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Original Article

Virological failure of first-line antiretroviral therapy in children living with HIV in Indonesia and associated factors

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Abstract

Background *The World Health Organization* (WHO) recommends viral load (VL) monitoring for HIV patients on antiretroviral therapy (ART). However, availability of VL monitoring in low-income countries remains limited.

Objective To investigate factors associated with virological failure in HIV-infected children treated without routine VL monitoring.

Methods This cohort study was done in children living with HIV (CLHIV) registered at Cipto Mangunkusumo General Hospital from 2004 to 2021. Viral load monitoring was not routinely done. Subjects with at least one VL result after 6 months on ART were included in the study. Virological failure was defined as a VL of >1,000 copies. Subjects' data were obtained from medical records, laboratory reports, and dispensing pharmacies. Statistical analysis was done following survival analysis with hazard ratio.

Results There were 384 children who had at least 1 VL result after ART was initiated. Median age at diagnosis was 30 months. Length of follow-up ranged from 6 to 216 months, with a mean frequency of VL monitoring of 0.7 times/person/year. Most subjects were already in clinical stages 3 and 4 (77.8%); 75% met severe immunodeficiency criteria. Virological failure was found in 45.8% of subjects after a median of 33 months on first-line ART, yielding an incidence of 3.3 per 1,000 person months. Independent associated factors were age at diagnosis of <60 months (HR 1.714; 95%CI 1.13 to 2.6), severe immunodeficiency (HR 1.71; 95%CI 1.15 to 2.54), referral cases (HR 1.70; 95%CI 1.23 to 2.36), and WHO clinical staging 3 (HR 1.987; 95%CI 0.995 to 3.969) and 4 (HR 2.084; 95%CI 1.034 to 4.201). Subjects with virological failure had lower weight-for-age z-scores [median 1.92; interquartile range (IQR) -3.003 to -0.81] and height-for-age z-scores [median -2.05; IQR -2.902 to -1.04] at the time of failure.

Conclusions In HIV-infected children treated without routine VL monitoring, age at diagnosis <60 months, severe immunodeficiency, WHO clinical stage 3 and 4, and referral from other centers were associated with virological failure. **[Paediatr Indones. 2022;62:295-303; DOI: https://doi.org/10.14238/pi62.4.2022.295-303**].

Keywords: *HIV; virological failure; severe immunodeficiency*

Human immunodeficiency virus (HIV) infection is a major public health problem worldwide. In 2020, there were 37.7 million people living with HIV (PLHIV), with 1.5 million new HIV infections and 680,000 deaths from AIDS-related causes.[1] An estimated 1.7 million children worldwide (age <15 years) were living with HIV and more than 80% of them were living in sub-Saharan Africa, of whom only an estimated 49% received antiretrovirals.[2,3]

The use of antiretroviral therapy (ART) that combines two or more drugs has significantly reduced morbidity and AIDS-related mortality among infected children.[4,5] The goal of ART is to suppress viral replication, resulting in decreased HIV-RNA VL.6 *The World Health Organization* (WHO) recommends routine viral load monitoring for all PLHIV on ART to assess treatment response and disease progression.[6-8] However, availability of VL monitoring remains

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scarce, particularly in low- and middle-income countries due to limited laboratory facilities and trained personnel.9 In Indonesia, VL monitoring is not routinely supported.

Missed opportunities to do routine viral monitoring lead to delays in identifying treatment failure and switching to second-line ART combinations. Virological failure and the development of drug resistance have become major issues in children living with HIV (CLHIV) due to weight-based dosing, poor tolerability of drugs, and suboptimal adherence.[10,11] Studies in sub-Saharan Africa showed that the prevalence of virological failure was significantly higher among children compared to adults and was reported to be 32.1% in Ugandan, 37% in Kenyan, and 66% in Malawian children based on cohort and cross-sectional studies of 12-24 months of therapy.[12-14] In South Africa, the incidence rate of virological failure was 18.7 per 100 person years follow up, while India, as Asia's representative, reported a 29% prevalence of viral failure.[9,15] Several factors that are known to increase the risk of virological failure on CLHIV include younger age at diagnosis or treatment initiation, WHO stage 3 and 4, lower CD4 count, nevirapine (NVP)-based regimen, and treatment interruption.[10,11,16-21]

This study aimed to determine the incidence of treatment failure with first-line ART in situations of limited VL monitoring in Indonesia, as well as to identify the predictors of treatment failure in order to assist clinicians in monitoring their patients more closely.

Methods

This retrospective cohort study included patients from the Dr. Cipto Mangunkusumo General Hospital registry observed from 2004 to 2021. Dr. Cipto Mangunkusumo General Hospital is the top national referral hospital in the capital region of Jakarta, Indonesia, with an HIV service established in the early 2000s. Universal ART coverage started in 2004 and any PLHIV who met the indication criteria was treated. The ART regimens were given according to the *Indonesian Guideline of HIV Management*, adapted from WHO guidelines. The first national guideline was published in 2008, with subsequent revised versions published in 2013, 2013, and 2019, incorporating continuous adjustments according to the global guidelines.6 Drug doses were based on the child's body weight. Children were reviewed every month after ART initiation and every 2-3 months for those whose HIV infections were under control.

Children aged <18 years living with HIV/AIDS who had their first-line ART initiation between January 2004 and March 2021 and had at least one viral load measurement after six months of ART initiation were included. The diagnosis of HIV infection was confirmed by virological test using polymerase chain reaction (PCR) of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) HIV for patients aged <18 months and serological test for patients aged ≥18 months (*Cobas TaqMan, Roche,* Basel and *GenXpert, Cepheid,* Sunnyvale, California). Children who transferred from other hospitals and initiated ART with complete information available were included in the study; otherwise, CLHIV with incomplete data were excluded.

The outcome variable was virological failure of CLHIV after starting ART. The sociodemographic characteristics collected were age at diagnosis, sex, the child's primary caregiver, disclosure of HIV status to the CLHIV prior to virological failure, and antiretroviral (ARV) treatment history (whether naïve or referral). Baseline clinical factors were WHO clinical stage and baseline CD4 according to age category. Treatment-related factors were type of initial regimen, form of medication use, time to treatment failure, age at treatment failure, timing of switch to second-line treatment after failure, type of second-line regimen, adherence, HIV status disclosure, and nutritional status at treatment failure. Time to failure was measured in months from the point of ART initiation until the point of first-line treatment failure. We determined adherence before and after failure in cross-sectional fashion.

Virologic failure was diagnosed as VL >1,000 copies/ml after at least 6 months of ART treatment.6 Baseline data were taken at the first clinic visit and included age at diagnosis, sex, the child's primary caregiver, WHO clinical stage at diagnosis, and whether the patient was a naïve or referral case. Adherence to highly active antiretroviral therapy (HAART) was measured for those with viral load >1,000 copies/ml, measured subjectively, and

expressed on a scale of 0 to 100 according to a visual analog scale (VAS). A VAS of 91-100 was considered as good, 81-90 as moderate, and <80 as poor adherence. CD4 count was categorized according to the WHO age-appropriate classification to describe immunosuppression level: children aged <1 year with a CD4 count of <1,500 cells/mm^3, 1-5 years with a CD4 count of <750 cells/mm^3, and >5 years with a CD4 count of <350 cells/mm^3 were categorized as immunocompromised.[22]

First-line ART regimens consisted of three drugs. The backbone was either nevirapine (NVP), efavirenz (EFV), lopinavir/ritonavir (LPV/r) or other drugs. The other two drugs were made up of a combination of either zidovudine (AZT), stavudine (D4T), didanosine (DDI), tenofovir (TDF), lamivudine (3TC), or emtricitabine (FTC) and abacavir (ABC). The forms of medications used are specific to Indonesia. Since most ART are available as adult tablets, we categorized the medication forms as crushed tablet, scored tablet, or full form tablet. When pediatric fixed drug combination was available and used, patients recorded it as full form tablet.

Time to treatment failure was calculated from the date of first ART dispensing from the pharmacy and the date of virological failure. Nutritional status, comprising body weight, body height and body mass index (BMI), was expressed as age- and sex-specific *z*-scores according to the *WHO Child Growth Standards*.[23] Z-scores were determined using WHO *Anthro®* software (WHO, Geneva) for children aged <5 years and *WHO AnthroPlus®* (WHO, Geneva) for children aged 5-18 years. The measurements collected were those done within two weeks before or after the date of treatment failure. Weight-for-age *z*-score (WAZ), height-for-age *z*-score (HAZ), and BMI *z*-score (BAZ) of <-2 were considered as undernutrition.[23]

Data were collected and collated from the hospital electronic data registry, physical medical records, laboratory reports, and ARV dispensing lists from the hospital pharmacy. Data were initially collected using *Microsoft Excel 2021®* (*Microsoft*, Redmond, Washington). Completeness of the data was checked manually. Data coding and entry were done using *SPSS version 28* (*IBM,* Armonk, New York). Data consistency was repeatedly checked by the investigators.

Retrospective data collection encompassing a period of 18 years has a high possibility of information bias. We expected data to be missing in several variables. The minimum required sample size was determined using a single population proportion formula, with the following statistical assumptions: an incidence rate of 1.5 per person months based on a study by Makatini *et al.*[15] in South Africa, a margin of error of 5%, and a $Z\alpha/2$ of 1.96, which was the corresponded to a 95% confidence interval (95%CI). Precision was determined at 1% and time of observation (T) was 216 months, resulting in a minimum sample size of 267 subjects.

Tables were used to present descriptive results. Additionally, frequencies, percentages, proportions, and median (with interquartile range) were used to summarize the study population characteristics. Two standard statistical methods were employed: the Kaplan-Meier method (a non-parametric method) and Cox proportional hazards regression model (a semi-parametric method). *Stata v.16 software* (*StataCorp,* College Station, Texas) was used to generate substitute values for missing data (imputate missing data) to use in multivariate analysis. The Kaplan-Meier method was used to estimate the rate of virological failure at different time points. The incidence of virological failure was calculated in person-years of observation. The Chi-square test was used to examine bivariate associations between independent variables and virological failure, using *Stata* and *SPSS*. We further analyzed all bivariate associations with a P value of <0.25 using Cox proportional hazards analysis to determine significant predictors of virological failure. The results are presented as hazard ratio (HR) with 95%CI. The level of significance was set at $p<0.05$.

This study was approved by the Health Research Ethics Committee, Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo General Hospital. To protect patient confidentiality, all records were anonymized and de-identified prior to analysis. All procedures in this study were conducted in accordance with the Declaration of Helsinki, as revised in 2013.

Results

There were 684 children with HIV registered from January 2003 to March 2021, which was the last

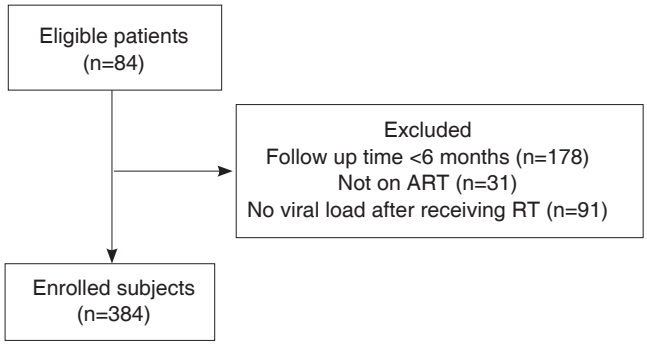

Figure 1. Subject recruitment

recruitment date for new patients in order to allow for 6 months of treatment observation. The study observation ended on 31 December 2021. We excluded 178 children who had not been under our care for at least six months, either due to death or having only one or two consultation visits with less than six months of follow up. Thirty-one children who were not on ART were excluded. Furthermore, 91 children were excluded because, although they met the six-month ART criteria, they had no data on VL monitoring. Hence, a total of 384 CLHIV were included in the final analysis (**Figure 1**).

Median age of HIV diagnosis was <3 years (26 months for those with failure and 30 months for those without failure). According to absolute CD4 count for age, most subjects were already in WHO clinical stage 3 or 4 with severe immunodeficiency (75%). Twenty-one percent of new cases in the study were referred from other HIV care centers. Most subjects had started ART one to 11 years before referral to our hospital, usually for failure diagnosis. Almost all subjects were infected through a perinatal route, but only four had received ART for prevention during the perinatal period. Subjects' mean frequency of VL examination was 0.73 times per person per year. A single parent or both parents were the primary caregivers for most subjects, with another 38% of subjects under the care of grandparents or other blood relatives. The basic sociodemographic characteristics of subjects before ART initiation are shown in **Table 1**.

The median time lag between diagnosis and ART initiation was 7 months in the failure group and 1.5 months in the non-failure group. Since pediatric ART formulations were scarce, adult ARV tablets were usually crushed or scored. Although 47.2% of subjects took crushed tablets (powder form), they used the full tablet form at later ages. **Table 2** shows the characteristics of ART treatment in subjects.

The longest follow-up time was 216 months (18 years). Disclosure was important for CLHIV once they reached the late school-age or teen years. In our study almost half of subjects were still at an inappropriate age for disclosure (**Table 1**).

More than 75% of subjects used nevirapine (NVP) as first-line ART backbone, which was in line with Indonesian guidelines for those aged <3 years. Use of efavirenz is contraindicated in this age group. A small number of subjects used ritonavir-boosted lopinavir (LPV/r) as first-line backbone; most had started ART overseas or had an allergy to nevirapine. In the past 5 years, we changed the backbone to LPV/r whenever possible, as the appropriate, child-friendly form was available.

Overall, almost half (45.8%) of the participants met our definition of virological failure (viral load >1,000 copies/mL) after at least six months of ART consumption (45.8%), as defined by the *2016 WHO Guideline*, measured 2 times apart with adherence support. In 2021, the WHO guideline was modified to allow a one-time VL result >1,000 copies/mL to define virological failure, which was more feasible in this study.6 Adherence measurements before and after the date of viral failure were available for 117 subjects, with 92% having good adherence (VAS 91-100). Data for adherence was missing for those in care before 2017, and this data was not imputed. At virological failure, median weight-for-age z-score was -1.92 (IQR -0.81 to -3.003), classified as undernutrition, and median height-for-age z-score was -2.05 (IQR -1.04 to -2.902), classified as short stature.

Table 1. Sociodemographic characteristics of subjects

Variables	Total (n=384)	Virological failure (n=176)	Non-failure (n=208)
Gender, n (%)			
Male	198 (51.6)	92 (52.3)	106 (50.9)
Female	186 (48.4)	84 (47.7)	102 (49.1)
Source of transmission, n (%)			
Perinatal	380 (98.9)	176 (100)	204 (98.1)
Blood products	3 (0.8)	0	3 (1.4)
Sexual	1 (0.3)	0	1 (0.5)
Age at diagnosis			
Median, months	29	26	30
IQR (Q3-Q1)	41 (53-12)	36 (50-14)	45 (57-12)
Age at diagnosis by group, n (%)			
≤60 months	312 (81.25)	149 (84.6)	163 (78.4)
>60 months	72 (18.75)	27 (15.4)	45 (21.6)
WHO clinical stage before ART, n (%)			
Grade 3 and 4	299 (77.8)	144 (81.8)	155 (74.5)
Grade 1 and 2	85 (22.2)	32 (18.2)	53 (25.5)
Type of cases, n (%)			
Referral	81 (21)	52 (29.5)	29 (13.9)
Naïve	303 (79)	124 (70.5)	179 (86.1)
Primary caregiver, n (%)			
Parents	227 (59.1)	93 (52.8)	134 (64.4)
Blood relatives	147 (38.3)	78 (44.3)	69 (33.2)
Other (foster parents)	10 (2.6)	5 (2.9)	5 (2.4)
Absolute CD4+ based on age			
Immunocompromised	289 (75.3)	46 (82.9)	143 (68.75)
Not immunocompromised	95 (24.7)	30 (17.1)	65 (31.25)
Disclosure status prior to viral failure (n=269, missing data= 115)			
Yes	82	27	45
Partial	3	1	2
No HIV disclosure due to age < 12 y.o.	179	89	90
Unknown	5	2	3
Nutritional status at virological failure or last VL* (n=344, missing data 40)			
Body weight (WAZ)	-1.72 (-0.578 to -2,83)	-1.92 (-0.81 to -3.003)	-1.54 (-0.33 to -2.63)
Body height (HAZ)	-1.73(-0.775 to -2.59)	-2.05 (-1.04 to -2.902)	-1.495 (-0.50 to -2.42)
BMI	-0.69(0.25 to -1.725)	-0.76 (0.04 to -1.77)	-0.66 (0.36 to -1.45)

*Median Z-score (Q3-Q1)

Using a life table calculation, the incidence rate of virological failure was 3.3 per 1,000 person months of follow-up. Most subjects with virological failure were male (52.3%). In subjects with virological failure, median age at HIV diagnosis was 26 (IQR 50-14) months. Median overall time to failure was 33 months. The proportion of failure was higher in referral cases (52/81; 64.1%). Out of all failure subjects, 29.5% were referral cases. Diagnosis of failure was the reason of referral in most subjects.

Before performing analysis on the association of determinants with virological failure, we imputed missing data on body weight and body height in 40 out of 384 subjects (10.4%) based on age at diagnosis and WHO clinical stage. Both bivariate and multivariate analyses were used to determine factors associated with virological failure. On bivariate analysis, age at diagnosis, WHO clinical stage, ART treatment history (referral or naïve), drug formulation, and absolute CD4 count were associated with virological failure with a P value of <0.25, therefore becoming candidate variables for the final regression model (**Table 3**).

Multivariate Cox regression analysis revealed four statistically significant determinants for virological

Table 2. Characteristics of ART in subjects

Variables	Total (n=384)	Virological failure (n=176)	Non-failure (n=208)
Age at ART initiation, months			
Median		33	31.5
IQR (Q3-Q1)		37 (53-16)	48 (62-14)
ART regimens, n (%)			
NVP-based	290	137 (77.8)	153 (73.56)
EFV-based	65	17 (9.6)	48 (23.07)
LPV/r-based	11	6 (3.4)	5 (2.4)
Other	18	16 (9.2)	2 (0.97)
Form of ART drugs (n=380, missing data=4			
Crushed tablet	290	137 (77.8)	153 (73.5)
Full or scored tablet	90	36 (20.5)	54 (25.9)
Adherence, (n=117, missing data= 267)*			
Poor		4 (3.4)	n/a
Moderate		5 (4.3)	n/a
Good		108 (92.3)	n/a

*Measured only in failure subjects, thus % is out of 117 total subjects; Adherence level: poor (VAS<80), moderate (VAS 80-90), good (VAS 91-100)

Table 3. Multivariate Cox regression analysis for virological failure among CLHIV

Variables	Bivariate analysis		Multivariate analysis			
			Initial model		Final model	
	HR (95%CI)	P value	HR (95%CI)	P value	aHR (95%CI)	P value
Gender	1.03 (0.76 to 1.38)	0.858	1.10 (0.14 to 1.49)	0.531		
Age at diagnosis <60 month	1.39 (0.92 to 2.10)	0.113	1.70 (1.058 to 2.73)	0.028	1.71444 (1.13 to 2.6)	0.012
WHO clinical staging:						
Stage 4	2.338 (1.165 to 4.693)	0.017	1.911 (0.938 to 3.892)	0.075	2.084 (1.034 to 4.201)	0.04
Stage 3	2.207 (1.016 to 4.041)	0.045	1.934 (0.964 to3.881)	0.64	1.987 (0.995 to 3.969)	0.052
Stage 2	1.963 (0.908 to 4.244)	0.086	1.790 (0.823 to 3.896)	0.142	1.798 (0.815 to 3.833)	0.149
Stage 1	1					
Referral cases	1.74 (1.26 to 2.40)	0.001	1.901 (1.337 to 2.704)	0.000	1.858 (1.336 to 2.585)	0.0001
ARV formulation	1.28 (0.89 to 1.85)	0.185	2.02 (1.423 to 2.873)	0.415		
Primary caregiver						
Parents	0.81 (0.33 to 1.99)	0.642				
Blood relatives	1.11 (0.45 to 2.74)	0.822				
Other (foster parents, orphaned)	1					
Absolute CD4+ based on age	1.662 (1.192 to 2.32)	0.003	1.66 (1.19 to 2.32)	0.0025	1.885 (1.341 to 2.65)	0.0001
Nutritional status						
BMI Z-score <0.1	0.164(0.806 to1.682)	0.418				

failure in the final model. Children who were aged <60 months at diagnosis were prone to treatment failure (HR 1.714; 95%CI 1.13 to 2.6; P=0.012). Referral cases were more likely to have virological failure compared to naïve cases (HR 1.858; 95%CI 1.336 to 2.585; P=0.0001). Baseline absolute CD4+ count categorized as immunocompromised (HR 1.885; 95%CI 1.341 to 2.65; P=0.0001) and severe WHO clinical stage (stage 3 and 4) were also significant predictors for virological failure (**Table 3**).

Discussion

This study provides important information about virological failure status among CLHIV in Jakarta. Current practice on treatment failure monitoring in Indonesia focuses on clinical deterioration or immunological failure, which are considered late findings.[24] Since 2016, the WHO has proposed annual viral load monitoring to detect earlier treatment failure.[22]

Determination of ideal virological failure was a challenge for our cohort, who underwent less than 1 test per person per year. Ideally, after one VL result of >1,000 copies/ml, the viral load test should be repeated, as it supports adherence. However, program constraints and lack of funding lead to few or no follow-up testing. Even a single viral load test result of >1,000 copies/ml may be considered as failure, especially in low-and middle-income countries with nucleoside/nucleotide reverse transcriptase inhibitors (NNRTI) as backbone first-line ARV.[25] The timing for follow-up VL tests is important, since there is evidence of emerging viral resistance in older regimens. Hence, the recommendation of 6-month, 12-month, and yearly testing after initiating ARV, thereafter.[22] Use of integrase inhibitor (INSTI) may change the need for an exact time of repeated viral load testing, since INSTI is considered to have higher resistance barrier.[26]

Prevalence of virological failure in our study (45.8%) was higher than reported in three studies in Africa and one study in India.[12-15] This difference could have been due to follow-up periods and study settings. The follow-up time for our cohort was 6 months to 18 years, which was longer than in other studies. Our unique position as the referral center for pediatric HIV care in the greater Jakarta region resulted in a distinctive group of subjects, whether they were naïve or had prior ART experience. The proportion of failure was higher in referral subjects (62%), which was not previously reported in any study. This is consistent with the diagnosis of treatment failure being the main reason for referral to our center. Such a diagnosis implies that subjects probably had immunological failure or clinical failure that occurred after virological failure and before they were referred to our hospital.

The incidence density of treatment failure in our study was 3.3 children per 1,000 person-months, which was higher compared to that in a South African study reporting an incidence density of 18.7 per 100 person-years (equivalent to 1.5 per 1,000 person-months).[15] The mean time from first-line therapy to virological failure was 29 months in our study, similar to that of 30 months reported by an Ethiopian study.[17]

For the last 15 years in Indonesia, ARV backbone regimens have been limited to nevirapine and efavirenz; both of which were reported to be ineffective among African populations with high perinatal exposure.[15] However, exposure risk was not a determinant of virological failure in our study, since almost all subjects had missed perinatal prevention. In subjects treated with nevirapine, the proportion of failure was much higher compared to those treated with efavirenz, but still comparable to findings of other studies reporting virological failure.[18,19] However, univariate analysis of first-line backbone regimens showed no statistically significant differences in hazard ratios.

Weight and height in CLHIV usually improve after ART. In our study, nutrition data was extracted at failure diagnosis. This approach differed from another study which used baseline data at diagnosis in order to measure its influence on failure occurrence. A study in South Africa showed that WAZ and HAZ at baseline had no relationship to virological failure.[15] In other studies, wasting and stunting were not always measured as separate factors, although WHO stage 3 or 4 was reported as an important factor in virological failure, with HIV wasting as one criteria.[10,14,15,17,20] Findings of WAZ <-1 and HAZ <-1.9 showed that clinical failure had already taken place. Ineffective regimen use and lack of scheduled VL monitoring may explain this late detection of virological failure.

Determinants associated with virological failure in the Cox proportional hazards (PH) multivariate final model were initial absolute CD4 counts categorized as immunocompromised, age at diagnosis <60 months, referral cases, and clinical stages 3 and 4 (**Table 3**). The proportion of immunocompromised status at baseline in our study was comparable to that in other studies. Form of medication (crushed or scored vs. whole tablet) a HR of >1, but the p value did not agree with the confidence interval. Since pediatric ART formulations were scarce, adult ARV tablets were usually crushed or scored. The practice of scoring or crushing ARV tablets may have led to a sub-standard pharmacological effect. These specific results could be pertinent to hospital characteristics which could be used to improve care during clinic monitoring.

Our study used a strong design and a longer follow-up duration to estimate the survival time and predictors of viral failure. However, our limitations associated with incomplete data may have led to underestimating or overestimating virological failure. Missing data on variables may have limited the range

of variables and the number of children that could be included in multivariate models. Imputation was only done for nutritional data, which accounted for 10.4% of missing data.

In conclusion, the prevalence and cumulative incidence of virological failure was high in our CLHIV subjects. Children who were <60 months of age at diagnosis, belonged to WHO clinical stage 3 and 4, had low absolute CD4 count, and were referral cases had a significantly higher risk of treatment failure. This observational study showed that early HIV case finding remains inadequate, since the median age at diagnosis was around 3 years. Late diagnosis may lead to treatment failure in the long term. Based on our findings, areas for improvement in HIV care practices based on our findings are early diagnosis, more effective ART, routine VL monitoring, and timely switching to a second-line treatment regimen.

Conflict of interest

None declared.

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