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*Full Length Research Paper*

# Prevalence of antiretroviral treatment failure and associated factors in HIV infected children on antiretroviral therapy at Gondar University Hospital, retrospective cohort study

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**As the use of highly active antiretroviral therapy (HAART) increases, the issue of drug resistance and subsequent anti-retroviral treatment (ART) failure appears as a challenge. The study aim to assess prevalence of ART treatment failure and associated factors amongst children on ART at Gondar University Hospital, North WEST Ethiopia, 2014. A retrospective cross-sectional study was conducted on children taking ART at Gondar University Hospital by using a systematic random sampling technique to include 225 under 15 Children on ART who took the drugs for at least six months. Data was collected from the patients' medical records and analyzed by SPSS version 16.0. Binary logistic regression with multivariate analysis was used. Data from 225 children was analyzed, where the mean age was 10.8 years. *The* majority of children (77.4%) were in advanced clinical stage before initiation of HAART. About 60% of children were started with regimen of AZT-3TC-NVP. The original first line regimen was substituted in 44.9% o f patients. About 101 patients who took ART for a mean of 60.3 months had poor adherence. There were 41 patients (18.2%) who had evidence of first line ART treatment failure of which the most common type is both clinical and immunological. Out of all children with first line ART treatment failure, only 14 patients (34%) were detected and started on second line regimens. ARV prophylaxis for PMTCT (p=0.041), advanced clinical stage 3(p=0.046) and stage 4(p=0.035), base line CD4 less than 200 cells or 10% (p<0.001), tuberculosis co-infection (p=0.045), substitution of original regimen (p=0.001), poor adherence during follow up (p= 0.002) and duration of ART above 60 months (p=0.033) were independent risk factors for ART treatment failure.**

**Key words:** HIV/AIDS, clinical and immunological treatment failure, risk factors, Ethiopia.

## INTRODUCTION

United nations programme on HIV/AIDS (UNAIDS)/World health organization (WHO) 2010 report estimated that, globally, about 33.3 million people are living with human immunodeficiency virus (HIV) in 2008 of which 30.8 million were adults and 15.9 million are women. Children under 15 years of age account about 2.5 million (7.5% of PLWHIV) (FMOH, 2010).

Estimated number of PLHIV in Ethiopia in 2010 were

1,216,908 (41% males and 59% females) of which, 79,871**(**6.6%) are children <15 years. 44,751 deaths occurred due to acquired immune deficiency syndrome (AIDS) in 2009 which made about 804,184 children AIDS Orphans in 2010.from the total anti-retroviral therapy Need in 2010(Universal Access Target) 397,818, about 26,053 were children (FHAPCO/MoH, 2007).

Many studies have reported the success of highly active anti retroviral therapy in improving clinical and immunologic outcomes of children. However, as the use of HAART increases, the issue of drug resistance and subsequent treatment failure presenting as one or more of clinical, immunological or virological ART failure appears as a challenge (Tigist et al., 2012). The World Health Organization advocates a public health approach to ART, recognizing the potential role for plasma HIV-1 RNA testing but recommending clinical and immunological monitoring in most situations. However, little work has been done to assess the sensitivity and specificity of clinical and immunologic criteria to predict virologic failure, and we are aware of no other study evaluating these criteria in children (Emmett et al., 2010). From retrospective cohort study amongst 456 patients on NNRTI-based ART in Soweto, after a median of 15 months on ART, 19% (n = 88) and 19% (n = 87) had failed virologically and immunologically respectively. A cumulative adherence of <95% to drug-refill visits was significantly associated with both virologic and immunologic failure ($p<0.01$).

In the final multivariable model, risk factors for virologic failure were incomplete adherence (OR 2.8, 95%CI 1.2 to 6.7), and previous exposure to single-dose nevirapine or any other antiretroviral (adj. OR 2.1, 95%CI 1.2–3.9), adjusted for age and sex. As a conclusion, one in five failed virologically after a median of 15 months on ART. Adherence to drug-refill visits works as an early warning indicator for both virologic and immunologic failure (El-Khatib et al., 2011).

In an Ethiopian university hospital, among children on first line ART, clinical treatment failure and immunologic treatment failure were diagnosed in 6.2 and 11.5% respectively. The presence of chronic gastroenteritis or the appearance of a new opportunistic infection afterstarting treatment was associated with immunologic treatment failure.

Having chronic malnutrition (height for age in the third percentile or less) at initiation of ART, low CD4 at base line, chronic diarrhea after initiation of first line ART, substitution of ART drugs and age less than 3 years old were found to be independent predictors of first line ART failure in children. Most of the first line ART failure cases were not detected early and those that were detected were not switched to second line drugs in a timely fashion. Children with the above risk factors should be closely monitored for a timely switch to second line highly active anti-retroviral therapy (World Health Organization (WHO) (2010).

ART failure is not a common diagnosis in most centers in Ethiopia. Very few patients among the needy are started on second line ART regimens. Previous studies have evaluated the patterns associated with switching from first line ART regimes to second line ART regimes; however, studies that evaluate the factors associated with first line ART regime failures in limited resource settings like Ethiopia and Africa at large are scarce (Workneh et al., 2009).

Hence, this study reported prevalence of first line ART treatment failure and associated factors which will help the personnel working on the ART program and clinicians to evaluate patients on ART in every visit for treatment failure and contributing factors. The study result can also be used as a baseline data for subsequent studies.

## METHODOLOGY

### Study setting

The study was conducted at Gondar University Hospital which is located in Gondar town. The Hospital is one of the teaching hospitals of Ethiopia, and referral hospitals in the Amhara Region with strong HIV /AIDS care and treatment center. The Hospital started delivering ART service in 2003. Free ART was started in 2005. Since the Hospital is the only referral hospital for the surrounding zones with wide catchment area, most patients have follow up in this hospital. Currently (up to June 30, 2013), there were 964 HIV positive children ever enrolled in chronic care. Of these children, 614 have ever started ART as to the National guide line. Patients are then followed based on the National guide line which recommends first visit after two weeks of initiation, every month for the next two to three months and every three months then after. They are followed with clinical staging at every visit and CD4 count /CD4 percentage every six month

### Study period

The study was conducted from September to December, 2014 in HIV infected children on HAART from 2005 to 2013.

### Study design

A retrospective cohort study was conducted on a children taking ART since March 2005 up to Dec 2013 at Gondar University Hospital to assess treatment failure and associated factors.

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**Study population**

All HIV infected children who took first line ART for at least six months at the Gondar University Hospital were included in the study with the following inclusion criteria:

1. Under15 years of age
2. A minimum of two follow-up visits with at least one visit six months post initiation of first line ART of any regimen.

**Exclusion criteria:**

1. If CD4 count/percentage not documented at least once after 6 month of ART.
2. If transferred out before treatment failure was detected.
3. If lost to follow up or died before detection of treatment failure.

**Sampling technique and sample size**

Systematic random sampling technique was used to select 259 patients from total of 614 patients on ART who took ^^for six months. The formula used to select the sample was:

$n_0 = Z^2Pq/d^2$, where
p=population proportion in problem (estimated prevalence) =0.5
q=1-p=0.5
d=degree of accuracy (estimated error) =0.05
Z=the standard normal value at confidence interval of 95%=1.96
$n_0$ = the minimum sample size from single population = 384

The final study sample (n) will be:

$$n = \frac{n_0}{\left(1+\frac{n_0}{N}\right)}$$

(Reduction Formula because the total population is less than 10,000) where
n=sample size to be calculated for study
$n_0$ = the minimum sample size above.
N=number of sampling population=patients on ART for at least six months= 614
So n=236+23 (10% contingency for loss of subjects from any reasons) =259
The data collected from 225 charts was analyzed (19 were excluded and 15 cards cannot traced)

**Data collection procedures**

Data was collected from the patients' medical records by using an English structured data retrieval form check list. Quality of data collected by data collectors was checked every day by principal investigator (author).

**Data analysis procedures**

The data was entered, cleaned and analyzed using SPSS version16.0. Cross tabulations between independent variables and dependent variable (treatment failure) were made to see relations. Binary logistic regression with multivariate analysis was used to see predictors of treatment failure (to compute p-value and adjusted odds ratio at 95% confidence interval) where p-value of less than 0.05 was taken significant

**Operational definitions**

Treatment failure is categorized as clinical, immunological and virological failure and defined as follows (FMH, 2008; Sebunya et al., 2013):

**Clinical failure**

Sever or recurrent infections or illness: recurrence or persistence of AIDS defining conditions (OIs and malignancies) or other serious infections.
Growth failure: persistent decline in weight growth velocity despite adequate nutritional support and without other explanation.
Progressive neurodevelopmental deterioration: lack/loss of neuro-developmental milestones or HIV encephalopathy.

**Immunological failure**

**Incomplete immunological response to therapy**: failure to improve CD4 values by ≥ 5 % in a child < 5 years with severe immune suppression (CD4 percentage< 15%) or failure to improve CD4 values by ≥ 50 cells/mm3 in a child 5 years or older and sever immune suppression (CD4 ,200 cells/mm3)

**Immunological decline**: sustained decline of 5% CD4 below baseline at any age or decline to below baseline in absolute CD4 count in children 5 years or older.

**Virologic failure**: was not used because of the complexity of defining ART failure in children using viral load and the in accessibility of routine virologic tests in Ethiopia

**Ethical consideration**

The study proposal was approved by ethical committee for health research of the University of Gondar, collage of medicine and health sciences. A formal letter was received from hospital administration to review patients' medical charts for data collection. Since it (the chart review) does not have direct contact with patients and doesn't harm the patients, and data kept confidential with coding consent was not taken from each patient.

## RESULTS

From the 225 children whose data was analyzed, 110 (48.9%) are males and 115 (51.1%) are females. Majority of children (59.5) lies in age group between 10 to 15 years and the mean age at time of study was 10.8 (range 3 to14 years). Only 7 patients (3.1%) took ARV prophylaxis (PMTCT) where single dose NVP, single dose NVP with one week AZT or four week AZT was used (Table 1). As shown in Table 2 from the 225 sampled children on ART, about 137(60.9%) children started HAART with eligibility criteria of both WHO clinical sage and CD4 number/percentage. Majority of the children were in advanced clinical stage (stage3 and 4) and severe immune suppression before initiation of

**Table 1**. Socio demographic characteristics of sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

| Variable | | Number | Percentage (%) |
|---|---|---|---|
| Age | 0-5 years | 8 | 3.6 |
| | 5-10 years | 83 | 36.9 |
| | 10-15 years | 134 | 59.5 |
| | Total | 225 | 100 |
| sex | Male | 110 | 48.9 |
| | Female | 115 | 51.1 |
| | Total | 225 | 100 |
| ARV prophylaxis | Yes | 7 | 3.1 |
| | No | 218 | 96.9 |
| | Total | 225 | 100 |

**Table 2**. Base line characteristics of sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

| Variable | | Number | Percentage (%) |
|---|---|---|---|
| WHO clinical stage | 1 | 22 | 9.8 |
| | 2 | 29 | 12.9 |
| | 3 | 134 | 59.6 |
| | 4 | 40 | 17.8 |
| | Total | 225 | 100.0 |
| CD4 level | Less than 200/ 10 % | 75 | 33.3 |
| | 200-350/10%-15% | 79 | 35.1 |
| | Above 350/15% | 71 | 31.6 |
| | Total | 225 | 100 |
| Tuberculosis co-infection | yes | 27 | 12 |
| | No | 198 | 88 |
| | Total | 225 | 100.0 |

HAART. About 60% (135 patients) of children started with regimen of AZT-3TC-NVP followed by D4T-3TC-NVP which accounts for 29.8% (67 patients). AZT-3TC-EFV, D4T-3TC-EFV, AZT-3TC-LPV/r and TDF-3TC-EFV are other first line regimens used. About 12% (27 cases) of patients have Tuberculosis co- infection during the initiation of the HAART.

As shown in Table 3, the original first line regimen was substituted in 101(44.9%) patients. The reasons for change were side effects, diagnosis of Tuberculosis, program shift from D4T to AZT or TDF and stock out of drugs. The side effects were common with AZT-3TC-NVP regimen, anemia being the commonest. About 27(12%) patients who were followed for a mean of 60.3 months (range 7 to 113 months), have poor adherence.

There were 41(18.2%) patients who had evidence of first line ART treatment failure of which the most common type is both clinical and immunological 20 (48.8%), followed by immunological failure 14 (34.2%). Clinical failure alone accounts for about 7(17.0%). Out of all children with first line ART treatment failure, only 14 (34%) patients were detected and started on second line regimens. Mostly prescribed second line regimen is ABC-ddi-LPV/r (78.6%) followed by TDF-3TC-keletra (14.3%). The rest 27(66.0%) patients were not detected even though the first line treatment had failed (Table 4).

As shown in Table 5 ARV prophylaxis, advanced clinical stage, low CD4 count and tuberculosis co-infection before initiation of ART are independent factors that increase risk of treatment failure. Substitution of original regimen

**Table 3**. Follow up data of sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

| Variable | | | Number | Percentage (%) |
|---|---|---|---|---|
| Substitution of first line | Yes | Side effect | 29 | 12.9 |
| | | Diagnosis of TB | 32 | 14.2 |
| | | Program shift | 32 | 14.2 |
| | | stock out | 5 | 2.2 |
| | | Other | 3 | 1.3 |
| | | Total | 101 | 44.9 |
| | No | | 124 | 55.1 |
| | Total | | 225 | 100.0 |
| Adherence | Good | | 186 | 82.7 |
| | Fair | | 12 | 5.3 |
| | poor | | 27 | 12.0 |
| | Total | | 225 | 100.0 |
| Duration on ART | Below 36 months | | 38 | 16.8 |
| | 36-60 months | | 71 | 31.6 |
| | Above 60 months | | 116 | 51.6 |
| | Total | | 225 | 100.0 |

**Table 4**. Treatment failure, type of treatment failure and second line drug intake among sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

| Variable | | | Number | Percentage (%) |
|---|---|---|---|---|
| Treatment failure | Yes | Immunological | 14 | 6.2 |
| | | Clinical | 7 | 3.1 |
| | | Both | 20 | 8.9 |
| | | Total | 41 | 18.2 |
| | No | | 184 | 81.8 |
| | Total | | 225 | 100.0 |
| Taking second line regimen | Yes | ABC-ddi-LPV/r | 11 | 26.8 |
| | | ddi-3TC-LPV/ r | 1 | 2.4 |
| | | TDF-3TC-keletra | 2 | 4.8 |
| | | Total | 14 | 34.0 |
| | No | | 27 | 66.0 |
| | Total | | 41 | 100.0 |

once or more for any reason and poor adherence during follow up had also increased the risk of ART treatment failure. Patients who took ART for longer duration (above 60 months) have high probability of first line ART treatment failure in comparison with those who took less than 60 months.

## DISCUSSION

From this study, there were 41(18.2%) patients who had evidence of first line ART treatment failure of which the most common type is both clinical and immunological 20 patients (8.9%), followed by immunological failure 14(6.2%). Clinical failure alone accounts about 7(3.1%).

From the study by PLATO II in many countries more than 1000 children were followed for a median of 4.2 years from the time of ART initiation. Risk for triple-class failure was estimated to be 12% by year 5 of ART and 20% by year 8 (Holly, 2011). From retrospective cohort study amongst 456 patients on NNRTI-based ART in Soweto, after a median of 15 months on ART, 19% (n =

**Table 5**. Independent variables as predictors of first line ART treatment failure among sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

| Covariates | | Treatment failure (%) | p-value | Adjusted odds ratio (95 CI) |
|---|---|---|---|---|
| ARV prophylaxis | | 2 (28.6) | 0.041 | 1.438 (1.223-2.453) |
| Clinical stage | Stage 1 | 5 (12.7) | 0.815 | - |
| | Stage 2 | 4 (13) | 0.622 | 0.872 (0.172.1.245) |
| | Stage 3 | 23 (17.2) | 0.046 | 1.401(1.389-3.336) |
| | Stage 4 | 9 (22.5) | 0.035 | 1.815 (1.499-6.593) |
| Base line CD4 | <200 cells/10% | 26 (34.7) | <0.001 | 5.748 (2.197-15.043) |
| | 200-350/10-15% | 9(11.3) | 0.089 | 0.436 (0.231-1.368) |
| | >350 cells /15 % | 6 (8.4) | 0.545 | - |
| TB co-infection | | 12 (44.5) | 0.045 | 2.943 (2.067-12.987) |
| Regimen shift | | 28 (27.7) | 0.001 | 3.275 (1.592-6.735) |
| Adherence | Good | 18 (9.6) | 0.257 | - |
| | Fair | 2 (16) | <0.001 | 32.667(11.670 -91.437) |
| | Poor | 21 (77.8) | 0.002 | 14.701(1.401-19.102) |
| Month on ART | Below 36 months | 8 (21) | 0.165 | - |
| | 36-60 months | 7 (9.8) | 0.861 | 1.083(0.443-2.648) |
| | Above 60 months | 26 (22.4) | 0.033 | 2.641(1.080-6.458) |

88) and 19% (n = 87) had failed virologically and immunologically respectively (El-Khatib et al., 2011). From case controlled study conducted in Uganda among 701 children on first line ART, 240(34%) failed on first line ART (Sebunya et al., 2013). From retrospective cohort study done in Nigeria the rate of first line regimen failure was 18.8% (Isaakidis et al., 2010).

In retrospective cohort study done at Jimma university specialized hospital, among children on first line ART, clinical treatment failure and immunologic treatment failure were diagnosed in 6.2% and 11.5% respectively (8). From the retrospective cohort study conducted in Addis Ababa, there were 167 (14.1%) children with HIV/AIDS who had evidence of first line ART failure of which 70 (5.9%) had clinical treatment failure, 79 (6.7%) immunologic failure and 18 (1.5%) developed both immunologic and clinical failure (Tigist et al., 2012). From all studies above the prevalence of the ART treatment failure was comparable except that of Ugandan study which was higher and explained by the nature of study being case control with possible risk factors.

In this study, out of all children with first line ART treatment failure, only 14 (34%) patients were detected and started on second line regimens but the rest 66% of patients were not detected even though they have evidence of treatment failure.

From study conducted at Addis Ababa, Out of all children with first line ART failure, only 24 (14.4%) were identified. The mean time of detection of treatment failure was 19.7 months (SD = 14 months) and the mean time to switch to second line ART regimen, for those switched, was 24 months (SD = 11.67 months) (Tigist et al., 2012). The detection rate was higher in the current study which can be due to the high prevalence of treatment failure and the increased awareness for treatment failure as time goes

In this study duration of ART above 60 months (p=0.033) was independent factor that increase the risk of ART treatment failure. From PLATO II study the factors for treatment failure were older age at time of study and longer duration on HAART (Holly, 2011). From the study conducted in Medical College and Research Institute of Bangalore, duration on ART for more than 3 years (*P*=0.0436) was associated with immunological failure. In multiple regression, duration on ART, age and nadir CD4 count (lowest ever) on treatment were predictors of immunological failure in these patients (Prabhakar et al., 2011). As it can be seen from these studies the chance of ART treatment failure was increasing as duration of ART increases which is 18.2% (in this study) with average duration of 60.2 months and 12% and 20% ( PLATO II study) with mean duration of 60 months and 96 months respectively.

This study showed that ARV prophylaxis for PMTCT (p=0.041), base line CD4 less than 200 cells/µl (p<0.001) and poor adherence during follow up (p= 0.002) were also independent factors for ART treatment failure. In Medical College and Research Institute of Bangalore, low

CD4 counts (<100cells/µl) at start of ART (*P*=0.0261), less than 50% gain in CD4 count (*P*=0.048) after one year of start of ART and duration on ART for more than 3 years (*P*=0.0436) were associated with immunological failure. In multiple regression, duration on ART, age and nadir CD4 count (lowest ever) on treatment were predictors of immunological failure in these patients (Prabhakar et al., 2011).

From Soweto study, a cumulative adherence of <95% to drug-refill visits was significantly associated with both virologic and immunologic failure (p<0.01). In the final multivariable model, risk factors for ART treatment failure were incomplete adherence (OR 2.8, 95%CI 1.2 to 6.7), and previous exposure to single-dose nevirapine or any other antiretrovirals (adj. OR 2.1, 95%CI 1.2 to 3.9), adjusted for age and sex (El-Khatib et al., 2011). From the studies conducted in Nigeria and Cambodia risk factors for ART treatment failure were ARV exposure and sever immunosuppression before start of HAART (Isaakidis et al., 2010). From a case control study conducted in Uganda, the factors associated with treatment failure were poor adherence ((OR = 10, 95 CI: 6.4 to 16.7) p < 0.001), exposure to single dose nevirapine (sdNVP) [(OR = 4.2, 95% CI:1.8-9.4), p = 0.005] and a NVP containing regimen ((OR = 2.2,95% CI:1.4-3.6), p < 0.001) (Robert et al., 2013). From a study conducted in Kenya, the factors were base line CD4 below 50 cells and imperfect Adherence. From these studies, the risk factors including low base line CD4, poor adherence and ARV prophylaxis were found to be significant associated factors for ART treatment failure.

In this study, advanced clinical stage 3(p=0.046) and stage 4(p=0.035), substitution of original regimen once or more for any reason (p=0.001) and tuberculosis co-infection as opportunistic infection (p=0.045) were also risk factors for treatment failure. In retrospective study conducted at Jimma university specialized hospital, the presence of chronic gastroenteritis or the appearance of a new opportunistic infection after starting treatment and clinical stage 4 were associated with immunologic treatment failure (Workneh et al., 2009). From retro-spective cohort study conducted in Addis Ababa Children under 3 years old, chronic malnutrition at ART initiation, chronic diarrhea after the start of ART, drug substitution during the course of ART, and having $CD_4$ count less than 50 at base line were independent predictors of increased risk of treatment failure(3). From these studies risk factors assessed in common including substitution of original regimen, advanced clinical stage before start of HAART and opportunistic infection (Tuberculosis co infection as OI in this case) were found to be significantly associated with ART treatment failure.

## CONCLUSION

The overall first line ART treatment failure was 18.2% (41 patients) in which the most common type is both clinical and immunological (8.9%) followed by immunological failure (6.2%), clinical failure alone accounts for 3.1%. Out of all children who have evidence for first line ART treatment failure, only 14 (34%) patients were detected and started on second line regimens. But about 37(66%) patients were not detected even though they have evidence of treatment failure during follow up. So close monitoring should be done to detect treatment failure early and shift to second line treatment.

ARV prophylaxis for PMTCT, advanced clinical stages (3 and 4), base line CD4 less than 200 cells/µl, tuberculosis co-infection, substitution of original regimen once or more for any reason , poor adherence during follow up and duration of ART above 60 months were independent factors that increase the risk of first line ART treatment failure.So this group of patients should be strictly evaluated for treatment failure at every visit since these factors increase the risk of first line ART treatment failure. Service providers should strengthen adherence counseling at every visit since it is a risk factor for treatment failure. Since there are many patients with first line ART treatment failure, second line drugs for children should be available.

The trend of shifting to second line treatment and the mean delay from detection of treatment failure and start of second line treatment was not determined in this study and can be studied in subsequent studies.

## Limitation of the study

CD4 was not determined regularly every six months for some patients/ not documented. There was lack of viral load determination to assess virological treatment failure.

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## Conflict of interests

The author has not declared any conflict of interests.

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