Published in final edited form as:

J Acquir Immune Defic Syndr. 2019 March 01; 80(3): 308–315. doi:10.1097/QAI.0000000000001921.

Early and late virologic failure following virologic suppression in HIV-infected Asian children and adolescents

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Abstract

Background: Virologic failure is a major threat to maintaining effective combination antiretroviral therapy, especially for children in need of lifelong treatment. With efforts to expand access to HIV viral load testing, our understanding of pediatric virologic failure is evolving.

Setting: An Asian cohort in 16 pediatric HIV services across six countries.

Methods: From 2005–2014 patients aged <20 years who achieved virologic suppression and had subsequent viral load testing were included. Early virologic failure was defined as a HIV RNA

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Conflicts of Interest

There is no conflicts of interest.

1,000 copies/mL within 12 months of virologic suppression, and late virologic as a HIV RNA 1,000 copies/mL after 12 months following virologic suppression. Characteristics at cART initiation and virologic suppression were described and a competing risk time-to-event analysis used to determine cumulative incidence of virologic failure and factors at virologic suppression associated with early and late virologic failure.

Results: Of 1,105 included in the analysis, 182 (17.9%) experienced virologic failure. Median age at virologic suppression was 6.9 years, and median time to virologic failure was 24.6 months following virologic suppression. The incidence rate for a first virologic failure event was 3.3 per 100 person-years. Factors at virologic suppression associated with late virologic failure included older age, mostly rural clinic setting, tuberculosis, protease inhibitor-based regimens, and early virologic failure. No risk factors were identified for early virologic failure.

Conclusions: Around 1 in 5 experienced virologic failure in our cohort after achieving virologic suppression. Targeted interventions to manage complex treatment scenarios, including adolescents, tuberculosis co-infection, and those with poor virologic control are required.

Keywords

Virologic failure; HIV; children; adolescents

INTRODUCTION

Maintaining effective antiretroviral therapy (ART) is one of the key challenges to managing children and adolescents living with HIV, with poor treatment adherence and drug resistance representing major threats to its success. HIV viral load testing is the preferred method to monitor response to ART and is an important tool in identifying issues with treatment adherence and drug resistance [1]. Assessing virologic response to ART is also an integral component of the UNAIDS “90-90-90” strategy [2], which calls for over 3 million infants, children, and adolescents living with HIV to have access to ART and HIV viral load testing [3]. If these targets set out in the UNAIDS strategy are to be accomplished, a comprehensive understanding of the burden of virologic failure and associated factors is imperative.

With efforts to expand access to ART and HIV viral load testing, the understanding of virologic failure is evolving [4–6]. Among pediatric studies published to date, virologic failure has been reported in 25–34% of children and adolescents receiving ART [6–8]. This highlights the need to better understand the burden of virologic failure in pediatric cohorts to guide development and implementation of targeted interventions to optimize the durability of ART regimens and HIV outcomes, as well as reach the UNAIDS target of viral suppression in 90% of those on ART by 2020. This study aims to describe the incidence of virologic failure and its associated factors within the TREAT Asia pediatric HIV Observational Database (TAPHOD) cohort, a regional study in South and Southeast Asia.

METHODS

Study population and settings

TApHOD is a regional observational database incorporating 16 pediatric HIV services across six countries in Asia (Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam). Information relating to patient demographics, clinical features, laboratory results, and treatment are collected during routine HIV care and transferred to the Kirby Institute, University of New South Wales, Sydney, Australia for data management and statistical analysis. Further details of the study cohort have been previously reported [9].

HIV-infected children and adolescents (<20 years of age) who initiated care at a TApHOD site between 1st January 2005 and 31st December 2014 were included if they: (i) received at least 6 months of continuous combination antiretroviral therapy (cART); (ii) had a documented suppressed viral load (<400 copies/mL) 5 to 12 months following cART initiation; and (iii) had at least one HIV viral load following virologic suppression before the age of 20 years. Data for these patients to the end of 2016 were included to allow sufficient time for HIV viral load testing following virologic suppression. Ethics approvals were obtained through the human research ethics committees at the respective sites, The Kirby Institute, and the coordinating center at TREAT Asia/amfAR (Bangkok, Thailand).

Definitions

Continuous cART was defined as an antiretroviral regimen consisting of at least 3 agents with no more than a 2-week treatment interruption. Virologic suppression was defined as receiving 6 months of continuous cART in conjunction with a documented HIV viral load of <400 copies/mL 5–12 months after commencing continuous cART. Virologic failure was defined as at least 1 HIV viral load of ≥1,000 copies/mL following virologic suppression. Early virologic failure was defined as virologic failure ≤12 months from initial virologic suppression, while late virologic failure was defined as virologic failure >12 months after initial virologic suppression. A viral blip was defined as a single detectable viral load of 400–999 copies/mL that was preceded and followed by a suppressed viral load (<400 copies/mL). Loss-to-follow-up (LTFU) was determined by either documentation of LTFU by the treating site, or a >12-month absence of reported clinical data prior to the date of the site's last data transfer. Anaemia was defined as haemoglobin (Hb) <10.0g/dL [10]. Weight-for-age z scores (WAZ) were determined using WHO 1977 Standards [11] and height-for-age z scores (HAZ) were determined using WHO 2007 Child Growth Standards [12, 13].

Statistical analyses

Descriptive statistics were used to report the demographic, immunologic, virologic, and clinical characteristics of patients at time of cART initiation and virologic suppression. Descriptive characteristics were compared between the included population and those excluded who had received ≥6 months continuous cART with no accompanying HIV viral load testing 5–12 months following cART initiation, and the Wilcoxon-Mann-Whitney test used to evaluate statistically significant differences in non-parametric continuous variables. A time-to-event analysis, with loss to follow-up (LTFU) and death as competing events, was used to determine the cumulative incidence of virologic failure stratified by age at time of

virologic suppression. A competing risk regression analysis (Fine and Gray method) [14], with LTFU and death as competing risks, was used to determine the subdistribution hazard ratio (sHR) and adjusted sHR (asHR) for factors at time of virologic suppression associated with (i) early virologic failure and (ii) late virologic failure. Covariates included sex, age, orphan status, primary caregiver, type of clinic setting, CD4%, WHO clinical stage, viral blip, WAZ, HAZ, hepatitis B/C infection, tuberculosis (TB) infection (diagnosed within the preceding 6 months), cART regimen, and calendar year. Early virologic failure was also evaluated as a covariate for late virologic failure. The period of observation for virologic failure for each patient started the date virologic suppression was achieved and finished when the patient either experienced a competing event (LTFU or death) or had their last clinic visit. Covariates with a p-value of <0.1 on univariate analysis were included in multivariate analyses. Multivariate analyses were conducted in a step-wise fashion maintaining co-variables that retained a p-value of <0.05. All statistical analyses were performed using Stata, version 14.2 (StataCorp LP, College Station, Texas, US).

RESULTS

Of the 4,601 HIV-infected children and adolescents that were enrolled in care at participating sites between 1st January 2005 and 31st December 2014, a total of 1,015 (22.1%) achieved virologic suppression and had subsequent viral load testing, and were included in the analysis. Their characteristics at the time of cART initiation and virologic suppression are summarized in Table 1. The median age at cART initiation was 6.1 [interquartile range (IQR) 3.0, 9.3] years and virologic suppression 6.9 [IQR 3.8, 10.3] years. The median time to achieve virologic suppression was 6.4 [IQR 5.8, 8.8] months. Median duration of continuous cART was 6.1 [IQR 3.7, 8.6] years. Approximately 90% of cART regimens included non-nucleoside reverse transcriptase inhibitors (NNRTI) at cART initiation and at virologic suppression. Of the 906 patients receiving NNRTI-based regimens at virologic suppression, 10 (1.1%) had either a PI-based or other initial cART regimen. Of the 103 patients receiving PI-based regimens at virologic suppression, 22 (21.4%) had either a NNRTI-based or other prior cART regimen. All PI-based regimens were boosted. During the period between cART initiation and virologic suppression, there were improvements in WAZ scores (34.2% vs 26.7% with WAZ -1), prevalence of anaemia (25.6% vs 7.6%), and overall median CD4% (11.0% vs 21.1%).

Of the 3,586 children and adolescents that were excluded: 845 (23.6%) received <6 months of continuous cART; 2,404 (67%) received ≥6 months of continuous cART but did not have HIV viral load testing 5–12 months following cART initiation; 284 (7.9%) received ≥6 months of continuous cART but had unsuppressed HIV viral loads 5–12 following cART initiation; and 53 (1.5%) received ≥6 months continuous cART and achieved virologic suppression within 5–12 months, but did not have subsequent HIV viral load testing. For the 2,404 who were excluded on the grounds of having received ≥6 months continuous cART but no accompanying HIV viral load testing 5–12 months following cART initiation, comparison with the included population showed no difference in sex (47.4% vs 51.2% female), initial cART regimen (93.6% vs 89.3% with NNRTI-based cART), median CD4% at cART initiation (11.5% [IQR 4.0, 18.2] vs 11% [IQR 4.6, 17], p=0.21), or WHO clinical stage at cART initiation (34.3% vs 37.9% with WHO clinical stage III/IV). However, this

excluded sub-population had a lower median age at cART initiation (4.5 [IQR 2.2, 7.4] years vs 6.1 [IQR 3, 9.3] years, $p<0.001$); a higher proportion from Vietnam (56.7% vs 12.2%), Indonesia (10.2% vs 0.8%), and India (4.1% vs 0.3%); and a higher proportion from urban clinic settings (77.2% vs 45.1%) compared to the included population. For the 284 who were excluded because despite having received 6 months continuous cART they had unsuppressed HIV viral loads 5–12 months following cART initiation, there was a higher proportion of males (59.9% vs 48.8%) and those with WHO clinical stage III/IV disease at cART initiation (44.4% vs 37.9%), and a lower median age at cART initiation (4.0 [IQR 1.6, 8.1] years vs 6.1 [IQR 3, 9.3] years, $p<0.001$) compared to the included population. This excluded sub-population also had a higher proportion from Malaysia (19.4% vs 10.9%) and Vietnam (22.9% vs 12.2%), and a lower proportion from Thailand (31.7% vs 47.2%) compared to the included population. There was no difference in the initial cART regimen (88.4% vs 89.3% NNRTI-based cART), median CD4% at time at cART initiation (11.0% [IQR 4.0, 18.5] vs 11.0% [IQR 4.6, 17], $p=0.88$), or the proportion of those being managed in an urban clinic setting (49.3% vs 45.1%) between this excluded sub-population and the included population.

Of the 1,015 who achieved virologic suppression and had subsequent viral load testing, there were 182 (17.9%) patients who experienced at least one virologic failure event. Median time to virologic failure was 24.6 [IQR 12, 54] months. The crude first virologic failure rate was 3.3 (95% confidence interval (CI) 2.9–3.9) per 100 person-years. The incidence of virologic failure in the study cohort gradually declined throughout the course of cART (Figure 1). The cumulative incidence of a first virologic failure event progressively increased as the age at virologic suppression increased (Figure 2). Of the 182 patients experiencing a virologic failure event, 101 (55.5%) would eventually achieve documented virologic suppression.

There were 38 patients who experienced an early virologic failure event, which represented 20.9% of those who experienced any virologic failure event. On regression analysis, there were no specific characteristics at virologic suppression identified as factors associated with early virologic failure (Table 2). There were 156 patients who experienced a late virologic failure event, representing 85.7% of subjects who experienced any virologic failure event. Of these, 12 (7.7%) had also experienced an early virologic failure event. On multivariate regression analysis the following characteristics at virologic suppression were associated with late virologic failure: *age >3 years compared to age <3 years* (3–4 years asHR 2.9 [95%CI 1.4, 5.9]; 5–9 years asHR 4.0 [95%CI 2.0, 7.8]; 10–14 years asHR 6.3 [95%CI 3.2, 12.2]; 15–19 years asHR 7.9 [95%CI 3.3, 18.8]); *receiving care in a mostly rural clinic setting compared to an urban setting* (asHR 3.6 [95%CI 1.6, 8.0]); *TB infection* (asHR 3.8 [95%CI 1.9, 7.6]); *receiving a PI-based cART regimen compared to an NNRTI-based regimen* (asHR 2.4 [95%CI 1.5, 3.9]); and *having experienced an early virologic failure event* (asHR 2.6 [95%CI 1.4, 4.7]) (Table 2).

DISCUSSION

This study presents valuable findings regarding the burden of virologic failure and associated risk factors in Asian children and adolescents. In particular, 18% of our cohort developed virologic failure following virologic suppression over a median of 6.1 years on

continuous cART. Factors at virologic suppression associated with virologic failure after 12 months included older age, a history of TB infection, receiving a PI-based regimen, and treatment in a mostly rural clinic setting. In addition, those who experienced virologic failure within 12 months of virologic suppression were more likely to experience subsequent virologic failure.

The proportion of children and adolescents experiencing virologic failure in our study cohort is less than the 25–34% reported in other pediatric cohorts, with a median age at ART initiation ranging from 4.6 to 9.3 years [6–8]. However, unlike the other studies, the estimates of virologic failure in our analysis incorporated a cohort of children and adolescents who had confirmed virologic suppression. This is likely to select out a subset of patients with a greater likelihood of treatment adherence, as well as reduce the impact of transmitted or prior drug resistance on virologic outcomes. The median time to virologic failure in our cohort was 2 years, and there was a pattern of decreasing incidence of virologic failure over time. This is consistent with results from a Thai pediatric cohort that reported a median time to virologic failure of 22 months and a decreasing trend in rate of virologic failure throughout the course of cART [4].

The most striking risk factor for late virologic failure was the age at which virologic suppression was initially achieved. Those who achieved virologic suppression >3 years of age were more likely develop virologic failure compared to those <3 years of age, with adolescents (aged 10–19 years) demonstrating the highest risk group. The better outcomes for the youngest cohort may reflect better engagement through the continuum of care from maternal and antenatal services to pediatric services. As for adolescents, our findings add further weight to the growing body of evidence regarding poorer virologic outcomes for adolescents, which has been demonstrated irrespective of the resource setting [15–18]. Given the median age at cART initiation of 6.1 years in our study, in a cohort where at least 86.7% acquired HIV perinatally, there have been considerable delays in commencing cART for our current surviving cohort of children with perinatally acquired HIV infection. This not only resulted in poorer virologic outcomes as demonstrated by our study, but also has implications for the degree of immune suppression and severity of clinical disease, which has been demonstrated to impact treatment outcomes in other studies [19, 20]. These results further re-iterate the importance of early diagnosis of perinatal HIV infection and prompt cART initiation to optimize immunologic, virologic, and clinical outcomes.

Studies evaluating the association between TB co-infection and late virologic failure have produced variable results. Our analysis, which reported a higher risk of virologic failure associated with TB, is consistent with previous observational data from pediatric cohorts in Mozambique and Uganda [21]. However, in a combined cohort of children, adolescents, and adults from Swaziland, TB coinfection was not associated with virologic failure [22]. In addition, a systematic review including 13 adult studies on the impact of TB treatment on virologic failure, found inconclusive evidence regarding the impact of TB treatment on virologic failure, which was largely due to the heterogeneity in definitions for virologic failure [23]. HIV/TB co-infection continues to be a significant global health concern, and given current WHO recommendations for concurrent ART and TB therapy to improve mortality outcomes [24], our results support the need for further longitudinal studies on the

virologic outcomes for children and adolescents with HIV/TB co-infection to identify potential areas to refine management [25].

Our finding of the association between boosted PI-based therapy and late virologic failure is not in keeping with previous pediatric studies. In a rural Tanzanian cohort, a higher likelihood of virologic failure was associated with NNRTI-based compared to PI-based therapy [6]; whilst a South African study found unboosted ritonavir, but not boosted ritonavir, containing cART regimens to have a higher likelihood of virologic failure compared to efavirenz containing ART regimens [5]. The higher risk of virologic failure for those receiving PI-based therapy demonstrated in our cohort may reflect the higher likelihood of using PI-based regimens as 2nd-line in our study cohort. Of those receiving a PI-based regimen at virologic suppression, 20% had initially commenced an NNRTI-based or other type of cART regimen; whereas only 1% of those who were receiving an NNRTI-based cART regimen at virologic suppression had initially commenced a PI-based or other type of cART regimen. Therefore, those who were on a PI-based regimen at virologic suppression in our study were more likely to have a complex history of ART exposure and/or possible issues with previous treatment adherence.

The differences in virologic outcomes based on type of clinic setting demonstrated in our study identifies the complex nature of HIV health infrastructures, and the need for pediatric expertise across the spectrum of services from centrally located specialized facilities to local clinics. This is particularly important given the shift to decentralize HIV services, which requires additional considerations regarding transfer of care, supply and access to effective cART regimens, and local clinic resources with adequate staffing and support from specialized centers through accessible referral systems.

Those who experienced an early virologic failure event in our cohort were shown to be at a two-fold higher risk of a subsequent virologic failure event. This could reflect ongoing issues with ART adherence or drug resistance, and the difficulties in implementing interventions to improve virologic outcomes. The reason no specific characteristics were identified as factors associated with early virologic failure could be due to the small number of early virologic failure events according to our criteria.

This study has several limitations. Firstly, clinical practice regarding HIV viral load testing has not been uniform across the region, with a considerable proportion either not having any HIV viral load results or not being tested within the 5–12-month study inclusion period following cART initiation. Those with viral load testing may have either come from higher resourced clinics or have been selected for testing due to concerns over adherence. Consequently, we may have over- or underestimated the burden of virologic failure within our cohort. Secondly, our criteria for virologic failure included only one HIV viral load >1,000, which is less stringent than that defined by the WHO (of two consecutive HIV viral loads >1,000 with optimal ART adherence); however, this was considered a reasonable approach given that we pre-specified prior virologic suppression, the prevalent use of NNRTIs in first-line regimens, the frequency of HIV viral load testing in our region during the study period, and prior studies using similar definitions [4, 26–28]. Thirdly, due to a lack of self- or clinic-reported adherence measures and the lack of HIV resistance testing, we

were unable to determine the impact of treatment adherence and drug resistance on virologic failure.

In conclusion, our study showed that approximately 1 in 5 children and adolescents in our Asian cohort who achieved virologic suppression after cART initiation experienced subsequent virologic failure at a median time of 2 years. Older age at cART initiation, a history of TB coinfection, use of PI-based regimens, treatment in rural clinic settings, and early virologic failure were associated with long-term virologic failure. These results suggest that if the targets of the UNAIDS “90-90-90” strategy are to be met in Asia, there needs to be improved capacity for early HIV diagnosis and cART initiation of HIV-exposed infants and children, regular HIV viral load testing, and targeted interventions for complex treatment scenarios, such as adolescents, TB coinfection, extensive ART exposure, and those with a history of poor virologic control. Adequate resource allocation across all clinic settings is integral if such measures to optimize virologic outcomes for children and adolescents living with HIV is achievable.

Acknowledgements

The TREAT Asia Pediatric HIV Network: PS Ly*, and V Khol, and R Seng, National Centre for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia; J Tucker, New Hope for Cambodian Children, Phnom Penh, Cambodia; N Kumarasamy*, and E Chandrasekaran, YRG CARE Medical Centre, CART CRS, Chennai, India; DK Wati*, D Vedaswari, and IB Ramajaya, Sanglah Hospital, Udayana University, Bali, Indonesia; N Kurniati*, and D Muktiarti, Cipto Mangunkusumo - Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia; SM Fong*, KJ Wong, and FB Daut, Hospital Likas, Kota Kinabalu, Malaysia; NK Nik Yusoff*†, and P Mohamad, Hospital Raja Perempuan Zainab II, Kelantan, Malaysia; TJ Mohamed*, and MR Drawis, Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; R Nallusamy*, and KC Chan, Penang Hospital, Penang, Malaysia; T Sudjaritruk*, V Sirisanthana, and L Aurpibul, Department of Pediatrics, Faculty of Medicine, and Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand; R Hansudewechakul*, P Ounchanum, S Denjanta, and A Kongponoi, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; P Lumbiganon*, P Kosalaraksa, P Tharnprisan, and T Udomphanit, Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; G Jourdain, PHPT-IRD UMI 174 (Institut de recherche pour le développement and Chiang Mai University), Chiang Mai, Thailand; T Puthanakit*, S Anugulruengkit, W Jantarabenjakul and R Nadsasarn, Department of Pediatrics, Faculty of Medicine and Research Unit in Pediatric and Infectious Diseases, Chulalongkorn University, Bangkok, Thailand; K Chokephaibulkit*‡, K Lapphra, W Phongsamart, and N Vanprapar, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; KH Truong*, QT Du, and TT Nguyen, Children's Hospital 1, Ho Chi Minh City, Vietnam; VC Do*, TM Ha, and VT An Children's Hospital 2, Ho Chi Minh City, Vietnam; LV Nguyen*, DTK Khu, and LT Nguyen, National Hospital of Pediatrics, Hanoi, Vietnam; ON Le, Worldwide Orphans Foundation, Ho Chi Minh City, Vietnam; AH Sohn*, JL Ross, and C Sethaputra, TREAT Asia/amfAR -- The Foundation for AIDS Research, Bangkok, Thailand; DA Cooper, MG Law*, and A Kariminia, The Kirby Institute, UNSW Australia, Sydney, Australia;

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Source of Funding:

This work was supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Cancer Institute, National Institute of Mental Health, National Institute on Drug Abuse as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA) [Grant number U01AI069907], the Australian Government Department of Health and Ageing, and the National Science and Technology Major Project of the Ministry of Science and Technology of China [Grant number 2012ZX10001004, 2014ZX10001002]. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above.

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Figure 1.

Incidence of virologic failure for each year of combination antiretroviral therapy following virologic suppression.

cART = combination antiretroviral therapy. VF = virologic failure.

Figure 2.

Cumulative incidence of virologic failure following virologic suppression by age at combination antiretroviral therapy initiation.

cART = combination antiretroviral therapy.

Table 1.

Characteristics at time of cART initiation and at virologic suppression for 1,015 children and adolescents included in the analysis.

	cART initiation (n=1015)	Virologic suppression (n=1015)
Age (years)		
Median [IQR]	6.1 [3.0, 9.3]	6.9 [3.8, 10.3]
<3	249 (24.5)	202 (19.9)
3–5	230 (22.7)	221 (21.8)
6–9	301 (29.7)	330 (32.5)
10–14	203 (20.0)	212 (20.9)
15–19	32 (3.2)	50 (4.9)
Sex		
Female	520 (51.2)	
Exposure		
Mother-to-child	880 (86.7)	
Other	20 (2.0)	
Unknown/missing	115 (11.3)	
Country of origin		
Cambodia	291 (28.7)	
India	3 (0.3)	
Indonesia	8 (0.8)	
Malaysia	110 (10.8)	
Thailand	479 (47.2)	
Vietnam	124 (12.2)	
Clinic setting		
Urban	458 (45.1)	
Mostly urban	534 (52.6)	
Mostly rural	23 (2.3)	
Orphan status		
No	722 (71.1)	717 (70.6)
Yes	216 (21.3)	247 (24.3)
Unknown/missing	77 (7.6)	51 (5.0)
Primary caregiver		
Immediate family	578 (56.9)	574 (56.6)
Extended family	173 (17.0)	204 (20.1)
Non-relative	61 (6.0)	71 (7.0)
Unknown/missing	203 (20.0)	166 (16.4)
CD4%		
25	69 (6.8)	313 (30.8)

	cART initiation (n=1015)	Virologic suppression (n=1015)
15–24	230 (22.7)	336 (33.1)
<15	574 (56.6)	209 (20.6)
Unknown/missing	142 (14.0)	157 (15.5)
Median [IQR]	11 [4.6, 17]	21.1 [15, 28]
HIV viral load (copies/ml)		
<400	19 (1.9)	1,015 (100)
400 and <1,000	4 (0.4)	
1,000 and <10,000	32 (3.2)	
10,000	434 (42.8)	
Unknown/missing	526 (51.8)	
Median log [IQR]	5.1 [4.7, 5.7]	
WHO clinical stage		
I or II	630 (62.1)	992 (97.7)
III or IV	385 (37.9)	23 (2.3)
Anaemia		
No	465 (45.8)	698 (68.8)
Yes	260 (25.6)	77 (7.6)
Unknown/missing	290 (28.6)	240 (23.6)
Weight for age Z score		
–1	271 (26.7)	347 (34.2)
–2 to <–1	271 (26.7)	353 (34.8)
<–2	435 (42.9)	276 (27.2)
Unknown/missing	38 (3.7)	39 (3.8)
Median [IQR]	–1.8 [–2.6, –0.9]	–1.4 [–2.1, –0.6]
Height for age Z score		
–1	236 (23.3)	259 (25.2)
–2 to <–1	255 (25.1)	287 (28.3)
<–2	432 (42.6)	418 (41.2)
Unknown/missing	92 (9.1)	51 (5.0)
Median [IQR]	–1.9 [–3.0, –0.9]	–1.7 [–2.7, –0.9]
Tuberculosis ^a		
No	915 (90.2)	989 (97.4)
Yes	100 (9.9)	26 (2.6)
cART regimen		
EFV-based	277 (27.3)	294 (29.0)
NVP-based	641 (63.2)	612 (60.3)
PI-based	88 (8.7)	103 (10.1)
Other	9 (0.9)	6 (0.6)

	cART initiation (n=1015)	Virologic suppression (n=1015)
NRTI agent		
3TC	995 (98.0)	
D4T	525 (51.7)	
AZT	452 (44.5)	
TDF	25 (2.5)	
ABC	9 (0.9)	

Values n (%) unless otherwise specified.

^aDiagnosed within the preceding 6 months.

3TC=lamivudine, D4T=stavudine, AZT= zidovudine, TDF= tenofovir, ABC=abacavir, EFV=efavirenz, NVP=nevirapine, PI=protease inhibitor, cART=combination antiretroviral therapy, IQR=interquartile range, NNRTI=non-nucleoside reverse transcriptase inhibitor, NRTI=nucleoside reverse transcriptase inhibitor.

Table 2.

Factors at virologic suppression associated with virologic failure.

	Early VF		Late VF			
	Univariate ^a		Univariate		Multivariate	
	sHR [95% CI]	p	sHR [95% CI]	p	asHR [95% CI]	p
Age (years)						
<3	1.0		1.0		1.0	
3 to <5	1.5 [0.5, 4.5]	0.5	2.5 [1.2, 5.2]	0.012	2.9 [1.4, 5.9]	0.004
5 to <10	1.5 [0.5, 4.2]	0.47	3.4 [1.7, 6.7]	<0.001	4.0 [2.0, 7.8]	<0.001
10 to <15	2.1 [0.7, 6.1]	0.17	5.5 [2.8, 10.8]	<0.001	6.3 [3.2, 12.2]	<0.001
15 to <20	1.6 [0.3, 8.3]	0.57	6.4 [2.7, 15.2]	<0.001	7.9 [3.3, 18.8]	<0.001
Sex						
Female	1.3 [0.7, 2.5]	0.4	1.3 [1.0, 1.8]	0.09	1.2 [0.9, 1.7]	0.29
Clinic setting						
Urban	1.0		1.0		1.0	
Mostly urban	0.7 [0.3, 1.2]	0.15	1.0 [0.7, 1.4]	0.95	1.2 [0.8, 1.6]	0.40
Mostly rural	-	-	2.4 [1.1, 5.1]	0.02	3.6 [1.6, 8.0]	<0.001
Orphan						
Yes	1.1 [0.5, 2.2]	0.84	1.2 [0.8, 1.7]	0.29	-	-
Primary caregiver						
Immediate family	1.0		1.0		-	
Extended family	1.3 [0.7, 2.8]	0.42	1.3 [0.9, 1.9]	0.16	-	-
Non-relative	0.7 [0.2, 3.1]	0.65	1.0 [0.6, 2.0]	0.89		
CD4%						
25	1.0		1.0		1.0	
15–24	1.3 [0.6, 3.2]	0.49	1.8 [1.2, 2.7]	0.008	1.3 [0.8, 2.0]	0.29
<15	1.3 [0.5, 3.4]	0.56	1.8 [1.2, 2.9]	0.009	1.2 [0.7, 1.9]	0.53
Viral blip						
Yes	1.0 [0.1, 7.0]	0.98	1.7 [0.8, 3.5]	0.18	-	-
WHO clinical stage						
I or II	1.0		1.0		-	
III or IV	2.7 [0.4, 18.9]	0.32	0.7 [0.2, 2.3]	0.59	-	-
Anaemia						
Yes	1.0 [0.3, 3.4]	0.99	1.0 [0.5, 1.7]	0.93	-	-
Weight for age z score						
-1	1.0		1.0		-	
-2 and <-1	0.8 [0.3, 1.7]	0.49	1.0 [0.7, 1.5]	0.91	-	-
<-2	1.4 [0.6, 2.9]	0.43	1.0 [0.7, 1.5]	0.86	-	-
Height for age z score						

	Early VF		Late VF			
	Univariate ^a		Univariate		Multivariate	
	sHR [95% CI]	p	sHR [95% CI]	p	asHR [95% CI]	p
-1	1.0		1.0		-	
-2 and <-1	2.1 [0.8, 5.6]	0.12	1.0 [0.6, 1.5]	0.87	-	-
<-2	1.8 [0.7, 4.5]	0.24	0.9 [0.6, 1.4]	0.78	-	-
TB infection						
Yes	-	-	2.6 [1.3, 5.1]	0.007	3.8 [1.9, 7.6]	<0.001
Calendar year						
2005–2007	1.0		1.0		1.0	
2008–2010	0.9 [0.4, 2.1]	0.76	1.4 [1.0, 2.0]	0.08	1.4 [1.0, 2.0]	0.09
2011–2013	1.3 [0.5, 3.0]	0.59	1.2 [0.7, 1.8]	0.51	1.0 [0.6, 1.6]	0.96
2014	2.0 [0.8, 5.4]	0.15	0.3 [0.08, 1.3]	0.11	0.3 [0.06, 1.2]	0.08
cART regimen						
NNRTI-based	1.0		1.0		1.0	
PI-based	1.8 [0.8, 4.4]	0.17	1.9 [1.2, 2.9]	0.006	2.4 [1.5, 3.9]	<0.001
Other	1.9 [0.3, 13.9]	0.51	1.5 [0.5, 4.6]	0.44	1.2 [0.4, 3.5]	0.77
VF 12 months						
Yes	-	-	2.7 [1.4, 5.0]	0.002	2.6 [1.4, 4.7]	0.003

aSHR = adjusted subdistribution hazard ratio. CI = confidence interval. cART = combination antiretroviral therapy. SHR = subdistribution hazard ratio. TB = tuberculosis. VF = virologic failure.

^a Multivariate analysis not conducted as no co-variables on univariate analysis proved significant.