Impact of Dolutegravir-based regimen on tolerance and virologic suppression, compared to non-dolutegravir regimen among PLHIV in Southern Senegal

Abstract :

Background:

In 2020,Senegal began a transition to aDolutgravir-based treatmentas a first-line regimen in all new ART initiators in accordance with WHO recommendations.

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 cross-sectional study based on retrospective data (from January 2nd, 2017 to June 30th; 2022) involving 469 patients, 219 people were initiated with Dolutegravir regimen ART between Jan 2nd, 2020, and June 30th, 2022,and 250 patients treated using the old protocol (non-dolutegravir regimen). Patients who had received both the old protocol then switched to a DTG based regimen were excluded from the study.
A single questionnaire was used to collect data. Sociodemographic, clinical and virological parameters and the last control of the virological load were analyzed with Stata 16 software.Descriptive statistics and univaried analysis were also carried-out.

Results: In the dolutegravir regimen ART group, 161 (73, 52%) of 219 were women and 58 (26.48) were men. The median participant age was 43·0 years (IQR 33·0–53·0) and the median time on ART was 28·0 months (23·0–36·0). The dolutegravir-based regimen combined tenofovir, lamivudine and dolutegravir. 15 (6, 85 %) were receiving tuberculosis treatment at the time of ART initiation. The proportion of patients screened at an advanced clinical stage of AIDS (WHO stage 3 or 4) were 63, 47%. People initiated on dolutegravir were more likely to be retained in care at 12 months (100% vs. 95.20%; p=0.075) and having viral suppression(96.80%vs. 96.40% ; p=0,810) compared with those initiated on non-dolutegravir-based regimens but the difference was not statistically significant. 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). In the dolutegravir based regimen the side effects were mainly vomiting, insomnia, and dizziness. The mean gain weight was 6,7± 8,2 kilograms.

For thenon-dolutegravir regimen group, 195 (78.00%) were women. The median participants age was 43·0 years (IQR 34·0–53·0)and the median time on ART was 55·0 years (48·0–65·0) months. 18 (7, 20%) were receiving tuberculosis treatment at time of ART initiation.The therapeutic protocol combined TDF, lamivudine, Efavirenz in 225 cases (90%). A percentage of 59.20% patients were screened at an advanced clinical stage of AIDS (WHO Stage 3 and 4). In this group the side effects were mainly nausea and insomnia and the mean gain weight was 7,2 ± 6,2 kilograms.

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

Keywords: Doluteglavir, Treatment, PLHIV, Senegal

Introduction:

HIV infection is a public health issue with an estimated 39 million persons living with HIV (PLHIV) worldwide, two-thirds of who reside in sub-Saharan Africa (SSA) [1].

Under WHO recommendations, a regimen based on efavirenz, a non-nucleotide reverse transcriptase inhibitors (NNRTI) was the preferred first-line treatment until 2018. Given the concerns about side effects, low genetic barrier and occurrence of drug resistance especially in low income settings as shown in several studies in Africa [2-3], where viral load and genotyping is not systematically realized, new recommendations have been made.For instance an alternative treatment based on dolutegravir, an integrase strand transfer inhibitor (INTSI) has been recommended by the World Health Organization. This molecule has shown a better efficiency based on studies run in Europe then in Africa[4-5] due to the improvement of the tolerance, reduction of treatment discontinuations with fewer cases of resistance.

Senegal is one of the first countries in sub-Saharan Africa to set up an access program to ART in 1998. It is also one of the first countries in Africa to have decided to make ART free in 2003[6].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 :

Study design and participants

The study took place in the HIV outpatient treatment unit at Kolda's health center (UTA) on patients enrolled from January 2nd,2017 to December 31st, 2022.

It is a cross-sectional and descriptive study on two groups of subjects: patients treatedusing the old protocol without DTG (from January 2nd, 2017 to December 31st, 2020) and patients treated with new protocol including DTG (from January 2nd, 2020 to June 30th, 2022) followed in the infectious diseases department of Kolda's hospital.

The old protocol associated two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitors(NNRTI) or two NRTI and one Protease inhibitors (PI). The new protocol associates two NRTI and one INTSI (DTG).

The duration of exposure to dolutegravir had to be at least 6 months. Each patient included had to have a monitoring of the viral load available after at least 6 months of ART. We excluded pretreated PLHIV with the old protocol who had switched to dolutegravir from the comparison group. Patients whose files were unusable due to lack of information were not included.

Data collection

Data was collected on a survey sheet. A questionnaire was developed to collect data on socio-demographic (age, sex, level of education,HIV status disclosure) clinical (duration of HIV infection, clinical stage at discovery of HIV, weight, presence of opportunistic infection), therapeutic (ART protocol, side effects), virological (viral load, virological failure, virological success) evolution (body mass index) parameters. The questionnaire was filled out using patients' medical records, patients' interrogation and the UTA's data base.

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

Statistical analysis

Data were computed using Excel 97- 2003 and analysed using Stata/Special 16 software (Stata Corporation, Texas, and USA). Results were expressed as mean ± standard deviation for continuous variables and proportion for categorical variables. Student t-test was used for mean comparisons and Pearson's chi-square test for categorical variables comparison. P values < 0.05 were considered significant for all analysis.

Results :

A total of 469 PLHIV were included in this study, with 219 who initiated treatment with a dolutegravir-based regimen and 250 with anon-dolutegravir

regimen. 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). (table1)

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 ARTbased on dolutegravir compared to patients on the non-dolutegravir group (21.00% versus 11.60%; P: 0.006). Tuberculosis was the revealing condition in 15 (6, 85 %) cases in the dolutegravir based regimen group and 18 (7, 20%) cases in the other group(Table 2).

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).According to the serological profile, HIV type-1 is predominant with 88.91% (n = 469). The mean duration on ART 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 ART regimen combining TDF, lamivudine, Efavirenz as first line treatment (Table2). 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) (Table3).In the dolutegravir based regimen the side effects were mainly vomiting (0,91%), insomnia (0,91%), and dizziness(0,46%) while in the non-dolutegravir group the side effects were mainly nausea(0,80%) and insomnia (0,80%).

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) (Table1).In the dolutegravir-based regimen, viral success was higher in females and patients aged less than 35year-old (Table4). As for the non-dolutegravir group, the viral success was higher in males and patients aged less than 35(table5). The viral suppression in PLHIV under tuberculosis treatment was higher in the dolutegravir group compared to the non-dolutegravir group (100% versus 94,44%) (Table4). Viral failure (Viral load>1000 copies/ml) was less

frequent in the dolutegravir group than in the group without dolutegravir (1 versus 3) (Table1). Mean body mass index at ART initiation 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). (Table1)

Discussion

In this study, we compared data on viral 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%). 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]. 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.

The median age in both groups was42·0 years (IQR 33·0–53·0. This result was similar to the ones found in multiple studies in Africa [7,8,9,10,11]. 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.

Majority of HIV infection in both groups were detected at an advanced clinical stage ofAIDS (WHO stage 3 or 4) (63.47% versus 59.20%, P = 0.344). However, this result is less than the ones found in studies run in Senegal in 2009 and 2011[10,11]. That difference can be explained by the strategy 95-95-95launched by UNAIDS in 2014 with the aim of ending AIDS pandemic by 2030. HIV diagnosis is the crucial first step of that strategy [41]. 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 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].

Senegalese guidelines recommend a double dose of dolutegravir in first line for patients under tuberculosis treatment. Theviral suppression in PLHIV under tuberculosis treatment was higher in the dolutegravir group compared to the non-dolutegravir group.This result is in accordance to the clinical trial INSPIRING that showed a good tolerance and an acceptable viral suppression [42].

Senegal guidelines recommend than dolutegravir for people initiating ART who are receiving the standard rifampicin-containing tuberculosis treatment. However, we found that over half of those receiving tuberculosis treatment in our study did receive dolutegravir and, among this group, the beneficial effect of dolutegravir on viral suppression was even stronger compared with those without tuberculosis.

After monitoring patients on ART 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 ART 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 ART 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 ART 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 ART 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 ART 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 ART 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 viral success rate (measured by the proportion of participants with a viral load <50 copies per milliliter after at least 6 months on ART) 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 viral 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 ART. This could

explain the difference in viral 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 viral failure and good tolerance similar or better than other regimens mainly with efavirenz. Other regimenseven 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.

Ethical Approval and Consent:

Prior to participation, participants were informed about the study's objectives and procedures, and their written consent was obtained. Both the regional health direction and the UTA's director gave their authorization. Each survey sheet was assigned an anonymous number.

Table1: Socio-demographic characteristics of Respondents

Characteristics	Dolutegravir-b regimen(N=219)	Non-dolutegravirregimen(N=250)	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%)	
Median (IQR)	43 (IQR 33·0–53	42 (IQR 34·0–53·0)	
Level of education			
Illetrate	111 (50.68 %)	144 (57.60%)	
Primary	82(37.44%)	74 (29.60%)	
Secondary	21(9.59%)	32 (12.80%)	
University	5 (2.28 %)	0 (0.00%)	
HIV status disclosure	|		
Yes	159 (72.94%)	155 (65.40 %)	0.083
No	59 (27.06%)	82 (34.60%)	
Viral success<50 copies/ml	212 (96.80%	241 (96.40%)	0.810
Viral failure >1000 copies/ml	1 (0.46%)	3 (1.20%)	
ART 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	219 (100 %)	238 (95.20%)	0.075
Lost of sight	0 (0,00%)	12 (4.80%)	
Mean BMIafter at least 12 months of ART treatment	22.19 ±4.4	22.42±4.5	0.581

Mean weight gain after 12months of treatment	6,7± 8,2	7,2 ± 6,2	0,503

Table2: Clinical characteristics of Respondents

	Dolutegravir-based regimen(N=219)	Non-dolutegravirregimen(N=250)	
WHO Stage at enrolmentno. (%)			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			
Hypertensionno. (%)	46 (21.00)	29 (11.60)	0.006
Diabetes no. (%)	17 (7.76)	20 (8.00)	0.924
HIV-HBV Co-infection no. (%)	12 (5, 48)	14 (5, 60)	
Tuberculosis at ART initiationno. (%)			
Knowntuberculosis	15 (6, 85)	18 (7, 20)	0.882
No tuberculosis	204 (93.15)	232 (92.80)	
HIV profileno. (%)			
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 admissionno. (%)			
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 ARTduration	28.95± 7.8	55.67± 11.93	0.0000

Viral success<50 copies/ml	212 (96.80)	241 (96.40)	0.810
Viral failure >1000 copies/ml	1 (0.46)	3 (1.20)	
ART 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)	

Table 3: repartition of side effects in both groups during their last 6 months of treatment

Type of side effects	**Dolutegravir-based regimen**(N=219)	**Non-dolutegravirregimen(N=250)**
Dizziness no. (%)	1 (0,46)	1 (0.40)
Acute diarrhea no. (%)	1 (0,46)	1 (0.40)
Vomiting no. (%)	2 (0,91)	0 (0.00)
Nausea no. (%)	0 (0.00)	2 (0.80)
Headache no. (%)	0 (0.00)	1 (0.40)
Insomnia no. (%)	2 (0.91)	2 (0.80)
Skin rash no. (%)	0 (0.00)	1 (0.40)
Total	6 (2.74)	8 (3.20)

Table4. Subgroup Analysis of Proportion of Participants under dolutagravir-based regimen with a Viral Load of Less Than 50 Copies per Milliliter after at least6 months of treatment.

Dolutegravir-based regimen (N=2019)	**Viral success<50 copies/ml (%)**	p-value

Gender		0.318
Female	157 (97, 52)	
Male	55 (94, 83)	
Age (years)		0.985
<35	57 (96.61)	
35 – 49	88 (96.70)	
> 50	67 (97.10)	
Tuberculosis at ART initiation		0.644
Knowntuberculosis	15 (100)	
No tuberculosis	107 (96.57)	

Table 5 . Subgroup Analysis of Proportion of Participants under a non-dolutegravir based regimen with a Viral Load of Less Than 50 Copies per Milliliter after at least 6 months of treatment.

Non-dolutegravir regimen	**Viral success < 50 copies/ml**	p-value
Gender		0.318
Female	187 (95, 90)	
Male	54 (98, 18)	
Age (years)		0.872
<35	70 (97.22)	
35 – 49	82 (96.47)	
>50	89 (95.70)	
Tuberculosis at ART initiation		
Knowntuberculosis	17 (94.44)	
No tuberculosis	224 (96.55)	

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