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Molecular Evaluation of the Efficacy of the TDF+3TC+EFV Therapeutic Regimen in the Treatment of HIV-1 Patients

Babacar Faye[1, 2, 3*], Mame Diarra Bousso Lam[1], Ismaïl Barkiré[4], Micailou Magassouba[5], Hameth Sarr[1], Aissatou Ngom[6] and Alioune Dièye[7]

[1]Laboratory of Molecular Biology, Military Hospital of Ouakam (HMO), Dakar, Senegal
[2]AIDS Program of the Senegalese Armed Forces, Military Hospital of Ouakam, Dakar, Senegal
[3]Molecular biology Service, Department of Pharmacy, Faculty of Medicine, Pharmacy and Odonto-Stomatology of the Cheikh Anta Diop University of Dakar, Dakar, Senegal
[4]Service of internal medicine, Military Hospital of Ouakam, Dakar, Senegal
[5]National Alliance of Communities for Health, Dakar, Senegal
[6]Service of Pediatric, Military Hospital of Ouakam, Dakar, Senegal
[7]Service of Immulogy, Department of Pharmacy, Faculty of Medicine, Pharmacy and Odonto-Stomatology of the Cheikh Anta Diop University of Dakar, Dakar, Senegal

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***Corresponding author:** Babacar Faye
Laboratory of Molecular Biology, Military Hospital of Ouakam (HMO), Dakar, Senegal

Abstract **Original Research Article**

Background: **A**ntiretroviral therapy (ART) has played an important role in the response to HIV infection and has significantly reduced morbidity and mortality worldwide. It allows control of plasma viral load (CV) to an undetectable level CV<50 copies/ml, an indicator of successful treatment. Assessing the effectiveness of ART makes it possible to make recommendations to limit failures in the treatment of HIV. Thus, the objective of this study is to evaluate the efficacy of the TDF+3TC+EFV therapeutic regimen in the treatment of HIV-1 infection. ***Materials and methods*****:** This is a retrospective study of the treatment of HIV-1 seropositive patients, at the Molecular Biology Laboratory of HMO in Dakar, Senegal, from 2014 to 2021. The main criterion for evaluating the effectiveness of the treatment was the proportion of patients whose viral load value was undetectable (CV<50 copies/ml) according to the duration of ART. Plasma viral load tests were performed on Abbott Real Time HIV-1® (m2000sp/rt) and COBAS®AmpliPrep/COBAS®TaqMan®(Roche) version 2.0. Variables with p<0.05 were considered statistically significant for all comparisons between groups. ***Results:*** Of a cohort of 2,704 HIV+ patients, 2,078 met the inclusion criteria and 626 were excluded due to death, transfer or loss to follow-up. The median age was 38 years, women represented 71% patients. At 6 months of treatment, viral suppression was achieved in 8.9% of men and 6.5% of women (P=0.04) and it was significantly greater in young patients aged 0 to 25 years, 11.4% of patients. 79% of women and 75.2% of men had an undetectable viral load at 12 months of ART (P=0.01). Significantly the suppression was better in men in the first 6 months of treatment, they had more virological success, while women responded better to treatment for a duration of 12 months (P=0.01). At the end of the 18-month study period, 85.5% of patients had a suppressed viral load, 5.3% had a decrease in viral load levels and 7.2% of patients had virologic failure. Gender and age were significantly related to treatment success. ***Conclusion:*** Our results showed the efficacy of the TDF+3TC+EFV regimen in the treatment of HIV-1 infection. Viral suppression was related to patient gender and age. The ideal duration to obtain a good rate of undetectability in our cohort was at least 12 months of treatment.

Keywords: HIV, ART, HIV Viral Load, TDF+3TC+EFV.

INTRODUCTION

The HIV pandemic remains the most serious infectious challenge in public health and AIDS remains the leading cause of death in Africa and in the world [1, 2].

According to UNAIDS reports, the number of people living with HIV in the world was estimated at 38.4 million in 2021. In sub-Saharan Africa about 25.6 million people are living with HIV or 67.5% of the total population infected with HIV. HIV globally [3]. The AIDS epidemic in Senegal is of the concentrated type with a low prevalence in the general population and high

in certain localities and among the most key populations [4]. According to data from the national report on the response to AIDS in Senegal for the year 2021, the estimated number of PLHIV (adults and children) is estimated at 40,277 people, including nearly 21,703 women and 3,957 children under the age of 15 [5].

The introduction of highly active antiretroviral therapy (HAART) as a treatment for HIV infection has dramatically reduced the morbidity and mortality of people living with HIV worldwide. From 2000 to 2021, AIDS-related deaths have been reduced from 1.7 million people to 650,000 globally [3]. New HIV infections have decreased by 32%, from 2.2 million to 1.5 million between 2010 and 2021. This gradual decrease in prevalence and new infections is possible thanks to free access to antiretroviral (ARV) treatment in several regions and the advent of triple antiretroviral therapy (ART). Indeed, efforts in terms of treatment and prevention to reach the "90-90-90" target for 2020 and "95-95-95" by 2025 have accelerated access to antiretroviral treatment which has increased by 560,000 to 28.7 million the number of HIV+ people on treatment between 2000 and 2021 worldwide so that 95% of PLHIV have an undetectable viral load [3].

ART has been adopted worldwide including West Africa [6]. Genetic variability can make HIV resistant to ARVs and is the cause of treatment failures. This genetic variability results from the rate of nucleotide incorporation errors carried out by the reverse transcriptase, during the retro-transcription of the viral RNA into DNA and this error rate is 1 to 10 mutations per genome and per cycle. This step is the target of INRT (TDF; AZT) and INNRT (EFV) family drugs by reverse transcriptase inhibition [7-8-9]. Also, poor compliance with treatment (forgetting to take ARVs, stopping then resuming them) can lead to resistance to ARVs [3]. Given the genomic variability of HIV and therapeutic resistance, the study of the effectiveness of ART regimens is necessary to give recommendations to national AIDS programs and clinicians in order to minimize treatment failures. Thus, it is important to update ART combinations, especially in regions with limited resources, to achieve the UNAIDS objectives in 2025

The UNAIDS targets for ending the HIV/AIDS epidemic by 2025 are: that 95% of people living with HIV know their status, that 95% of people living with HIV receive antiretroviral therapy and that 95% of people receiving antiretroviral therapy achieve viral suppression [10]. Several countries, cities and communities in different contexts have already achieved the 95-95-95 targets, indicating that achieving the global three 95s by 2025 is both achievable and attainable if we resolutely address the gaps in the HIV testing and treatment cascade [10]. Today, while the overall situation in the fight against AIDS shows encouraging results in terms of screening, access to treatment and monitoring of the viral load, West Africa and Central Africa present a delay in achieving objectives [11]. For the third "95", West and Central Africa has an undetectable viral load coverage rate for people living with HIV of 59% compared to 90% globally in 2021 [11]. A "silent" epidemic has persisted, particularly among vulnerable populations, and access to testing remains the most important objective to achieve in order to also improve therapeutic management and viral load suppression. In Senegal, in 2019, 87% of diagnosed PLHIV are on treatment and 81% for viral suppression. This coverage increased from 71% in 2017 to 80% in 2019. ARV coverage increased from 54% to 70% from 2017 to 2019. As for access to viral load, it increased from 41% to 57% [12] from 2017 to 2019. Antiretroviral therapy should render the patient's viral load undetectable (< 50 copies/ml), promoting immune restoration, decreasing the risk of viral resistance to ARVs and reducing clinical events associated with HIV [13]. Early initiation of antiretroviral therapy leads to a rapid drop in viral load, which reduces the risk of HIV transmission [14].

The UNAIDS goal of ending the HIV epidemic by 2030 will be achieved primarily through the achievement of the three 95s by 2030, and in particular the third 95, which consists of achieving an undetectable level of viremia thanks to effective ART.

Several studies showing the limits of CD4 measurement in the management of HIV-positive patients have made viral load the main marker for prognosis, evolution and therapeutic monitoring [15]. The measurement of the plasma viral load makes it possible to evaluate the progression of the infection, the effectiveness of the antiretroviral treatment and the appearance of resistant genotypes of HIV. Inaccurate viral load measurement can lead to inappropriate patient management.

It is in this context that we conducted this study with the main objective of evaluating the therapeutic efficacy of Tenofovir in combination with lamivudine and efavirenz (TDF+3TC+EFV) in Senegalese HIV-1 patients.

MATERIAL AND METHODS

Study population

Seropositive plasma samples were collected at the Molecular Biology Laboratory of the AIDS Program of the Senegalese Armed Forces at the Ouakam Military Hospital in Dakar from 2014 to 2021. All plasma samples are from HIV-1 seropositive patients. Consent was not required for these patients as plasma VL was performed as part of their clinical follow-up for their ART but the data for the study were anonymised. The evaluation of the TDF+3TC+EFV combination was carried out from the initiation of treatment until the 18th month (from M0 to M18) with a six-monthly or annual follow-up. To be eligible, HIV-1 positive patients had to

have been receiving the TDF+3TC+EFV treatment regimen for at least 6 months.

Sample collection

Whole blood was collected in 5 ml BD K2E (EDTA) tubes (ref 368861) (Becton Dickinson, NJ, 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.

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.

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 of plasma, 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 [15]. 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. 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.

Roche COBAS® AmpliPrep/TaqMan

The COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 v2.0 (Roche Molecular Systems, Inc, NJ, USA) is a real-time reverse transcriptase PCR test. The extraction is done using the COBAS® AmpliPrep, using 1 ml of plasma [16]. 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 20-10,000,000 (1.3-7 log10) copies/ml [17]. 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.

Treatment efficacy endpoint

The primary endpoint of treatment efficacy was the proportions of patients with undetectable plasma viral load values (CV < 50 copies/ml) by treatment duration. Virological success was defined by a plasma viral load below the detection limit of the test used (CV<50 copies/ml), the virological evolution as being a reduction in the level of plasma CV (CV<1000 copies /ml) but not resulting in an undetectable viral load. Virological failure was defined as either viral load rebound (CV > 1000 copies/ml after previously being undetectable) or after measuring two successive viral load values >1000 copies/ml after 18 months of treatment.

Statistical analysis

Data acquisition and analysis were carried out using Excel 2013 and SPSS version 21 software. Descriptive statistics were used to describe the demographic and virological characteristics in terms of percentage or median values. Statistical crossing 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.

RESULTS

1.1 Demographic characteristics of the study population

Of 2,704 treatment naïve patients, there were 2,078 meeting the inclusion criteria and 626 were excluded due to death, transfer and loss of follow-up. The median age was 38 years with extremes of 1 year and 84 years and the majority of patients were aged 25 to 45 years (54.2%). Women represented 71% patients and men 29% with a sex ratio M/F = 0.41%.

1.2 Effectiveness of ART, TDF+3TC+EFV

At 18 months of treatment, 87.5% of patients had a suppressed viral load, 5.3% had a favorable outcome, i.e., a significant decrease in the viral load rate (CV<1000copies/ml) and 7.2% of patients had virologic failure (Table I). Viral load was undetectable in 7.3% and 78.2% of patients after 6 and 12 months of ART respectively.

1.3 Efficacy of treatment according to patient gender

At 6 months of treatment, viral suppression was achieved in 8.9% of men and 6.5% of women (P=0.04). 79% of women and 75.2% of men had an undetectable viral load at 12 months of ART (P=0.01). Significantly the suppression was better in men in the first 6 months of treatment, they had more virological success, while women responded better to treatment for a duration of 12 months (P=0.01) and 18 months (P=0.04; Table I). Virological failure (CV>1000 copies/ml) was 9.1% versus 6.2% respectively in men and women (P=0.04) after 18 months of treatment (Table I). Overall, we found that gender had a significant association with patient treatment success.

1.4 Efficacy of treatment according to patient age

After 6 months of treatment, virological suppression was significantly greater in young patients aged 0 to 25 years, 11.4% of patients. For the same duration of treatment, patients in the 25-45, 45-65 and over 65 age groups had virologic suppression rates of 7.4%, 5.5% and 5.9% respectively. The response to ARV treatment is better in young people at 6 months (P=0.02).

At 12 months of ART, viral suppression was significantly greater in older subjects than in younger ones with 69.9%, 76.5%, 83.4% and 82.4% respectively in 0–25-year-olds, 25-45 years olds, 45-65 years olds and over 65 (P=0.002; Table II). Virological failure was 7.8%, 7.3%, 7.1% respectively in patients aged [0–25 years [, [25-45 years [, [45-65 years [(P=0.08; table II). Our results had shown a link between age and viral suppression at 6 months and 12 months of treatment.

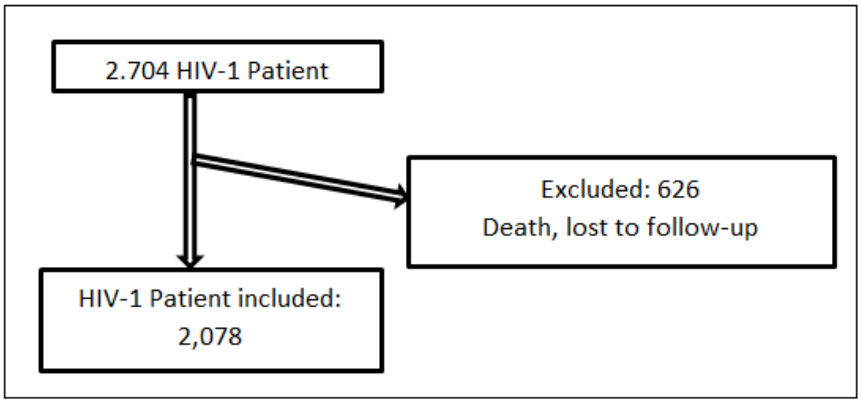

Figure 1: Patient Selection

Table I: Treatment efficacy according to gender.

	Viral Load Suppression Rate			
	Male (710) n (%)	**Female (1368) n (%)**	**Totat population (2078) n (%)**	**P-value**
Undetectable at 6 months	63 **(8.9 %)**	89 **(6.5 %)**	152 **(7.3%)**	0.04
Undetectable at 12 months	534 **(75.2 %)**	1091 **(79.8 %)**	1624 **(78.1%)**	**0.01**
Undetectable at 18 months	8 **(1.1 %)**	33 **(2.4 %)**	41 **(1.9%)**	0.04
Virological evolution	41 **(5.8%)**	70 **(5.2%)**	111 **(5.3%)**	0.04
Virological failure	64 **(9.01 %)**	85 **(6.2 %)**	150 **(7.2%)**	0.04

n = number of patient

Table II: **Treatment efficacy by age group**

	Viral Load Suppression Rate				
age [years], (N)	**6 months; n (%)**	**12 months; n (%)**	**18 months; n (%)**	**Virological evolution n (%)**	**Virological failure n (%)**
[0-25[(282)	32 **(11.4%)**	197**(69.9%)**	8 **(2.8%)**	24 **(8.5%)**	22 **(7.8%)**
[25-45[(1158)	85 **(7.4%)**	886 **(76.5%)**	21 **(1.8%)**	49 **(4.2%)**	84 **(7.3%)**
[45-65[(604)	33 **(5.5%)**	504 **(83.4%)**	10 **(1.7%)**	37 **(6.12%)**	43 **(7.1%)**
>65 (34)	2 **(5.9%)**	28 **(82.4%)**	2 **(5.9%)**	1 **(2.9%)**	1 **(2.9%)**
P-value	**0.02**	**0.002**	0.3	0.08	0.08

n = number of patient

DISCUSSION

Achieving and maintaining viral suppression is the ultimate goal of antiretroviral therapy. Sustained suppression of HIV replication depends on the use of potent and well-tolerated ARVs that are easy to adhere to. Studying their effectiveness remains important for making recommendations for patient treatment regimens in HIV/AIDS programs. Thus, we carried out a retrospective study whose main objective was to evaluate the therapeutic efficacy of the TDF+3TC+EFV combination in the management of HIV-1 patients. During this study, we included 2,078 patients followed in the molecular biology laboratory of HMO from 2014 to 2021. The virological parameters are considered for each patient for at least 18 months in order to assess the effectiveness of antiretroviral treatment in these HIV-1 patients.

We observed in this a female predominance with a frequency of 71%. Other studies have shown similar results such as those obtained by Laurent in 2004, Labhardt *et al*., in 2015 who found a prevalence of 68% and 66.4% respectively [19, 20]. Indeed, in sub-Saharan Africa, women and girls accounted for 63% of all new HIV infections in 2021 [3]. This feminization of HIV infection is explained on the one hand by the fact that women are more vulnerable than men and that they are anatomically more susceptible to contracting infections. The mucosa exposed to the virus during sex is greater in women and the fragility of the vaginal walls offers multiple entry routes for the virus [21]. On the other hand, the studies carried out by Zouiten *et al*., in 2007; Kietiburanakul., 2007 had reported a male predominance with 51% and 68.1% respectively [22, 23]. The majority of patients were between 25 and 45 years old, i.e. 54.2% of the population with a median age of 38 years. This description is comparable to those reported by Maiga in Mali in 2008, which reported a predominance of the 25-39 age group [24]. In 2002, WHO reports showed that at least 10% of adults aged 25-49 had contracted HIV [25]. These results show that the sexually active adult population is more affected by HIV infection. In addition, in this study, 14% of the patients were between 0 and 24 years old. This may be due, on the one hand, to the fact that 90% of HIV infections in children are acquired through mother-to-child transmission, i.e. during pregnancy, breastfeeding or childbirth [26], but also because the majority of new infections occur in young people between the ages of 15 and 24 [25]. West and Central Africa has the highest proportion of adolescents giving birth before the age of 18 (33%), with 3.5% giving birth before the age of 15. Of the ten countries with the highest percentages of adolescent pregnancies, seven are in the WCA region. In Niger, for example, the percentage is 51%, the highest in the world. In Senegal, 17% of adolescent girls had a live birth before the age of 18, 2.1% of women aged 15-18 and 3.6% of women aged 20-24 had their first sexual experience before the age of 15 [25]. In sub-Saharan Africa, the risk of HIV infection is twice as high among adolescent girls [3].

Measuring the amount of HIV RNA present in the blood is the best way to monitor the effectiveness of antiretroviral therapy, i.e., viral suppression, and to detect virological failure in a resource context limited.

Our results indicated a good response to TDF+3TC+EFV treatment, after the 18-month study period, 85.5% of patients had an undetectable viral load for all patients. Studies done in Senegal by Diop *et al*., in 2013 and Ladman *et al*., in 2009 showed similar results with lower percentages for a longer duration, 71% and 72.5% of patients respectively showing virological suppression after 24 months [27-28]. Moreover, the study made by Cassetie *et al*., in 2007 in the USA showed proven efficacy of TDF+3TC+EFV with a virologic success rate of 84% for a longer duration of 36 months [29]. Our study showed a positive virological evolution was noted in 5.3% of patients showing a good reduction in the rate of CV (less than 1000 copies / ml) therefore a good efficacy of treatment with TDF + 3TC + EFV. Virological failure was noted in 7.2% of patients, probably due to poor compliance or HIV-1 resistance mutations.

At 6 months, 7.3% patients had an undetectable plasma viral load. This result is different from those obtained by Dolo in 2011 in Mali [1] and by Bar in 2016 in Senegal [30] which showed virological suppression of 36.4% and 46.7% after 6 months of treatment. At 12 months, 78.2% of the patients had an undetectable viral load, virologic suppression was greater after 12 months of treatment, this suggests that most patients need a treatment duration of one year to show virologic success and not a period of 6 months. These results are similar to those reported by Boender *et al*., in 2015 and Barthel *et al*., in 2010 in resource-limited settings that found viral suppression rates of 80% and 76% respectively at 12 months [31, 32]. We also found that gender had a significant influence on patients' treatment success. Viral suppression was significantly greater in women 79% against 75.2% (p= 0.01) in men after 12 months of treatment with a higher rate of virological failure (CV>1000 copies/ml) in men 9.1% against 6.2% in women (P=0.04) after 18 months of treatment. We also presented that at 6 months, virological suppression was significantly greater in patients aged 0 to 25 years (11.4%). One hypothesis to be tested would be to compare compliance with treatment between men and women and between age groups. After 12 months of treatment, virological success was significantly greater in patients aged 45 to 65 (83.4%) and in those over 65 (82.4%) than in the youngest (69.9%). Adults need a longer treatment time to have an undetectable viral load, i.e. one year of treatment was needed to achieve a good rate of virologic suppression. At the end of our study, we observed significant virological success rates and proven efficacy of the TDF+3TC+EFV regimen in the treatment

of HIV-1 patients. Indeed, in 2013 the WHO recommended the combination of TDF+3TC+EFV as first-line treatment for the treatment and prevention of HIV infection because of its efficacy, ease of use, of its safety profile and its unique resistance profile [33]. The WHO guidelines are supported by our results. However, antiretroviral potency, immunovirological reconstruction, tolerability and drug-related toxicity are important factors to include in evaluating the efficacy of antiretroviral therapy. Since the patient information sheet did not include information on treatment adherence, adverse drug reactions and ARV resistance, we could not study the link between virological failure, adherence and patient resistance to treatment and to assess the adverse effects and toxicity of ARVs in this study.

CONCLUSION

Our results showed the efficacy of the TDF+3TC+EFV regimen in the treatment of HIV-1 infection. Viral suppression was related to patient gender and age. The ideal duration to obtain a good rate of undetectability in our cohort is at least 12 months of treatment. Treatment failure was low after 18 months of treatment. Our results support the WHO recommendation to use TDF+3TD+EFV as first-line therapy. However, studying the side effects linked to TDF+3TD+EFV would be necessary for a good completeness of this study. In addition, a study on resistance genotyping due to the use of TDF+3TC+EFV taking into account patient compliance will be useful. Despite a UNAIDS recommendation to switch to dolutegravir-based treatment because of better efficacy and tolerance, this regimen remains effective and can still be used.

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