# Impact of dolutegravir as first-line antiretroviral treatment on the tolerance and virological suppression among PLHIV in the southern region of Senegal


## Abstract :

**Aims:**To determine the virological suppression and the tolerance on patients under a dolutegravir-based regimen by comparison with patients on a regimen without dolutegravir after at least 6 months of treatment.

**Materials and methods**: A retrospective, descriptive, analytical and comparative study covering data from 469 patients with 219 treatment-naive patients under a dolutegravir based regimen and 250 patients pretreated with triple therapies not including dolutegravir, followed at the HIV treatment center of Kolda from January 1st, 2017 to December 31st, 2022. The inclusion criteria were: Patients HIV-1 and/or HVI-2 positive, aged> 15 years, with a viral load achieved after at least 6 months of ARV treatment. Undetectable threshold is defined as a viral load< 50 copies/ml.

**Results:** The proportions of patients screened at an advanced clinical stage of AIDS (WHO stage 3 or 4) were significant in both groups of patients under dolutegravir and without dolutegravir respectively (63.47% versus 59.20%, P= 0.344). The mean duration on ARV treatment was significantly higher in patients pretreated with therapeutic regimens not including dolutegravir (55.67±11.93 versus 28.95±7.80) (P < 0.0001) (Table 2). The dolutegravir-based regimen combined tenofovir, lamivudine and dolutegravir while the majority (90%) of pretreated patients were on an ARV regimen combining TDF, lamivudine, Efavirenz in first line (Table). Fewer patients presented side effects due to triple therapy in the dolutegravir-based regimen group compared to the non-dolutegravir group (2.74% vs. 3.20%; p=0.77). The rate of undetectable viral load was slightly higher in the doluteglavir-based regimen group, compared to the group without doluteglavir but the difference was not statistically significant (97.72% vs 97.60%; p = 0.933). There was less Virological failure (viral load >1000 copies/ml) in the dolutegravir group than in the group without dolutegravir (1 versus 3). The mean of the body mass index did not differ in the two groups. The weight gain was lower in the dolutegravir based regimen group but the difference was not statistically significant 6,7± 8,2 kg versus 7,2 ± 6,2 kg. The occurrence of obesity was not significantly different in the two groups [23.74%] versus [23.20%], P = 0.89).

**Conclusion**: The results of our study show a high rate of virological success, and good tolerance of the dolutegravir-based regimen in a decentralized setting.



**Keywords:** Dolutéglavir, Treatment, PLHIV, Senegal


## Introduction:

Sub-Saharan Africa remains the most heavily affected region by HIV in the world, holding more than two-thirds (67%) of all people living with HIV [1].

With the significant progress in antiretroviral therapy, HIV infection has become a chronic infection which, failing to be eradicated can be controlled.

Better tolerated and/or more effectiveARVs on sensitive or resistant viruses have been developed in recent years, belonging either to old classes or to new classes, such as integrase inhibitors and CCR5 inhibitors.

The effectiveness of integrase inhibitors has been established in studies of treatment-naive and pretreated patients [3,4]. Dolutegravir as a first-line treatment has shown an improved safety profile compared to EFV which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) [4]. It is estimated that around 15 million people will be taking Dolutegravir by 2025 and it will replace first-line Efavirenz-based regimens [5,6]. These ARVs have a beneficial role not only in terms of individual health but also in the drastic reduction of contagiousness when plasma viral replication is controlled under treatment. This fundamental data regarding the possible reduction of transmission associated with the individual benefits of earlier treatment led to the concept of TasP (Treatment as Prevention) and Test and Treat [2].

Senegal is one of the first countries in sub-Saharan Africa to set up an access program to ARV treatments in 1998. It is also one of the first countries in Africa to have decided to make ARV treatments free in 2003.

In 2020, Senegal began a transition to Dolutegravir-based treatment regimens in accordance with WHO recommendations. This regimen was first initiated in newly infected patients then gradually in patients under other protocols. After three years of switching to dolutegravir, we conducted this study with the aim of comparing the tolerance and effectiveness of these new protocols to those pre-existing regimens, especially based on NNRTI in a decentralized environment.

**Methodology :**

The study took place in the HIV outpatient treatment unit at Kolda's health center (UTA) from January 1$^{st}$ ,2017 to December 31$^{st}$, 2022.

It is a descriptive, analytical and comparative observational study based on data from patients who initiated their first-line treatment with the dolutegravir-based ARV regimen between April 2020 and December 2022. Our comparison group consisted of PLHIV pretreated with an ARV regimen without dolutegravir. The duration of exposure to dolutegravir had to be at least 6 months. Each patient included had to have a virological assessment available after at least 6 months of ARV treatment. We excluded pretreated PLHIV who had switched to dolutegravir from the comparison group. Patients whose files were unusable due to lack of information were not included.

The viral load was considered undetectable when it was less than 50 copies per milliliter of blood. Viral suppression was a viral load below 1000 copies per milliliter of blood.

Patients' medical records in the center's cohort served as the source of data collection. The data was collected on a survey sheet. Each survey sheet was assigned an anonymous number. To meet our objective, the epidemiologic, clinical parameters (age, sex, level of education, duration of HIV infection, clinical stage at discovery of HIV, weight, presence of opportunistic infection, side effects) and virological parameters (viral load) were studied. A Chi test allowed the comparison of qualitative variables. The significance threshold was set at 5%.

Data were entered into Excel 2016 after cleaning and coding, then analyzed using the Stata version 13 software, before categorizing the different variables according to the defined methods.

**Results :**

A total of 469 PLHIV were included in this study, with 219 who initiated treatment with a dolutegravir-based regimen and 250 with other regimens. The patients' average age did not differ significantly between the two groups (41.63±12.89 versus 39.56±1298, P=0.085) respectively. We also noted in both groups a female predominance (73.52% versus 78.00%, P= 0.257), a significant proportion of married people (77.31% versus 72.29%, P= 0.214), and patients who haven't shared their HIV status with their partners (27.06% versus 34.60%, P= 0.083). The majority of patients were illiterate (50.68% versus 57.20%, P = 0.158). The proportions of comorbidities found: the proportion of diabetes did not differ in the two groups (7.76% versus 8.00%, P = 0.924), however hypertension was significantly higher among patients on ARV based on dolutegravir compared to patients on other regimens (21.00% versus 11.60%; P: 0.006). The proportions of patients presenting weight loss (BMI < 18.5 kg/m2) at inclusion did not differ significantly between the two groups (47.03% versus 43.20%, P = 0.405). HIV-HBV co-infection was similar in both groups (5.48% versus 5,60 %, P= 0.545). The proportions of patients screened at an advanced clinical stage of AIDS (WHO stage 3 or 4) were significant in both groups (63.47% versus 59.20%, P= 0.344). The mean duration on ARV was significantly higher in patients pretreated with therapeutic regimens not including dolutegravir (28.95±7.80) versus 55.67±11.93) (P < 0.0001)(Table 2). The dolutegravir-based regimen combined tenofovir, lamivudine and dolutegravir while the majority (90%) of pretreated patients were on an ARV regimen combining TDF, lamivudine, Efavirenz as first line treatment (Table1).

Fewer patients experienced side effects related to triple therapy in the dolutegravir-based regimen group compared to the non-dolutegravir group (2.74% vs 3.20%; p=0.77).

The undetectable viral load rate was slightly higher in the doluteglavir-based regimen group compared to the non-doluteglavir regimen group, but the difference was not statistically significant (97.72% vs 97.60%; p = 0.933). Virological failure (Viral load>1000 copies/ml) was less frequent in the dolutegravir group than in the group without dolutegravir (1 versus 3). Mean body mass index did not differ in the two groups. The weight gain was lower in the dolutegravir based regimen group but the difference was not statistically significant6,7± 8,2 kg versus 7,2 ± 6,2 kg. The occurrence of obesity was not significantly different in the two groups [23.74%] versus [23.20%], P = 0.89).

**Discussion**

In this study, we compared data on virological suppression and tolerability of dolutegravir based regimens of219treatment-naive patients with those of 250 patients pretreated with a non-dolutegravir regimen for HIV-1 and HIV-2 in decentralized and resource-limited settings.

We observed in both groups a female predominance (75.9%) and an average age of 40 years. These results are in agreement with data from the CNLS (National council for the fight against AIDS) 2021 in Senegal [13]. This female predominance has also been found in several studies in Africa: [7, 8,9,10,11,12]. Indeed, HIV infection mostly affects the sexually active age group corresponding to the population of young adults due to their exposure to certain risk factors, especially economic insecurity and the relaxation of social control, notably in urban areas. However, a meta-analysis of 13 cohorts by Egger [14] bringing together European and North American countries suggested a male predominance. This difference between the countries of the North and the South finds two explanations: on one hand, the predominance of heterosexual transmission in the South associated with female vulnerability; on the other hand the relatively high role of homosexuality and injection drug use in the North in the transmission of the disease.

Most patients in both groups were detected at an advanced clinical stage of AIDS (WHO stage 3 or 4) (63.47% versus 59.20%, P = 0.344). This diagnostic delay has been observed in several African studies [10,11]. The advanced clinical stage is a vulnerability factor for patients both to the disease itself and the opportunistic conditions. It illustrates a diagnostic delay which remains frequent in our developing countries; the reasons for this delay can be explained

by poverty, lack of information, the attitude of hiding the disease because of the risk of stigmatization and discrimination from the populations, the geographical and especially financial inaccessibility to healthcare structures [10]. This despite the freeness and efforts made to decentralize the screening in Senegal.

The proportion of weight loss (BMI < 18.5 kg/m2) at inclusion was significant and did not differ significantly between the two groups (47.03% versus 43.20%, P = 0.405). Studies have revealed that in the very advanced stages of AIDS there is a reduction in nutritional intake, an increase in energy expenditure linked to basal metabolism due to viral replication [15,16,17]. This viral presence triggers proteolysis which leads to muscle damage, thus causing an imbalance in the nitrogen balance and an exaggerated loss of lean tissue [15].

According to the serological profile, HIV type-1 is predominant with 88.91% (n = 469). This high prevalence of HIV-1 is explained by its greater virulence, which is characterized by greater transmissibility both sexually and from mother to child. This is how HIV-1 constitutes the serotype solely responsible for the current pandemic [18].

After monitoring patients on ARV for at least six months, we observed a progressive increase in weight gain in both groups. This increase was slightly greater in the group without dolutegravir with a mean weight gain of 7.2 ± 6.2 and a BMI of 22.42 ± 4.5 kg/m2 compared to a mean weight gain of 6.7 ± 8.2 kg and BMI 22.19 ±4.4 in the dolutegravir group but the difference was not statistically significant (p: 0.58). This variation in weight gain in the two groups could be due to the fact that the average duration of ARV treatment is longer in the group without dolutegravir (55.67 ± 11.93 versus 28.95 ± 7.80; (P < 0.0001). The usage of anthropometrics parameters including BMI as a marker of the effectiveness of ARV treatment has been described and remains important in settings with limited resources [19,20] [21, 22]. This weight gain in our study is close to the one found in patients followed in South Africa [21] [23]. However, several studies have found the occurrence of significant weight gain under ARV based on dolutegravir in Bouaké[22,24,23,25]. Dolutegravir would therefore play a role in patients weight gain. According to the literature, various mechanisms explain weight gain in PLHIV. Weight gain has recently appeared as a main side effect of antiretroviral treatment, potentially increasing the associated cardiovascular risks and having a negative impact on the quality of life of people living with HIV. This weight gain undoubtedly has a multifactorial origin and is of variable magnitude depending on the anti-integrase, the associated ARVs, the sex, the previous weight, the CD4 nadir and

ethnic origin. We studied, in patients switching from triple therapy based on dolutegravir (DTG) to dual therapy, the evolution of weight gain [26]. Indeed, HIV infection and ARV treatment itself would lead to intestinal lesions causing an increase in fungal translocation and therefore an increase in the Beta D glucan (BDG) marker. A higher BDG would be associated with greater fat gains under antiretroviral treatment [27].

Retention for 12 months was significant among patients newly initiated to ARV treatment including dolutegravir in our cohort. This finding was observed in a therapeutic trial where people initiated to dolutegravir were more likely to be retained in care for 12 months (adjusted RR 1.09, 95% CI 1.04 to 1.14; adjusted risk difference 5.2%, 2.2 to 8.4). This high rate of retention of patients on dolutegravir-based ARV could be explained by increased tolerance [28,29,30]. Indeed, in our study, fewer patients experienced side effects linked to triple therapy in the dolutegravir-based regimen group compared to the group without dolutegravir (2.74% vs 3.20%; p= 0.77).

The virological success rate (measured by the proportion of participants with a viral load <50 copies per milliliter after at least 6 months on ARV) was slightly higher in the doluteglavir-based regimen group, compared to the non-doluteglavir regimen group however there was not a statistically significant difference (97.72% vs 97.60%; p = 0.933). This virological success rate observed in our study was higher compared to those found in several others: 88% in the group having received dolutegravir, abacavir and lamivudine in the SINGLE2 trial [31] and 90% in the group that received dolutegravir and two NRTIs in the FLAMINGO trial [32]. Studies have shown viral suppression was impaired in participants with a high baseline viral load. However, in our study, the baseline viral load was not measured in our patients before starting ARV. This could explain the difference in virological success rates. Furthermore, an improvement in viral suppression over 12 months with dolutegravir was observed in treatment-naïve patients in two clinical trials in Africa. [28,33]. Public health data from Brazil showed good safety outcomes [34] and better viral suppression over 12 months in people initiated on dolutegravir compared to those on efavirenz [35], but the proportion on dolutegravir was low and there was no assessment of retention in care.

In our study we did not look for resistance to ARVs, particularly to dolutegravir. Studies from Malawi, Lesotho, and Uganda suggest low levels of HIV resistance mutations to dolutegravir and high levels of viral suppression in people who transitioned to dolutegravir, but did not compare results with those of people remaining on dolutegravir-free regimens [35,36,37].A retrospective

cohort study of 3,108 people from four African countries have found that people who transitioned to dolutegravir had better viral suppression than those who remained on the same first- or second-line treatment.[38] . Dolutegravir-based regimens are associated with a reduced need to switch to other antiretrovirals and there is a lower risk of developing major antiretroviral resistance mutations compared to efavirenz-based regimens [39,40 ].

**Conclusion :**

This study showed that patients on treatment based on dolutegravir have a high rate of virological success, a low rate of virological failure and good tolerance similar or better than other regimens mainly with efavirenz. Other diets even though the improvements in terms of retention in care and viral suppression are modest, constitutes an asset for achieving the 95-95-95 objectives in our context.

Table 1 : Demographic characteristics of DTG and other diets

| **Characteristics** | **DTG diet** | **Other diets** | **P-value** |
|---|---|---|---|
| **Gender** | | | |
| Female | 161 (73.52%) | 195 (78.00%) | 0,257 |
| Male | 58 (26.48%) | 55 (22.00%) | |
| **Age (years)** | | | |
| <35 | 59 (26.94%) | 72 (28.80%) | |
| 35 - 49 | 91 (41.55%) | 85 (34.00%) | |
| >50 | 69 (31.51%) | 93 (37.20%) | |
| **Sharing of HIV viral status with partner** | | | |
| Yes | 159 (72.94%) | 155 (65.40 %) | 0.083 |
| No | 59 (27.06%) | 82 (34.60%) | |
| **Clinical stage WHO** | | | 0,344 |
| 1 | 41 (18, 72%) | 45 (18, 00%) | |
| 2 | 39 (17, 81%) | 57 (22, 80%) | |
| 3 | 118 (53, 88 %) | 125 (50, 00%) | |
| 4 | 21 (9, 59 %) | 23 (9, 20%) | |
| **Co-morbidity** | | | |
| **High blood pressure** | 46 (21.00%) | 29 (11.60%) | 0.006 |
| **Diabetes** | 17 (7.76 %) | 20 (8.00%) | 0.924 |
| **Dual infection HIV-HBV** | 12 (5, 48%) | 14 (5, 60%) | |

| | | | |
|---|---|---|---|
| **HIV profile** | | | |
| Type 1 | 194 (88.58%) | 223 (89.20%) | 0.576 |
| Type 2 | 18 (08.21%) | 17 (06.8%) | |
| Type 1+2 | 7 (03.17%) | 10 (04.00%) | |
| **BMI at admission** | | | |
| **Mean** | 22.19 ±4.4 | 22.42 ± 4.5 | |
| < 18,5 | 103 (47.03%) | 108 (43.20%) | 0.443 |
| 18,5- 24,9 | 87 (39.73%) | 114 (45.60 %) | |
| 25 – 29,9 | 23 (10.50%) | 24 (9.60%) | |
| 30 – 34,9 | 6 (2.74%) | 3 (1.20 %) | |
| 35 – 39,9 | 0 (0.00 %) | 1 (0.40%) | |
| **Mean ARV treatment duration** | 28.95± 7.8 | 55.67± 11.93 | 0.0000 |
| **Virogical success<50 copies/ml** | 212 (96.80%) | 241 (96.40%) | 0.810 |
| **Virological failure >1000 copies/ml** | 1 (0.46%) | 3 (1.20%) | |
| Sides effects | | | |
| **Sides effects sides** | 6 (2.74%) | 8 (3.20%) | |
| Dizziness | 1 (0.46%) | 1 (0.40%) | |
| Acute diarrhea | 1 (0.46%) | 1 (0.40%) | |
| Vomiting | 2 (0.91%) | 0 (0.00%) | |
| Nausea | 0 (0.00%) | 2 (0.80%) | |
| Headache | 0 (0.00%) | 1 (0.40%) | |
| Insomnia | 2 (0.91%) | 2 (0.80%) | |
| Skin rash | 0 (0.00%) | 1 (0.40%) | |
| **ARV regimen** | | | |
| TDF+3TC+DTG | 219 (100%) | 0 | |
| TDF+3TC+EFV | 0 (0.00%) | 225 (90%) | |
| TDF+3TC+LPv | 0 (0.00%) | 12 (4,80%) | |
| AZT+3TC+LPv | 0 (0.00%) | 8 (3,20%) | |
| AZT+3TC+NVP | 0 (0.00%) | 4 (1,60%) | |
| ABC+3TC+EFV | 0 (0.00%) | 1 (0,40%) | |
| **Patients after 12months** | | | |
| Regularly followed | 172 (78.54%) | 245 (98.00 %) | |
| Lost of sight | 0 (0,00%) | 4 (1.60%) | |
| Transfers | 47 (21.46%) | 1 (0.40%) | |

| | | | |
|---|---|---|---|
| **Mean BMIafter at least 12 months of ARV treatment** | 22.19 ±4.4 | 22.42±4.5 | 0.581 |
| **Mean weight gain** | 6,7± 8,2 | 7,2 ± 6,2 | 0,503 |

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