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ORIGINAL RESEARCH

Virologic Efficacy of Recycling Tenofovir and Lamivudine/Emtricitabine in Second-Line Antiretroviral Treatment with Dolutegravir: A Non-Inferiority-Matched Cohort Study in Senegal

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Abstract

Background: The World Health Organization (WHO) now recommends dolutegravir (DTG)-based regimens as the preferred option for first-line and second-line antiretroviral therapy (ART) for all people living with HIV (pwHIV). However, exposure to tenofovir (TDF) in first-line antiretroviral therapy (ART) could compromise its efficacy (K65r mutation). Our study aimed to assess whether recycling TDF and lamivudine or emtricitabine (XTC) with DTG as second line ART is non-inferior to optimized nucleotide reverse transcriptase inhibitor (NRTI)-based regimens.

Methods: This multicenter noninferiority-matched cohort study included pwHIV (> 18 years) who switched to second-line ART between october 2013-october 2023 in six HIV clinics in Senegal. The test group consisted of pwHIV on TDF + XTC +DTG with ≥ 2 years of TDF exposure in the first-line regimen, while those receiving other second-line ART with no history of prior TDF exposure composed the control group. We used propensity score matching analysis to balance the two groups. The primary outcome was viral load (VL) suppression (VL < 400 copies/mL) at week 48. Noninferiority was considered when the lower limit of the one-sided 95% confidence interval (95% CI) of the difference in VL suppression rates between groups was > -12%.

Results: Overall, 254 out of 907 pwHIV who were switched to second-line ART during our study period, were included in the matching process. Ultimately, 126 participants (63 pairs) were enrolled with optimal standard mean differences (SMDs). Of the 126 participants included, 86 (68.3%) were female, and the median age was 38 years (interquartile range [IQR]: 27-46 years). Seventy-two (64.3%) participants had a CD4 count < 200 cells/mm^3, and 33 (26.2%) were classified as WHO stage 4. At the week 48, 58 pwHIV in the test group (92.1%) and 51 in the test group (81.0%) had VL < 400 copies (difference: 11.10% 95% CI [1.23-20.97]), which met the noninferiority criterion.

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Conclusions: DTG-based regimen with recycled TDF was noninferior to alternative second-line regimens at the 48-week endpoint. However, further studies are needed to evaluate its efficacy over extended periods.

Keywords

Dolutegravir, Recycling-NRTIs, Senegal, Second-line antiretroviral therapy, Noninferiority

Abbreviations

HIV: Human Immunodeficiency Virus; pwHIV: people living with HIV; 1 L: First-Line; 2 L: Second-Line; ART: Antiretroviral Treatment; VL: Viral Load; DTG: Dolutegravir; TDF: Tenofovir Disoproxil Fumarate; TLD: Tenofovir, Lamivudine, Dolutegravir; FTC: Emtricitabine; DRV/r: Ritonavir-boosted Darunavir; 3TC: Lamivudine; RAL: Raltegravir; AZT: Zidovudine; DDI: Didanosine; LPV/r: Ritonavir-boosted Lopinavir; ATV/r: Ritonavir-boosted Atazanavir; ABC: Abacavir; WHO: World Health Organization; cell: cells, mm^3: cubic millimeter; HBsAg: Hepatitis B surface Antigen; CI : Confidence Interval; cp/mL: Copies per millimeter

Introduction

Antiretroviral (ARV) resistance has become a global challenge, with low-income countries being the most affected [1,2]. Approximately 15% to 35% of patients in sub-Saharan Africa experience virological failure within 12 months of starting antiretroviral therapy (ART) [3]. The prevalence of resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) has exceeded 50% in the region [2,4,5]. Approximately 95% of people living with HIV (pwHIV) received tenofovir (TDF)-based first-line ART in 2020, a notable increase from 80% in 2016 [6]. This scale-up is paralleled by increasing viral resistance through the selection of the K65r mutation, whose prevalence varies between 6% and 35% in African cohorts [7,8]. According to the TenoRes study, 57% of people with first-line treatment failure in Eastern and Southern African cohorts had developed resistance to TDF [2].

The introduction of dolutegravir (DTG), a second-generation integrase inhibitor with a high genetic barrier, has led to a significant shift in treatment approaches [9]. Trials such as VISEND and D2EFT have shown the noninferiority of DTG paired with TDF and either lamivudine or emtricitabine (XTC) compared to standard-of-care ritonavir-boosted protease inhibitors such as lopinavir (LPV/r), atazanavir (ATV/r), and darunavir (DRV/r) for second-line treatment [10,11]. Notably, the DAWNING study, involving 624 People living with HIV (pwHIV) who failed first-line nonnucleoside reverse transcriptase inhibitor (NNRTI)-based ART, demonstrated the superior efficacy of DTG over LPV/r. Additionally, DTG offers reduced pill burden, better tolerability, and improved cost-effectiveness when combined with dual nucleoside reverse transcriptase inhibitor therapy (NRTIs) [12]. Consequently, the World Health Organization has recommended DTG-based regimens as the preferred option for both first-line and second-line ART for all pwHIV [13]. However, the recommendation outlined that consideration should be given to substituting TDF with zidovudine after failing a first-line NNRTI-based regimen with TDF/XTC [1,13] in low and middle income countries (LMICs) where access to antiretroviral resistance testing is limited. This substitution ensures the presence of an active NRTI backbone, as the resistance mutation selected for by TDF (K65R) does not compromise the activity of zidovudine [14].

People who fail a first-line drug regimen in sub-Saharan Africa have limited options for an optimized NRTI backbone [1,15]. The recurrent stockouts of antiretroviral (ARV) medications compound these challenges [16]. Recycling available ARVs has therefore become a research priority in African settings [17-19]. Recent clinical trials have highlighted the potential of recycling TDF and lamivudine (3TC) with dolutegravir (TLD) in second-line ART after first-line NNRTI-based ART failure, leveraging both the superior virologic efficacy and greater genetic barrier offered by DTG [10,11,19-22]. Evidence from non-trial or real-world cohorts, where treatment adherence may be relatively lower than in trial settings, remains limited. We aimed to assess whether recycling TDF and XTC with DTG was as effective as an optimal NRTI-based regimen 48 weeks after initiating NNRTI-based first-line ART.

Methods

Study design and setting

We conducted a multicenter noninferiority-matched cohort study across six HIV-care referral clinics located in four regions of Senegal. These included three university hospitals in Dakar, one district hospital, and three regional hospitals in Ziguinchor, Kaolack, and Kolda. HIV care at these diverse sites adheres to the guidelines outlined by the Senegalese National AIDS Council (CNLS). VL testing was routinely performed 6- and 12-months following ART initiation and subsequently every 12 months. Therapeutic failure was defined based on the WHO guidelines [23].

Participants and data collection

For this study, we considered adults (> 18 years) who were switched to a second-line ART regimen between October 1, 2013, and October 30, 2023. Patients who underwent at least two years of follow-up since first-line ART failure were eligible for inclusion. We excluded participants who had missing viral load data at the endpoint. Participants were divided into two groups: The test group, which included those who recycled TDF and XTC with DTG in their second-line ART regimen, and the control group, which included individuals receiving the standard of care (SOC: ritonavir boosted protease inhibitor (PI/r) or DTG + 2NRTIs with a rotation of nucleosides and no prior history of exposure to TDF).

Data were collected from pre-defined follow-up sheets designed by the CNLS for HIV clinics to facilitate

timely retrieval of key indicators. This included patient demographics (age, sex, marital status, occupation and place of residence), WHO clinical stages, history of tuberculosis and positive Hepatitis B surface Antigen (HBsAg), CD4 count and HIV ARN, ART regimens and follow-up outcomes (ART failure, loss to follow-up, transfer out, and death) along with their specific dates. Additional information such as therapeutic adherence, opportunistic diseases, and genotype testing results was directly checked for in the patients' files. The data were initially collected retrospectively from October 2013 to October 2022 and subsequently supplemented with a one-year prospective collection period.

Outcomes

The primary outcome was VL suppression, defined as a VL < 400 copies/mL at 48 weeks after the initiation of second-line ART. Two secondary analyses described VL suppression, defined as < 50 copies/mL and < 1000 copies/mL, respectively. Because viral loads are not always completed regularly in routine care, we defined the 48-week window as the closest viral load to 24 months between 12 and 36 months.

Sample size and statistical analysis

To reduce the effect of selection bias, we performed a 1:1 ratio nearest neighbour propensity scores matching analysis between the test and control groups. Propensity scores were estimated by using a logistic regression model adjusted for age, sex, marital status, education level, income-generating activity, and history of opportunistic diseases, including tuberculosis, WHO stages, CD4 count, HBsAg positivity, first-line ART regimen, and site of follow-up. The obtained matched dataset was then checked for balance using standardized mean differences (SMDs) with the margin for optimal balance set at 0.2. Based on previous studies [19-21], we assumed that 80% of participants in the test group and 90% in the control group would have a viral load suppression of less than 400 copies per millimeter. With a noninferiority margin of -12% and a unilateral alpha risk of 5%, we calculated that 126 participants (63 per group) would provide 90% power to show noninferiority. Noninferiority was considered when the lower limit of the one-sided 95% confidence interval (CI) of the absolute difference in viral load suppression rates between groups was greater than -12%. We used the Dunnett-Gent chi-square test to compute the noninferiority p values.

Results

Figure 1 depicts the participant selection process. A total of 254 out of 907 pwHIV who were switched to second-line ART regimens during our study period were

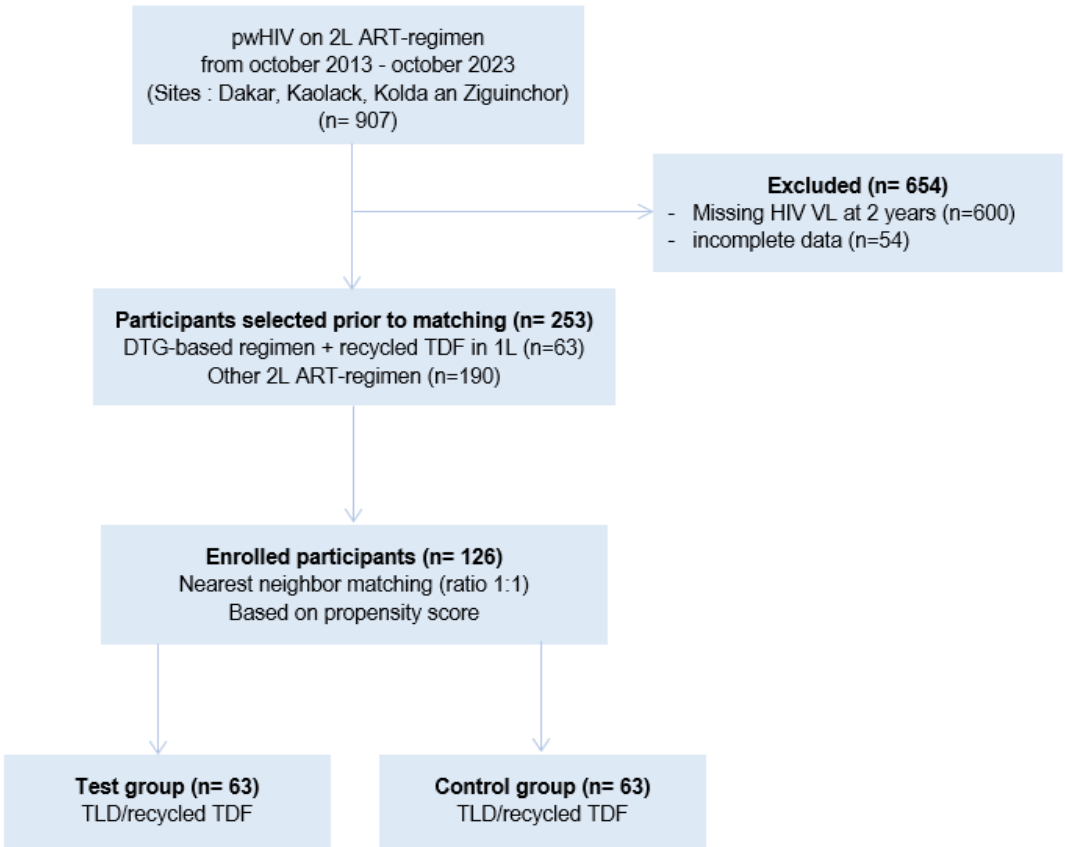

Figure 1: Study recruitment, enrollment and propensity score matching.

Abbreviations: HIV: Human Immunodeficiency Virus; pwHIV: people living with HIV; 1L: First-Line; 2L: Second-Line; ART: Antiretroviral Treatment; VL: Viral Load; DTG: Dolutegravir; TDF: Tenofovir Disoproxil Fumarate; TLD: Tenofovir, Lamivudine, Dolutegravir

Table 1: Baseline characteristics of participants before and after matching.

Characteristics	Overall			Propensity score matched		
	Control group N = 190	Test group N = 63	p	Control group N = 63	Test group N = 63	p
Age (years)	38 (29-44)	37 (25-46)	0.6	38 (31-45)	37 (25-46)	0.4
Female	118 (62.1)	44 (69.8)	0.3	42 (66.7)	44 (69.8)	0.7
Married	89 (46.8)	29 (46.0)	0.9	32 (50.8)	29 (46.0)	0.6
Education level			0.2			0.9
Under secondary level	78 (41.1)	19 (30.2)		19 (30.2)	19 (30.2)	
At least secondary level	46 (24.2)	15 (23.8)		13 (20.6)	15 (23.8)	
Missing	66 (34.7)	29 (46.0)		31 (49.2)	29 (46.0)	
Employment [Active]	109 (57.4)	32 (50.8)	0.4	34 (54.0)	32 (50.8)	0.7
Opportunistic diseases	118 (62.1)	59 (93.7)	< 0.001	59 (93.7)	59 (93.7)	0.9
WHO stage 4	50 (26.3)	16 (25.4)	0.9	17 (27.0)	16 (25.4)	0.8
CD4 < 200 (cell/mm^3)	140 (54-219)	140 (60-256)	0.6	140 (69-223)	140 (60-256)	0.9
HBsAg-Positive	13 (6.8)	5 (7.9)	0.8	6 (9.5)	5 (7.9)	0.8
Baseline-ART regimen			< 0.001			0.9
AZT/D4T-based	126 (66.3)	26 (41.3)		26 (41.3)	26 (41.3)	
TDF/ABC/DDI-based	64 (33.7)	37 (58.7)		37 (58.7)	37 (58.7)	
ART duration (years)	14.1 (10.5, 16.8)	13.1 (10.0, 17.7)	0.4	13.7 (9.7, 16.9)	13.1 (10.0, 17.7)	0.9
From Dakar sites	160 (84.2)	52 (82.5)	0.8	51 (81.0)	52 (82.5)	0.8

Categorical variables are presented as numbers (%), and quantitative variables are presented as medians (IQRs).

Abbreviations: WHO: World Health Organization; CD4: Class of Differentiation 4; HBsAg: Hepatitis B surface Antigen; ART: Antiretroviral Treatment; AZT: Zidovudine; D4T: Stavudine; TDF: Tenofovir Disoproxil Fumarate; ABC: Abacavir; DDI: Didanosine

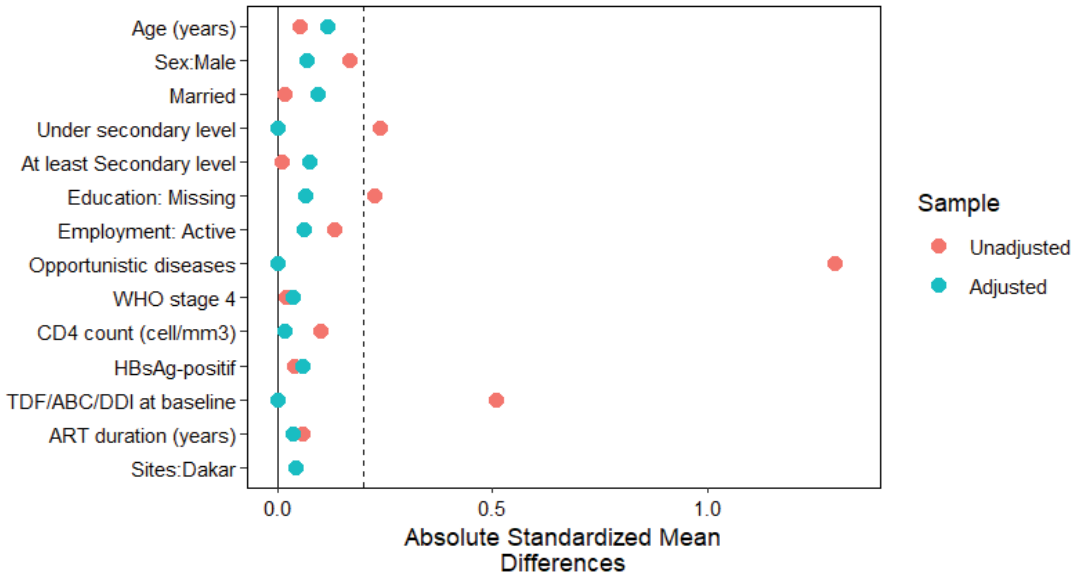

Figure 2: Balance of covariate distribution between treatment groups.

Abbreviations: WHO: World Health Organization; cell: cells; mm^3: Cubic Millimeter; HBsAg: Hepatitis B surface Antigen; TDF: Tenofovir Disoproxil Fumarate; DDI: Didanosine; ABC: Abacavir; ART: Antiretroviral Treatment

included in the matching process. Ultimately, 63 pairs were enrolled, and the SMDs for all covariates were < 0.2, indicating successful and optimal group matching, as illustrated in Figure 2. Of the 126 participants (63 per group) included, 86 (68.3%) were female, and 11 (8.7%) were coinfected with HBV. The median age and CD4 count were 38 years (interquartile range [IQR]: 27-46 years) and 140 cells/mm^3 (IQR: 64–230 cells/mm^3),

respectively. Seventy-two (64.3%) participants had a CD4 count < 200 cells/mm^3, and 33 (26.2%) were classified as WHO stage 4. The first-line ART at enrollment included TDF/ABC or DDI (didanosine)-based regimens for 74 (58.7%) participants and AZT/D4T (stavudine)-based regimens for 52 (41.3%) participants. Table 1 provides an overview of the baseline characteristics of participants in each treatment group, before and after the matching process. More than one-third of participants in the control group were on ritonavir-boosted protease inhibitors regimens as shown in Figure 3.

At the 48-week endpoint, 51 (81.0%) PLHIV had a viral load < 400 copies in the control group compared to 58 (92.1%) in the test group (difference: 11.10% 95% CI [1.23-20.97], p = 0.002), which met the prespecified noninferiority criterion (Figure 4).

Discussion

Assessing the effectiveness of recycling TDF and XTC as NRTI backbones is particularly crucial in Senegal. Local studies have shown that ~20% of individuals who fail TDF-based first-line ART develop the K65R mutation within 12 months of treatment initiation [1,7]. Such a strategy would be beneficial because tenofovir is better tolerated than zidovudine, and TLD is available as a single fixed-dose tablet taken once daily, while zidovudine requires twice-daily administration [24]. In this multicenter noninferiority-matched cohort study using routine data from 6 HIV-care referral centers in Senegal, we showed that recycling TDF and XTC with DTG in a second-line ART regimen was noninferior to SOC, achieving high virologic suppression rates at the 48-week follow-up: 77.8% vs. 69.8% (VL < 50 copies/mL) and 93.7% vs 95.7% (VL < 400 copies/mL).

Our findings were consistent with those of existing clinical trials assessing the efficacy of recycling TDF in second-line ART regimens. Among 464 participants in the NADIA trial with first-line treatment failure (≥ 1000

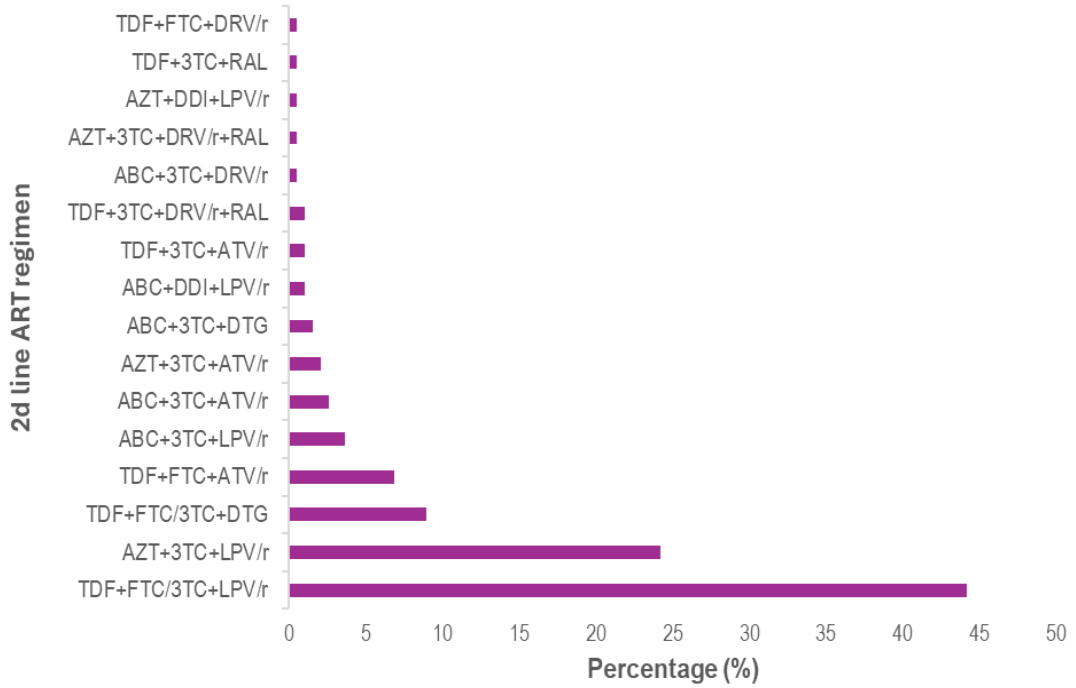

Figure 3: Antiretroviral treatment regimen of participants enrolled in the control group.

Abbreviations: ART: Antiretroviral Treatment; TDF: Tenofovir Disoproxil Fumarate; FTC: Emtricitabine; DRV/r: Ritonavir-boosted Darunavir; 3TC: Lamivudine; RAL: Raltegravir; AZT: Zidovudine; DDI: Didanosine; LPV/r: Ritonavir-boosted Lopinavir; ATV/r: Ritonavir-boosted Atazanavir; ABC: Abacavir; DTG: Dolutegravir.

Outcomes	Test group	Control group	Difference (90% CI)	p−value
HIV VL(cp/mL)	n/N(%)	n/N(%)		
<50	49/63 (77.8)	44/63 (69.8)	8.00 (−4.83 to 20.83)	0.004
<400	58/63 (92.1)	51/63 (81.0)	11.10 (1.23 to 20.97)	0.002
<1000	59/63 (93.7)	54/63 (85.7)	8.00 (−0.83 to 16.83)	<0.001

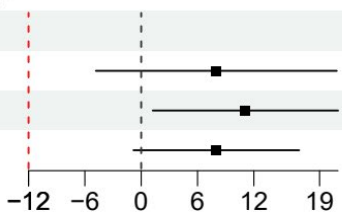

Figure 4: Viral suppression by recycled TDF vs other second-line regimens.

Abbreviation: CI: Confidence Interval; HIV: Human Immunodeficiency Virus; VL: Viral Load; cp/mL: Copies per millimeter.

copies/ml) on an NNRTI-based regimen with a TDF/XTC backbone, the use of recycled tenofovir for second-line treatment was noninferior at week 48 (92.2% vs. 89.67%) and superior (92% vs. 85%) at week 96 to the use of zidovudine combined with dolutegravir or darunavir for viral suppression (< 400 copies/ml) [19,20]. Preliminary results from the VISEND [10] and D2EFT [11] trials also revealed that TLD or a regimen of dolutegravir with tenofovir alafenamide and emtricitabine was noninferior for achieving viral suppression of ritonavir-boosted lopinavir or atazanavir (VISEND) and darunavir (D2EFT) at 48 weeks. This was achieved despite more than half of the participants not having fully active NRTIs on resistance testing in the recycled-TDF arm. In the single-arm ARTIST trial, which included participants who underwent recycling of the TDF-XTC backbone with DTG, 95% (57/60) and 84% (52/62) of the patients were virologically suppressed (VL < 400 copies/mL) at weeks 24 and 48, respectively [21,22]. Differences in suppression rates could be due to differences in patterns of adherence between the study populations as well as differences in cohort baseline virologic failure and postbaseline viral suppression thresholds.

Our study did not include genotype analysis. However, observational studies based on routine data, like ours, have found comparable results despite the presence of TDF resistance mutations in some cases. In a large cohort study including 1892 participants who switched to TLD in Malawi, 97.9% achieved viral load suppression (< 50 copies/mL) at week 48, although 88.3% of them were initially viremic. No increased risk of viremia or virological failure was observed in those with baseline NRTI resistance [25]. A retrospective cohort study with routine data from 59 clinics in South Africa, the authors did not find evidence of a significant difference in retention (85.7% vs. 76.9%) or viral suppression (80.6% vs. 84.8%) between TDF/XTC/DTG and AZT/XTC/DTG at the twelve-month follow-up [26].

All studies mentioned above [25,26], including our own, advocate of the routine recycling of TDF in settings with limited access to genotype testing. However, attention should be drawn toward resistance to DTG. Data from eight HIV cohorts, seven from high-income countries and one from an upper-middle-income country, showed that individuals with intermediate or high-level NRTI resistance were thirteen times more likely to develop DTG resistance than were those with fully active NTRIs [27]. According to the World Health Organization's (WHO) latest HIV Drug Resistance (HIVDR) Report, the prevalence of DTG resistance ranges from 3.9% to 8.6%, reaching 19.6% among people who experienced treatment and transitioned to DTG-containing ART while having high HIV viral loads [1]. Although these data are based only on four countries, monitoring remains important to prevent resistance at the individual and population levels and ensure the long-term sustainability of ART.

Our study is one of the few real-world cohort studies, addressing the reuse of TDF and XTC with DTG in low-income countries where access to genotype tests is limited. The results from this study are of interest to clinicians and researchers in the field of HIV research, as well as to policymakers, as it addresses pertinent public health questions regarding antiretroviral resistance.

One of the main limitations of this study is that therapeutic failure was defined based on clinical and immunological criteria because genotype tests are not routinely recommended for switching individuals from first- to second-line ART in Senegal. While this may lead to an overestimation of therapeutic failure, the definitions of ART failure based on clinical events and CD4 count that we used are still recommended by the WHO in settings with limited access to genotype tests. We excluded many participants due to missing HIV viral load data at the endpoint. However, this issue, common in observational studies, did not impact our results, as our sample size was sufficient to address our research question.

Conclusion

Aligned with results from the NADIA trial and similar studies, our study supports the routine recycling of TDF and XTC with DTG as a second-line ART regimen in settings where timely access to genotype testing is limited. However, further studies are required to assess its long-term efficacy. Active surveillance and strategies to mitigate and promptly detect dolutegravir resistance are strongly recommended. This approach would streamline implementation and ensure that this effective, well-tolerated, and cost-effective regimen is accessible to millions of patients.

Declarations

Ethics approval and consent to participate

This research analyzed routinely collected medical data from five HIV clinics in Senegal. The opening of the medical files, follow-up, and ART initiation at all sites were done with the patients' consent. The protocol was approved by the UNIGOM Institutional Review Board. UNIGOM/CEM/04/2022.

Availability of data and materials

The data presented in this study are available on request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Declaration of generative AI

During the preparation of this work the authors used ChatGPT in order to improve readability and language. After using this tool, the authors reviewed and edited

the content as needed and take full responsibility for the content of the publication.

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