



# Virologic Failure in Different Antiretroviral Regimens Among Pediatric Patients with HIV Referring to a Voluntary Counseling and Testing (VCT) Center in Tehran, Iran (2004 - 2017)

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## Abstract

**Objectives:** This study aimed to evaluate the virologic failure rate of treatment for various types of antiretroviral treatment (ART) regimens in pediatric patients with HIV.

**Methods:** The present study was conducted among 75 HIV-positive pediatric patients characterized by the presence of a viral load of 200 or more copies per mL after six months of effective, continuous ART regimen. Therefore, treatment failure was defined based on virologic failure. We designed a questionnaire that included patients' demographic characteristics, viral load markers, TCD4+ count, antiretroviral regimen received, and the probable treatment failure, along with the results of the drug resistance tests.

**Results:** In total, 22 (29.2%) children experienced treatment failure. The most common primary antiretroviral regimen was Zidovudine (AZT)/Lamivudine (3TC)/Nevirapine (NVP) (59.2%), followed by AZT/3TC/Efavirenz (EFV) (29.6%). The highest rate of virologic failure was related to the AZT/3TC/NVP regimen (68.2%). In children who used NVP, the virologic failure was significantly higher than in children on other regimens ( $P = 0.02$ ).

**Conclusions:** The present study showed that patients receiving ART regimens based on reverse transcriptase non-nucleoside inhibitors, especially NVP, experienced more treatment failure than patients receiving other regimens.

**Keywords:** HIV/AIDS, Pediatric, Virologic Failure, Antiretroviral Therapy, Iran

## 1. Background

The successful prevention and treatment of pediatric HIV infection in developed countries have not been replicated in the developing world where children continue to be infected with HIV and die of AIDS. Children are understated among the recipients of antiretroviral therapy (ART) in almost every country in the world where treatment programs are putting in place. It took almost 10 years after the initiation of pediatric ART to achieve the opportunity for treating a large number of HIV-positive children in developing nations (1).

There have been a few studies of pediatric HIV infection in Iran and even most specialists have little experience with this disease (2, 3). The HIV transmission pattern mainly occurs through injecting drug use (IDU). However,

we have been rapidly moving toward a sexual transmission pattern in recent years, which has resulted in the increased perinatal HIV infection (4, 5).

In Iran, there were 480 HIV-infected under-five children in 2017 and the number of HIV-infected patients among children aged 11 to 15 years was 134 (6).

The complete suppression of viral replication is the most important goal of ART in patients with HIV infection (7, 8). Before 2008, 40 to 70% of ART programs encountered failure (9). Resistance to anti-HIV drugs is on the rise with the intensification of ART coverage (10-12). The existing data indicate that around 10% - 17% of patients receiving ART in developed countries have viral strains that are resistant to at least one of the ART drugs (13-16). There has also been a remarkable increase in transmitted drug resistance in middle-income countries (17). This growing resis-

tance to medications mediated by HIV genome mutations is the main cause of virologic failure (18, 19).

The most prescribed first-line regimen in Iran is Efavirenz (EFV), Tenofovir disoproxil (TDF), and Emtricitabine (FTC) for adult patients (20). The antiretroviral drugs in pediatric patients who have not received medication before is a combination of two reverse nucleoside transcriptase inhibitors and a protease inhibitor as a primary treatment. Zidovudine (AZT), Lamivudine (3TC), and Nevirapine (NVP) are allowed to be prescribed to children at any age (21, 22). The ART regimen published by the Iranian Ministry of Health in 2013 recommended AZT + 3TC + NVP for children less than 3-years-old as the first choice and AZT + 3TC + EFV for children aged 3 - 10 or adolescents of less than 35 kg. For adolescents between 10 and 19 or more than 35 kg, the first-line treatment was TDF+3TC or FTC + EFV (23). Based on the published report in 2016, AZT + 3TC + LPV/r is the first-line treatment for children less than 3-years-old and AZT + 3TC + EFV for children aged 3 - 10 or adolescents of less than 35 kg. For adolescents between 10 and 19 or more than 35 kg, the first prescribed regimen is TDF+3TC/ FTC + EFV, TDF + 3TC, or FTC + DTG (23).

Monitoring the recipients of ART drugs is of great importance in successful treatment and identification of barriers to adherence to treatment and can determine the time of drug change in treatment failure cases (24).

## 2. Objectives

The purpose of this study was to evaluate the virologic failure rate of treatment for various types of ART regimens in pediatric patients with HIV.

## 3. Methods

### 3.1. Participants

We examined 75 pediatric patients living with HIV at Voluntary Counseling and Testing (VCT) center of Imam Khomeini Hospital in Tehran from 2004 to 2017.

### 3.2. Instruments

A questionnaire was assigned to gather data on patients' demographic characteristics, viral load markers, TCD4+ count, ART regimen, and probable treatment failure. Also, a drug resistance test was performed to investigate the resistance against each drug.

In this study, virologic failure in pediatric patients, according to the latest edition of the Aids Info Instructions in 2017 (<https://aidsinfo.nih.gov/guidelines>), was determined by the presence of a viral load of 200 or more copies per mL after six months of ART regimen. The ART started based on

the guidelines for the use of ART in the HIV-positive pediatric patients published by the Iranian Ministry of Health in 2016 (23). The number of patients registered before 2016 and received other first drugs is shown in Figure 1 (25). The first-line regimen was AZT + 3TC + LPV/r for children less than 3-years-old and AZT + 3TC + EFV for children aged 3 - 10 or adolescents of less than 35 kg. For adolescents aged 10 to 19 or more than 35 kg, the first prescribed regimen was TDF+3TC/ FTC + EFV, TDF + 3TC, or FTC + DTG.

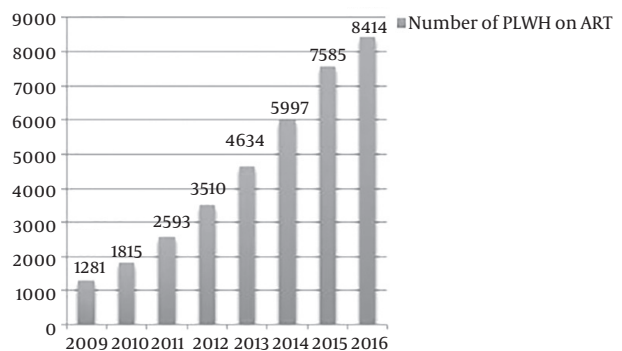


Figure 1. The number of people living with HIV on ART from 2009 to 2016, Iran (25)

Physicians and health care providers usually do not live with the patient or his/her family to see if the patient is taking medications timely and regularly; therefore, there is no choice except for trusting and referring to the patient's report. We also inquired about the patient's admission to treatment in each of the periodic and regular visits (for which the patient referred to the AIDS clinic), and the data were recorded in the patient's file.

### 3.3. Statistical Analysis

The data were entered into SPSS software (version 22) and analyzed by paired *t*-test and Pearson's chi-square test.

## 4. Results

### 4.1. Study Population

We examined 75 patients (43 boys and 32 girls) in this study. Of them, 58 (77.3%) were more than five-years-old (Table 1), 71 (92%) had a completed vaccination program, and 71 (94.7%) had an HIV-positive member in their family. Table 2 shows the anthropometric characteristics. Mother-to-child transmission was the most common route (94.7%). Seven (9.3%) patients had another disease while 68 (90.6%) were only infected with HIV.

**Table 1.** Demographic Characteristics of Children Living with HIV, Tehran, Iran, 2004 - 2017

Demographic Characteristics	Number (%) <sup>a</sup>
<b>Gender</b>	
Male	43 (57.3)
Female	32 (42.7)
<b>Age group, y</b>	
0 - 2	5 (6.7)
2 - 5	12 (16)
> 5	58 (77.3)
<b>HIV infection duration, y</b>	
0 - 5	37 (49.3)
5 - 10	33 (44)
> 10	5 (6.7)
<b>Adherence to treatment</b>	
Yes	65 (90.3)
No	7 (9.7)
<b>Reasons for missed case or lack of adherence</b>	
Lack of referral	2 (28.6)
Unwillingness to take drug	1 (14.3)
Irregular visits	2 (28.5)
Lack of access to the patient	1 (14.3)
Irregular drug intake	1 (14.3)

<sup>a</sup>Subgroups do not always add up to total due to missing data.

#### 4.2. ART Regimens

The most common primary ART regimen was AZT/3TC/NVP (59.2%), followed by AZT/3TC/EFV (29.6%). Patients receiving the AZT/3TC/NVP regimen experienced virologic failure (68.2%) more than other patients. The most common secondary ART regimen was TDF/FTC/LPV/r (60%) (Table 3).

#### 4.3. Virologic Failure

In total, 22 (29.2%) children experienced treatment failure. The resistance to Abacavir (ABC), 3TC, and FTC group was higher (17.3%) (Table 4). No patients under 2-years-old experienced virologic failure, while 3 (13.6%) patients aged 2 - 5 and 19 (86.4%) patients aged more than 5 presented virologic failure. The patients merely infected with HIV (76.2%) faced virologic failure three times the patients with concomitant diseases (23.8%) (Table 5). The duration of ART in patients with virologic failure was 6 months to 2 years for 11 (52.4%) patients and 2 - 5 years for 8 (38.1%) patients while only two (9.5%) patients encountered virologic failure after more than five years of ART. The patients who

received the AZT/3TC/NVP regimen faced virologic failure more than the others (68.2%).

The TCD4+ cell count was significantly lower at the time of virologic failure ( $629 \pm 536$  cells/ $\mu$ L) than at the beginning of ART ( $807 \pm 766$  cells/ $\mu$ L). The viral load was significantly lower at the time of virologic failure ( $77899 \pm 127888$  copies/mL) than at the beginning of ART ( $3042510 \pm 5576600$  copies/mL).

The mean interval between ART beginning and virologic failure was  $30.3 \pm 201$  months. The viral load six months after secondary ART was measured and it was under 47 copies per mL in 20 (91%) patients while only had two (9%) patients a viral load of more than 47 copies per mL.

There was no significant association between virologic failure and patient's gender ( $P = 0.50$ ), regular drug administration ( $P = 0.57$ ), and associated diseases ( $P = 0.08$ ). There was a statistically significant difference between primary TCD4+ count and TCD4+ measured after virologic failure ( $P = 0.01$ ).

There was no relationship between virologic failure and administration of EFV ( $P = 0.22$ ), Stavudine ( $P = 0.11$ ), ABC ( $P = 0.59$ ), LPV/r ( $P = 0.59$ ), TDF ( $P > 0.9$ ), AZT ( $P > 0.9$ ), and 3TC ( $P = 0.49$ ). The virologic failure was significantly higher in children who used NVP than in those who used other regimens ( $P = 0.02$ ).

## 5. Discussion

In the present study, the total virologic failure rate was 29% among children receiving ART. In addition, the present study showed that patients receiving ART regimens based on reverse transcriptase non-nucleoside inhibitors, especially NVP, experienced more treatment failure than patients receiving other regimens. Therefore, it seems reasonable to propose protease inhibitor drugs as primary ART regimens in children living with HIV instead of NVP-based regimens.

As ART is expanding in developing countries, virologic failure is becoming more and more important in children living with HIV (26). In the present study, 29% of children receiving ART experienced virologic failure, while in a similar study on 1 - 16-year-old children and adolescents, the rate of failure was 6.3% (27). In another study on children in South Africa, 19.4% of patients experienced virologic failure (26) and in another study, 20% of children under the age of 18 faced virologic failure after receiving ART (19).

In the present study, there was no significant association between virologic failure and the patient's gender ( $P = 0.50$ ). In a study of second-line antiretroviral therapy following virologic failure in HIV-infected patients in rural areas of South Africa, which was conducted on 210 patients (including 39 children) who initiated PI-based second-line

**Table 2.** The Anthropometric Indices of Children Living with HIV According to Age Group, Tehran, Iran, 2004 - 2017

Age Group Characteristics	Mean (SD)	Median	Min	Max
<b>0 - 2 years</b>				
Body weight (kg)	8.3 (2.8)	7.6	5.7	12
Height (m)	0.7 (0.1)	0.7	0.6	0.8
Body mass index (BMI)	14.9 (0.3)	14.8	14.5	15.5
<b>2 - 5 years</b>				
Body weight (kg)	16.9 (2.3)	17.0	13.5	21.5
Height (m)	1.0 (0.09)	1.1	0.8	1.1
Body mass index (BMI)	14.6 (2.3)	13.9	12.2	20.3
<b>&gt; 5 years</b>				
Body weight (kg)	29.8 (13.1)	26.0	11.9	75
Height (m)	1.3 (0.1)	1.2	1.0	1.6
Body mass index (BMI)	16.1 (3.4)	15.2	8.4	27.5

therapy, there was no association between treatment failure and gender of patients (28). Also, in another study investigating the risk of triple-class virologic failure in children with HIV, no significant difference was found in the risk of failure by sex, year of ART beginning, type of initial ART regimen, previous ART exposure for the prevention of mother-to-child transmission, CD4 percentage, or viral load at ART initiation (29).

In our study, there was no significant association between virologic failure and regular drug administration ( $P = 0.57$ ). Regular drug intake directly affects adherence to therapy in patients. In a study conducted by Bangsberg et al. (30), the investigation of 148 individuals that were highly adherent to ART revealed that high levels of adherence did not prevent the population levels of drug resistance. In contrast, in another study of treatment failure and ARV drug resistance among HIV-1-infected children, adherence to treatment was low in 50% of children experiencing treatment failure; therefore, adherence to therapy was likely to be an important contributory factor in treatment failure (31).

Clinical and immunological monitoring of children in resource-limited settings may be even more challenging than the monitoring of adults because of the high baseline risk of infections, the normal age-linked drop in TCD4+ lymphocyte counts, and frequent lack of availability of TCD4+ (27). Therefore, due to poor access to viral load monitoring in these settings, there are limited data on virologic failure in children living with HIV (26).

In a study conducted for the prediction of pediatric virologic failure in a Referral Center in Tanzania, 206 children with HIV infection aged 1-16 years who received more than six months of ART experienced treatment failure. It was shown that 65 (6.3%) patients experienced virologic

failure that was associated with lower age, TCD4+ of less than 25%, and loss of adherence. Patients receiving NVP experienced virologic failure more than those with EFV regimens (27).

In another study of the failure of pediatric ART, 19.4% of 5485 South African children who received ART experienced treatment failure. In line with our study, the ART regimen with NVP or Ritonavir showed more virologic failure than other regimens (26).

In a study of the prediction of virologic failure in children under the age of 18 years who received ART based on NNRTIs, 20% of 202 children experienced virologic failure and in 16% of children, virologic failure occurred in the first year of treatment. In agreement with our results, children who received NVP experienced treatment failure 3.7 times the children receiving EFV (19).

In a study of virologic failure and drug resistance in children and adolescents receiving long-term ART (48 months) in an African country, Togo, 283 people living with perinatal HIV comprising 167 (59%) adolescents and 116 (41%) children were investigated. The results showed that 228 (80.6%) of them received an ART regimen containing AZT/3TC and NVP or EFV. Only received 28 (9.9%) of them a protease-inhibitor-based regimen. Moreover, 146 (51.6%) patients experienced virologic failure. In 85.6% of them, genotypic resistance tests were performed, showing that 88% were resistant to both NRTI and NNRTI drugs. Only was a single patient resistant to NRTI and four of them were resistant to NNRTI. Three people were resistant to all three drugs (32).

In another study to assess the virologic response to first-line ART based on EFV or NVP in 836 children aged 3 years or more in Africa (Uganda and Zimbabwe), 445 (53%) children received EFV and 391 (47%) received NVP. The pre-

**Table 3.** Primary and Secondary Antiretroviral Therapy (ART) in Children Living with HIV Based on Age Group, Tehran, Iran, 2004 - 2017

Age Group Primary ART Regimen	No. (%)
<b>0 - 2 years</b>	
AZI/3TC/NVP	5 (100)
<b>2 - 5 years</b>	
AZI/3TC/EFV	2 (16.7)
AZI/3TC/NVP	10 (83.3)
<b>&gt; 5 years</b>	
ABC/3TC/EFV	1 (1.7)
ABC/3TC/Kaletra	1 (1.7)
AZI/3TC/EFV	19 (32.8)
AZI/3TC/Kaletra	1 (1.7)
AZI/3TC/NVP	27 (46.6)
d4T/3TC/NVP	1 (1.7)
D4T/3TC/NVP	1 (1.7)
TDF/FTC(Truvada)/EFV	2 (3.4)
TDF/FTC/EFV(Vonavir)	1 (1.7)
<b>Secondary ART Regimen</b>	
<b>0 - 2 years</b>	
	0 (0)
<b>2 - 5 years</b>	
AZI/3TC/Kaletra	1 (8.3)
AZI/3TC/NVP	1 (8.3)
<b>&gt; 5 years</b>	
ABC/3TC/Kaletra	1 (1.7)
AZI/3TC/Kaletra	1 (1.7)
AZI/3TC/NVP	1 (1.7)
TDF/FTC/Kaletra	12 (20.7)
TDF/FTC/NVP	1 (1.7)
TDF/FTC/ATV/r/Raltegravir	1 (1.7)

mature viral inhibition was more frequent in the EFV recipients during the 36 - 48 weeks of treatment (33).

In a study conducted in Kampala, Uganda, which compared the therapeutic effect of two regimens based on NVP or LPV/r, 329 infants or children receiving NVP-based ART regimen experienced a clear risk of virologic failure and death more than LPV/r recipients (9.1 times) (34). The present study revealed that the rate of virologic failure was high (29%) among children who received ART; therefore, it is very important to choose the most proper ART regimen. NVP-based regimens face the virologic failure more than the other ones. Hence, it seems reasonable to propose PI better than reverse transcriptase non-nucleoside inhibitors as the primary ART regimen in children.

In another study by Mullen et al., the effect of adher-

ence to therapy was investigated on HIV drug resistance among children living with HIV. They assessed 26 pediatric patients for virologic failure. HIV RNA sequence data were obtained for 21 out of 26 children. Mutations leading to resistance were detected in the protease gene of 7 (33%) and reverse transcriptase gene of 19 (90%) children. Genotypic resistance was widespread in children treated with 3TC (91%), NVP (75%), and AZT (64%). Children who were receiving other nucleoside reverse transcriptase inhibitors and protease inhibitors encountered fewer mutations than the others. In 50% of children, drug adherence was above 90% (31).

In a study conducted in Addis Ababa in 2008 to investigate the adherence of pediatric patients living with HIV, 339 (86.9%) out of 390 children were adherent to ART for the last seven days based on caregivers' reports. Parents' payment for treatment [OR = 0.39 (95%CI: 0.16, 0.92)] and the lack of nutritional support from the clinic [OR = 0.34 (95%CI: 0.14, 0.79)] had reductive effects on adherence. Receiving Co-Trimoxazole syrup besides ARV [OR = 3.65 (95%CI: 1.24, 10.74)] and ignorance of serostatus [OR = 2.53 (95%CI: 1.24, 5.19)] had positive effects on adherence (35). In our study, 65 (90.7%) patients were adherent to therapy and the reasons for the lack of adherence were lack of referral for 2 (28.6%) patients, unwillingness to take drug in one (14.3) case, irregular visits for 2 (28.5) children, and irregular drug intake for one (14.3%) patient; however, we did not have access to one of our patients (14.3%) to follow treatment adherence.

According to a study by Bangsberg et al. (36), 11 patients merely infected with HIV (76.2%) faced virologic failure three times the patients with concomitant diseases (23.8%). In our study, the patients only infected with HIV (76.2%) faced virologic failure three times the patients with concomitant diseases (23.8%). In another study by Lowenthal et al. (37) in Botswana in 2002 - 2011, the comparison of initiated EFZ-based and NVP-based ART among 421 and 383 HIV-infected children respectively, revealed that the prevalence of virologic failure was significantly lower among children receiving EFZ-based ART than among those receiving NVP-based regimen. Similarly, our finding demonstrated that ART regimens based on reverse transcriptase non-nucleoside inhibitors, especially NVP, were most associated with treatment failure.

Our study has several limitations, such as the low number of children meeting guidelines for virologic failure. They may have been influenced by death, loss to follow-up of clinic attendees, and use of second-line therapy. The missing data limited the range and number of children that could be included in the study.

Although we investigated a multitude of patients' files of more than 10 years, due to the inclusion criteria, the sample size increment was not feasible. It is worth men-



**Table 4.** HIV Resistance Levels Based on Medication Class in Children Living with HIV, Tehran, Iran, 2004 - 2017<sup>a</sup>

Medication Class	High-Level Resistance	Intermediate-Level Resistance	Low-Level Resistance	Susceptible	Total Resistance
AZT	2 (2.6)	5 (6.7)	1 (1.3)	6 (8)	8 (10.6)
TDF	0 (0)	1 (1.3)	4 (5.3)	9 (12)	5 (6.6)
ABC	1 (1.3)	5 (6.7)	7 (9.3)	1 (1.3)	13 (17.3)
3TC	13 (17.3)	0 (0)	0 (0)	1 (1.3)	13 (17.3)
FTC	13 (17.3)	0 (0)	0 (0)	1 (1.3)	13 (17.3)
EFV	6 (8)	5 (6.7)	0 (0)	3 (4)	11 (14.7)
NVP	9 (12)	3 (4)	0 (0)	2 (2.7)	12 (16)
LPV/r	0 (0)	0 (0)	0 (0)	14 (18.6)	0 (0)
ATV/r	0 (0)	0 (0)	1 (1.3)	13 (17.3)	1 (1.3)
DRV/r	0 (0)	0 (0)	0 (0)	14 (18.6)	0 (0)

<sup>a</sup>Values are expressed as No. (%).

**Table 5.** Concomitant Diseases in Pediatric Patients Living with HIV, Tehran, Iran, 2004 - 2017

Concomitant Diseases	No. (%)
Autism-ADHD	1 (1.3)
Glioblastoma	1 (1.3)
Hemophilia	1 (1.3)
Autoimmune hepatitis	1 (1.3)
Tuberculosis	1 (1.3)
Mental retardation and seizure	1 (1.3)
Other mental disorders	1 (1.3)

tioning that the sample size of our study was not enough for the descriptive and analytic purposes of the study. Therefore, further studies in this regard would be valuable and useful.

Based on our findings, ART regimens based on reverse transcriptase non-nucleoside inhibitors, especially NVP, were most associated with treatment failure.

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### Footnotes

**Authors' Contribution:** Study concept and design: Mehrnaz Rasoulinejad and SeyedAhmad SeyedAlinaghi; analysis and interpretation of data: Mohammad Sarraf; drafting of the manuscript: Zeinab Najafi; statistical analysis: Banafsheh Moradmam Badi; critical revision of the manuscript for important intellectual content: Mohammad Reza Salehi and Fabrício Azevedo Voltarelli.

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