo of ART, copies/mL		
6VL < 400 & 12VL < 400	-	Ref
6VL ≥ 400 & 12VL < 400	-	3.05 (1.3–7.2)
6VL < 400 & 12VL ≥ 400	-	8.47 (4.2–17.1)
6VL ≥ 400 & 12VL ≥ 400	-	44.52 (24.2–82.0)
Demographic and confounding factors		
Gender		
Female	Ref	Ref
Male	1.90 (1.1–3.2)	1.72 (1.0–2.9)
Age, y		
18–24	Ref	Ref
25–34	1.01 (0.4–2.9)	1.10 (0.4–3.2)
35+	0.33 (0.1–1.0)	0.41 (0.1–1.2)

Abbreviations: 6VL, viral load at 6 months of ART initiation; 12VL, viral load at 12 months of ART initiation; ART, antiretroviral therapy; CI, confidence interval; Model E, 12-month VL indicator + confounders (age, gender); Model H, 6- and 12-month VL composite indicator + confounders (age, gender).

disengagement from care or prolonged VF, which could result in drug resistance and onward HIV transmission. Although these are real risks, we feel that the use of VL monitoring opens a window to improve the way ART is provided in our setting, both in terms of resource utilization and patient satisfaction.

The risk of VF can be influenced by other factors such as drug adherence [23, 24] and effective drug adherence interventions have been shown to reduce VF risk [25]. Any differentiated care strategies that reduce either patient visit or VL measurement frequency would need to include careful adherence monitoring as well. Patient age, gender, ART regimen type, and presence of primary drug resistance also affect the risk of VF [21, 22]. We did not assess drug adherence or resistance, but we believe these factors are reflected in any detectable VL at 6 and 12 months.

Our analysis has several limitations. It was a retrospective analysis of an ART cohort with 6-monthly routine VL monitoring and was not designed to evaluate virologic risk stratification prediction models. The study used a cutoff of 400 copies/mL for undetectable viral load, which may result in some patients not being identified who had low-level viremia. The study was performed in 1 rural setting in sub-Saharan Africa, which may limit generalizability.

VL test results performed at 12 months after ART initiation can adequately predict which HIV patients on ART are at risk of subsequent VF. Ninety percent of patients have suppressed VL <400 copies/mL at 12 months after ART initiation with low likelihood of subsequent VF, and thus could be considered for less frequent VL monitoring. Most VFs occur among patients with VL >2000 copies/mL at 12 months after ART initiation. Such patients may benefit from more intensive long-term monitoring. These findings suggest the possibility of differentiated VL monitoring with less frequent VL testing for patients who have achieved VL suppression at 12 months after ART initiation.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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