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RESEARCH ARTICLE

Virological Failure and Associated Risk Factors among HIV/AIDS Pediatric Patients at the ART Clinic of Jimma university Medical Center, Southwest Ethiopia

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Abstract:

Background:

Pediatric antiretroviral treatment failure is an under-recognized issue that receives inadequate attention in the field of pediatrics and within HIV treatment programs. Despite the reduction in morbidity and mortality, a considerable proportion of patients fail to achieve a sustained virologic response to therapy. Thus virological failure is an increasing concern globally.

Objective:

This study aimed to assess the virological failure and associated risk factors among HIV/AIDS pediatric patients at Antiretroviral Treatment (ART) follow up clinic of Jimma University Medical Center, southwest Ethiopia.

Methods:

An institution based cross-sectional study was conducted at the ART follow-up clinic of Jimma University Medical Center. A structured English version checklist was developed and used for data extraction from patients' charts from April -May 2019. Then the data was coded and entered using epi data 4.2 and exported to statistical package for social science (SPSS version 22) for analysis. Descriptive analysis was conducted for categorical as well as continuous variables. Multivariable logistic regression was performed in a backward, step-wise manner until a best-fit model was found.

Results:

Of 140 HIV/AIDS pediatric patients enrolled in this study, 72(51.4%) were male and the mean age was 9.7±3.3 Years. ABC-3TC-NVP was the commonly used ART medication in this population, which was 37.1% followed by AZT-3TC-EFV(32.1%). The mean duration of antiretroviral treatment (ART) follow-up was 63.8±29.4 months. Among the study population, 11.0% of them had virological failure. Weight at ART initiation [OR=1.104, 95 CI% [1.013-1.203], p=0.024] and WHO clinical stage 3 [AOR=0.325, 95CI, 0.107-0.991,P=0.048] were the significant risk factors for the virological failure.

Conclusion:

A significant proportion of HIV/AIDS pediatric patients had virological failure. Weight at ART initiation and patients having WHO clinical stage 3 were risk factors associated with virological failure in this study. Governmental and non-governmental concerned bodies should invest their effort to devise strategies for the achievement of HIV/AIDS treatment targets.

Keywords: HIV/AIDS, Treatment failure, Virological failure, Associated factors, Pediatrics, Children, JUMC.

Article History

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1. INTRODUCTION

There were approximately 36.9 million people worldwide

living with HIV/AIDS in 2017. Of these, 1.8 million were children (<15 years old): among them, an estimated 66.0% live in sub-Saharan Africa. Estimated 1.8 million individuals worldwide were newly infected with HIV in 2017, about 5,000 new infections per day. Of these, 180,000 were children (<15 years). Most of these children lived in sub-Saharan Africa and

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were infected by their HIV-positive mothers during pregnancy, childbirth or breast feeding [1, 2].

Globally in 2018, around 78%[69–82%] of people were living with HIV who knew their status and were on treatment, of this 86%[72–92%] had viral suppression (it accounts 63.1% of all HIV/AIDS patients), while 15.0% of them did not achieve viral suppression with the expected time range [2]. The Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 targets the goal of achieving viral suppression in 90.0% of the patients on sustained Antiretroviral Treatment (ART) [3].

Pediatric ART failure is an under-recognized issue that receives inadequate attention in the field of pediatrics and within HIV treatment programs. Pediatric ART failure rates range from 19.3% to over 32.0% in resource-limited settings [4]. Treatment failure is the suboptimal response or the lack of a sustained response to ART, which can be determined using clinical, immunologic or virologic criteria, either singly or in concert [5]. Virologic suppression is the hallmark of successful HIV treatment in both adults and children. However, due to early immunologic damage and high viral loads found in many children, attaining rapid virologic suppression in children is critical [6]. Despite the reduction in morbidity and mortality, a considerable proportion of patients fail to achieve a sustained virologic response to therapy [7]. Thus virological failure is an increasing concern globally.

World Health Organization (WHO) recommends viral load estimation as the preferred monitoring approach to diagnose as well as to confirm treatment failure. Viral Load (VL) testing has thus become essential for accurate management and decision-making for children on ART [6, 8]. Virological failure of the three original drug classes (nucleoside or nucleotide reverse transcriptase inhibitors (NRTI), non-NRTIs (NNRTI), and Protease Inhibitors (PIs) during childhood severely limit future treatment options; therefore, the rate of triple-class virological failure should be monitored, to estimate the number of children transferring to adult care in probable need of treatment with new drugs [9].

Delay in detecting the virological failure and switching to second-line combination Antiretroviral Therapy (cART) is often observed in human immunodeficiency virus-infected children [10] of low-middle-income countries. There are a few studies in resource-limited settings describing the various treatment outcomes and factors that are associated with ART outcomes [5].

Despite studies done on ART failure in Jimma zone [11 - 13], Ethiopia, studies focusing on assessing virological failure in the pediatrics population are lacking. This study aimed to assess virological failure in HIV/AIDS pediatric patients and its associated factors at the ART clinic of Jimma University Medical Center (JUMC).

2. MATERIALS AND METHODS

2.1. Study Design, Area and Period

An institution-based cross-sectional study was conducted at the ART clinic of JUMC, in Jimma town. It is around 346

km from Addis Ababa, the capital city of Ethiopia. JUMC is the only teaching and referral hospital in southwest Ethiopia. ART clinic of JUMC is the only clinic that provides integrated ART services including voluntary counseling and testing, prevention of mother to child transmission, antiretroviral therapy, follow up services, treatment of opportunistic infection services, and viral load testing at Jimma town, Southwest Ethiopia. The clinic also provides services to patients from surrounding rural villages and nearby towns. This study was conducted by abstracting information from medical charts of eligible patients from April -May 2019.

2.2. Eligibility Criteria

2.2.1. Inclusion criteria

HIV/AIDS patients aged <15 years, on ART drugs for at least 6 months, and had a documented viral load test at least two times during the study period (data abstraction time) were included.

2.2.2. Exclusion criteria

- Only a single viral load report documented
- <6 months on ART

2.3. Sample Size and Sampling Technique

All HIV/AIDS pediatric patients' charts available during the study period at the ART clinic of JUMC were assessed for eligibility criteria. Finally, 140 HIV/AIDS pediatric patients' charts fulfilling the inclusion and exclusion criteria were selected for this study.

2.4. Data Collection Instruments

A structured English version checklist was developed and used for data extraction from the patients' medical records on the Federal Ministry of Health ART follow up form and pediatrics HIV intake form. Data were collected from the patients' medical charts. Baseline demographic data at the time of ART initiation was recorded, including gender, age at ART initiation, and weight at ART initiation. Baseline laboratory data such as complete blood count, viral load, and CD4 count were collected. Data on the WHO clinical stage at ART initiation, the recent complete blood count, viral load and CD4 count were recorded. Other findings including comorbid illnesses, baseline AIDS-defining illnesses at ART initiation, years on highly active antiretroviral treatment (HAART), history of treatment interruption, the status of adherence to ART regimen, and the history of ART regimen change are reported.

2.5. Data Collection Procedures and Quality Assurance

One day training was given to chart abstracters on the data extraction, data collection tools and objectives of the study. To assure the quality of data, the data collection checklist was pretested. After the pretest, the necessary modifications to the data collection tool were made. Strict follow-up and supervision were carried out during the data collection period by principal investigators and feedback to chart abstracters

were given on a daily basis. The data was screened for inconsistencies, missing values, and checked for completeness before data entry.

2.6. Data Analysis

The screened data were coded and entered using epi data 4.2 and then exported to statistical package for social science (SPSS version 22) for analysis. Descriptive analysis was conducted for categorical as well as continuous variables. Univariate and multivariate logistic regression analyses were conducted to determine associated risk factors of virological failure. Factors tested in the univariate analysis were gender, residency, age at ART initiation, weight at ART initiation, baseline blood count, viral load, and CD4 count, initial ART regimen, WHO clinical stage at ART initiation, comorbid illnesses, years on ART, history of treatment interruption, the status of adherence to ART regimen, and history of ART regimen change. Variables with a p-value of <0.25 on univariate analyses were selected for multivariate logistic regression analysis to identify independent risk factors of virological failure. Multivariable logistic regression [reported with Adjusted Odds Ratios with 95% Confidence Intervals (95% CI)] was performed in a backward, step-wise manner until a best-fit model was found. Variables having a P-value <0.05 on the final model of multivariate logistic regression were considered as significantly associated risk factors for virological failure and presented accordingly.

2.7. Operational Definition

2.7.1. Pediatrics

Individuals age less than 15 years old.

2.7.2. Virological failure

Documented plasma viral load above 1000 copies/ml (based on two consecutive viral load measurements gaped by 3 months with enhanced adherence support) after at least 6 months of ART treatment.

2.7.3. Treatment interruption

Any documentation regarding missing a dose of ART for at least 1 day during consecutive ART clinic follow up.

2.7.4. Adherence

Adherence was assessed by pill count and categorized as “good” when the patient misses three or fewer doses, as “fair” if between three and eight doses are missed, and “poor”, if more than eight doses per month are missed. This was documented on patients’ charts abstracted accordingly.

2.7.5. ART regimen change

HIV patients who took at least one drug substituted from the initial ART regimen.

2.7.6. WHO clinical staging

Patients are assigned to a particular stage when they demonstrate at least one clinical condition in the criteria of that stage [14].

3. RESULTS

3.1. Patient Enrollment

One hundred eighty HIV/AIDS pediatric patients’ charts were assessed for eligibility criteria. Of these 140 charts were found eligible and used in this study. Fourteen patients’ charts (n=40) were excluded, where only a single viral load report was documented (n=25), <6 months on ART (n=13), and age>15 years at pediatric ART clinic during the study period (n=2).

3.2. Baseline Characteristics

From a total of 140 study population, 72(51.4%) were male and the rest were females. One hundred eighteen (84.5%) of them were living in urban areas. The mean age of the study population was 9.7±3.3 years. Thirty-one of them had a comorbid illness (22.1%). One hundred seven people (76.4%) of the study population had a history of TB treatment. The presence of opportunistic infection was documented in 80 people (57.1%) of the study population. The mean weight at ART initiation was 28.4±9.3kg. One hundred twenty-nine(92.1%) of them had good adherence to their ART medication. Fifty-eight (41.4%) of the patients were in WHO clinical stage one and 53(37.9%) of them were at WHO clinical stage 3 at ART initiation. The mean duration of ART take was 63.8±29.4 months. ABC-3TC-NVP was the most commonly used ART medication in this population, which was 52 (37.1%) followed by AZT-3TC-EFV45(32.1%) (Table 1).

Table 1. Baseline characteristics of HIV/AIDS pediatrics patients at the ART clinic of Jimma University Medical Center from April -May 2019.

Variables		Frequency (N=140)	Percentage (%)
Sex	Female	68	48.6
	Male	72	51.4
Residency	Urban	118	84.3
	Rural	22	15.7
Age (Mean±Std. Deviation) 9.7±3.3Years			
Weight (Mean±Std. Deviation) 28.4±9.3kg			
Comorbid Illness*	Yes	31	22.1
	No	109	77.9

(Table 1) contd.....

Variables		Frequency (N=140)	Percentage (%)
History Of TB Treatment	Yes	107	76.4
	No	33	23.6
Opportunistic infections***	Yes	80	57.1
	No	60	42.9
Adherence	Good	129	92.1
	Fair	10	7.2
	Poor	1	0.7
Change of HAART regimen	Yes	16	11.4
	No	124	88.6
WHO Clinical Stage	1	58	41.4
	2	23	16.4
	3	53	37.9
	4	6	4.3
ART regimen	ABC +3TC+NVP	52	37.1
	AZT+3TC+EFV	45	32.1
	ABC +3TC+LPV/r	38	27.1
	TDF+3TC+EFV	5	3.6
Mean duration on ART (mean± std. deviation) 63.8±29.4 months			
History of treatment interruption	Yes	11	7.9
	No	129	92.1

* Diabetes mellitus hepatitis, anemia, asthma ***Tuberculosis, Pneumocystic Pneumonia, Candidiasis, Toxoplasmosis, cryptococcal meningitis WHO-World Health Organization, ART-antiretroviral treatment, ABC-abacavir, AZT-Zidovudine, 3TC-lamivudine, LPV/r-Lopinavir/ritonavir, NVP-nevirapine, EFV-efavirenz, TDF-tenofovir.

Table 2. Baseline and recent laboratory findings of HIV/AIDS pediatric patients at the ART clinic of Jimma University Medical Center from April -May 2019.

Variables	Baseline (Mean±std.deviation)	Recent (Mean±std.deviation)
White blood cell ($10^3/\mu\text{L}$)	8.0±2.5	12.2± 48.0
Red blood cell ($10^6\text{cell}/\mu\text{L}$)	4.8± 3.8	5.4± 6.0
Hemoglobin (g/dl)	11.8 ±1.8	14.6± 15.3
Platelet count($10^3\text{cell}/\mu\text{L}$)	348.9 ±100.5	349.4± 99.1
CD4 count (cell/ mm^3)	619.0 ±479.0	969.4± 1278.4
Viral load (copies/ml)	4810.10±43895.6	141.16±302.3

3.3. Laboratory Findings

Baseline mean of red blood cell count (RBC) was $4.8\pm 3.8 \times 10^6\text{cell}/\mu\text{L}$ and the recent one was $5.4\pm 6.0 \times 10^6\text{cell}/\mu\text{L}$. Hemoglobin count was $11.8\pm 1.8\text{ g/dl}$ (mean ± std.deviation) at baseline and $14.6\pm 15.3\text{ g/dl}$ was the recent. The baseline mean viral load was $4810.1\pm 43895.6\text{copies/ml}$ and the recent was $141.1\pm 302.3\text{ copies/ml}$. The mean values of baseline and recent CD4 count were $619.0\pm 479.0\text{ cell}/\text{mm}^3$ and $969.4\pm 1278.4\text{ cell}/\text{mm}^3$, respectively (Table 2).

3.4. Prevalence of Virological Failure

Of the total study population (n=140) that were assessed in this study; sixteen (11.0%) [95%CI, 6.7-17.9%] of them had a

virological failure when studied.

3.5. Risk Factors Associated with Virological Failure

In order to identify the risk factors that may be associated with virological failure, a logistic regression analysis adjusting for several factors was performed. All variables showing a P-value of less than 0.25 in univariate analysis were further tested in the multivariate logistic regression models. On the final model of multivariate logistic regression; weight at ART initiation [AOR=1.104, 95%CI, 1.013-1.203, P=0.024] and WHO clinical stage 3 [AOR=0.325, 95CI, 0.107-0.991, P=0.048] were the significant risk factors for the virological failure. The mean weight at ART initiation of the study population with virological failure was 20.2 ± 6.2 . While those virally suppressed had a mean weight of 16.5 ± 6.2 , which is significantly different from those who had a virological failure (P=0.03) (Table 3).

4. DISCUSSION

A total of 140 HIV/AIDS pediatric patients' charts were included in this study; 11.0% of them had virological failure.

The prevalence of virological failure in this study was lower than a report from Thailand (32.7%) [15]. This difference could be due to the differences in study design (prospective cohort study vs. cross-sectional study) and study year (2011 vs. 2019); scaled-up use of viral load test for monitoring effectiveness of ART in recent years.

The prevalence of virological failure in a few other studies was higher than this study such as in the United Kingdom (UK) and Ireland 34.0% [16], and in Nepal 14.5% [17]; the possible justification could be the difference in the study design which was a multicenter national cohort (UK and Ireland).

Table 3. Factors associated with virological treatment failure among HIV/AIDS pediatric patients at the ART clinic of Jimma University Medical Center from April -May 2019.

Variables		Virological Failure		COR[95% CI]	P-value	AOR [95%]	P-Value
		No	Yes				
Weight(kg) at ART initiation(mean ±std.dev)		16.4±6.2	20.2±6.2	1.096[1.009-1.190]	0.03	1.104[1.013-1.203]	0.024
Residency	Urban	103(73.6)	15(10.7)	3.058[0.383-24.42]	0.201	3.72[0.434-32.022]	0.231
	Rural	21(15.0)	1(0.7%)	1		1	
WHO clinical stage 3	No	81(57.9%)	7(5.0%)	0.413 (0.144-1.1885)	0.100	0.325[0.107-0.991]	0.048
	Yes	43(30.7%)	9 (6.4%)	1		1	
Recent hematocrit (mean ±std.dev)		38.4±5.5	40.7±5.6	1.09 [0.98-1.22]	0.111	1.111[0.984-1.252]	0.090

COR-crude odd ratio, AOR-adjusted odd ratio.

The prevalence of virological failure in previously conducted studies in South Africa ranged from 19.3%-38.0% [18, 19], in Cameroon 16.0% [20], and in Tanzania 31.6% [21]. Those were higher than the current findings. The possible reason for this difference might be the difference in the coverage of HIV /AIDS treatment and monitoring as in recent years, special attention has been given to meet the WHO's 90-90-90 objectives. Greatly increased access to ART will certainly be a game-changer in the global response to HIV.

Studies conducted in Ghana identified a virological failure prevalence ranging from 6.5%-16.7% [22, 23]. The inconsistency with findings from this study may be due to the difference in the study design and study population (inclusion criteria).

The current findings are in line with previously conducted studies in Ethiopia [Bahr Dar 10.7% [24], Gonder 13.0% [25]. This similarity might be due to similarity in the HIV control and prevention program of the two setups and scaled up viral load testing as a national monitoring strategy adopted for patients on ART in response to the WHO's recommendations and utilization in clinical care in Ethiopia.

The current findings are lower compared with the study conducted in Amhara Region referral hospitals, where the prevalence of virological failure among HIV children was 48.9% [26]. This might be justified by the previous study conducted for over 7 years (2011-2018), focusing on a viral load test that was performed only if a person showed signs and symptoms of a severe disease. Another possible explanation might be the fact that the previous study was a multicenter study.

A study conducted in Uganda [27] revealed male gender, baseline CD4% <5.0% and treatment with d4T/3TC/NVP versus ZDV/3TC/EFV as independent predictors of viral failure in children. A study conducted in Tanzania [21] reported that the administration of nevirapine vs. efavirenz-based regimen, CD4% <25.0%, and physician documentation of maladherence were associated with virological failure.

Several factors were investigated for possible independent association with virological failure. Weight at ART initiation and patients having WHO clinical stage 3 were associated risk factors of virological failure in this study. With every one-kilogram increase in the weight of the patient, during the initiation of ART, the odds of having virological failure is increased by 1.1 unit. This might be explained by poor

continuous weight record practice at ART follow up clinic and the retrospective nature of data collection in this study (*i.e* it hindered direct weight measurement for each patient). Patients who were not at WHO clinical stage 3 had the odds of 0.34 times less likely to develop virological failure *i.e* patients having WHO clinical stage 3 were 67.0% more likely to develop virological failure. There is established evidence that virological failure occurs first, followed by an immunological failure, and then clinical failure [28]. Clinical failure (*i.e.* new WHO clinical stage 3 or 4) may have a high correlation with the unsuppressed viral load [29]. Pulmonary tuberculosis, pneumonia, meningitis, and recurrent oral candidiasis are among the WHO clinical stage 3 medical conditions recorded in this study. They weaken the immune system, which in turn facilitates viral replication (increase viral load) [30].

Despite being a pioneer study from the Jimma region assessing virologic failure in the pediatric population, it has some limitations. Mainly, this study was conducted via medical chart review. As medical record data was not collected for research purposes, it lacked certain important variables, including the socioeconomic status of the family, serostatus of the family as well as HAART regimen related side effects and toxicity. Additionally, this study was conducted at a single-center, leading to a small sample size, therefore, it lacks generalizability.

CONCLUSION

In conclusion, this study showed a significant number of HIV/AIDS pediatric patients having virological failure. Weight at ART initiation and patients having WHO clinical stage 3 are risk factors associated with virological failure. Further studies should be conducted to develop concrete evidence on the status of antiretroviral treatment towards virological suppression targets. Health policymakers and other governmental and non-governmental concerned bodies should make effort to devise strategies towards the improvement of HIV/AIDS treatment (90-90-90 targets).

LIST OF ABBREVIATIONS

3TC	= Lamivudine
AIDS	= Human immunodeficiency virus / Acquired Immune Deficiency Syndrome
AOR	= Adjusted Odd Ratio
COR	= Crude Odd Ratio

ART	= Anti-Retroviral Treatment
EFV	= Efavirenz
HAART	= Highly Active Antiretroviral Treatment
HIV	= Human Immune Deficiency Virus
JUMC	= Jimma University Medical Center
LPV/r	= Lopinavir/ritonavir
NNRTI	= Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	= Nucleoside Reverse Transcriptase Inhibitor
NVP	= Nevirapine
PI	= Protease Inhibitor
TDF	= Tenofovir
TB	= Tuberculosis
UNAIDS	= United Nations Programme on HIV and AIDS
UK	= United Kingdom
VL	= Viral Load
WHO	= World Health Organization
AZT	= Zidovudine

AUTHORS' CONTRIBUTIONS

MA contributed to the design of the study, analysis, interpretation, and write up of the manuscript. Data collection was managed by MA and FA. MA drafted the manuscript. Both authors (MA and FA) participated in editing, feedback, and revisions of the manuscript. Both authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical clearance and approval were obtained from the Institutional Review Board (IRB) of Jimma University, Ethiopia under the reference number of 106/2019.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from each participant prior to the study.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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CONFLICT OF INTEREST

The authors herein declare that, in the conception, ethics, data collection, and the drafting of this paper, have no conflicts of interest in any form.

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