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Population-Specific Predictors of Immunologic Reconstitution Following Initiation of Combined Antiretroviral Therapy in Children: A Retrospective Observational Study from a 15-Year Cohort of HIV-Positive Children and Adolescents in Eritrea

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Background: In the landscape of HIV treatment, combined antiretroviral therapy (cART) is a cornerstone in managing viral loads and boosting CD4+ T-cell counts. Nevertheless, disparities in treatment outcomes remain persistent, and a subset of children fail to achieve adequate immunologic reconstitution (IR). This study aims to investigate the demographic and clinical factors associated with inadequate IR in HIV-infected children in Eritrea.

Methodology: A retrospective observational study was conducted on 822 children followed at Orotta National Pediatric Referral Hospital between 2005 and 2020. Two distinct analyses were performed, with univariate and multivariate logistic regression models employed to investigate risk factors contributing to inadequate immunologic reconstitution (IR) at the study endpoints of 6- and 12-months post-cART initiation.

Results: From the initial cohort of 822 patients [53.4% were males, cohort median age at cART initiation was 78 (IQR: 48–101) months and median absolute CD4 count 270 (151–441) cells/μL]. Two separate analyses were conducted on two cohort subsets with complete data, including 456 children at the 6-month mark and 495 children at 12 months of follow-up. Following 6 months on cART, Immunologic reconstitution was achieved in 87.8% (95% CI: 84.3–91.2) and increased to 90.4% (95% CI: 87.3–93.5) after 12 months of treatment. Independent predictors of inadequate IR after 6 months of cART were higher baseline absolute CD4 counts (aOR = 1.003, (95% CI: 1.002–1.005); p-value <0.001) and NNRTI (EFV: aOR = 3.9, (95% CI: 1.3–11.9); p-value = 0.01). Meanwhile, gender (females: aOR = 0.3, (95% CI: 0.1–0.9, p-value = 0.03) and higher baseline absolute CD4 counts (aOR = 1.003, (95% CI: 1.002–1.005); p-value < 0.001) were independent risk factors of inadequate IR after 12 months of treatment.

Conclusion: The study underscores the interplay of baseline CD4 count, gender, and regimen choice in shaping the effectiveness of cART in children. Lower baseline absolute CD4 count was associated with IR after starting cART. Notably, children on EFV had a higher likelihood of inadequate IR after 6 months, and male children were more prone to insufficient IR at 12 months. Targeting these population-specific factors may be pivotal in advancing gender-responsive therapeutic strategies and improving health outcomes for HIV-infected children in sub-optimal clinical settings and resource-constrained environments.

Keywords: risk factors, CD4, pediatrics, HIV, ART, immunologic reconstitution, Eritrea

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Introduction

The World Health Organization (WHO) estimates that 1.8 million [1.3 million–2.2 million] children aged 0–14 years are living with HIV-1 infection worldwide, 90% of whom are from Sub Saharan Africa. Since 2010, new HIV infections among children have declined by 52%, from 310,000 [200,000–500,000] in 2010 to 150,000 [94,000–240,000] in 2019. At the same time, AIDS-related deaths decreased steadily from 1.1 million [830,000–1.6 million] in 2010 to 690,000 [500,000–970,000] in 2019. As of June 2020, 53% [36–64%] of the children aged 0–14 years were living with HIV and receiving antiretroviral therapy.[1] The UNAIDS has established a 90–90-90 target towards ending the global HIV/AIDS threat by 2030.[2,3] However, children have fallen behind in achieving sustainable development goals due to suboptimal treatment and lower viral suppression rates compared to adults.[4] In Eritrea, the preliminary antenatal care reports drawn in 2019 indicated a landmark reduction in national HIV prevalence, which dropped from 2.4% in 2003 to 0.36% by the end of 2019. More than 8956 patients receive treatment nationwide, marking a coverage rate of 73%. Among these patients, children under 15 make up 4% of the treatment targets.

The initiation of potent antiretroviral therapy (ART) in the mid-1990s has substantially improved HIV-associated morbidity and mortality globally.[5,6] Antiretroviral treatment reduces HIV-associated burden by suppressing HIV replication to undetectable levels.[7,8] Pediatric evidence generated from various observational and randomized clinical trial studies upon receiving the diagnosis of HIV has demonstrated that the initiation of cART leads to an improvement of immunological status,[9–11] followed by an increment of CD4+ count features.[12] The restoration of absolute CD4+ count was observed in HIV children regardless of the pre-treatment status of the peripheral CD4+ count.[13] Several studies following successful cART implementation observed notable reductions in viral loads and evident improvements in T cell immunological parameters.[8,14]

Prior studies have reported the beneficial effects that successful cART has on CD4 activation and its subsequent role in the recovery path of immune function.[8,15,16] CD4+ counts are essential markers for assessing treatment response, making immune reconstitution (IR) a vital outcome measure of cART.[8,10,14,16–19] Indeed, results from a large multicenter study of immunological response to cART in (HIV-Positive) children discovered a clear association between the CD4+ count and viral load at 12 months of therapy (28% of children with a CD4 < the 25th percentile had shown undetectable HIV viral load as compared with 77% of children with a CD4 > the 75th percentile).[20] However, several studies outlined there was a significant immunological response variation that had been witnessed among patients initiated on ART drugs, resulting from HIV pathogenesis,[16,21] thymopoiesis activity,[8,14] sustained co-infections,[14,22] nutritional status[14] and medication adherence issues.[19] Despite the existing wisdom of conventional traditional risk factors, a subset of individuals failed to achieve an adequate threshold of CD4+ T cell count reconstitution due to unobserved variances, uncaptured variables, or a parameter shortage of capabilities on fully measuring the differences in personal traits and population compounded factors.[16,23]

Lately, the clinical significance of immune reconstitution has been the subject of attention in low and middle-income countries, where the widespread efficacy and success rate of ART is hampered by emerging incidences of lowered immune reconstitution (IR) responses.[14,22] Globally, the incidence of IR ranges from (10–40%), compromising a broad spectrum of classification categories that include non-immune respondents, immune non-discordant, and immunologic failure to treatment response in HIV patients.[10,16,22] More worldwide consensus and standard operational guidelines must be agreed upon when employing various definitions and diagnostic criteria pertaining to IR. In different studies, inadequate IR has been defined as either a failure to meet the prescribed CD4+ T-cell count threshold (eg, > 200 or > 250 or > 350) or a specified percentage of CD4+ T-cell increase over baseline (eg, < 5% or < 20% or < 30%).[10] Moreover, many children are inclined to exhibit poor immunologic response due to the variations arising from the response to therapy that may increase their risk of morbidity and mortality despite the widespread use of cART.[23,24]

In prior studies, a multitude of sociodemographic and clinical parameters have been found to influence IR in HIV-infected pediatric patients following cART initiation: Baseline CD4+ lymphocyte count, cART group, WHO clinical stages, initial nutritional status, tuberculosis and the presence of anemia have all been found to influence CD4+ count reconstitution.[23,24] Nonetheless, with the existing data and the lines of evidence, the depth of knowledge in the Sub-Saharan context remains sparse. Furthermore, the available literature from the findings of relevant studies could not be generalized, especially in Eritrean settings, due to the variability of clinical standards of practice and the differences in the set-up of public health services. Identifying population-specific predictors, understanding the role of contextual factors, and developing targeted

interventions are crucial for advancing HIV eradication efforts and optimizing immunological outcomes for high-risk children in endemic regions.

Here, in a retrospective longitudinal cohort of HIV-infected children, we aim to identify specific clinical and socio-demographic baseline characteristics that assist in predicting the immune reconstitution status following cART initiation and examining the short-term immunological responses at 6 and 12-month fixed time points. In SSA countries such as Eritrea, where access to the broader choices of ART regimens is restricted and evidence-based decisions are driven from settings with limited resources, scaling up potential new intervention strategies and optimizing avenues to personalized treatment could transform the outcomes of HIV children considerably. The study set out to explore the magnitude of Inadequate immunologic reconstitution and the sociodemographic and clinical factors associated with inadequate immunologic reconstitution at 6 and 12 months after treatment initiation with cART. Furthermore, the findings from the study will assist in the identification of those children who have a higher risk of developing poor CD4 outcomes and who are disadvantaged with the odds of manifesting insufficient immunologic response, thereby requiring closer monitoring to satiate the vulnerable needs of those children who are prone to have a weakened state of immune reconstitution.

Methodology

Study Design and Setting

A retrospective cohort study was conducted using paper charts and electronic medical records extracted from HIV-infected pediatric patients who initiated cART at Orotta National Pediatric Referral Hospital (ONPRH), Asmara, Eritrea, from January 2005 to December 2020. Since the commencement of the pediatric HIV/AIDS follow-up clinic in Orotta Pediatric Hospital in 2005 which is located in the central zone, 822 children under the age of 18 have received service in the clinic. In this study, we used three distinct guidelines for cART initiation according to the recommended criterion stated by WHO, following the quantification of peripheral blood CD4 T lymphocytes. Notably, the WHO guideline of 2010[25] advocated the initiation of cART when the CD4+ count plummeted to ≤350 cells/μL. Subsequently, the WHO guideline 2013[26] revised the cART initiation, increasing the threshold to 500 cells/μL. Conversely, the WHO guidelines of 2016[27] recommended an immediate initiation of cART, irrespective of CD4+ count, after diagnosis of HIV infection. Once a child is initiated on cART, regular and complete clinical assessments are conducted to check responses to cART at regular intervals.

Study Cohort Description

All children ≤ 18 years old living with HIV/AIDS who attended the NPRH HIV follow-up clinic from 2005–2020 were enrolled in the study. Those with a follow-up duration of < 6 months, missing key baseline data, unavailable CD4+ cell count follow-up data, and received protease inhibitor were excluded from the study. All eligible children and adolescents received free treatment for HIV, according to the national ART Guidelines. The guidelines endorsed the use of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) as the standard first-line treatment regimens. Of note is that these assessments were undertaken at the discretion of the attending physician/clinician, and the Eritrean government entirely covered the cost of the treatment.

Data Collection Tool and Approach

Data was collected in the ONPRH cART follow-up program electronic database (ART DHIS 2). The data was exported from the electronic record database to the Microsoft Excel platform. The retrieved data was robustly reviewed and cross-referenced with patients' clinical chart registries. The following baseline data were exported into a Microsoft Excel database: date of birth, gender, residence, age at enrollment and cART initiation date, cART regimen, clinical stage, height, weight, and baseline laboratory results, including absolute CD4+ count, CD4 percentages, and hemoglobin. Further, follow-up data were extracted on absolute CD4+ counts at 6 and 12 months and cART toxicity and cART changes following cART initiation. Baseline parameters are the measurement at cART initiation, whereas 6 and 12-month absolute CD4+ counts are taken as the nearest measurement within ± 2-month window, in line with reports in the literature.[28]

Operational Definitions

Immunologic reconstitution (IR): Absolute CD4+ count increment >10% after 6 months and 12 months of cART initiation with adherence counselling, whereas an increment of ≤10% was defined as inadequate immunologic reconstitution. These definitions are based on the WHO guideline classification of immunological failure for children[25] and adolescents[27] and other reports in the literature.[28] Duration on cART was defined as the time, expressed in units of weeks, from the point of cARt initiation (week 0) till the follow-up time of absolute CD4 measurement was taken at 6 months (24 weeks) and 12 months (48 weeks).

WHO standard deviations (SD) for growth monitoring were calculated to define the nutritional status of participants. Underweight was defined as weight for age < −2 SD while stunted were participants that had height for age < −2 SD. Wasting was defined as the body mass index for age < −2SD.

Residence outside the central zone was defined as children who reside outside the central zone, the administrative zone of Eritrea.

WHO clinical stage was defined as early- WHO stage 1 and stage 2 while WHO stages 3 and 4 were categorized as Advanced WHO disease stage.

AZT+3TC refers to NRTI backbones of Zidovudine and Lamivudine while AZT+3TC else refers to backbone Abacavir + Lamivudine, Stavudine + Lamivudine and Tenofovir + Lamivudine.

Data Analysis

To investigate the baseline variables associated with immune reconstitution, we used two separate analysis groups of children with distinct endpoints, where measurements of absolute CD4 count, denoted with an increment in percentages of CD4 T cell recovery, were taken at the time intervals of 6 months and 12 months, respectively. All analyses were conducted using SPSS version 26 for Windows (SPSS Inc., Chicago, Illinois, USA). Where appropriate, demographic and HIV-related characteristics of patients were summarized using percentages and median (IQR). Descriptive analyses were stratified by IR at the 6-month and 12-month interval in all key variables at baseline using Pearson's Chi-square test or Fisher's exact test and Mann–Whitney *U*-test for continuous data. Normality tests were performed before running any statistical computations. Multivariate logistic regression analysis was subsequently undertaken – only variables with a p-value of ≤ 0.30 in the bivariate analysis were included in the model. The cutoff (p-value ≤ 0.30) for variable inclusion in the multivariate logistic regression model was chosen based on the model's overall goodness of fit. During model selection, including variables with a p-value < 0.30 provided the best multivariate model fit. Further, the potential for collinearity was minimized by not including pairs of variables with a Spearman r > 0.60 in the same model. Results are presented as crude odds ratios (cOR) and adjusted odds ratio (aOR) with 95% CIs. A p-value < 0.05 was considered as significance level of statistical interference.

Ethical Consideration

Ethical approval was obtained from head of the Ministry of Health (MOH) research Ethics and Protocol review committee with a letter of reference (Approval Number: Ref: 01/21). Since the research design is observational and the study is retrospective, the head of the Ministry of Health (MOH) research Ethics and Protocol review committee [Eritrean Ministry of Health (MOH) Research Ethical Committee] waived the need for informed consent. All the information gathered was de-identified and held with the utmost confidentiality. All the study procedures followed the recommendations of the Helsinki Convention.

Results

Baseline Patient Characteristics: Sociodemographic and Clinical Characteristics of the Study Participants

A total of 822 patients were enrolled for care in the treatment centre from 2005–2020 [410 (49.9%) ≤ 2010, 280 (34.1%) 2011–2015, and 132 (16.1%) > 2015]. Out of these, 345 (42%) had complete data available. Those with a follow-up duration of < 6 months, missing baseline data and unavailable follow-up CD4+ cell count were excluded (Figure 1). The median age (IQR) at enrollment was 78 (48–101) months. At the initiation of treatment, the majority of patients were

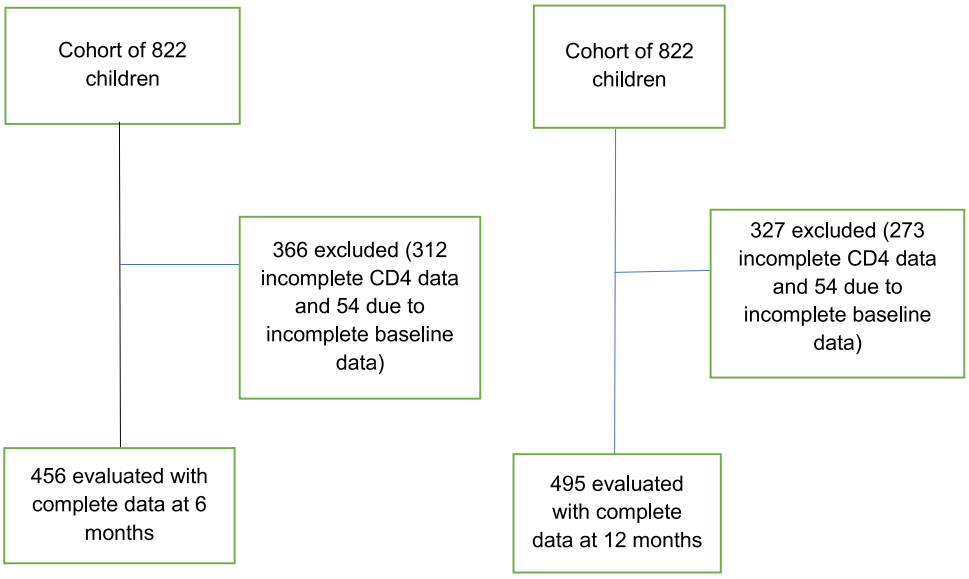

Figure 1 Flow diagram of study recruitment in children receiving cART in National Referral Pediatric Follow-up Clinic, 2005–2020.

> 60 months of age [634 (77.1%)], males [439 (53.4%)], and from the central zone [592 (72.3%)]. Concerning the clinical profile of patients, the majority had advanced WHO clinical stage [496 (61.1%)], WAZ < −3 [228 (42.8%)] and HAZ < −3 [341 (43.3%)] whereas BAZ > −2 was evident in the majority of patients [433 (59.9%)]. Moreover, the median (IQR) baseline CD4+ count, CD4 percentage, and Hgb were 270 (151–441) cells/ µL, 12 (8.2–17) %, and 10.8 (9.5–11.8) gm/dl. Regarding cART, most of the patients were initiated on AZT+3TC backbone [579 (70.7%)] while nearly half were started on EFV [393 (48.2%)]. Ninety-nine (12%) patients had cART toxicity, and 160 (19.5%) had cART changes (See Table 1 for details).

Table 1 Baseline Characteristics of Children Included in the Study

Cohort Characteristics	Total, N (%)
Overall	345 (42)
Age at initiation in months, median (IQR)	83 (50–104)
Age ≤ 60	78 (22.6)
Age > 60	267 (77.4)
Gender	
Male	179 (51.9)
Female	166 (48.1)
Residence	
Central zone	225 (73.9)
Outside central zone	90 (26.1)
Cohort Year	
≤ 2010	176 (51)
2011–2015	125 (36.2)
>2015	44 (12.8)

(*Continued*)

Table 1 (Continued).

Cohort Characteristics	Total, N (%)
Clinical Stage	
Early	137 (40.2)
Advanced	204 (59.8)
CD4 count cells/μL, median (IQR)	268 (156–449)
CD4 percentage, median (IQR)	12 (7.3–17.6)
Baseline Hgb in gm/dl, median (IQR)	10.9 (9.5–11.9)
Anthropometric Measurements	
Weight for age Z-score, median (IQR)	−2.4 (−3.3--1.6)
Normal, well nourished (Z >-2)	78 (14.6)
Moderately Underweight (−3 ≤ Z ≤ −2)	57 (25)
Severely Underweight (Z < −3)	93 (40.8)
Height for age Z-score, median (IQR)	−2.4 (−3.4--1.5)
Normal (Z >-2)	117 (35.5)
Moderately Stunted (−3 ≤ Z < −2)	77 (23.3)
Severely Stunted (Z < −3)	136 (41.2)
BMI for age Z-score, median (IQR)	−1.3 (−2.1--0.3)
Normal (Z >-2)	183 (25.3)
Moderately wasted (−3 ≤ Z ≤ −2)	52 (17.3)
Severely wasted (Z < −3)	65 (21.7)
Initial cART regimen	
NRTI	
AZT+3TC	274 (79.7)
AZT+3TC ELSE	70 (20.3)
NNRTI	
NVP	179 (52)
EFV	165 (48)
cART Toxicity	
No	310 (89.9)
Yes	35 (10.10)
cART changes	
No	273 (79.1)
Yes	72 (20.9)

Notes: 3TC, lamivudine; Z-score-WHO standard deviations.
Abbreviations: AZT, zidovudine, cART, combined antiretroviral therapy, EFV, Efavirenz; Hgb, Hemoglobin; IQR, interquartile range; N, number; NVP, Nevirapine.

Inadequate IR and Associated Factors After 6 Months on cART

Following 6 months of treatment on cART, IR was achieved in 399 out of 456 (87.8%; 95% CI: 84.3–91.2) patients. In this analysis, patients initiated on cART in the later cohort year categories had a higher proportion of inadequate IR [38.6% in > 2015 and 35.1% in 2011–2015 vs 26.3% ≤ 2010, p-value < 0.001]. Moreover, inadequate IR was associated with the early WHO clinical stage as compared to the advanced stage [31 (54.4%) vs 26 (45.6%) respectively, p-value = 0.01] and EFV as compared to NVP [37 (64.9%) vs 20 (35.1%), respectively, p-value = 0.04]. Furthermore, participants with inadequate IR at 6 months had a significantly higher median baseline CD4 cell count, CD4 percentage, and Hemoglobin. See Table 2 for details.

Table 2 Factors Associated with Inadequate IR at 6 Months Following Treatment Initiation on cART

Cohort Characteristics	Adequate IR at 6 Months, N (%)	Inadequate IR at 6 Months, N (%)	N (%)	*P*-value (χ2)
Overall	399 (87.2)	57 (12.5)	456	
Age at initiation	86 (56–103)	73 (32–104)	80 (48–101)	0.5[a]
≤ 60	76 (19)	16 (28.1)	92 (20.2)	0.1 (2.5)
< 60	323 (81)	41 (71.9)	364 (79.8)	
Gender				
Male	211 (52.9)	27 (47.4)	238 (52.2)	0.4 (0.6)
Female	188 (47.1)	30 (52.6)	218 (47.8)	
Residence				
Central zone	289 (72.4)	41 (71.9)	330 (72.4)	0.9 (0.006)
Outside central zone	110 (27.6)	16 (28.1)	126 (27.6)	
Cohort Year				
≤ 2010	206 (51.6)	15 (26.3)	221 (48.5)	<0.001 (36.6)
2011–2015	153 (38.3)	20 (35.1)	173 (37.9)	
> 2015	40 (10)	22 (38.6)	62 (13.6)	
Clinical Stage				
Early	149 (37.8)	31 (54.4)	180 (39.9)	0.01 (5.7)
Advanced	245 (62.2)	26 (45.6)	271 (60.1)	
TB-Status				
Not symptomatic	348 (97.5)	51 (100)	399 (97.8)	0.2 (1.3)
Symptomatic and under treatment	9 (2.5)	0 (0)	9 (2.2)	
CD4 count cells/μL, median (IQR)	288 (181–445)	654 (437–959)	298 (177–478)	<0.001[a]
CD4 percentage, median (IQR)	11.9 (8.1–15.8)	20.7 (13.1–29.6)	11 (7.9–17)	<0.001[a]
Baseline Hgb, median (IQR)	11 (9.7–12.1)	11.9 (10.1–13)	11.1 (9.7–13.3)	0.01[a]
Anthropometric Measurements				

(*Continued*)

Table 2 (Continued).

Cohort Characteristics	Adequate IR at 6 Months, N (%)	Inadequate IR at 6 Months, N (%)	N (%)	*P*-value ($\chi 2$)
Weight for age Z-score, median (IQR)	−2.7 (−3.6--1.7)	−2.5 (−3.4--1.6)	−2.7 (−3.7--1.7)	0.2[a]
Normal, well nourished (Z > −2)	80 (30.9)	14 (40)	165 (31)	0.3 (2)
Moderately Underweight (−3 ≤ Z ≤ −2)	65 (25.1)	10 (28.6)	140 (26.3)	
Severely Underweight (Z < −3)	114 (44)	11 (31.4)	228 (42.8)	
Height for age Z-score, median (IQR)	−2.6 (−3.8--1.5)	−2.6 (−3.9--1.7)	−2.7 (−3.9--1.7)	0.6[a]
Normal (Z > −2)	128 (33.1)	21 (39.6)	149 (33.9)	0.6 (0.8)
Moderately Stunted (−3 ≤ Z < −2)	96 (24.8)	12 (22.6)	108 (24.5)	
Severely Stunted (Z < −3)	163 (42.1)	20 (37.7)	183 (41.6)	
BMI for age Z-score, median (IQR)	−1.3 (−2.2--0.45)	−0.8 (−1.6--2.9)	−1.3 (−2.3--0.4)	0.1[a]
Normal (Z > −2)	212 (59.9)	33 (71.7)	245 (61.3)	0.1 (3.3)
Moderately wasted (−3 ≤ Z ≤ −2)	67 (18.9)	4 (8.7)	71 (17.8)	
Severely wasted (Z < −3)	75 (21.2)	9 (19.6)	84 (21)	
Initial cART regimen				
NRTI				
AZT+3TC	313 (78.6)	42 (73.7)	355 (78)	0.3
AZT+3TC else	85 (21.4)	15 (26.3)	100 (22)	
NNRTI				
NVP	215 (54)	20 (35.1)	235 (51.6)	0.007 (7.1)
EFV	183 (46)	37 (64.9)	220 (48.4)	
cART Toxicity				
No	349 (87.5)	55 (96.5)	404 (88.6)	0.04 (4)
Yes	50 (12.5)	2 (3.5)	52 (11.4)	
cART changes				
No	314 (87.5)	46 (80.7)	360 (78.9)	0.7 (0.1)
Yes	85 (21.3)	11 (19.3)	96 (21.1)	

Notes: Superscripts: a-Mann–Whitney *U*-test. 3TC, lamivudine; Z-score-WHO standard deviations.
Abbreviations: AZT, zidovudine, cART, combined antiretroviral therapy, CI, confidence interval; EFV, Efavirenz; Hgb, Haemoglobin; IQR, interquartile range; N, number; NVP, Nevirapine; TB, Tuberculosis.

Inadequate IR and Associated Factors After 12 Months on cART

Following 12 months of treatment on cART, IR was achieved in 442/495 (90.4%; 95% CI: 87.3–93.5) patients. In this analysis, patients initiated on cART in the later cohort year categories had a higher proportion of inadequate IR [35.8% in > 2015 and 34% in 2011–2015 vs 30.2% ≤ 2010, p-value < 0.001]. Concerning the hematologic parameters, participants with inadequate IR at 12 months had significantly higher median baseline CD4+ cell count, CD4 percentage, and Hemoglobin. See Table 3 for details.

Table 3 Factors Associated with Inadequate IR at 12 Months Following Treatment Initiation on cART

Cohort Characteristics	Adequate IR at 12 Months, N (%)	Inadequate IR at 12 Months, N (%)	N (%)	*P*-value (χ2)
Overall	442 (89.3)	53 (10.7)	495	
Age at initiation	80 (56–101)	66 (34–88)	78 (48–113)	0.7[a]
≤ 60	90 (20.4)	15 (28.3)	105 (21.2)	0.1 (1.7)
> 60	352 (76.9)	38 (71.7)	390 (78.8)	
Gender				
Male	229 (51.8)	31 (58.5)	260 (52.5)	0.3 (0.8)
Female	213 (48.2)	22 (41.5)	235 (47.5)	
Address				
Central zone	327 (74)	38 (73.1)	365 (73.9)	0.8 (0.02)
Outside central zone	115 (26)	14 (26.9)	129 (26.1)	
Cohort Year				
≤ 2010	245 (55.4)	16 (30.2)	261 (52.7)	<0.001 (31.5)
2010–2015	154 (34.8)	18 (34)	172 (34.7)	
> 2015	43 (9.7)	19 (35.8)	62 (12.5)	
Clinical Stage				
Early	173 (39.7)	24 (45.3)	197 (40.3)	0.4 (0.6)
Advanced	263 (60.3)	29 (54.7)	292 (59.7)	
CD4 count cells/μL, median (IQR)	288 (175–445)	730 (450–1449)	314 (181–514)	<0.001[a]
CD4 percentage, median (IQR)	11.8 (8–16.1)	20.7 (11.3–36.3)	12.2 (8.2–17.6)	<0.001[a]
Baseline Hgb, median (IQR)	11 (9.5–11.9)	11.4 (9.5–12.1)	10.8 (9.5–11.8)	0.01[a]
Anthropometric Measurements				
Weight for age Z-score, median (IQR)	−2.4 (−3.3--1.6)	2.2 (−3.1--1.3)	2.6 (−3.5--1.7)	0.4[a]
Normal, well nourished (Z >-2)	105 (35.4)	12 (41.4)	117 (35.9)	0.7 (0.5)
Moderately Underweight (−3 ≤ Z ≤ −2)	78 (26.3)	6 (20.7)	84 (25.8)	
Severely Underweight (Z < −3)	114 (38.4)	11 (37.9)	125 (38.3)	
Height for age Z-score, median (IQR)	−2.5 (−3.5--1.4)	−2.7 (−3.9--1.7)	−2.7 (−3.7--1.7)	0.5[a]
Normal (Z > −2)	147 (34.8)	17 (34)	164 (34.7)	0.3 (2.2)
Moderately Stunted (−3 ≤ Z < −2)	103 (24.3)	8 (16)	111 (23.5)	
Severely Stunted (Z < −3)	173 (40.9)	25 (50)	198 (41.9)	
BMI for age Z-score, median (IQR)	−1.3 (−2.1--0.4)	−0.6 (−1.6--0.2)	−1.3 (−2.3--0.4)	0.5[a]
Normal (Z > −2)	246 (63.2)	29 (67.4)	275 (63.7)	0.8 (0.3)
Moderately wasted (−3 ≤ Z ≤ −2)	68 (17.5)	6 (14)	74 (17.1)	
Severely wasted (Z < −3)	75 (19.3)	8 (18.6)	83 (19.2)	

(*Continued*)

Table 3 (Continued).

Cohort Characteristics	Adequate IR at 12 Months, N (%)	Inadequate IR at 12 Months, N (%)	N (%)	*P*-value (χ2)
Initial cART regimen				
NRTI				
AZT+3TC	348 (78.9)	39 (75)	387 (78.5)	0.5 (0.4)
AZT+3TC else	93 (21.1)	13 (25)	106 (21.5)	
NNRTI				
NVP	228 (51.8)	21 (41.2)	249 (50.7)	0.1 (2)
EFV	212 (48.2)	30 (58.8)	242 (49.3)	
cART Toxicity				
Yes	55 (12.4)	6 (11.3)	61 (12.3)	0.8 (0.05)
No	387 (87.6)	47 (88.7)	434 (87.7)	
cART changes				
No	349 (79)	37 (69.8)	386 (78)	0.1 (2.3)
Yes	93 (21)	16 (30.2)	109 (22)	

Notes: Superscripts: a-Mann–Whitney *U*-test. 3TC, lamivudine; Z-score-WHO standard deviations.
Abbreviations: AZT, zidovudine, cART, combined antiretroviral therapy, EFV, Efavirenz; Hgb, Haemoglobin; IQR, interquartile range; N, number; NVP, Nevirapine.

Absolute CD4+ Cell Count Kinetics Following cART Initiation

The median CD4+ count at baseline was 270 (IQR: 151–441) cells/μL. However, a significantly higher median absolute CD4+ cell count was achieved following cART [521 (IQR: 330–771) cells/μL, p-value < 0.001 and 650 (IQR: 425–885) cells/μL, p-value < 0.001] (Figure 2). In addition, the median CD4+ cell count was compared across different categories of patient characteristics. In this section, children under 60 months of age had a significantly higher CD4+ count at 6

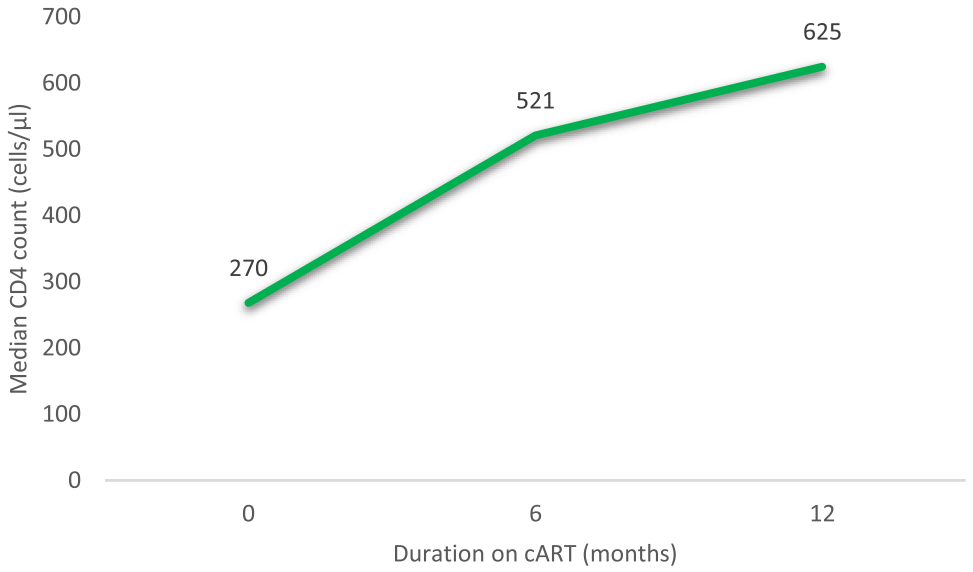

Figure 2 Immunologic reconstitution following cART.

months and 12 months as compared to those older than 60 months [808 (IQR: 525–1140) vs 471 (IQR: 303–669), p-value < 0.001] and [886 (IQR: 580–1407) vs 599 (IQR: 391–779), p-value < 0.001) respectively] (Figure 3) while patients in the cohort year category > 2015 had significantly higher median CD4+ cell count at 6 and 12 months [672 (IQR: 498–984) and 699 (IQR: 549–1099)] (Figure 4). Moreover, patients initiated on NVP had a significantly higher median CD4+ cell count at 12 months as compared to EFV [669 (IQR: 457–900) vs 592 (IQR: 415–842), p-value = 0.01] (Figure 5).

Table 4 compares the rate of CD4+ count increment across categories of patient characteristics. This analysis observed a significantly higher CD4+ count increase following six months on cART in Children ≤60 months of age, cohort year categories ≤2010 and 2011–2015, and those initiated on NVP (see Table 4 for details).

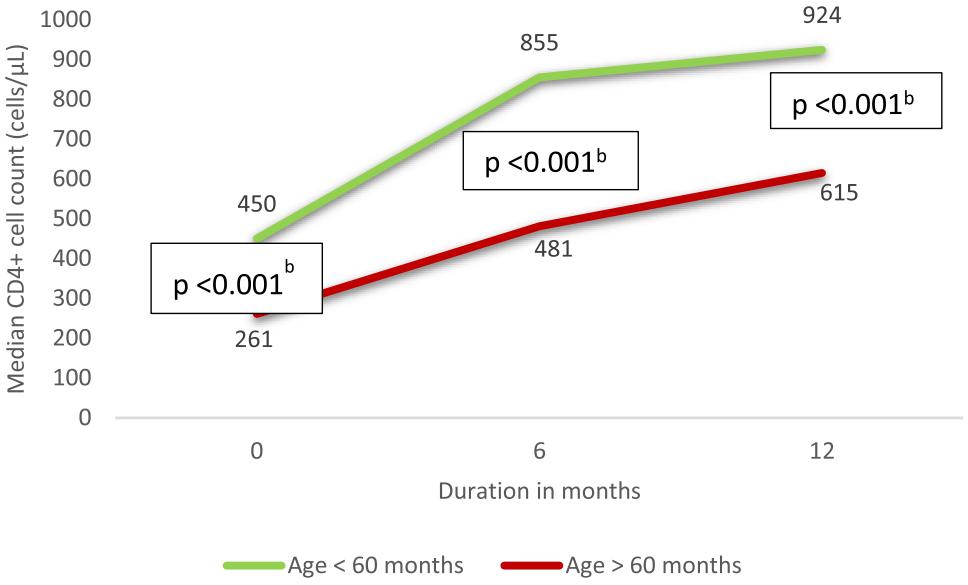

Figure 3 Comparison of median absolute CD4+ count across different age categories.
Note: Superscripts: b- Mann–Whitney *U*-test.

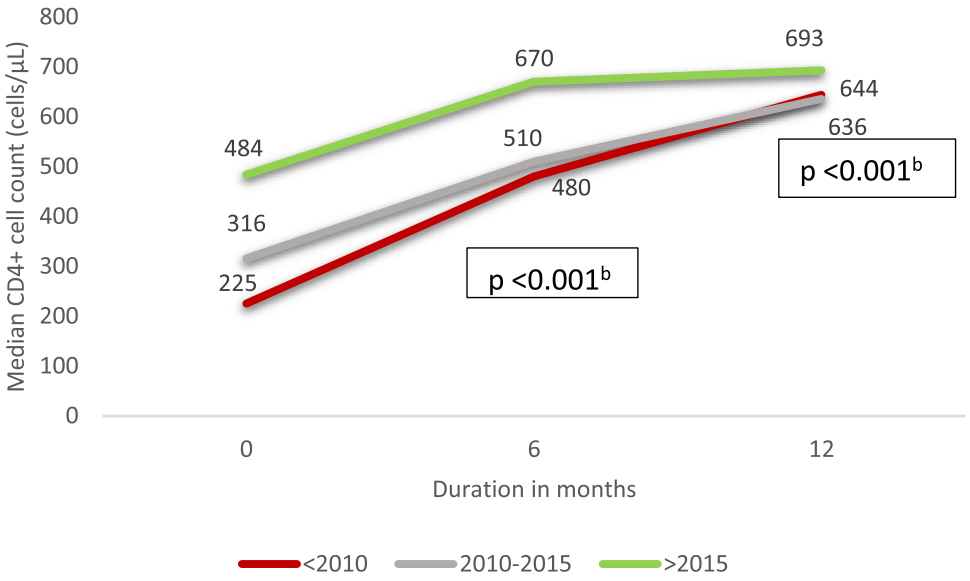

Figure 4 Comparison of median absolute CD4+ count across different cohort year categories.
Note: Superscripts: b- Mann–Whitney *U*-test.

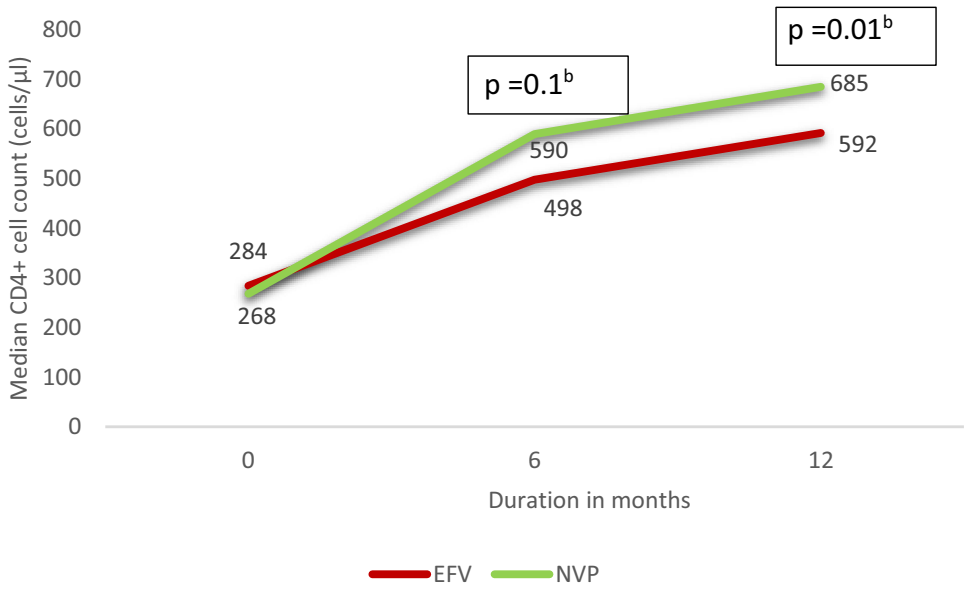

Figure 5 Comparison of median absolute CD4+ count across different categories of NNRTI.
Note: Superscripts: b- Mann–Whitney *U*-test.

Longitudinal Changes of Patients Characteristics: Association Among Cohort Year, Baseline, and Follow-Up CD4+ Count

Figure 6 shows the distribution of the proportion of children across cohort year categories stratified by baseline CD4+ count and IR following 6 months and 12 months on cART. HIV patients that initiated cART ≤ 2010 had a significantly higher percentage. CD4+ count < 200 cells/µL at baseline compared to 2011–2015 and > 2015. However, following cART patients initiated in the category ≤ 2010 showed a significantly higher proportion of IR at 6 and 12 months (See Figure 6 for details).

Table 4 Median $CD4^+$ Cell Count in Cells/ µL /Month (IQR) Change per Month During the First Years of cART

	Rate 0–6 Months	p-value	Rate 6–12 Months	p-value
Cohort year				
≤ 2010	42.6 (22–70)	< 0.001[b]	19.6 (0.5–41.2)	0.1[b]
2010–2015	39.2 (19.1–67.2)		13.6 (−7.7–34.8)	
>2014	19 (−4.3–45.2)		9.7 (−2.8–36.3)	
Age in months				
≤ 60	67.6 (31.9–106.5)	< 0.001[a]	17.8 (−20.2–53.3)	0.9[a]
> 60	33.8 (17.3–57.1)		15.4 (0.08–35)	
NNRTI				
NVP	48.2 (24–76.8)	< 0.001[a]	15 (−7.8–41.2)	0.7[a]
EFV	33.1 (18.1–60.1)		16.8 (−3-34.6)	

Notes: Superscripts: a Mann–Whitney *U*-test, b- Wilcoxon signed-rank.
Abbreviation: EFV-Efavirenz, NVP-Nevirapine.

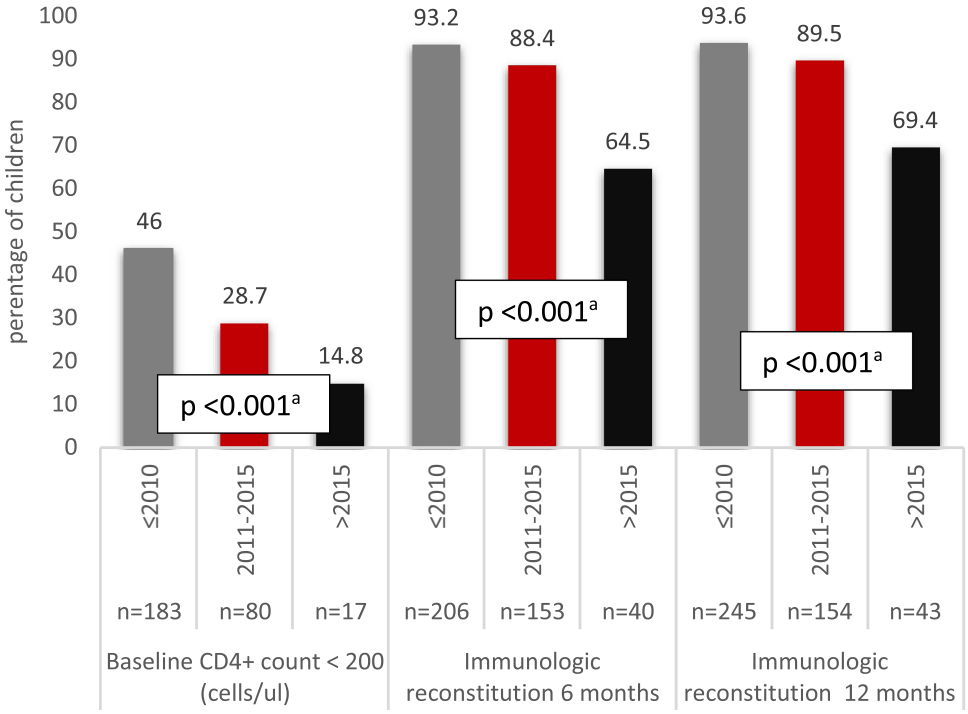

Figure 6 Comparison of baseline CD4+ count and good immunologic Response at 6 and 12 months against cohort year categories.
Note: Superscript: a- Chi-square test.

Univariate Regression of Factors Associated with Inadequate IR at 6- and 12-Months Following cART Initiation

Univariate logistic regression was performed to evaluate patient characteristics associated with inadequate IR at 6- and 12-months following treatment initiation on cART. Table 4 shows the unadjusted relative odds ratio of poor CD4 recovery. In this analysis, higher odds of poor CD4 recovery at 6 months was observed in: cohort year (> 2015: cOR = 7.5 (95% CI: 3.6–15.8), p-value < 0.001), higher baseline CD4+ count (cOR = 1.003 (95% CI: 1.002–1.004), p-value < 0.001), higher baseline Hgb (cOR = 1.2 (95% CI: 1.03–1.4, p-value = 0.02), early WHO clinical stage (cOR = 1.2 (95% CI: 1.03–1.4), p-value = 0.01) and NNRTI (EFV: cOR = 2.1 (95% CI: 1.2–3.8), p-value = 0.009). Similarly, higher odds of poor CD4 recovery following 12 months of treatment on cART were observed in cohort year (>2015: cOR = 6.7 (95% CI: 3.2–14.1), p-value<0.001), higher baseline Hgb (cOR = 1.2 (95% CI: 1–1.4), p-value = 0.01) and higher baseline CD4+ count (cOR = 1.003 (95% CI: 1.002–1.004), p-value < 0.001) (Table 5).

Multivariate Analysis for Independent Predictors of Inadequate IR at 6- and 12-Months Following cART

Table 6 shows the multivariate analysis for independent predictors of inadequate IR at 6 months and 12 months following treatment on cART. In this analysis, the higher adjusted odds ratio of inadequate IR at 6 months was associated with a higher baseline CD4+ count (aOR = 1.003, (95% CI: 1.002–1.005), p-value<0.001) and NNRTI (EFV = 3.9, (95% CI: 1.3–11.9), p-value = 0.01). Similarly, higher baseline CD4+ count was an independent predictor for inadequate IR at 12 months, whereas females were observed to have a lesser risk of poor recovery (aOR = 0.3, 95% CI: 0.1–0.9), p-value = 0.03).

The percentages of the final models for the 6-month and 12-month analyses that were accurately classified were 89% and 90%, respectively, using the Hosmer and Lemeshow goodness-of-fit test (p values = 0.95 and p values = 0.79, respectively), indicating that the models fit well.

Table 5 Univariate Logistic Regression for Inadequate IR at 6 Months and 12 Months Following Treatment Initiation on cART

Cohort Characteristics	cOR for Inadequate IR at 6 Months (95% CI)	*P*-value	cOR for Inadequate IR at 12 Months (95% CI)	*P*-value
Age at initiation, in months				
≤60	*1 (Ref)*		*1 (Ref)*	
>60	0.6 (0.3–1.2)	0.1	0.6 (0.3–1.1)	0.1
Gender				
Male	*1 (Ref)*	0.4	*1 (Ref)*	0.3
Female	1.2 (0.7–2.1)		0.7 (0.4–1.3)	
Residence				
Central zone	*1 (Ref)*	0.9	*1 (Ref)*	0.8
Outside central zone	1.02 (0.55–1.9)		1.04 (0.5–2)	
Cohort Year				
≤2010	*1 (Ref)*		*1 (Ref)*	
2011–2015	1.7 (0.8–3.6)	0.1	1.7 (0.8–3.6)	0.1
>2015	7.5 (3.6–15.8)	<0.001	6.7 (3.2–14.1)	<0.001
Clinical Stage				
Advanced	*1 (Ref)*	0.01	*1 (Ref)*	0.4
Early	1.9 (1.1–3.4)		0.7 (0.4–1.4)	
Baseline Hgb (grm/dl)	1.2 (1.03–1.4)	0.02	1.2 (1–1.4)	0.01
Baseline CD4 count (cells/μL)	1.003 (1.002–1.004)	<0.001	1.003 (1.002–1.004)	<0.001
Anthropometric Measurements				
Weight for age Z-score				
Normal, well nourished (Z >-2)	*1 (Ref)*		*1 (Ref)*	
Moderately Underweight (−3 ≤ Z ≤ −2)	0.8 (0.3–2.1)	0.7	0.6 (0.2–1.8)	0.4
Severely Underweight (Z < −3)	0.5 (0.2–1.2)	0.1	0.8 (0.3–1.9)	0.7
Height for age Z-score				
Normal (Z >-2)	*1 (Ref)*		*1 (Ref)*	
Moderately Stunted (−3 ≤ Z < −2)	0.7 (0.3–1.6)	0.4	0.6 (0.2–1.6)	0.3
Severely Stunted (Z < −3)	0.7 (0.3–1.4)	0.3	1.2 (0.6–2.4)	0.5
BMI for age Z-score				
Normal (Z >-2)	*1 (Ref)*		*1 (Ref)*	
Moderately wasted (−3 ≤ Z ≤ −2)	0.3 (0.1–1.1)	0.08	0.7 (0.2–1.8)	0.5
Severely wasted (Z < −3)	0.7 (0.3–1.6)	0.5	0.9 (0.3–2)	0.8

(*Continued*)

Table 5 (Continued).

Cohort Characteristics	cOR for Inadequate IR at 6 Months (95% CI)	*P*-value	cOR for Inadequate IR at 12 Months (95% CI)	*P*-value
Initial cART regimen				
NRTI				
AZT+3TC	*1 (Ref)*		*1 (Ref)*	0.5
AZT+3TC else	1.3 (0.6–2.4)	0.3	1.2 (0.6–2.4)	
NNRTI				
NVP	*1 (Ref)*		*1 (Ref)*	0.1
EFV	2.1 (1.2–3.8)	0.009	1.5 (0.8–2.7)	
cART Toxicity				
Yes	*1 (Ref)*		*1 (Ref)*	0.8
No	3.9 (0.9–16.6)	0.06	1.1 (0.4–2.7)	
cART changes				
No	*1 (Ref)*		*1 (Ref)*	0.1
Yes	1.1 (0.5–2.2)	0.7	0.6 (0.3–1.1)	

Notes: 3TC, lamivudine; Z-score-WHO standard deviations.
Abbreviations: AZT, zidovudine, cART, combined antiretroviral therapy, CI, confidence interval; EFV, Efavirenz; Hgb, Hemoglobin; IQR, interquartile range; N, number; NVP, Nevirapine.

Table 6 Independent Predictors of Inadequate IR at 6 Months Following Treatment Initiation on cART

Cohort Characteristics	aOR for Inadequate IR at 6 Months (95% CI)	*P*-value	aOR for Inadequate IR at 12 Months (95% CI)	*P*-value
Gender				
Male	*1 (Ref)*	0.4	*1 (Ref)*	0.03
Female	1.2 (0.7–2.1)		0.3 (0.1–0.9)	
CD4 count	1.003 (1.002–1.005)	<0.001	1.003 (1.002–1.005)	<0.001
NNRTI				
NVP	*1 (Ref)*	0.01	*1 (Ref)*	
EFV	3.9 (1.3–11.9)		1.7 (0.8–3.5)	0.1

Abbreviations: aOR- adjusted odds ratio, CI- Confidence interval, cOR-crude odds ratio, EFV-Efavirenz, NVP-Nevirapine.

Discussion

This study investigated the demographic and clinical factors affecting short-term IR in HIV-infected children starting cART in Eritrea. The findings highlight population-specific factors that shape the immune recovery trajectory in children with HIV following short-term immunologic response of cART initiation. Our results demonstrated that children with higher baseline CD4 counts were independently associated with inadequate IR following treatment with cART. Additionally, those initiated on EFV had a 3.9-fold higher likelihood of developing inadequate IR compared to children on Nevirapine after 6 months on cART. Furthermore, girls exhibited 30% lower odds of inadequate IR compared to boys after 12 months of cART.

ART is widely and freely accessible for all HIV patients and those who are vulnerable in Eritrea. The increasing accessibility and use of antiretroviral therapy (ART) can assist in suppressing the HIV viral load and increase the CD4+ T-cell counts, resulting in diminished AIDS-related morbidity and mortality.[5–10] Despite the monumental benefits of cART, disparities in response remain eminent, and many HIV patients exhibit inadequate CD4 reconstitution, which subsequently increases the burden of morbidity and mortality.[10,14,16,22,23] To our knowledge, this is the first longitudinal study that explores the distribution patterns of CD4 T-lymphocyte cells, baseline patient indicators, and short-term immunological responses (Immune Reconstitution) of HIV-positive children in Eritrea after the initiation of cART retrospectively. In this study, immunologic reconstitution (IR) was observed in 87.8% of patients after 6 months of receiving combined antiretroviral therapy (cART), with the proportion increasing to 90.4% after 12 months of treatment. These IR rates are notably higher than those reported in previous studies. Indeed, in their study, Kye-Hyung Kim et al noted immunologic response of 45% and in another study by Kelly CF et al significantly lower immunologic response rates were documented.[29,30]

Interestingly, a study conducted in South Africa demonstrated that the proportion of IR was 73% at six months and increased to 89% at 12 months.[23] Furthermore, a comparative analysis conducted among children followed in Uganda/Kampala and UK/Ireland discovered a lower proportion of immune reconstitution as compared to our study, 46% and 44% in Ireland and Kampala, respectively, after 6 months of cART, and an increment was observed reaching to 64% and 65%, respectively after 12 months of cART.[28] The variability in the results can be explained by the heterogeneity of study populations and the discrepancy in the definition of IR. Indeed, the prevalence of Immunologic Response varies between 6–90%[16,17,22] as studies deploying lower cut-off points of CD4+ tend to report a higher prevalence of immune reconstitution. Nonetheless, the duration of cART significantly affects the magnitude of IR in HIV-1-infected patients, as a higher proportion of IR tends to occur following a longer duration of cART.[10]

In our study, the median baseline CD4+ count was 270 (IQR: 151–441) cells/μL. Generally, patterns and distributions of CD4+ count are influenced by various physiological factors such as age, gender, geographical location, and genetics.[8,12,13,16] In addition, pathological conditions, including drug administration, coinfections, autoimmune antibodies,[8,16,18,31] and contextual parameters that compromise clinical methodologies, setting performance level, and inter-laboratory proficiency[13] tend to cause baseline CD4+ count fluctuations among HIV patients. In our study, the median average of baseline CD4+ count was 270 (IQR: 151–441) cells/μL. This finding is higher than other reports from Ethiopia, 115 cells/μL[32] and 177 cells/μL.[33] Similarly, a lower median CD4+ count was reported from Kenya, 152 cells/μL,[34] 238 cells/μL in Liberia,[35] and 234 cells/μL in Uganda.[28] Nonetheless, investigators from other studies report a higher median CD4+ count in Ireland (350 cells/μL)[28] and in Tanzania (834 cells/μL).[36] The observed variation may be explained by differences in the minimum standards of CD4+ count used for early initiation of cART treatments and delayed initiation of cART.[37]

Aside from the relatively high proportion of immune reconstitution and high initial CD4+ count reported in this study, unexpected findings have been observed in our results; the data demonstrates that the participants with a lower baseline absolute CD4+ count had better IR than those with higher counts at the initiation of cART. Indeed, as noted in the adjusted multivariate model, participants with a lower baseline CD4+ count tend to show more robust immunologic recovery than those with a higher CD4+ count; this finding concurs with prior literature reports.[12,38,39] Notably, a multicenter cohort study of nearly 600 children who started cART across 14 resource-limited countries (10 in Africa) reported good Immune Response among those patients with CD4%<5% at the initiation of treatment.[40] Furthermore, in their study, Kekitiinwa et al noted that children initiated on cART in the UK/Ireland with the lowest CD4% at cART initiation had a better reconstitution to cART compared to children receiving treatment in Uganda/Kampala in which better IR was observed in children with higher baseline CD4%.[28] Better immune recovery among the most immunocompromised children in the United Kingdom/Ireland may relate to their better nutritional status and other environmental factors, such as a lower burden of coinfections, giving a more remarkable ability to "bounce back" once the virus has been suppressed.[28] Similar factors may also be accountable for the observed findings in this cohort. We hypothesize that these results in our cohort could be linked to the redistribution role of sequestered cells played by T-lymphocyte cells after the administration of ARTs and leading to the gradual increase of naïve cells attributed to the diminishing antigenic pressure.[41]

Additionally, we stratified the trend of CD4+ count across different cohort year categories. The study uncovered that baseline CD4+ count was significantly lower in those patients that had been initiated on cART before ≤ 2010 as

compared to the latter cohort year categories [CD4+ count <200 at baseline, ≤2010 = 46%, 2011–2015 = 28.7% and >2015 = 14.8%]. However, following cART, these groups showed a significantly higher proportion of IR [IR, ≤2010 = 93.2%, 2011–2015= 88.4% Vs >2015 =64.5%] and [IR, ≤2010 = 93.6%, 2011–2015 = 89.5% Vs >2015 = 69.4%] at 6- and 12-months following cART respectively. Similarly, the median rate of CD4+ count was significantly higher in the early cohort year category. Multiple potential factors could explain these findings associated with the initiation of cART among the different year categories. Primarily, the provision of cART services was centralized before 2010, and the guidelines for initiation of cART were <350 cells/μL. While services were decentralized from 2010 onwards, the guidelines for initiation for cART were amended to <500 cells/μL and then updated regardless of the CD4+ count in the year categories of (2011–2015) and (>2015), respectively. We used the year categories as a surrogate indicator for adherence to cART. Treatment adherence is assumed to be improved linearly due to the established awareness, accumulated knowledge, and a gradual attitude shift from the progress made through an Eritrean national health campaign and educational initiatives. However, various psycho-social and behavioral factors could confound the practices of children, parents and caregivers. The non-linear trajectory of absolute CD4 percentages increment throughout the cohort year categories might have contributed to the confounding community variables such as HIV-related stigma, discrimination, profound fear of stigmatization, and isolation from social circles.[42] Moreover, the data shows that the advanced WHO clinical stage was significantly associated with IR following 6 months of cART initiation.

Interestingly, children in this cohort who were initiated with Nevirapine (NVP) NNRT Inhibitor regimens, after initiation of cART showed a better CD4 T-cell recovery. The current study revealed a higher risk of inadequate IR in children initiated on an EFV-based cART. Our results are incongruent with previous research findings, which reported a better immunological response to cART among children initiated on EFV-containing regimen.[31,43,44] Although a slight difference in the CD4+ count was documented in several comparison studies, there is insufficient evidence indicating EFV's superiority over Nevirapine (NVP) in the induction of apoptosis of T-lymphocytes and immune activation.[45,46] Strikingly, a study involving children from diverse ethnic origins conducted by Soeria-Atmadjaet et al investigated genetic variants in CYP2B6 and CYP2A6 tend to explain the inter-individual variation in Efavirenz plasma concentration.[47] The results showed significant variability (9-fold measured as mean EFV plasma concentration across the participants) due to genetic polymorphism.

Furthermore, prior reports have described a positive relationship between the EFV plasma concentrations and CD4+ count evolution following cART initiation.[48,49] Such factors may be decisive in interpreting results and extrapolating data extracted from the study analysis of this cohort as well. We found gender was independently associated with IR in our adjusted multivariate analysis. Females, as compared to males, had a significantly lower likelihood of inadequate IR following 12 months of treatment. Similar studies have also shown that females responded better to cART than males.[28,37,50] Sex-based immune disparities between males and females modulate HIV infection dynamics, affect disease pathogenesis, alter the response to cART, and lead to differential IR outcomes.[8,16] Immunologic, pharmacodynamics and pharmacokinetic profile differences between males and females were noticed during the initiation of cART, and sex-linked variations were observed in the absorption, concentrations of antiretroviral drugs and the number of pro-inflammatory cytokines circulating in the plasma.[21,51] We speculated that the expression of T-lymphocyte subsets in girls had a better response capacity and a higher affinity to cART regimens than in boys. Various epidemiological and clinical studies have demonstrated that a female's immunological sex advantages over a male's can be correlated to a better innate and adaptive response,[52] a greater CD4+ T-cell count and a higher CD4/CD8 ratio.[53]

Moreover, we reported the relationship between the child's age at the time of cART initiation and the magnitude of CD4+ T-cell restoration after cART treatment. The effect of increasing age on a poor CD4+ response upon initiation of ART in SSA countries has been documented in several clinical HIV studies[16,54–57] as a result of deteriorating thymic output,[16,56,58] which is linked to the exhaustion of immune system due to a higher level of T-lymphocyte cell activation[56,59] and the decline of de-nova CD4 production accompanied by a high turn-over rate of T-cells.[56,60] Naturally, the distribution course of T-cells and CD4+ counts in healthy children is predominately higher than in adults.[61] Our data complements previous pediatric studies, which suggested that younger children at cART initiation tend to show a better IR.[11,18,28,62] In this cohort, children < 60 months of age at the initiation of treatment had a significantly higher rate of absolute CD4+ count increase, a higher median absolute CD4+ count at 6 months of therapy, and a significantly higher median absolute CD4+ count following 12 months on cART. Age at the time of

diagnosis has repeatedly been found to have a crucial impact on the recovery of CD4+ count, HIV viral load suppression, and, therefore, a considerable effect on the future progression of the disease itself.[11] Indeed, the CASCADE collaboration study found a similar age effect correlating with a CD4+ count, with younger pediatric patients showing better CD4 response following cART.[63] More importantly, a cohort-based modeling study involving 1206 pediatric patients from SSA demonstrates that higher long-term CD4+ count was predicted for those starting cART at a younger age.[14]

The complex interaction between HIV infection and the maturation of the immune system in children has been invoked to explain the observed association. In contrast, age-related immune homeostatic variations significantly affect the T-lymphocyte cells' regenerative capacity.[54,56,57,59,60] Indeed, in the study evaluating the influence of variation of thymic output with age and HIV infection on thymic lymphocyte numbers in HIV-infected children, Kirschner et al discovered a combined negative effect on CD4+ T-lymphocytes in children with increasing age.[64] Another explanation is that the immune system develops with age, and children at younger ages are more effective at combating infections better than during the developmental stage. However, HIV tends to target specifically an activated immune system, which potentially renders children more susceptible to HIV infection as they age.[65] Generally, the existing evidence emphasizes the importance of receiving an early diagnosis and the availability of cART for children living with HIV, intending to enhance initiatives of integrated health services and ensure more sustained responses to treatment.

The strength of our study is the relatively long duration of the cohort (15 years) and the robust representation of clinical data. However, we must acknowledge that our research has several limitations. Firstly, the study's retrospective nature can be linked with missing data on candidate variables of interest that hinder an in-depth investigation of time-dependent covariates due to the unavailability of follow-up information on CD4+ T-cell count. Secondly, patients' data on adherence to medication and HIV-RNA viral load was unavailable at the time of data collection, as was the case in most of the resource-limited countries. Furthermore, socio-economic and programmatic data on maternal HIV status, children's parent, guardians, and their caregivers were not collected. Hence, the generalizability of our study has been confined to populations with suboptimal adherence levels or virologic responses; the effect of the viral load on IR could not be inferred from these findings due to methodological drawbacks. However, our data suggests that there is a distinct consideration to be made of the baseline characteristics such as gender, CD4+ count, and class of HIV regimen, which are detrimental to gaining better immune reconstitution outcomes. In addition, rigorous research is imperative to comprehend further biological, psychosocial, and contextual factors that contribute to optimum health for HIV children receiving ART in endemic SSA, where the constructs of clinical practices are principally guided and in which treatment plans are significantly bound within the metrics of constrained settings and in-country competing resources.

Conclusion

The success of initiating cART on HIV-positive children is likely to include factors associated with the elevation of CD4 T-lymphocyte count. Effective immunologic reconstitution (IR) following cART is crucial for improving clinical outcomes and reducing the risk of AIDS-related complications. However, the current working knowledge and evidence regarding clinical practices for immunosuppressed HIV children in resource-limited settings and endemic regions of SSA countries remains remarkably sparse. The findings of the study underscore the importance of considering baseline CD4 counts, selecting appropriate antiretroviral regimens, acknowledging gender differences when initiating cART in HIV-infected children, and addressing a range of related factors. Key insights reveal that a discernible fraction of children within the HIV-positive populace exhibit inadequate IR, and the percentage of the outcome was relatively low, yet the cohort findings were noteworthy. Furthermore, the study elucidated that inadequate IR was associated with baseline absolute CD4+ count and EFV after 6 months of therapy, while baseline absolute CD4+ count and gender were predictive indicators following one year of cART. In addition, younger children who were initiated on cART in the earlier cohort year category (2005–2010) and had weakened cell-mediated immunity (advanced WHO clinical stage) were observed to have higher median CD4+ counts following treatment. Understanding the intricate interplay between population-specific indicators of children's immune responses and factors shaping the dynamics of cART utilization will be essential for maximizing setting-optimum treatment options, devising improved intervention strategies, and alleviating the immunological needs and vulnerabilities of children with high HIV risk profiles. Overall, these findings highlight the positive impact of cART on the immunologic parameters of HIV-infected children, and the insights gained

from this retrospective cohort are crucial for advancing pediatric HIV treatment paradigms and enhancing patient outcomes in limited and in-country resources competing settings.

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Author Contributions

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