



Highly Active Antiretroviral Treatment of HIV-1 Patients, Molecular Evaluation of AZT+3TC+EFV Regim

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Abstract: *Background:* Antiretroviral therapy (ART) is an effective way to reduce the risk of HIV transmission. Several studies have demonstrated a reduction of sexual transmission of HIV in people on ART treatment and the main objective of antiretroviral treatment is to avoid the increase of, morbidity and mortality associated to AIDS. Furthermore, the 2030 UNAIDS target requires the achievement of the 3 “95s”, with the 2nd and 3rd linked to the establishment and success of treatment. This is why the evaluation of therapeutic regimens is necessary to achieve these targets. The aim of our study was therefore to assess the effectiveness of the AZT+3TC+EFV regimen in the antiretroviral therapy of HIV-1 infection. *Material and methods:* This is a retrospective study on the treatment of HIV-1 positive patients. For this study, 372 HIV positive patients were included and followed at the molecular biology laboratory of the HIV/AIDS program at Ouakam Military Hospital in Dakar, Senegal from 2014 to 2021. All plasma samples came from HIV-1 positive patients. Plasma viral load were performed on Abbott Real-Time HIV-1[®] (m2000sp/rt) and COBAS[®] AmpliPrep TaqMan[®] (Roche) v.2.0. p-value<0.05 was considered statistically significant. *Results:* 372 patients met the selection criteria, 62.1% were women and the sex ratio M/F was 0.61. The largest age group [40-60] represented 40.1% and those aged 60 was the smallest group with 5.4%. At 6 months, 12 months and 24 months of treatment, viral suppression was 41.1%, 65.9% and 80.6%, respectively. At 24 months of treatment, virological suppression was linked to age. Virological success at 24 months was 95%, 78.5%, 86.3%, 72.2% respectively for patients aged 65 or over, [45-65] years, [25-45] years and [0-25] years, (P= 0.02). At 12 months, the undetectable viral load was significantly higher in women with 70.1% than in men with 58.2% (P=0.02). The rate of therapeutic failure after 24 months of treatment was higher in men (22.7%) than in women (17.3%) (P=0.2). Therapeutic failure was significantly higher among the youngest aged [0-25] years with 27.8%. It was 13.7%, 21.5% and 5% for the groups [25-45] years, [45-65] years and 65 years or more respectively (P=0.02). *Conclusion:* AZT+3TC+EFV treatment gives HIV-1 patients a high virological suppression rate at 24 months. Sex was associated with viral suppression at 12 months being significantly higher in women. It was significantly greater in the elderly at 24 months of treatment. Therapeutic failure was linked to age after 24 months of treatment and higher in young people. This treatment remains effective and inexpensive, hence its interest for countries with limited resources.

Keywords: HIV-1, Antiretroviral-Therapy, Sub-Sahara, Viral Load, AZT+3TC+EFV

1. Introduction

Forty-two years after its discovery, HIV/AIDS remains a public health problem despite the efforts of the international community.

According to the latest UNAIDS report in 2023, the number of people living with HIV worldwide was estimated at 39 million. In sub-Saharan Africa, approximately 25.6 million people are living with HIV, or 66.6% of the total HIV-infected population globally and declines in the number of new HIV infections are the steepest [1]. The AIDS epidemic in Senegal is concentrated with a low prevalence in the general population of 0.3% and high in certain localities and among the most vulnerable populations [2].

From 2000 to 2022, free access to HIV treatment has prevented nearly 20.8 million AIDS-related deaths with a 69% reduction in deaths since the peak in 2004 [1]. Since 2010, new HIV infections, estimated at 1.3 million in 2022, have been the lowest. Declines in new HIV infections are greatest in sub-Saharan Africa [1]. This gradual reduction in prevalence and new infections is made possible by the free access and effectiveness of antiretroviral therapy (ART) in several regions. Indeed, efforts in terms of treatment and prevention to achieve the “95-95-95” objective by 2025 have made it possible to facilitate access to antiretroviral treatment. The number of people put on treatment has grown massively in sub-Saharan Africa, Asia and the Pacific, which together are home to around 82% of all people living with HIV [1].

Thanks to antiretroviral therapy (Highly Active Antiretroviral Treatment, HAART), HIV/AIDS infection can now be regarded as a chronic disease. While waiting for an effective vaccine, there are now ART which have improved the health of infected patients, considerably reduced their mortality rate and increased their life expectancy [3].

Antiretroviral therapy aims to make the patient's viral load undetectable, restore the HIV patient's immunity and reduce the risk of viral drug resistance and clinical events associated with HIV [4]. Its early initiation leads to a rapid drop in viral load, which reduces the risk of HIV transmission [5].

The viral load has been retained as the main prognostic marker for the evolution and therapeutic monitoring in the management of HIV-positive patients, compared to the measurement of CD4 which has shown its limits [6]. Measuring plasma viral load makes it possible to assess the progression of infection, the effectiveness of antiretroviral treatment and the appearance of resistant HIV genotypes. Imprecise measurement of viral load can lead to inappropriate patient care.

HIV resistance to ARVs and therapeutic failures are consequences of the genetic variability and instability of the virus. National HIV/AIDS programs in resource-limited settings recommended nucleoside reverse transcriptase inhibitors (NRTIs: AZT, TDF, 3TC and d4T) and non-

nucleoside reverse transcriptase inhibitors (NNRTIs: NVP and EFV) in initial antiretroviral therapy [7-9]. Although current WHO guidance calls for putting patients on TDF+3TC+DTG, other combinations deserve to be considered as effective and more affordable alternatives [10].

ART combination therapies are limited by virological failure in HIV-1 patients due to the emergence of resistance to antiretroviral drugs (ARVs) [11]. Although the genetic barrier to resistance derives the threshold of mutations required for a clinically significant loss of drug sensitivity [12], the drug's structure can also influence the emergence of resistance [13], the inhibitory quotient [14] and pharmacokinetic tolerance [15]. Sustained suppression of HIV replication is the maintenance of a potent and tolerable regimen that the patient can adhere to. Compliance is necessary to prevent the emergence and replication of drug-resistant strains of the virus [16]. The close link between the genomic variability of HIV and its resistance to ARVs requires continuous evaluation of ART regimens to provide recommendations to national AIDS programs and clinicians in order to minimize therapeutic failures. For effective triple therapy allowing successful antiretroviral treatment, avoiding treatment failures and HIV-related deaths, it is important to evaluate the available antiretroviral regimens. This evaluation of the effectiveness of ART regimens is done by measuring viral load using molecular techniques.

Thus, it is important to update ART combinations, especially in regions with limited resources, to achieve the UNAIDS objectives in 2030 [17].

The general aim of this study is to assess the effectiveness of the AZT+3TC+EFV regimen in the management of HIV-1 patients in Senegal.

2. Materials and Methods

2.1. Populations and Study Type

This is a retrospective and analytical study focusing on patients living with HIV on ART, AZT+3TC+EFV.

The patients were cared for by clinicians in 21 health centers and hospitals in Dakar and came to have their biological monitoring, in particular their viral loads, between 2014 and 2022 at the molecular biology laboratory of the AIDS control program of the Armed Forces at the Military Hospital of Ouakam Dakar, Senegal.

The patients came from the following health structures: Centre hospitalier Dominique (CHD), centre hospitalier Roi Baudoin (CHRB), Centre hospitalier Youssou Mbargane Diop (CHYMD), au Centre de promotion de la sante Cardinal Hyacinthe Thiandoum (CPSCHT), centre de sante Keur Massar (CSKM), Hôpital militaire de Ouakam (HMO), centre de sante Rufisque polyclinique (CSRP), centre de sante Serigne Abdou Aziz Sy (CSAASY), centre de sante de Ouakam (CSO), centre de sante de Mbaou (CSM), centre de

sante Medina (PMI), établissement public de sante de Tivaouane (EPST), institut d'hygiène sociale polyclinique (IHS), hôpital général Idrissa Pouye (HOGIP), centre de santé Philipe Madjilene Senghor (CSPMS), hôpital principal de Dakar (HPD), hôpital des enfants Albert Royer (HEAR), centre de sante de Diamniadio (CSD), centre de sante Gaspard Kamara (CSGC), centre de sante de HIM (CSHLM) et centre de sante Nabil Choucair (CSNC).

The inclusion criteria were: 1) having a positive HIV-1 serology, 2) Treated with AZT+3TC+EFV antiretroviral

treatment for at least two years, 3) having completed their viral load measurement at the molecular biology laboratory of the armed forces AIDS program at the military hospital of Ouakam, Dakar, Senegal.

Patients whose viral load results and records were unavailable, incomplete or unusable, who were not on AZT+3TC+EFV treatment were not included in the study.

Identifying information from patients is strictly confidential and remains anonymous.

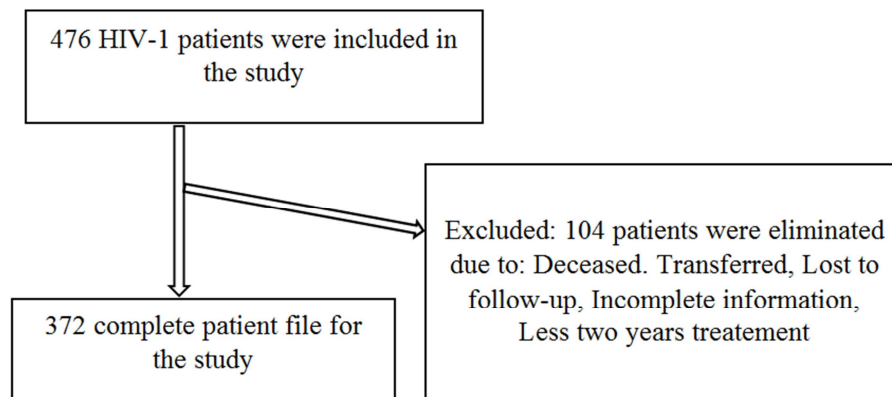


Figure 1. Selection of patients.

2.2. Sample Collection

Whole blood was collected in 5 ml BD K2E (EDTA) tubes (ref 368861) (Becton Dickinson, New Jersey, USA). After centrifugation at 6000 rpm for 20 minutes at 4°C, two aliquots of plasma were prepared for each patient, one for testing on Roche or Abbott and the other in reserve, immediately frozen at -80°C until testing. For each sample taken, an analysis report was submitted to each patient with the patient's identifier, age, sex, patient's HIV status, duration of ART and virological data.

2.3. HIV Viral Load Measurement Techniques

Each plasma sample was processed on either Abbott (m2000sp/m2000rt) or Roche (COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 v2.0) for HIV-1 RNA quantification.

2.3.1. Abbott Real Time HIV-1® (m2000sp/rt)

The Abbott Test (m2000sp/m2000sp) is a real-time reverse transcriptase PCR Test for the quantitative determination of HIV-1 RNA in HIV-1 positive plasma. Extraction is done using 0.6 mL⁻¹ of plasma and reverse transcriptase is followed by real-time amplification and detection of a fragment of the integrase region of the pol gene (pol/IN) of the genome of the HIV-1 with the m2000rt fluorescent probe test kit [18]. The Abbott platform detects the majority of HIV-1 M variants, A-H subtypes and CRFs such as CRF01-AE and CRF02-AG and also N and O divergent groups, in a range of linearity ranging from 40 to 107 copies mL⁻¹. Plasma samples are tested in the m2000sp/m2000rt instrument

according to the manufacturer's instructions. The Abbott instrument is a closed automation system combining extraction, reverse transcriptase, PCR and real-time detection, reducing the risk of contamination. Each series of tests includes three controls (one negative, one strong positive and one weak positive). The analyzer automatically validates the manipulation and determines the presence or absence of HIV-1 nucleic acids according to a threshold cycle value (Ct value) which corresponds to the PCR cycle from which the signal detected indicates the presence of the amplicons. The analyzer automatically validates the manipulation and determines the presence or absence of HIV-1 nucleic acids according to a threshold cycle value (Ct value) which corresponds to the PCR cycle from which the signal detected indicates the presence of the amplicons.

2.3.2. Roche COBAS® AmpliPrep/TaqMan

The COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 v2.0 (Roche Molecular Systems, Inc., New Jersey, USA) is a real-time reverse transcriptase PCR test. The extraction is done using the COBAS® AmpliPrep, using 1 mL of plasma according to the manufacturer's protocol. Next, reverse transcriptase is initiated automatically, followed by in vitro amplification and simultaneous detection of the highly conserved region of the Gag gene and the LTR (long terminal repeat) region of the HIV-1 genome using a TaqMan fluorescent probe (COBAS® TaqMan® 96). This test quantifies RNA over a range of 20-10⁷ (1.3-7 log10) copies mL⁻¹ [19]. Plasma samples are tested in the Roche CAP/CTM96 instrument according to the manufacturer's instructions. The CAP/CTM instrument is a closed automation. The Abbott instrument is a closed automation

system combining extraction, reverse transcriptase, PCR and real-time detection, reducing the risk of contamination. Each series of tests includes three controls (one negative, one strong positive and one weak positive). The analyzer automatically validates the manipulation and determines the presence or absence of HIV-1 nucleic acids according to a threshold cycle value (Ct value) which corresponds to the PCR cycle from which the signal detected indicates the presence of the amplicons. The quantification of VL using the Roche system was subject to an external quality assessment in 2018 by the College of American Pathologists (CAP) which deemed the results reliable.

2.4. Statistical Analysis

Data acquisition and analysis were performed using Excel 2013 and SPSS version 21 software. Statistical cross-referencing was used for data comparison using the Chi-square Test for proportions and Fisher's exact Test for dichotomous variables with a theoretical significance level of 5% ($p < 0.05$), considered statistically significant for all comparisons between groups.

3. Results

3.1. Sociodemographic Characteristics of Patients

Of 476 treatment-naïve HIV-1 patients, 372 met the inclusion criteria and 104 were excluded for reasons of death, transfer, loss to follow-up, incomplete information, etc. (figure 1). The median age was 37 years with extremes of 04 and 75 years. Patients aged 40 to 60 were the largest group representing 40.1% followed by those aged 20-40 with 33.3%. Women represented 62.1% and men 37.9%, i.e. a M/F sex ratio of 0.61.

3.2. Effectiveness of the AZT+3TC+EFV Regimen

Successful treatment corresponds to an undetectable load ($VL < 50$ copies mL^{-1}) after a period of 1 to 24 months.

Therapeutic failure corresponds to a detectable viral load after 24 months of treatment. In the overall population, 41.1% of patients had virological suppression after 6 months of treatment. This virological success was 65.9% and 80.6% after 12 months and 24 months of treatment respectively. The virological failure rate after 24 months of treatment was 19.4%. (Table 1).

Table 1. Effectiveness of AZT+ 3TC+ EFV treatment according to sex.

Sex Tx Efficacy	Men (141) n (%)	Women (231) n (%)	Total population (372) n (%)	P-value
Undetectable at 6 months	52 (36.9)	101 (43.7)	153 (41.1)	0.19
Undetectable at 12 months	83 (58.9)	162 (70.1)	245 (65.9)	0.02
Undetectable at 24 months	109 (77.3)	191 (82.7)	300 (80.6)	0.20
Failure at 24 months	32 (22.7)	40 (17.3)	72 (19.4)	0.20

3.3. Efficacy of AZT+ 3TC+ EFV According to Sex

At 6 months of treatment the viral load was undetectable in 36.9% and 43.7% in women ($P=0.19$). At 12 months undetectable viral load was significantly higher in women with 70.1% than in men with 58.2% ($P=0.02$). At 24 months of treatment, therapeutic success was high in both sexes, 77.3% in men versus 82.7% in women ($P=0.2$).

The rate of therapeutic failure after 24 months of treatment seemed higher in men (22.7%) than in women (17.3%) but was not significant ($P=0.2$; Table 1). The success of the treatment was only linked to the sex of the patients after one year of treatment.

3.4. Efficacy of AZT+ 3TC+ EFV According to Patient Age

At 6 months of treatment, the age groups [0-25], [25-45], [45-65] and 65 years or older had respective viral loads of 44.3%, 42.7%, 38.9% and 35%. ($P=0.78$; Table 2).

At 12 months of treatment, the rate of undetectable viral load increased with age. Rates of 59.5%, 66.1%, 67.8%, 75% were obtained for the age groups [0-25], [25-45], [45-65] and 65 years or older respectively ($P=0.49$; Table 2). At 24 months of treatment, treatment success was linked to age. Virological success was 95%, 78.5%, 86.3%, 72.2% respectively for patients aged 65 or over, [45-65] years, [25-45] years and [0-25] years, ($P=0.02$; Table 2).

Table 2. Monitoring of AZT+ 3TC+ EFV treatment according to age group.

Tx Efficacy Age group (N)	Undetectable at 6 months n (%)	Undetectable at 12 months n (%)	Undetectable at 24 months n (%)	Failure at 24 months n (%)
[0-20 years [(79)	35 (44.3)	47(59.5)	57(72.2)	22(27.8 %)
[20-40 years [(124)	53 (42.7)	82 (66.1)	107(86.3)	17(13.7 %)
[40-60 years [(149)	58 (38.9)	101(67.8)	117(78.5)	32(21.5 %)
≥ 60 years (20)	7 (35)	15 (75)	19(95)	1(5 %)
Total population (372)	153 (41.1)	245 (65.9)	300 (80.6)	72 (19.4)
P-value	0.78	0.49	0.02	0.02

Therapeutic failure was significantly higher among the youngest aged [0-25] years with 27.8%. It was 13.7%, 21.5%

and 5% for the groups [25-45] years, [45-65] years and 65 years or more respectively ($P=0.02$; Table 2).

4. Discussion

Treatment effectiveness was measured by the proportion of patients with an undetectable plasmatic viral load ($VL < 50$ copies mL^{-1}) within 6 to 24 months of treatment. Virological success was defined by a plasma viral load below the detection limit of the test used ($CV < 50$ copies mL^{-1}). Virological failure refers to either a rebound in the viral load ($CV > 1000$ copies mL^{-1} after being undetectable), or a viral load > 1000 copies mL^{-1} following two successive measurements after 24 months of treatment.

To provide recommendations to HIV/AIDS programs on the best triple therapy regimens to administer to HIV-1 patients in order to limit treatment failures, evaluating the effectiveness of ARV treatment remains important in the response to HIV/AIDS.

In our cohort, women were more represented, i.e. 62.1% and men 37.9%, i.e. a F/M sex ratio of 0.61. These results agree with those of Labhardt et al., 2015 of which women represented 66.2% [20]. Early sexuality, the high frequency of STIs and the anatomy of the female genital tract are factors that make women vulnerable to HIV. The insufficiency of support infrastructures for women living with HIV/AIDS, the poverty of women, the inequitable distribution of roles between the sexes, segregation and differentiation, are responsible for the phenomenon of feminization of HIV infection according to a study from Zimbabwe [21].

The median age was 37 years. The median age of our study was lower than 47.3 years of Labhardt et al (2015) and similar to that of Paengsai et al en (2022), 36.8 years [20-22].

Patients aged [40-60] years represented the largest group with 40.1% and those aged between [20-40] years and [0-20] years represented 33.3% and 21.2% respectively, i.e. 54.5% for patients below 40 years old. These results can be compared with the study in Lesotho and South Africa where we observed that patients whose age was less than 40 years represented 47.3% [20]. Our patients aged 60 and over were in the minority with 5.4% like those in the study by Paengsai et al in (2022) where they represented 2% [22]. These results show that HIV infection predominantly affects the sexually active population.

These data can be superimposed on the HIV prevalence of women and men increasing with age in Senegal. In women, HIV prevalence is very low among those under 20 but increases with age to reach 1.2% at 45-49 years [23].

Effective treatment with an undetectable viral load has become an effective way to prevent mother-to-child transmission and sexual transmission. There are three main categories of HIV viral load measurements: Unsuppressed (> 1000 copies mL^{-1}), detected but < 1000 copies mL^{-1} and undetectable (viral load not detected by the test used) according to the latest report of WHO from July 2023.

For the effectiveness of the AZT+3TC+EFV regimen, viral load suppression (undetectable) was 41.1%, 65.9% and 80.6% respectively at 6 months, 12 months and 24 months in the general population. Our lower 6-month suppression rate

is lower than the 88.1% in a study in South Africa [20]. An undetectability rate of 71.4% after 7.5 months of treatment was found in a Ugandan study of AZT+3TC+EFV, which means that virological suppression was earlier [24].

At 12 months of treatment, our proportion of viral suppression is slightly lower than the 73% virological suppression in 12 months of Gallant et al in (2006) [25].

Pozniak et al en (2006) had 62% viral suppression (viral load < 400 copies/ml) in 24 months of treatment which was lower than our 24 month rate, 80.6% [26].

Arribas et al in (2008) had a rate of 58% in 36 months of treatment, which is much lower than our rates. [27].

The therapeutic failure rate after 24 months of treatment was 19.4% and in agreement with the 18% of a study in South Africa [19]. On the other hand, lower failure rates of 9% and 11% were found respectively by Gallant et al and Malhotra et al after 12 months of treatment [25, 28].

Viral suppression was greater in women than in men at 6 months, 12 months, and 24 months of treatment. This viral suppression was linked to sex and significantly higher in women ($P=0.02$). There is no data explaining this gender difference. The better results in women suggest a hypothesis that women may have better treatment compliance.

Therapeutic failure after 24 months of treatment had no link with sex ($P=0.2$). Several factors can contribute to failure: poor compliance, drug stock shortages and contamination by resistant HIV genotypes. Patient genetic differences in ARV metabolism may also play an important role.

Age was linked to virological suppression, and this was higher in the elderly than in young patients ($p=0.001$) and conversely, therapeutic failure was higher in young people.

Treatment success was age at the highest at 24 months of treatment, patients aged 65 and over had a higher undetectability rate and [0-20] years had the highest rate ($P=0.02$).

The age group [0-20] years had more treatment failure (27.8%), whereas those aged 60 and over had more success (95%) at 24 months of treatment ($P=0.02$). Both failure and success of treatment at 24 months are age-related. This could be due to the fact that young people adhere less to ARV treatment compared to the elderly, even if associated factors have been noted elsewhere. This is the case of Gallant who reported a link between insufficient virological effectiveness and the low concentration of ARVs (non-compliance with treatment, drug interaction with an associated treatment or even self-medication) [25]. This is also the case of Anude et al in (2013), who found a significant association between age less than 30 years, a hemoglobin level less than 10g/dl, low level of compliance and failure virological [29].

Lack of information on adherence, observation, treatment side effects and ARV resistance was the limitation of this study. Antiretroviral potency, immunological reconstruction, tolerability and toxicity are important factors to include in evaluating the effectiveness of antiretroviral therapy. The patient's information file did not contain this information so that their link with virological failure could not be studied.

5. Conclusion

AZT+3TC+EFV treatment gives HIV-1 patients a high virological suppression rate at 24 months. Viral suppression was associated with sex at 12 months of treatment and significantly higher in women. It was significantly greater in the elderly than in the young at 24 months of treatment. Therapeutic failure was linked to age after 24 months of treatment and higher in young people. This treatment remains effective and less expensive, hence its interest for countries with limited resources. The patient profiles most associated with treatment failure were those aged between 0-20 years and belonging to male gender.

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Conflicts of Interest

The authors declare no conflicts of interest.

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