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# CLINICAL OUTCOMES IN CHILDREN AND ADOLESCENTS WITH CHRONIC HIV INFECTION IN ZIMBABWE

## PRELIMINARY REPORT OF THE PAP1 STUDY RESULTS

AIDSTAR-One
AIDS SUPPORT AND TECHNICAL ASSISTANCE RESOURCES

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# CONTENTS

**Acronyms** ..... **v**

**Introduction** ..... **1**

**Methods** ..... **5**

Study Site ..... 5

Treatment Guidelines ..... 5

Adherence Evaluation ..... 7

Data Analysis ..... 7

**Results of Retrospective Chart Review** ..... **9**

Sociodemographic Characteristics ..... 9

Clinical Characteristics ..... 10

Tuberculosis ..... 11

**Retention in Care** ..... **13**

Linked to Care but Not Engaged in Care ..... 13

Initiated on ART ..... 14

Retention in Care ..... 15

**Cross-sectional Cohort Analysis** ..... **17**

Sociodemographic Characteristics of Children Retained in Care ..... 17

Immunologic and Virologic Response to ART ..... 19

Adolescent Outcomes on ART ..... 23

Drug Resistance ..... 26

**Discussion** ..... **29**

**References** ..... **33**

# ACRONYMS

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| AIDS | acquired immunodeficiency syndrome |
| ART | antiretroviral therapy |
| ARV | antiretroviral (therapy) |
| AZT | zidovudine |
| d4T | stavudine |
| ddI | didanosine |
| DNA | deoxyribonucleic acid |
| EFV | efavirenz |
| FTC | emtricitabine |
| HIV | human immunodeficiency virus |
| IQR | interquartile range |
| LPV | lopinavir |
| NNRTI | nonnucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NVP | nevirapine |
| PHFCC | Parirenyatwa Hospital Family Care Centre |
| PMTCT | prevention of mother-to-child transmission |
| PCR | polymerase chain reaction |
| RTV | ritonavir |
| sdNVP | single-dose nevirapine |
| TAM | thymidine analogue mutation |
| TB | tuberculosis |
| TDF | tenofovir disoproxil fumarate |
| USAID | U.S. Agency for International Development |
| WHO | World Health Organization |

# INTRODUCTION

The global burden of pediatric HIV infection is high, with more than 2.5 million children infected with HIV. In sub-Saharan Africa, 2.3 million children are infected with HIV, and 1.84 million are in need of antiretroviral therapy (ART). By the end of 2010, only one in five children in need of ART was receiving it [1]. In Zimbabwe, it is estimated that more than 120,000 children between the ages of 0 and 14 years are living with HIV [2]. In 2008, only 24,958 children were registered in ART clinics in Zimbabwe [2].

The vast majority of children in HIV care acquire HIV infection at birth through mother-to-child transmission. In the absence of ART, survival is low among HIV-infected children, with an estimated 65% survival at one year and 48% at two years, with a steady decrease in survival rates through to adolescence [3]. Having a mother who is HIV-positive, or being an HIV-infected infant, is associated with high mortality. The two-year mortality among infants born to HIV-positive mothers, irrespective of the child's HIV status, ranges from 19.6% to 23.3% for Zimbabwean infants [4, 5]. In a large longitudinal study of HIV infection among infants in Harare prior to the availability of ART for prevention of mother-to-child transmission (PMTCT) services or treatment, intrauterine HIV infection (defined by positive HIV DNA PCR at birth) was associated with 67.5% mortality at two years, intrapartum infection (defined by positive HIV DNA PCR at six weeks) was associated with 65.1% mortality at two years, and postpartum infection (with positive HIV DNA PCR after six weeks) was associated with 33.2% mortality at two years [5].

The high mortality rates among infants with HIV infection in Africa [3] have led to initiatives to prevent HIV infection in infants through the widespread provision of PMTCT services. Among infants who are perinatally infected, there has been a marked increase in access to treatment services, with increasing evidence supporting early treatment initiation [6, 7]. The Children with HIV Early Antiretroviral Therapy (CHER) trial showed a 76% reduction in mortality and a 75% reduction in disease progression among children who were initiated on ART early [8]; as a result, the most recent pediatric ART treatment guidelines by the World Health Organization (WHO) and the Department of Health and Human Services [9] recommended treatment initiation among all infants regardless of their CD4 counts or clinical staging (Table 1). The current treatment guidelines in Zimbabwe reflect the WHO recommendations for early initiation of ART among children; however, most children currently on treatment were initiated prior to the guideline changes [10].

Treatment outcomes among children receiving ART in Africa are variable. An analysis of outcomes among children receiving HIV care in a consortium of clinics throughout Africa, the KIDS-ART-LINC, found that the two-year risk of death after ART initiation was 6.9, with a 10% risk of loss to follow-up [11]. In a West African pediatric ART cohort, 12-month mortality was 8.3% and loss to follow-up at 12 months was 23.1% [12]. Higher rates have been reported in the Malawi national treatment program, with mortality rates for children and infants on ART of 24.3 per 100 person-years in the first three months on ART, decreasing to 5.9 per 100 person-years in months 4–12. Across the entire population receiving ART care, early mortality was higher in infants < 2 years (47 per 100 person-years) and young adults than in any other age group. In addition, infants had the highest rates of loss to follow-up over 12 months, at 24.7 per 100 person-years. Interestingly, retention rates were highest in children ages 2–5 and 6–14 years [12]. These data suggest that infants

and adolescents are a vulnerable population and interventions should be designed to reduce the risk of mortality and improve adherence and retention in care.

Adherence to ART is required to achieve good clinical outcomes. ART has been shown to improve clinical outcomes among children [13, 14]; however, good outcomes are dependent on high rates of adherence. Adherence rates among children in developed countries are generally suboptimal. In a U.S. cohort of perinatally infected children, only 68% of children on treatment had a suppressed viral load [15]. An adherence assessment for children in a clinical trial found that 74% of caregivers reported full adherence, with only 79% of those children with reported full adherence having undetectable viral loads [16]. Adherence in children is often complicated by poor choice of regimens, scheduling of therapy, and patient refusal [17]. Determining accurate adherence levels in sub-Saharan Africa has been hampered by methodological differences across cohorts [18]. A meta-analysis of adherence rates among children on ART found that most studies reported > 75% adherence in sub-Saharan Africa, while most studies from high income countries also reported < 75% adherence [19]. These findings likely reflect methodological differences. Cohorts from high-income countries largely include children from families of lower socioeconomic status, racial minority groups, and marginalized communities who may experience additional challenges to adherence. Despite high adherence rates, high rates of virologic failure have been noted in resource-limited settings. A meta-analysis of treatment outcomes among children on ART in low-income countries found a pooled estimate of virologic suppression of only 70% after 12 months of ART [20].

Adherence rates among children and adolescents receiving ART in Zimbabwe remain largely unknown. A recent survey of children in HIV care in Zimbabwe asked staff in HIV clinics to identify some of the challenges faced by children on ART. Staff cited malnutrition, lack of availability of pediatric formulations, and inconsistent caregivers leading to poor clinic attendance as primary challenges [21]. Many children with HIV are orphaned and have a variety of caregivers with different levels of responsibility and concern for the child's welfare. Caregivers are often limited in their ability to provide for the children, or afford food, transport costs, ensure adherence, and attend clinic visits on a regular basis [22]. Among adolescents, psychosocial problems, poor medication compliance, and lack of disclosure have been identified as key factors leading to poor adherence and clinic attendance [21].

In addition to adherence, long-term retention in care is required to ensure good clinical outcomes among children on ART. Monitoring loss to follow-up rates and determining factors that lead to patient loss are important for all pediatric programs. Loss to follow-up rates are variable across programs in sub-Saharan Africa. In a cohort of children in care in a rural ART program, retention at four years was estimated at 67% of enrolled children [23]. Attrition occurred early, within three months of ART initiation, largely due to mortality after ART initiation [23]. A retrospective analysis of pediatric patients receiving ART from specific nongovernmental organization (NGO)–supported clinics throughout South Africa showed an increase in monthly enrollment rates between 2004 and 2009. Over time, the number of children with advanced clinical disease (WHO stages 3 and 4) decreased, while the median CD4 percentage increased [24]. Program retention was high. After four years of ART, retention in care was 84.1% and mortality was 10.7%. Identifying the factors that facilitate high retention in some programs and not in others is essential for strengthening pediatric programs [24].

Outcomes among children and adolescents receiving HIV care in public HIV treatment programs in Zimbabwe remain largely unknown. In addition, the various stages along the pediatric treatment cascade have been poorly defined for children and adolescents receiving public HIV/ART in low-

income countries such as Zimbabwe. One of the largest public pediatric ART clinics in Zimbabwe is located at Parirenyatwa Hospital in Harare. The hospital is affiliated with the University Of Zimbabwe College Of Health Sciences and serves as the primary teaching hospital of the medical school. It functions as a national center for HIV care and trains health personnel on the management of HIV and AIDS in Zimbabwe. This study evaluated the clinical outcomes among children and adolescents receiving HIV care at Parirenyatwa Hospital.

# METHODS

The team conducted a retrospective chart review of all children and adolescents, ages 0 to 19 years, enrolled in care at Parirenyatwa Hospital Family Care Centre (PHFCC) between January 2005 and December 2012. We established an electronic database and extracted key data elements from the patients' charts. The data were manually extracted from paper charts and verified by a second data entry clerk prior to entry into the database. Another data clerk, who was not involved with the initial entry, subsequently rechecked data entry.

A cross-sectional evaluation of clinical and laboratory parameters to determine outcomes was undertaken, with assessments of adherence among children and adolescents who were currently retained in care. During the course of the study, all children and adolescents receiving care at the clinic were given the opportunity to enroll in the cross-sectional evaluation component. Study procedures included history taking and clinical evaluation by study nurses as well as a blood draw for laboratory assays, primarily CD4 absolute, CD4 percentage, and viral load. In a subset of individuals with viral loads > 1,000 copies/mL, genotyping was performed following extraction of proviral DNA.

Written informed consent was required for all study participants. For children under the age of 12 years, informed consent was obtained from the child's legal guardian. For children between the ages of 12 and 17 years, informed consent was obtained from the child's legal guardian and assent was obtained from the child. For adolescents ages 18 and 19 years, consent was obtained from the adolescent.

## STUDY SITE

The study was conducted at Parirenyatwa Hospital Family Care Centre. PHFCC is the hospital's designated comprehensive HIV/AIDS Treatment and Care clinic. It was established at the end of 2004, when antiretroviral therapy (ART) became available through the national treatment program. To date, more than 14,000 adults and children have been enrolled in care at the clinic. All staffing and resource requirements, including drug supplies for the clinic, are provided through the Ministry of Health and Child Welfare.

The clinic is staffed by one senior physician, one senior pediatrician, two full-time doctors, four staff nurses, two nursing assistants, four counselors, and several peer counselors. In addition, at any given time, several junior house officers and senior house officers are completing rotations in the clinic. The clinic dispenses ART and cotrimoxazole free of charge, and no fee is required for pediatric consultation.

## TREATMENT GUIDELINES

The clinic follows national treatment guidelines for ART initiation and regimen choice. Patients are registered at the clinic, are clinically staged, obtain baseline laboratory studies, including CD4 counts with CD4 percentage, and receive cotrimoxazole prophylaxis. Children who are eligible for ART are initiated on therapy with monthly clinic follow-up visits until they are stable; visits can be spaced out to every two to three months. Height and weight are determined at each visit. CD4 count and CD4

percentage should be determined every three to six months, depending on staffing and reagent availability. However, this goal is rarely met as a result of staffing issues and lack of reagent availability. Most children receive repeat CD4 counts at 6–12-month intervals.

The national guidelines for treatment initiation among children have evolved over time since clinic initiation and have always closely followed World Health Organization (WHO) guidelines, with current guidelines listed in Table 1.

**Table 1. WHO Recommendations for ART Initiation among Infants and Children**

| Age Category | Recommendations |
|---|---|
| Infants (age <1 year) | • Initiate ART in all HIV-infected infants diagnosed in the first year of life irrespective of CD4 count or WHO clinical stage |
| Children | • Initiate ART in all HIV-infected children between ages 12–24 months irrespective of CD4 count of WHO clinical stage<br>• Initiate ART in all HIV-infected children between 24–59 months of age with CD4 count <=750cells/mm$^3$ or CD4 percentage <=25%, whichever is lower, irrespective of WHO clinical stage.<br>• Initiate ART in all HIV-infected children more than 5 years of age with a CD4 count of <=350cells/mm$^3$ irrespective of WHO clinical stage.<br>• Initiate ART in all HIV-infected children with WHO clinical stages 3 and 4, irrespective of CD4 count.<br>• Initiate ART in any child less than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection. |

From *WHO Antiretroviral Therapy for HIV Infection in Infants and Children* [9].

Available pediatric formulations have changed over time, but currently include liquid formulations of 3TC, ABC, AZT, d4T, LPV/RTV, and NVP. Tablet formulations of ABC, AZT, d4T, EFV, and fixed-dose formulations of ABC+3TC, AZT+3TC, AZT+3TC+NVP, d4T+3TC, d4T+3TC+NVP, and LPV/RTV are also available. The recommended pediatric first- and second-line regimens are shown in Table 2.

**Table 2. Recommended First-Line and Second-Line ART Regimens in Use at PHFCC**

| Patient Group | First-Line Regimen | Second-Line Regimen |
|---|---|---|
| **Infants** | | |
| Infant or child < 24months not exposed to ART | NVP + AZT/3TC NVP + d4T/3TC | LPV/RTV + ABC + 3TC<br>LPV/RTV + ABC + ddI |
| Infant or child < 24 months exposed to NNRTI | LPV/RTV + AZT + 3TC<br>LPV/RTV + d4T/3TC | NVP + ABC + 3TC NVP + ABC + ddI |
| Infant or child < 24 months with unknown ARV exposure | NVP + AZT/3TC NVP + d4T/3TC | LPV/RTV + ABC + 3TC<br>LPV/RTV + ABC + ddI |
| **Children** | | |
| Children 24 months–3 years | NVP + AZT/3TC NVP + d4T/3TC | LPV/RTV + ABC + 3TC<br>LPV/RTV + ABC + ddI |
| Children > 3 years | NVP or EFV + AZT/3TC NVP or EFV + d4T/3TC | LPV/RTV+ ABC + 3TC<br>LPV/RTV + ABC + ddI |

NNRTI = nonnucleoside reverse transcriptase inhibitor.
Adapted from WHO and Zimbabwe Pediatric Treatment Guidelines [9].

# ADHERENCE EVALUATION

All children receiving care during the course of the study underwent a standardized adherence assessment that was administered to the primary caregiver and the child (if above five years). However, as routine care at the clinic does not require pill counts, these were not routinely done. In addition, independent assessment through pharmacy pickup records could not be obtained due to the manual pharmacy record keeping system.

# DATA ANALYSIS

We compared baseline characteristics in children enrolled in care using descriptive statistics, and the Pearson chi square and Mann-Whitney tests for categorical and continuous variables, respectively. All analyses were performed using Stata version 9 (College Station, Texas, USA).

# RESULTS OF RETROSPECTIVE CHART REVIEW

## SOCIODEMOGRAPHIC CHARACTERISTICS

A total of 2,293 children between the ages of 0 and 19 years were enrolled into care at PHFCC from 2004 to 2012. The baseline characteristics of the study patients are described in Table 3.

The median age at enrollment was 71 months. Despite growing evidence that early initiation of ART results in improved clinical outcomes, only 26.2% of children were enrolled into care in infancy (< 24 months). More than half of the children were enrolled into care over the age of 5 years, with 27.5% enrolled as adolescents, at ages 10–19 years. In the cohort of enrolled adolescents, 78% were enrolled into care before age 15 years. The majority of these adolescents were likely infected through mother-to-child transmission, and many exhibit the sequelae of chronic HIV infection, such as stunting and chronic respiratory and viral skin infections. An even gender distribution was noted within the patient cohort.

Clinical outcomes in children and adolescents are strongly linked to a stable socioeconomic environment. We evaluated characteristics of the primary caregivers of the children within the cohort. Mothers continue to be the largest group of primary caregivers for the children in care, representing 52.6% of caregivers. Biological fathers were primary caregivers for 11%, grandmothers for 8.9%, and other relatives for 27.6% (aunts, uncles, siblings, family friends). With increasing age of the child, the mother was less likely to be the primary caregiver at the time of enrollment, while the "other" relative played a greater role as the primary caregiver. For 49.1% of adolescents, an "other" relative was listed as the primary caregiver, compared with 8.5% of infants. This likely reflects parental loss secondary to mortality as the children age.

**Table 3. Baseline Characteristics of Study Participants**

| Characteristics | Overall Median (IQR) or N (%) | Infants (0–<2 years) | Young Children (≥2–<5 Years) | Older Children (≥5–<10 Years) | Adolescents (≥10–19 Years) |
|---|---|---|---|---|---|
| Number of children in each age group (N = 2,291) | 71 (22,120) | 599 (26.2%) | 425 (18.6%) | 635 (27.7%) | 630 (27.5%) |
| Female (N = 2,289) | 1,135 (49.6%) | 283 (47.3%) | 187 (44%) | 320 (50.4%) | 354 (54.8%) |
| Mother as caregiver (N = 2,289) | 1,203 (52.6%) | 485 (81%) | 263 (61.9%) | 292 (46%) | 163 (25.9%) |

| Characteristics | Overall Median (IQR) or N (%) | Infants (0–<2 years) | Young Children (≥2–<5 Years) | Older Children (≥5–<10 Years) | Adolescents (≥10–19 Years) |
|---|---|---|---|---|---|
| WHO clinical stage 1 (N = 2,093) | 508 (24.3%) | 169 (31.2%) | 115 (28.7%) | 112 (19.2%) | 112 (19.8%) |
| WHO clinical stage 2 | 476 (22.7%) | 73 (13.5%) | 97 (24.2%) | 170 (29.2%) | 136 (24%) |
| WHO clinical stage 3 | 941 (45%) | 247 (45.6%) | 173 (43.1%) | 267 (45.8%) | 254 (44.8%) |
| WHO clinical stage 4 | 168 (8%) | 53 (9.8%) | 16 (4%) | 34 (5.83%) | 65 (11.46%) |
| History of TB (N = 2,217) | 352 (15.9%) | 64 (11.1%) | 60 (14.6%) | 125 (20.3%) | 103 (16.8%) |
| CD4 cell count (N = 1,617) | 412 (178, 839) | 940 (511, 1,380) N = 344 | 667 (383, 1,073) N = 300 | 366 (162, 612) N = 489 | 208 (77, 396) N = 482 |
| CD4 percentage (N = 1,496) | 15% (8, 22) | 17% (12, 25) N = 353 | 18% (11, 26) N = 324 | 14% (7.3, 21) N = 453 | 11% (6) N = 366 |
| Hemoglobin (g/dL) (N = 1,402) | 10.3 (9.1, 11.4) | 9.2 (8.4, 10.3) N = 328 | 10.2 (9.4, 11.2) N = 293 | 10.6 (9.5, 11.6) N = 414 | 11 (9.9, 11.9) N = 367 |

IQR = interquartile range.

# CLINICAL CHARACTERISTICS

An assessment of clinical parameters revealed that more than half of the patients who presented to care presented with late-stage disease. Median height for age, or weight for age, Z-score, suggests significant malnutrition and stunting across all age groups (Table 4). Older children and adolescents were found to have marked stunting.

This is possibly due to the long-standing consequences of chronic infection, with chronic inflammation affecting growth and biologic development.

**Table 4. Median Weight for Age, and Height for Age Z-Scores for Enrolled Children**

| Age Group | Median Weight for Age (Z-Score [IQR]) | Median Height for Age ((Z-Score [IQR]) |
|---|---|---|
| 0–12 months | -1.2 (2.9) | -1.5 (2.3) |
| 13–24 months | -2.3 (2.4) | -2.6 (2.3) |
| 25–60 months | -1.4 (2.0) | -2.2 (1.9) |
| 61 months–9 years | -1.5 (1.7) | -2.2 (1.7) |
| 10–14 years | -1.9 (1.7) | -2.6 (1.4) |
| 15–19 years | -2.0 (2.4) | -4.1(2.4) |

IQR = interquartile range.

Clinical staging is routinely used for evaluation of children in outpatient care as well as determining treatment eligibility. More than half of the children (53%) enrolled into care presented with WHO stage 3 or 4 disease. Most of these children presented with WHO stage 3 disease, and a smaller number presented with WHO stage 4 disease.

The baseline CD4 count was defined as the CD4 count within six months of registration and was available for 1,617 (70%) children. The median CD4 count was 412 cells/mm$^3$ across the entire cohort. Given the variability of CD4 count with age, CD4 percentage is a more appropriate comparison of CD4 trends across the age groups. The median CD4 percentage was lower in older children and adolescents compared with children under the age of five years (Table 3). The progressive decline with increasing age suggests the chronicity of infection and likely reflects that the older children and adolescents are true perinatally infected long-term survivors.

Anemia is an important predictor of clinical outcomes among individuals and has been associated with poor outcomes among HIV-infected individuals. Severe anemia, with hemoglobin above 7 g/dL, was relatively uncommon, occurring in 2.3% of patients who were enrolled. Moderate anemia, with hemoglobin 7–12 g/dL, was very common, occurring in 56% of enrolled patients. Median hemoglobin across all ages was 10.3 g/dL, and was lower in infants (9.2 g/dL) compared with adolescents (11 g/dL).

# TUBERCULOSIS

Tuberculosis remains a major cause of morbidity and mortality among both children and adults with HIV infection in sub-Saharan Africa. However, pediatric TB infection remains challenging to diagnose in the region. TB history was documented for 2,219 patients, of whom 353 (15.9%) indicated a history of TB infection at the time of enrollment into care. An additional 79 participants were reported as having developed tuberculosis while in the HIV/ART program. The characteristics of children who report TB infection compared with those who do not are indicated in Table 5.

**Table 5. Clinical Characteristics of Children and Adolescents with a History of TB Compared to Those Without**

| Characteristic | History of TB Median (IQR) or N (%) | No History of TB Median (IQR) or N (%) | p-value* |
|---|---|---|---|
| Age | 84 (33, 132), N = 353 | 64 (20, 120) N = 1,866 | 0.0001 |
| Female | 152 (43.1%) | 947 (50.7%) | NS |
| Mother as primary caregiver | 178 (50.42%) | 988 (52.9%) | 0.019 |
| CD4 absolute | 349 (151, 588), N = 276 | 437 (187, 887) N = 1,305 | 0.0000 |
| CD4 percentage | 11% (6, 17) N = 245 | 15% (9, 24) N = 1,220 | 0.0000 |
| Initiated on ART | 53.8% (N = 190) | 55% (N = 1,027) | NS |
| Hemoglobin (g/dL) | 10.1 (8.9, 11.4) N = 227 | 10.4 (9.2, 11.4) N = 11,50 | NS |

*p values < 0.05 are significant; IQR = interquartile range; NS = not significant.

The highest TB history rate was in the older children, 20% of whom reported a history of TB, compared with 11% of infants. The median age of children with TB was 84 months and significantly higher than the median age of 64 months in children who did not report a history of TB. Children who have a history of TB likely are presenting to care secondary to their diagnosis of TB, and often present with lower CD4 count and CD4 percentage, compared with those who do not have a history of TB. There was no significant difference between those with a history of TB and those without in terms of median hemoglobin and primary caregiver status.

WHO clinical staging criteria indicate that pulmonary TB is a WHO stage 3 condition, and all individuals should be initiated on ART if they are in WHO stage 3 regardless of CD4 count. Despite these guidelines, only 53.8% of children with a history of TB at the time of registration were initiated on ART, compared with 55% of those without a history of TB.

The median time to ART initiation for the cohort was 2.1 months (IQR 0.47, 9.3). The median time to ART initiation was delayed in children with TB compared to those without TB.

# RETENTION IN CARE

## LINKED TO CARE BUT NOT ENGAGED IN CARE

To achieve successful outcomes, individuals need to be aware of their HIV status, linked into care, and most importantly, effectively engaged in care. We identified a cohort of children who were successfully linked into care but not adequately engaged in care. We defined "linked but not engaged in care" as individuals who registered at the clinic but were engaged in care for less than three months. "Engaged in care" individuals were those who were engaged for at least three months. A total of 50 children who were enrolled through the prevention of mother-to-child transmission (PMTCT) program and were subsequently tested HIV-negative were dropped from the analysis. A total of 704 (31.4%) children were linked into but not engaged in care, while 1,539 (68.6%) were engaged for at least three months (Table 6).

**Table 6. Baseline Characteristics of Children Who Were Linked but Not Engaged (LNE) in Care and Those Who Were Engaged in Care**

| Characteristics | LNE Median (IQR) or N (%) | Engaged in Care Median (IQR) or N (%) | p-value* |
|---|---|---|---|
| Age (months) | 55 (13, 108) N = 702 | 72 (27, 120) N = 1539 | 0.0000 |
| Female | 349 (49.6%) | 766 (49.8%) | NS |
| Mother as caregiver | 390 (55.4%) | 778 (50.6%) | 0.033 |
| WHO clinical stage 1 and 2 | 233 (38.3%) | 733 (50.6%) | 0.000 |
| WHO clinical stage 3 and 4 | 376 (61.7%) | 715 (49.4%) | 0.000 |
| CD4 percentage | 13% (6, 20) (N = 297) | 15% (9, 23) (N = 1,179) | 0.05 |
| Hemoglobin (g/dL) | 9.7 (8.4, 11) (N = 291) | 10.4 (9.3, 11.5) (N = 1,096) | NS |
| History of TB | 118 (17.6%) | 233 (15.5%) | 0.2 |

*p values < 0.05 are significant; IQR = interquartile range; NS = not significant.

Among those with a history of TB at the time of enrollment, one-third (33.6%) were linked into but not engaged in care. It is likely that a large proportion of those individuals may have had early mortality secondary to their TB infection. Those who were linked and not engaged were also more likely to be in WHO clinical stage 3 or 4 than in stages 1 or 2. It is highly likely that most of these children subsequently died before full engagement in care. Median CD4 percentage counts and hemoglobin levels were lower in the children who were linked into but not engaged compared with those who were engaged in care.

# INITIATED ON ART

We evaluated the number of children who were enrolled in care and initiated on ART. ART initiation in Zimbabwe is done according to Zimbabwe national guidelines, which closely follow WHO guidelines. Over the course of the data collection period (late 2004–12) treatment guidelines did evolve, with the most up-to-date guidelines when the study was initiated being those highlighted in Table 1. These guidelines recommended initiation of ART in all infants (age above two years) regardless of CD4 count. In children aged above two years, ART was to be initiated in all individuals regardless of CD4 count if they had evidence of WHO stage 3 or 4 disease. In children aged above two years who do not have WHO stage 3 or 4 disease, if they are below five years of age, ART initiation should occur for CD4 count < 750 cells/mm$^3$ or CD percentage of 25%. For children above age five, ART should be initiated at a CD4 count < 350 cells/mm$^3$.

Of children who were engaged in care, 65% were initiated on ART. The most common ART regimens used were in accordance with national guidelines, with 35.5% initiated on AZT/3TC/NVP and 47.8% initiated on d4T/3TC/NVP. A comparative analysis of children initiated on ART versus those who were not initiated on ART is shown in Table 7.

**Table 7. Characteristics of Children Initiated on ART Compared with Those Who Were Not Initiated on ART**

| Characteristics | Initiated on ART Median (IQR) or N (%) (Overall N = 1,251) | Not Initiated on ART (Overall N = 992) | p* Value |
|---|---|---|---|
| Age | 84 (30, 132) (N = 1,250) | 50 (15, 106) (N = 991) | 0.0000 |
| Female | 622 (49.7%) | 493 (49.7%) | NS |
| Mother as caregiver | 575 (45.9%) | 593 (59.8%) | 0.000 |
| WHO clinical stage 1 and 2 | 520 (44.3%) | 446 (50.6%) | 0.005 |
| WHO clinical stage 3 and 4 | 665 (55.7%) | 436 (49.4%) | 0.0000 |
| CD4 percentage | 13% (7, 20) (N = 934) | 18% (10, 25) N = 542 | 0.0000 |
| Hemoglobin (g/dL) | 10.4 (9.2, 11.5) (N = 876) | 10.2 (8.9, 11.2) (N = 511) | 0.01 |
| History of TB | 189 (15.6%) | 162 (16.9%) | NS |
| Duration in care | 38 (21.5, 59) (N = 1,244) | 1 (0, 9) (N = 982) | 0.0000 |

*p values < 0.05 are significant; IQR = interquartile range; NS = not significant.

There was no observed gender bias with regard to whether or not a child was initiated on ART. The median age at enrollment was higher among children who were initiated on ART compared to those who were not. Among those who were initiated on ART, the mother was the primary caregiver in

45.9% of cases. The mother was the primary caregiver for almost 60% of children who were not initiated on ART.

In accordance with Zimbabwe national guidelines, all children with WHO stage 3 or 4 disease should be initiated on ART. However, 49.4% of children who presented with WHO stage 3 or 4 disease were not initiated on ART. The majority (83%) of the children who had WHO stage 3 or 4 disease at baseline and were not initiated on ART were linked but not engaged. It is likely that some of these children who were lost from care early are deceased. The overall prevalence of TB among those initiated and those not initiated on ART was 15.1% and 16.3%, respectively. The CD4 percentage at baseline was considerably lower among those who were initiated on ART compared with those who did not start ART. The median duration in care was significantly higher among those initiated on ART compared to those who were not initiated on ART. Lack of ART initiation is a primary driver of loss from care.

# RETENTION IN CARE

Although linkage, engagement, and initiation on ART are important in improving short- term survival among children on ART, retention in care is critical for successful long-term outcomes. We defined children as being retained in care if they had been seen in care within six months of the censoring date (May 1, 2013). Only children who were enrolled in the clinic from were included in the analysis. Of the children who were enrolled and confirmed to be HIV-positive, 783 (34.9%) were still actively engaged in care, while 1,460 (65%) were considered lost to follow up.

This analysis excludes children who are characterized as linked but not engaged in care (i.e., those who were enrolled in care at the clinic for less than three months). The transfer rate was low, as decentralization of care for pediatric patients has proceeded at a slower pace than decentralization of care for adult patients. A total of 80 patients were documented as having transferred, accounting for 3.5% of the patient population. The six-month retention rate was 92%, dropping to 81% at 12 months, with a gradual decline such that the five-year retention rate had dropped to 49%.

ART initiation is a major driver of retention in care. At 12 months following enrollment, 90% of children who were initiated on ART were still in care. However, only 55% of children who were not initiated on ART were still in care at six months. This rate dropped precipitously, such that at five or more years following enrollment in care, 67% of those who were initiated on ART were still retained in care compared with only 16% of those who were not initiated on ART.

# CROSS-SECTIONAL COHORT ANALYSIS

## SOCIODEMOGRAPHIC CHARACTERISTICS OF CHILDREN RETAINED IN CARE

The goal of ART is to achieve maximal virologic suppression to ensure immune recovery and decrease immune activation and inflammation. Viral load monitoring is not available as part of routine care for patients in the public HIV/ART program in Zimbabwe. To determine outcomes including virologic suppression rates in the patient cohort, we conducted a cross-sectional analysis of children in care on ART and determined CD4 counts and viral loads in the children.

A total of 665 children were enrolled in the cross-sectional study, representing 85% of the children who were still actively engaged in care. All the children were on ART. The demographic characteristics of these children prior to ART initiation are listed in Table 8.

**Table 8. Baseline Characteristics of Study Participants**

| Characteristics | Total No. of Children N = 665 | Overall Cohort Median (IQR) or N (%) | Infants (0–<2 Years) N = 82 | Children (≥2–<5 Years) N = 105 | Children (≥10–19 Years) N = 181 | Adolescents (≥10–19 Years) N = 273 |
|---|---|---|---|---|---|---|
| Age | | 11 (6, 15) | | | | |
| Female | | 51.6% | 51% | 53.9% | 49.2% | 52.6% |
| Mother as caregiver | | 49.3% | 68.4% | 74% | 50.6% | 33.1% |
| WHO clinical stages 1 and 2 | N = 166<br>476 (22.7%) | 26%<br>73<br>(13.5%) | 25.6%<br>(N = 21) | 31.4%<br>(N = 33) | 25.4%<br>(N = 46) | 24.4%<br>(N = 66) |
| WHO clinical stages 3 and 4 | N = 473<br>168<br>(8%) | 64%<br>53<br>(9.8%) | 74.4%<br>(N = 61) | 68.6%<br>(N = 72) | 74.6%<br>(N = 135) | 75.6%<br>(N = 205) |

| | | | | | | |
|---|---|---|---|---|---|---|
| CD4 cell count at enrollment | N = 554 | 347 (142, 705) | 1123 (666, 1,620) | 550 (286, 867) | 370 (169, 662) | 208 (65, 374) |
| CD4 percentage at enrollment | N = 492 | 13% (7, 20) | 19% (11, 26) | 14.5% (10, 22) | 12.5% (7, 17) | 10% (5, 17) |
| Hemoglobin (g/dL) | N = 431 | 10.8 (9.6, 11.9) | 10.3 (9, 11.5) | 10.4 (9.4, 11.2) | 10.6 (9.6, 11.5) | 11.4 (10.1, 12.3) |

IQR = interquartile range.

The median age of the cohort was 11 years (IQR 6, 15). We categorized the children into infants (age < 2 years), young children (age 2–< 5 years), older children (ages 5–< 10 years), and adolescents (aged 10–19 years). Adolescents formed the largest single group, as 43% of the cohort. The gender distribution was even across all the age groups.

The mother served as the primary caregiver for 49.3% of the children. Fathers were 8.7% of primary caregivers, grandmothers 14.2%, and other relatives 27.9%. Older children and adolescents were less likely to have their mother as the primary caregiver compared with infants and younger children. The primary caregivers were overwhelmingly female, with women representing 82% of all caregivers. The median caregiver age was 38 years (IQR 31, 46). Among the caregivers, 24% indicated that they were employed full-time, 54% were unemployed, and 16% were self-employed. A large proportion of the caregivers had achieved secondary education (57.6%), while 15.5% had achieved skilled job training or a university education.

Parental mortality was high, with 32% having a deceased mother and 35% having a deceased father. A total of 301 (47.3%) of the children had mothers who had been on ART, whereas only 219 (34.7%) of children had a father who was on ART.

Most children in the cohort had WHO stage 3 or 4 disease at baseline. WHO stage 3 disease had occurred in 57.3% and WHO stage 4 disease in 16.7% at the time of clinic enrollment. Pulmonary TB was the most common opportunistic infection, with 36% of the cohort having had pulmonary TB at baseline. Fourteen children reported having had TB meningitis prior to enrollment into care.

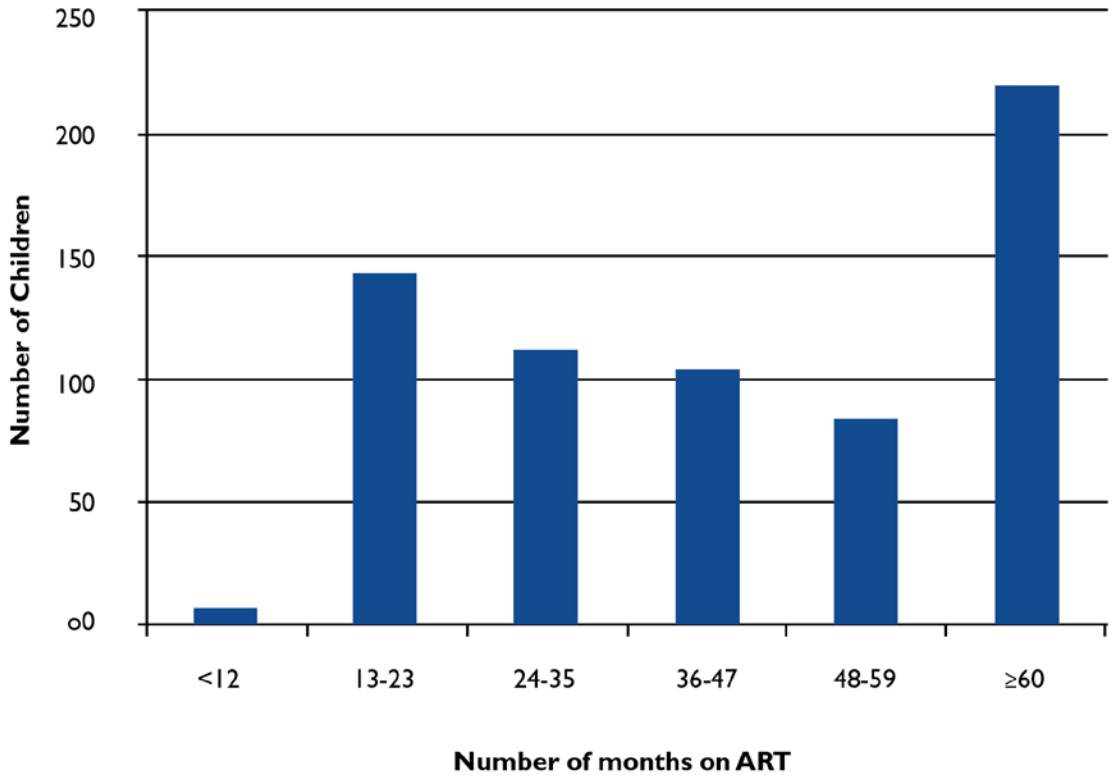
The CD4 percentage at baseline was notably higher in infants than it was in older children, reaching its lowest level of 10% among the adolescents. Many of these children likely were perinatally infected long-term survivors and presented to care late with more advanced disease.

All the children in the cohort were on ART. The median time to ART initiation was 1.15 months (IQR 0, 6.87). The median time to ART was shorter for adolescents, at 0.47 months (IQR 0, 3.43), compared with other children, whose median time to ART ranged from 1.37 to 1.6 months after clinic registration.

The majority of children in the cohort were on a 2NRTI+1NNRTI regimen, with the most common regimen being a stavudine-based regimen (d4T/3TC/NVP), which was used by half of the children in the cohort. The remaining were on regimens of d4T/3TC/EFV, AZT/3TC/NVP, or AZT/3TC/EFV. Only 46 children were on a protease inhibitor–based regimen. Two children were on a regimen containing TDF.

Study participants had to be on ART for at least 12 months at the time of study enrollment. The median time on ART was more than three years (39.7 months [IQR 23.8, 58.1]). Thirty-two percent of the children had been on ART for five or more years (see Figure 1).

**Figure 1. Duration on ART for Study Participants**




# IMMUNOLOGIC AND VIROLOGIC RESPONSE TO ART

The children had good responses to ART, and the overall median CD4 percentage rose from 13% at baseline to 24.9% (12.1, 38.9). However, the median CD4 percentage remained quite low for adolescents, being considerably lower than that observed for infants and older children. The baseline median CD4 percentage for adolescents rose from 10% to 14.6%. The median absolute CD4 count, however, rose from 208 to 480 cells/$mm^3$ (Tables 8 and 9).

**Table 9. Median Absolute CD4 and CD4 Percentage Counts in Response to ART**

| Age Group | Median Duration on ART | Median Absolute CD4 (N) | Median CD4 Percentage (N) |
|---|---|---|---|
| Infants (0–<2 years) | 33.8 (18.7, 46.4) (N = 74) | 1225 (975, 1,601) (N = 81) | 36.9% (22.3, 47.4) (N = 76) |
| Children (≥2–<5 years) | 32.4 (20.1, 54.1) (N = 95) | 1091 (700, 1,402) (N = 103) | 33.4 (22.2, 43.7) (N = 96) |
| Children (≥5–<10 years) | 44.4 (23.8, 60.7) (N = 159) | 800 (500, 1064) (N = 180) | 25.46 (16.1, 37.9) (N = 139) |
| Adolescents (≥10–19 years) | 42.7 (28.5, 59.3) (N = 235) | 480 (272, 756) (N = 270) | 14.6 (6.3, 31.2) N = 224 |

Virologic suppression was defined as a viral load of < 1,000 copies/mL. The overall viral suppression rate was 68.2%. The lowest virologic suppression rates were in adolescents, who achieved virologic suppression rates of only 63% as compared with 73% in children ages 5–10 years (Figure 2). The lower rates of virologic suppression in adolescents are largely due to adherence-related problems. Virologic suppression rates remained relatively stable over time, ranging from 73% among those who had been on ART for less than two years to 63% among those on ART for between four and five years (Figure 3).

**Figure 2. Virologic Suppression Rates by Age Group**

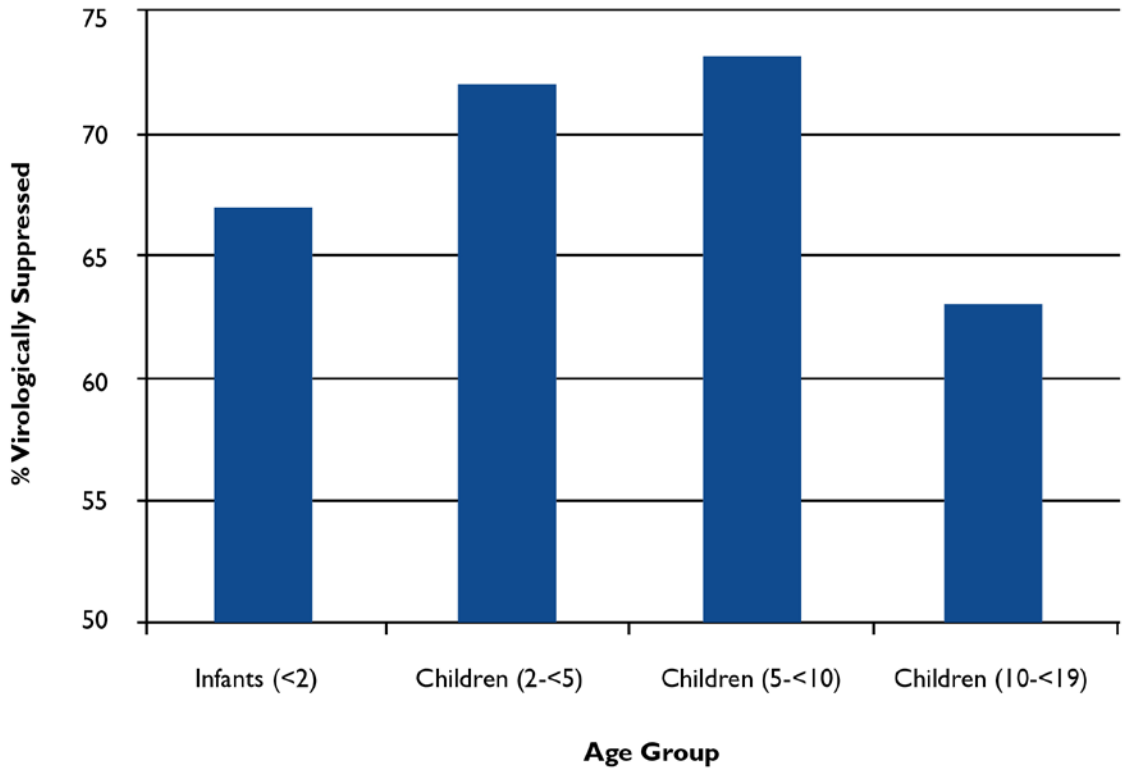
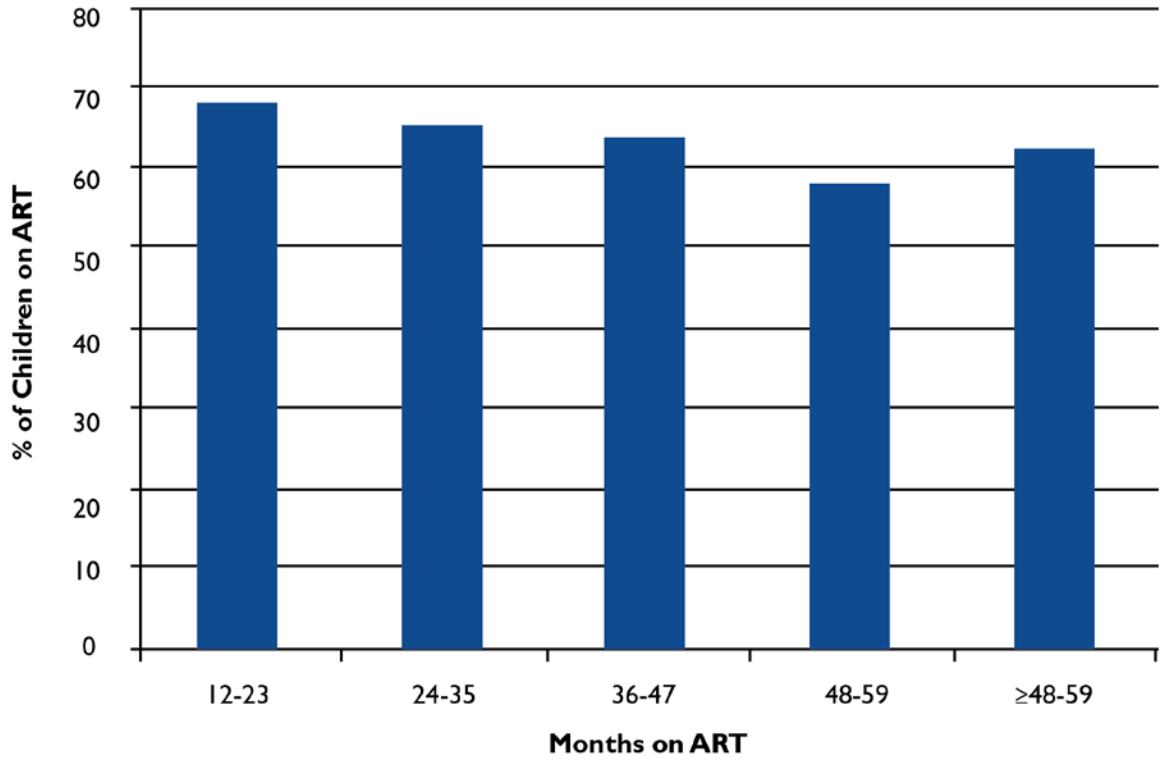


**Figure 3. Virologic Suppression Rates by Duration on ART**




The factors associated with virologic failure were assessed (Table 10). Age was significantly associated with virologic suppression. Children younger than 10 years had significantly lower virologic suppression rates than did children older than 10 years.

Although the difference was not statistically significant, virologic suppression rates were higher in children whose primary caregiver was either the mother or father (71% and 68.5%, respectively) compared with those who were cared for by either the grandmother or another relative (64% and 65%, respectively).

We subsequently determined if maternal or paternal condition would determine virologic suppression. We particularly compared those who indicated that their father or mother was either dead or chronically ill to those who indicated that their parent was healthy. The association between maternal mortality and chronic illness with virologic suppression in the child was not found to be significant. The virologic suppression rate in children whose mother had died or was chronically ill was 62.4% compared with 69% in children whose mothers were reported as healthy ($p = 0.095$). Paternal health was associated with virologic suppression; 62.8% of those whose father had died or was chronically ill were virologically suppressed compared with 72% of those whose fathers were healthy ($p = 0.021$). Zimbabwe is a very patrilineal society and it is likely that paternal mortality has the greatest socioeconomic and cultural impact on a family, such that it may more severely perturb the child's psychosocial and socioeconomic security.

We found no significant association between the child's virologic suppression status and whether or not the caregiver was on ART. There was no association between the caregiver's employment status as either employed/self-employed or unemployed or their level of educational attainment with virologic suppression in the child.

**Table 10. Factors Associated with Virologic Suppression**

| Factor | | N | Virologic Suppression N (%) | Virologic Failure N (%) | p-value* |
|---|---|---|---|---|---|
| Age | <10 | 368 | 264 (71.7%) | 104 (28.3%) | 0.019 |
| | ≥ 10 | 273 | 172 (63%) | 101 (37%) | |
| Gender | Female | 341 | 227 (66.6%) | 114 (33.4%) | NS |
| | Male | 316 | 219 (69.3%) | 97 (30.7%) | |
| Primary caregiver | Parents | 371 | 262(70.6%) | 109 (29.4) | NS |
| | Other | 265 | 172 (64.9%) | 93 (35.1) | |
| Attends school (age > 10 years) | Yes | 228 | 148 (64.9%) | 80 (35.1%) | NS |
| | No | 30 | 17 (56.7%) | 13 (43.3%) | |
| Duration on ART | < 3 years | 260 | 186 (71.5%) | 74 (28.5%) | NS |
| | ≥ 3 years | 405 | 267 (65.9%) | 138 (34.1%) | |
| WHO clinical stage | 1 and 2 | 172 | 112 (65.1%) | 60 (34.9%) | NS |
| | 3 and 4 | 491 | 341 (69.5%) | 150 (30.6%) | |
| CD4 percentage | <10% | 195 | 129 (66.2%) | 66 (33.8%) | NS |
| | >10% | 310 | 219 (70.7%) | 91 (21.4%) | |
| Disclosure | Yes | 402 | 256 (63.9%) | 146 (36.2%) | 0.002 |
| | No | 263 | 197 (74.9%) | 66 (25%) | |
| Year of enrollment | < 2008 | 314 | 109 (51.7%) | 205 (45.4%) | NS |
| | ≥ 2009 | 349 | 102 (48.3%) | 247 (54.7%) | |

*p values <0.05 are significant; NS = not significant.

There was also no statistically significant association between virologic suppression and history of TB or WHO clinical stage at the age of enrollment. We evaluated school attendance and performance at school as a proxy for social stability and functional status. The school attendance rate in Zimbabwe is quite high, so only a small number of children who were school eligible were not attending school (30 children). Although a larger proportion children who were not attending school had virologic failure (43%) compared to those attending school (35%), this difference was not statistically significant ($p = 0.38$).

Being in the correct grade for age was used as proxy for both social stability and cognitive developmental function. Children and caregivers were asked if the child was in the correct grade for their age, and 458 responses were collected. Of these children, 62.9% were in the correct grade, while 37.1% were not and most of these were at least one grade below the appropriate grade for age. There was no significant association between being in the correct grade and virologic suppression.

There was no significant association between duration on treatment and virologic suppression, despite those in care for less than three years having overall higher suppression rates (72.5%) than those in care for three or more years (65.9%). Although there may be some element of treatment fatigue with longer duration in care, as has been described in adults on ART, in this cohort it does not appear to cause a significant difference in virologic suppression rates.

Age-appropriate disclosure of HIV status is encouraged with children to help facilitate understanding and acceptance of their HIV status as well as adherence. We found, however, that HIV nondisclosure was significantly associated with virologic suppression, with individuals who had not been disclosed to having higher virologic suppression rates than those who had undergone disclosure (74.9% compared with 63.9%, $p = 0.002$). This differs from what is expected and has been previously reported and likely reflects the strong association between disclosure and age. Among the adolescents, 93% had had their HIV status disclosed to them, compared with only 37% of children below 10 years of age ($p = 0.000$). We also evaluated the disclosure rates based on primary caregiver, and the children whose primary caregiver was a father or mother were less likely to have undergone disclosure (48.3%) than those whose caregivers were grandparents or other relatives (77%) ($p = 0.000$). A higher proportion of children whose mother had died or was chronically ill had received disclosure of their HIV status than children whose mother was healthy (81.5% compared with 49.1%, $p = 0.000$). The same pattern was observed regarding the health status of the father. A larger proportion of children whose fathers had died or were chronically ill had been disclosed to compared to those with healthy fathers (75.9% and 46%, respectively, $p = 0.000$). This may reflect the reluctance of parents to disclose the HIV status of the child to the child as this would result in disclosing their own HIV status to their child, and potentially to the community if the child inadvertently disclosed the information to others. It may also indicate the natural instinct of a parent to protect their child from harm, given the degree of stigma that continues to be associated with HIV infection.

# ADOLESCENT OUTCOMES ON ART

Adolescents are generally defined as falling within the 10–19-year-old age group. This period is accompanied by a number of developmental and psychosocial changes, which make this group more vulnerable than children or young adults. We conducted additional analyses focusing primarily on the adolescents within the cohort. We divided the cohort of adolescents into young adolescents, who were at least 10 but not yet 15 years, and older adolescents, defined as older than 15 and less than 19 years. Many of the young adolescents had enrolled in care during childhood, while the older

adolescents had enrolled at an older age. We compared the sociodemographic parameters as well as the clinical outcomes in the two groups of adolescents (Table 11).

The median age of adolescents in care was 13.5 years (IQR 11.6, 16). The mother was the caregiver for 37% of younger adolescents and for 27% of the older adolescents.

There was no significant difference in WHO clinical staging in older compared to younger adolescents. In both age groups, 75% presented in stage 3 or 4. The majority presented with WHO stage 3 disease, and 19% presented with WHO stage 4 disease.

A higher proportion of adolescents (49%) indicated having a history of TB compared with younger children (32.9%, p = 0.000).

**Table 11. Characteristics of Younger (Ages 10–<15) and Older Adolescents (Ages 15–19)**

| Characteristics | Young Adolescents Median (IQR) or N (%) N = 177 | Older Adolescents Median (IQR) or N (%) N = 96 | p-value* |
|---|---|---|---|
| Age | 13.5 (11.6, 16) | | |
| Female | 91 (51.7%) | 52 (54.2% | NS |
| Parent as caregiver | 75 (44.3%) | 33 (36.3%) | NS |
| WHO clinical stage 1 and 2 | 44 (24.9%) | 22 (23.4%) | NS |
| WHO clinical stage 3 and 4 | 133 (75.1%) | 72 (76.6%) | NS |
| History of TB | 78 (46.2%) | 51 (54.8%) | NS |
| CD4 cell count at enrollment | 234 (86, 400)<br>(N = 160) | 142 (29, 340)<br>N = 79 | 0.03 |
| CD4 percentage at enrollment | 11 (5, 17.2)<br>(N = 123) | 9 (4, 13)<br>N = 46 | NS |
| Hemoglobin (g/dL) | 11 (9.9, 12.1) | 11.8 (10.7, 12.6) | 0.02 |
| Hemoglobin (g/dL) | (N = 117) | (N = 62) | 0.02 |
| Median CD4 count at evaluation | 555 (295, 821)<br>(N = 176) | 406 (259, 593)<br>(N = 94) | 0.0009 |
| Median CD4 percentage at evaluation | 21.5% (9.9, 35.4)<br>(N = 144) | 8.9 (4.6, 15.7)<br>N = 80 | 0.0000 |
| Duration in care (months) | 45.2 (28.6, 62.6) N = 176 | 37.2 (26,1, 52, 1) | 0.04 |
| Virologically suppressed | 112 (63.3%) | 60 (62.5%) | NS |

*p values < 0.05 are significant; IQR = interquartile range; NS = not significant.

Older adolescents were enrolled into care at lower median CD4 counts and CD4 percentage than the younger adolescents. This may reflect the longer duration of HIV infection in older adolescents, who were also likely infected perinatally. As a result of the low baseline CD4 count and CD4 percentage at enrollment, immune recovery may not be as robust in the older adolescents compared with the younger adolescents. The duration in care was longer for the younger adolescents than for the older adolescents, with many of the younger adolescents having been enrolled into care as older children (5–10 years). The virologic suppression rates were similar in the younger and older adolescents.

The factors associated with virologic suppression in the adolescents were assessed. Primary caregiver, duration on ART, WHO clinical stage, and CD4 absolute and percentage counts were all not significantly associated with virologic suppression in older compared with younger adolescents (Table 12).

**Table 12. Factors Associated with Virologic Suppression Rates in Older and Younger Adolescents**

| | | N | Virologic Suppression N (%) | Virologic Failure N (%) |
|---|---|---|---|---|
| Age | 10–<15 | 177 | 112 (63.3%) | 65 (36.7%) |
| | 15–19 | 96 | 60 (62.5%) | 36 (37.5%) |
| Gender | Female | 143 | 84 (58.7%) | 59 (41.3) |
| | Male | 129 | 87 (67.4%) | 42 (32.6%) |
| Primary caregiver | Parents | 108 | 68 (63%) | 40 (37%) |
| | Other | 152 | 97 (63.8%) | 55 (36.2%) |
| Duration on ART | <3 years | 84 | 52 (61.9%) | 32 (38.1%) |
| | ≥3 years | 189 | 120 (63.5%) | 69 (36.5%) |
| WHO stages | 1 and 2 | 66 | 43 (65.2%) | 23 (34.9%) |
| | 3 and 4 | 205 | 129 (62.9%) | 76 (37.1%) |
| CD4 percentage | <15% | 121 | 79 (65.3%) | 42 (34.7%) |
| | >15% | 48 | 29 (60.4%) | 19 (39.6%) |
| CD4 absolute | ≥350 | 171 | 105 (61.4%) | 66 (38.6%) |
| | >350 | 67 | 44 (65.7%) | 23 (34.33%) |

# DRUG RESISTANCE

We evaluated drug resistance patterns among 125 children who had evidence of virologic failure (viral load > 1,000 copies/mL). Most of the children sequenced had at least one mutation, although 39 (31.2%) had no detectable mutations despite elevated viral loads.

Most of the children with virologic failure had at least one drug-resistant mutation detected on genotyping. Only one mutation was detected in 21% of the children, two to five mutations were detected in 62% of the children, and 17% of the children had more than five drug resistance mutations. One child had 12 drug resistance mutations noted. The most common mutations identified are indicated in Table 13.

At least one thymidine analogue mutation (TAM) was present in 30.2% of isolates, with at least one drug resistance mutation. A greater proportion of the isolates contained TAM2 mutations than contained TAM1 mutations. Most of the isolates with a TAM (14/26) had only one mutation; however, 47% of the isolates containing TAMs had more than one TAM detected. In 6 of 26 isolates, two mutations were detected, and in 9 of 26 isolates between three and five TAMs were detected. In general, the M184V mutation will present before TAMs present. TAMs typically present sequentially, and the presence of more than one TAM suggests prolonged exposure to a failing regimen.

**Table 13. Frequency of Common Drug Resistance Mutations in Children and Adolescents on ART**

| Drug Resistance Mutation | Confers Resistance To | Frequency | Percentage of Isolates (N=86) |
|---|---|---|---|
| **NRTIs** | | | |
| M184V | 3TC/FTC | 53 | 61% |
| TAM1 (M41L, L210W, T215Y) | d4T/AZT | 13 | 15.1% |
| TAM2 (D67N, K70R, 219Q) | d4T/AZT | 18 | 20.9% |
| K65R | TDF | 2 | 2.3% |
| L74V | ABC/ddI | 4 | 4.7% |
| Q151M | AZT/d4T, all NRTIs except TDF | 1 | 1.2% |
| **NNRTIs** | | | |
| K103N | EFV | 29 | 33.7% |
| Y181C | NVP | 34 | 39.5% |
| Other (L100I, V106A/M, Y181C/I, Y188L, G190S, M230L) | 3 or more of these mutations confer resistance to etravirine | 53 | 61.6% |

| **Protease inhibitors** | | | |
|---|---|---|---|
| L10F/I/R/V, V32I, M46I/L, I54V/M/L, V82A/F/T/S, I84V/A/C, L90M | | 5 | 5.8% |

The frequencies indicate the frequency of the mutation among the 86 individuals with one or more drug resistance mutations detected on genotyping.

The presence of resistance mutations that typically develop following exposure to efavirenz or nevirapine were quite common within the cohort. The K103N mutation associated with efavirenz exposure was present in 33.7% of isolates, and the Y181C mutation associated with nevirapine exposure was present in 39.5% of the isolates. The K013N mutation was present in 29 isolates; in 16 of the 29 isolates with a K103N mutation, these children had not been exposed to EFV, but had been on NVP-based regimens. However, additional efforts will be made to ensure that they may not have had any inadvertent exposures caused by events such as stockouts. The Y181C/I/F mutation occurred almost exclusively in children who were known to have received nevirapine.

The other NNRTI mutations are less commonly noted. The V106A/M mutation was noted in six isolates (14%), Y188L occurred in one isolate, G190A/R was found in 10 isolates, M230L occurred in one isolate. The presence of three or more of the other NNRTI isolates, including Y181C (L100I, V106A/M, Y181C/I, Y188L, G190S, M230L), confers resistance to etravirine, an NNRTI that works in the presence of the efavirenz mutation K103N.

Four isolates had three or more of these mutations, whereas 61% of all isolates had at least one of these NNRTI mutations.

The presence of a protease mutation was generally rare, with only five isolates exhibiting only one of the common general protease mutations either L10V (three isolates), M46I (one isolate) or L90M (one isolate). All the children had been exposed to lopinavir/ritonavir, and none had been exposed to atazanavir/ritonavir, which has recently become the preferred protease inhibitor regimen.

Among those with at least one mutation, only 26 had their ART regimen switched, with the majority switched to an inappropriate regimen that does not take into account the drug resistance patterns that had emerged on their failing regimen. The majority of switches were lateral switches made because of stockouts or programmatic changes. Eight children had been switched to protease inhibitor–containing second-line regimens.

# DISCUSSION

This study provides one of the most comprehensive analyses of outcomes among children and adolescents receiving HIV care in a public HIV/ART program in Zimbabwe. The government through its key development partners, including the U.S. Agency for International Development, the UK Department for International Development, the Global Fund, and others, largely supports the program. However, all staff are paid as government employees, and all resources are obtained through government funds. ART is obtained through the national government, but is supplied to the government largely by its international donor partners. As a consequence, this clinic reflects outcomes at a tertiary institution in sub-Saharan Africa that is primarily run as a government institution, and not as a stand-alone research site or an internationally funded organization. The outcomes at this center are important as they reflect what outcomes would be in the absence of substantial foreign funding and involvement in an HIV treatment and care program in a low-income sub-Saharan African country.

Although the clinic is government supported, it is also important to note that this clinic is attached to a tertiary institution and medical school. However, much of the pediatric care is provided by senior house officers. These are typically doctors who have completed one to two years of additional clinical training following completion of medical school.

The primary medical providers in the program are therefore largely low-to-medium-level doctors who do receive once-weekly support from a consultant pediatrician. Although nurses have recently begun to provide pediatric care at the center, it largely remains doctor driven.

Interpretation of this data is best done in the context of the pediatric HIV treatment cascade, as the results of the study highlight the challenges of getting children into care in infancy, engaging them in care, retaining them, and ensuring that they are successfully suppressed on ART. The treatment cascade in children begins with prevention efforts in the PMTCT programs and progresses though to virologic suppression rates among children and adolescents on ART. Although the implementation of the national PMTCT program is widespread, the follow-up care and diagnostic testing of exposed infants in the postnatal period are limited, contributing to the large number of children and adolescents who are enrolled in care later in life.

We evaluated data from the *2010 National PMTCT Report*, which suggests that at least 88% of pregnant women are receiving HIV testing either in antenatal care or during labor. Based on the frequency of positive HIV tests among HIV-positive women in antenatal care, we estimated that a total of 52,782 pregnant women were HIV-positive. Among these women, 83% received some form of ART. Fully active triple ART is the most effective strategy for PMTCT; however, only 10% of pregnant women received triple ART. Ninety percent received sdNVP at delivery, while 42% also received a zidovudine-based regimen from 14 weeks.

Based on this data, it can be concluded that 17% of exposed infants received no effective therapy, and less than 10% received the most effective therapy, triple therapy, or full ART. This suggests that a large proportion of exposed infants remained at risk.

In the postnatal period, clinical and diagnostic follow-up of infants also remained poor. Based on the national data, we estimated that 67% of HIV-exposed children received some form of post-exposure ART. Some received sdNVP only, while others received sdNVP plus AZT. The current

guidelines recommend six weeks of daily nevirapine in children who are breastfeeding. Zidovudine may be used as an alternative in infants receiving replacement feeds. Forty-seven percent of infants received cotrimoxazole prophylaxis, which is recommended for all exposed infants and serves a proxy for whether or not the child is at least interacting with the HIV treatment program in the context of an HIV exposure.

DNA PCR testing was done in only 31% of exposed infants, whereas the data on serologic testing at 18 months were not available. This suggests that more than 50% of exposed uninfected children are not receiving adequate follow-up care. As a consequence, many of these children end up presenting at clinics such as PHFCC as infected older children and adolescents.

In the clinic, only 26% of children presented to care in infancy. The Children with HIV Early Antiretroviral Therapy (CHER) trial showed that early initiation on ART, regardless of CD4 count or CD4 percentage, in HIV-positive children ages 6–12 weeks resulted in a 76% reduction in mortality and a 75% reduction in disease progression [28]. These findings were important and resulted in changes in the WHO treatment guidelines. Additional data from the same study group also showed significant neuro-cognitive benefits associated with early treatment. Efforts should be made to increase enrollment into care in the early postnatal period; however, this requires immediate linkage of exposed infants to HIV/ART treatment facilities and strong diagnostic support services to ensure that children undergo DNA PCR testing early. A large number of children in Zimbabwe are not accessing care in the postnatal period, as confirmed by national data showing that only 47% of exposed babies make it into care and receive cotrimoxazole prophylaxis. As a consequence, a large proportion of exposed children who become infected likely die, and those who do survive present to care as older children or adolescents with the sequelae of chronic HIV infection.

The median age at enrollment of the cohort was close to six years. The study showed that among children enrolling in care increasing age was associated with a lower baseline CD4 percentage and more advanced WHO stage 3 and 4 disease. The failure of the health care system to identify HIV-positive children early in life and refer them to care may have consequences in terms of immunologic recovery on ART, chronic inflammation in children, and long-term outcomes. Routine testing should be offered to children whenever they encounter the health care system, either at the time of receiving immunizations or when they present with routine childhood problems such as respiratory and gastrointestinal infections. This early testing should be linked to referral for HIV care.

In addition to linkage to care from testing, engagement into care is critical to facilitate long-term retention in care. We found that 31.4% of patients presenting to care were linked but not engaged in care. Those who were linked but not engaged had lower CD4 percentage and higher clinical stages, and although outcomes are not known, many are likely to have died. This is a significantly large proportion of the children who are enrolled, and indicates patient vulnerability in the first three months of care. It also highlights the critical need to ensure that children are tested and engaged in care early, before they develop progressive disease with the associated high mortality rates.

The 12-month retention rates in those who were engaged in care were comparable to those documented elsewhere. The 12-month retention rates were 81% overall; 90% for those who were on ART, and 55% for those who were not. ART initiation is clearly an important driver of retention in this cohort. This study is one of the few to report long-term retention rates among children in public treatment programs, and our findings suggest a steady decline in retention with time. The greatest decline in retention is among those who are never initiated on ART. Among those on ART, retention after 60 months in care was 67%, while it was only 16% in those not initiated on ART, and

in the cohort overall retention rate was 49%. A study to determine the factors associated with loss to follow-up is critically needed to identify reasons for programmatic loss, and to guide the development of appropriate interventions

Virologic suppression is a marker of successful ART. We found lower virologic suppression rates among children on ART than anticipated, particularly in the first 12–24 months on treatment. For children on ART for 12–23 months, the virologic suppression rate was only 73% and remained relatively stable, dropping to 66% for those on ART for more than five years. The poor virologic suppression rates at one to two years are cause for concern and may reflect dosing and/or adherence challenges with pediatric ART. The strongest association with virologic failure in the cohort was age at enrollment, and disclosure of HIV status. Children who start treatment at older ages were more likely to have higher viral loads than those started in treatment earlier on. Some of these challenges may result from children becoming responsible for their own ART without supervisory support from an adult at an early age, stigma, and the psychosocial challenges that emerge particularly in adolescence.

Among children who had evidence of virologic failure, it was notable that 31% had fully susceptible virus. This supports the approach of promoting adherence first in a resource- limited setting where genotyping is not available, and subsequently rechecking viral load prior to switching therapy. Among those with evidence of resistance, most children had two or more resistance mutations mostly against NRTIs, suggesting that many of these children had prolonged exposure to a failing drug regimen. Routine availability of viral load testing is an important intervention to help facilitate early identification of virologic failure and prevent children from remaining on failing regimens for too long.

The data obtained give us some important insights into the outcomes among children and adolescents in care. The failure of the early infant diagnosis program and linkage to care has huge consequences for HIV care in children and results in many children presenting to care late and with advanced disease. Among those who are engaged in care, efforts need to be made to strengthen retention. These efforts may include establishing a follow-up system for contacting caregivers and children if they have missed appointments and creating a clinic environment that is conducive to family-oriented visits, including minimizing patient waiting times as the clinic. Among those who have been retained in care, efforts must be made to ensure that they achieve full virologic suppression. These efforts include strengthening and supporting adherence. Strengthening institutional capacity for viral load monitoring is needed, as is providing support to children, particularly adolescents, around adherence and coping with other psychosocial factors that may influence their ability to adhere to medications and care. In addition, efforts must be made to integrate care for children into the lives of children, including school and examination schedules. A systematic evaluation of the factors associated with failure within our patient cohort would provide some important insights into the local systems that need to be developed to support improved care and clinical outcomes.

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