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Research Article

Efficacy of Lamivudine and Dolutegravir simplification therapy compared with triple therapy in Northeast Brazil (LAMDO Study)

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Abstract

Background: Modern antiretroviral therapy provides numerous effective and well-tolerated treatment options for individuals living with HIV. However, due to medication tolerability, toxicity, and cost optimization associated with the emergence of highly potent drugs, dual therapy has emerged as a new therapeutic alternative for patients with viral suppression. Observational studies worldwide are being conducted to assess the effectiveness of dual therapy in people living with HIV/AIDS. A real-world study is important to validate the findings obtained in controlled studies.

Objective: Assess the effectiveness of dual therapy with lamivudine and dolutegravir compared to triple therapy in real-life settings.

Methods: The study was conducted at São José Infectious Diseases Hospital, a tertiary referral hospital in the state of Ceará, northeast Brazil, for the treatment of PLWHA.

Results: A total of 521 patients were taking double therapy with lamivudine plus dolutegravir and 450 patients were in triple therapy, mostly in the use of association with dolutegravir, were analyzed. Patients on dual therapy had a higher median age compared to those on triple therapy. A statistically significant higher viral suppression was observed in patients on dual therapy compared to triple therapy ($p < 0,001$). Viral suppression on dual therapy under 200 copies was 97.2%. There was a statistically significant higher percentage of patients with higher CD4/CD8 ratio using triple therapy compared to dual therapy.

Conclusion: The current study suggests a higher effective response to dual therapy compared to triple therapy in PLWHA in the real-world, supporting therapy simplification as a sustainable option to maintain virological suppression in patients experiencing toxicity or comorbidities.

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Introduction

The Human Immunodeficiency Virus (HIV), identified in 1983 by French virologists, acts on T lymphocytes, destroying these cells and rendering the patient susceptible to opportunistic infections, leading to the Acquired Immunodeficiency Syndrome (AIDS) [1]. Since this new disease discovery, it has been a challenge for treatment that could provide surveillance and quality of life (QoL) to people living with HIV/AIDS (PLWHA). With the Advent of Antiretroviral Therapy (ART), AIDS, once a potentially fatal disease, became controllable and transformed into a chronic condition [2]. PLWHA gained a greater and improved life expectancy, but quality was a continued issue since toxicity and high numbers of pills were a restrictive barrier to better life quality. ART can improve survival, reduce the incidence of HIV-related opportunistic infections, and improve patients' QoL. Clinical improvement in HIV-infected patients on ART has often been measured by reductions in mortality, opportunistic infection rates, or severe AIDS-related symptoms. However, general assessments of the QoL of PLWHA have also become a focus of interest as more effective and simpler regimens have become available [3]. The ability to detect, diagnose, and treat HIV has improved significantly, enabling more PLWHA to achieve a life expectancy similar to that of the general population. However, PLWHA is at excess risk of age-related comorbidities, which can be exacerbated by late diagnosis and can affect mental health and physical functioning. In addition, enduring societal and structural issues, including stigma, poverty, syndemics, and social isolation, continue to threaten their QoL [4].

HIV treatment regimens have undergone changes over the years, initially starting with monotherapy using Zidovudine to the current combined antiretroviral therapy. Triple combination therapy with three antiretroviral drugs has been recommended since 1996, based on the use of at least two different drug classes including protease inhibitors [5]. Currently, triple therapy is highly effective, since the integrase inhibitors started to be used as a preferential regimen, with most patients achieving undetectable viral loads, thus accomplishing the primary treatment goal [1]. For most patients with HIV infection and opportunistic infections, initial therapy should include an Integrase Strand Transfer Inhibitor (INSTI)-based ART regimen, even in advanced cases. INSTI-based ART has been shown to reduce HIV viral load more quickly than Protease Inhibitor (PI) or Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based ART regimens. Therefore, severely immunocompromised patients may be at an increased risk of Immune Reconstitution Inflammatory Syndrome (IRIS) with INSTI-based ART, besides HIV's highly suppressed effect. A study demonstrated that the incidence of IRIS within 6 months of ART initiation was 9.4%, and there were no significant differences in baseline characteristics and incidence of IRIS between the matched groups [6].

Integrase inhibitors have also shown to be effective and well-tolerated in patients co-infected with tuberculosis and HIV/AIDS. They can be considered as an alternative to efavirenz in clinical protocols. However, the need to take this medication twice a day may compromise treatment adherence [7]. However, due to medication tolerability, toxicity, and cost optimization associated with the emergence of highly potent drugs, dual therapy has emerged as a new therapeutic alternative for patients with viral suppression [8]. For pregnant women with HIV, ART plays a key role in the prevention of perinatal transmission. Newer antiretroviral regimens now contain integrase strand transfer inhibitors, which have been found to rapidly suppress HIV viral load in nonpregnant women and are also the first recommended option in WHO guidelines [9,10].

Modern antiretroviral therapy provides numerous effective and well-tolerated treatment options for individuals living with HIV, whether they are initiating treatment for the first time or have prior treatment experience. The introduction of INSTI, such as Dolutegravir (DTG), which exhibits high potency and a robust genetic barrier, has expanded the possibilities for initiating and simplifying ART. One study even tried monotherapy, of the 101 patients randomized, 68 were assigned to simplification to dolutegravir monotherapy and 33 to continuation of triple ART. At week 48 in the per-protocol population, 67/67 (100%) had virological response in the dolutegravir monotherapy group vs 32/32 (100%) in the ART group. This showed the noninferiority of the dolutegravir monotherapy at the prespecified level [11]. Another study evidenced that virologic failure (VF) at 24 weeks was lower on dual therapy than on monotherapy (adjusted odds ratio: 0.10, 95% CI 0.03-0.30). Therefore, DTG-based dual therapy seems to be a promising simplification strategy for individuals with a suppressed HIV viral load on triple-ART, while VF is relatively common in DTG maintenance monotherapy [12]. Additionally, recent advancements in clinical practice have introduced ART strategies involving fewer drugs, gaining widespread use globally. This trend allows for increasingly personalized therapies that balance efficacy and tolerability while enhancing lesser medication intake for PLWHA, thereby contributing to an improved quality of life [13].

Moreover, the availability of Single Tablet Regimens (STRs) appears to align with patient preferences and enhances treatment adherence. The utilization of two-drug regimens containing DTG, particularly in combination with lamivudine (3TC), emerges as one of the most promising approaches to simplify HIV treatment management without compromising its effectiveness and safety. STRs offer the potential benefit of avoiding selective non-adherence, where the patient takes part of a regimen but not the full regimen. Simplification of combination antiretroviral therapy has been associated with improved QoL. Although other factors may temper this effect, better adherence, higher QoL, and patient preferences are all important factors that can contribute to the long-lasting efficacy and durability of ART. All studies have highlighted the favorable tolerability profile of newer STRs. All of the drugs have demonstrated excellent efficacy. More recent formulations have improved safety and tolerability. Several other STRs are anticipated, including combinations of different drugs such as abacavir (ABC) plus lamivudine (3TC)/dolutegravir, innovative formulations of older drugs like tenofovir alafenamide fumarate, or the use of bioequivalent drugs such as lamivudine

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(3TC) plus ABC/EFV. The future challenge is to develop completely alternative short tandem repeats (STRs), such as protease inhibitors or new molecules, to extend the advantages of simplicity to heavily pre-treated individuals [14]. The DTG/3TC once-daily, single-tablet regimen is the first dual ART recommended for the initial treatment of HIV-1 infection in treatment-naïve adults. In the GEMINI studies, DTG and 3TC were compared with a regimen of DTG and tenofovir disoproxil fumarate/emtricitabine and demonstrated noninferiority for the primary endpoint of virological suppression at up to 96 weeks. No treatment-emergent resistance mutations were found in a small group of participants who did not achieve virological suppression. The treatment regimen is well-tolerated, with the most frequently reported adverse events in trials being headache, diarrhea, nausea, insomnia, and fatigue [15].

Observational studies worldwide are being conducted to assess the effectiveness of dual therapy in people living with HIV/AIDS. A retrospective observational study included 112 HIV-1-infected patients in China. The study found that the 3TC + DTG dual therapy demonstrated excellent virological efficacy against HIV-1 infections and had an acceptable safety profile, with predominantly mild adverse events. The virological suppression rates of male patients who have sex with men and patients with a CD4+ T-cell count of less than 350 cells/μL were higher than the baseline value ($p < 0.05$) at week 24 [16]. The DOLAMA study at week 48, demonstrated that 82.4% of patients achieved a viral load of less than 50 copies per microliter using an Intention-To-Treat (ITT) analysis. The modified ITT (mITT) analysis showed an increase of 89.6%, and the Per-Protocol analysis showed an increase of 96.7%. The incidence of Virological Failure (VF) was only 3.3%. The combination of lamivudine (3TC) and Dolutegravir (DTG) was a safe and effective option for simplifying ART in pretreated and virologically stable HIV-positive patients. This combination is cost-effective and offers the same effectiveness as the triple therapy it replaces [17]. However, due to it being a recent recommendation, long-term studies are necessary to evaluate the virological suppression and immunological control of patients who have undergone a treatment switch [5]. Therefore, real-world studies are important to validate the findings obtained in controlled studies. The aim of this current study is to evaluate efficacy related to virological suppression and immunological control in PLWHA using dual therapy after simplification compared to maintaining triple therapy.

Statement of the problem and study justification

In Brazil, triple therapy with tenofovir, lamivudine, and dolutegravir is recommended as the initial regimen. The initiation of dual therapy is not allowed because patients do not undergo pre-therapy genotyping tests as routine. However, simplification to dual therapy with lamivudine and dolutegravir is allowed after 6 months of viral suppression. At the time of the study, therapy was administered using non-combined formulated tablets. Therefore, patients on triple therapy used a combination of two tablets (1 combined formulated tablet of tenofovir and lamivudine, and 1 tablet of dolutegravir), and those on dual therapy used three tablets (2 lamivudine tablets and 1 dolutegravir tablet). Therefore, therapy simplification in Brazil is not aimed at reducing the number of pills per day but rather at toxicity control, especially related to tenofovir fumarate [18]. The population of PLWHA has a longer survival, but still with a high incidence of comorbidities such as diabetes mellitus and systemic arterial hypertension, which further contribute to renal toxicity [19]. Numerous studies indicate that PLWHA exhibits a higher occurrence of multimorbidity, and comorbidity compared to the general population. This heightened prevalence can be attributed to factors such as premature aging, the side effects of antiretroviral therapy, and the biological impacts of HIV infection [20-22]. Among the most common comorbidities associated with HIV are cardiovascular diseases, cancers, diabetes, dyslipidemia, chronic renal disease, hepatitis B, and hepatitis C [20]. Globally, there is a rising population of older adults (aged over 50 years) living with HIV, naturally leading to an uptick in the prevalence of HIV-related comorbidities [23]. Additionally, the aging process itself and the risk of osteopenia and pathological fractures make it challenging to maintain triple therapy in the older population. The present study aims to analyze whether, even without the impact of reducing the number of tablets, it is possible to maintain the good efficacy of dual therapy compared to triple therapy in real-life PLWHA [24].

Objectives of the study

The overall objective of the study was to assess the effectiveness of dual therapy with lamivudine and dolutegravir compared to triple therapy, in real-life settings. Secondary objectives included evaluating the maintenance of immunological response and the CD4/CD8 ratio as a marker of inflammation. Epidemiological characterization data were also taken into consideration.

Methodology

Study location

The study was conducted at São José Infectious Diseases Hospital, a tertiary referral hospital in the state of Ceará for the treatment of people living with HIV/AIDS (PLWHA). The state of Ceará is in the Northeast region of Brazil, an area considered to have greater economic limitations and a population with lower income compared to the southern and southeastern regions of the country. In this region, late diagnosis of HIV and delayed initiation of treatment are current concerns due to their impact on mortality. The hospital currently manages around 11,000 patients on antiretroviral treatment and has approximately 130 beds for inpatient care.

Study population

The study population consisted of PLWHA from the outpatient clinic of Hospital São José de Doenças Infecciosas do Ceará, which is a state reference for monitoring this specific population. A list of patients using dual therapy and triple therapy with dolutegravir was randomly obtained based on those who picked up medication in the last 6 months during data collection (May to November 2023). Patients with similar epidemiological profiles and treatment durations were selected.

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Data collection

In Brazil, the surveillance of AIDS epidemiology relies on data from reported cases in the Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação - SINAN) and recorded deaths in the Mortality Information System (Sistema de Informação sobre Mortalidade - SIM), but also incorporates information from two additional systems: the Laboratory Tests Control System (Sistema de Controle de Exames Laboratoriais - SISCEL) and the Medication Logistics Control System (Sistema de Controle Logístico de Medicamentos - SICLOM). These systems collectively form the foundation of the National HIV/AIDS registry in Brazil [25].

The SISCEL system is designed to monitor CD4 T lymphocyte (CD4+ T-cell) counts and HIV Viral Load (VL) assessments [25]. From May 2023 to November 2023, patients were voluntarily enrolled during their follow-up visits at the HIV outpatient clinic. Variables examined included age, gender, viral load, CD4 count, CD4/CD8 ratio, and the regimen of triple or dual therapy.

The Cobas 4800 HIV-1 kit with a detection limit of 14.2 copies/mL, and the Cobas 5800 HIV-1 kit detection limit of 13.2 copies/mL when using a sample volume of 500 mL for analysis are used to detect viral load. The linearity for quantification of both kits (Cobas 4800 HIV-1 and Cobas 5800 HIV-1) is from 20 to 10,000,000 copies/mL. In other words, the methodology can identify the presence of the virus in the sample when there is a concentration of at least 13.2 copies/mL (when using Cobas 5800 HIV-1) or 14.2 copies/mL (when using Cobas 4800 HIV-1), and it is capable of quantifying viral particles from 20 copies/mL for both kits. Individuals who previously had a detection/quantification limit of 40 copies/mL may now have detectable viral loads due to the lower detection/quantification limit of the current supplier's tests. Therefore, it's important to understand that the sensitivity of the new methodology may lead to the detection of cases that would not have been detected using the previous methodology. Below the lower limit of quantification (< LLOQ): This refers to the methodology being able to detect HIV RNA but unable to quantify it. This corresponds to the amount of virus that is between the analytical sensitivity value and the lower limit of quantification of the method [26].

Methodology used for CD4 and CD8: Flow Cytometry / Rapid CD4. This methodology allows for the counting of CD4+ and CD8 T lymphocytes, without evaluating other cellular populations. Patients with a CD4 count below 350 cells/mm3 should be reported by the physician in SINAN. It is recommended to investigate opportunistic infections in these patients, as well as to assess the indication for treatment for LTBI, according to the Clinical Protocol and Therapeutic Guidelines for the Management of HIV Infection (PCDT). There is no need for a new request for CD4+ T lymphocyte count exams for patients with results above 350 cells/mm3 in two consecutive tests, with a 6-month interval, in Brazil [26].

Ethic declaration

This is a cross-sectional, quantitative study that adhered to ethical principles regulated by Resolution No. 466/12 of the National Health Council (2012). The research project was submitted to the Research Ethics Committee of Unichristus - Plataforma Brasil. It is emphasized that in accordance with Resolution CNS No. 196/96, confidentiality, anonymity, and non-utilization of information to the detriment of individuals were ensured. There were no risks to the research subjects, and the data were used only for the purposes outlined in this study. The benefits obtained from this study were intended to benefit people living with HIV/AIDS (PLWHA) and the scientific community for the better management of antiretroviral therapy. The approval number from the Ethics Committee is 4.078.405, and the Certificate of Presentation for Ethical Consideration (CAAE) is 31342020.4.0000.5049.

Statistical analysis

Data were presented as absolute and percentage frequency or mean and standard deviation and were associated with antiretroviral therapy (ART) using Fisher's exact test, Pearson's chi-square test, or Student's t-test (parametric data). All analyses were conducted with a 95% confidence level using SPSS v20.0 software for Windows.

Results

ARV regimens analysis

Table 1 shows the patients who were initially selected using dual therapy and triple therapy. A total of 521 patients were taking double therapy with lamivudine plus dolutegravir and 450 patients were in triple therapy, mostly in use in association with dolutegravir.

We observed that the most used regimens were: 3TC/DTG, TDF/3TC/DTG, and ABC/3TC/DTG, all combinations in double or triple therapy with dolutegravir. Few patients were taking Efavirenz or Darunavir. This shows that integrase inhibitor therapy prevails in Brazil. A previous study examined the independent effect of different ART regimens on cumulative HIV viremia during the first 12 months of treatment, using

Table 1: Regimens used for patients in the initial evaluation.

Regimen ARV	n (%)
3TC/DTG	521 (53.7)
TDF/3TC/DTG	337 (34.7)
ABC/3TC/DTG	94 (9.7)
TDF/3TC/EFZ	8 (0.8)
TDF/3TC/DRVr	2 (0.2)
AZT/3TC/DTG	1 (0.1)
AZT/3TC/EFZ	1 (0.1)
DRV/RTV/DTG	1 (0.1)
EFZ/TDF/3TC	1 (0.1)
TDF/3TC/DRV	1 (0.1)
TDF/3TC/NVP	1 (0.1)
ATV/RTV/TDF/3TC	1 (0.1)
DRV/RTV/ETR/DTG	1 (0.1)
TDF/3TC/DTG/DRV/RTV	1 (0.1)

Data is presented in the form of absolute frequency and percentage.
3TC: lamivudine; DTG: Dolutegravir; TDF: Tenofovir Fumarate; ABC: Abacavir; EFZ: Efavirenz; DRVr: Darunavir, Ritonavir; AZT: Zidovudine; NVP: Nevirapine; ATVr: Atazanavir; ETR: Etravirine.

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programmatic data from the Ministry of Health of Brazil. The ART regimen with dolutegravir associated with a tenofovir-lamivudine backbone was superior to regimens with efavirenz or boosted atazanavir in reducing HIV VL, as shown by cumulative viremia during the first 12 months of treatment. The superiority persisted after adjustment for potential confounders [27]. Another study measured adherence and compared the use of "backbone" tenofovir/lamivudine plus efavirenz one tablet once-daily (STR) or dolutegravir in multi-tablet once-daily (MTR-DTG), or other multi-tablet regimens (MTR-other). A total of 393 patients were included, and analysis showed a higher chance of adherence among patients using MTR-DTG, those who received and understood counseling about their treatment, and those with a higher quality of life. Prior use of illicit drugs in the lifetime was associated with poorer adherence. Overall adherence was low, highlighting the need for strategies focusing on counseling about medicines and substance use. Pill burden was not an issue for patients using MTR-DTG once daily, who achieved better results [28].

Demographic characterization

Table 2 demonstrates a correlation between age and sex, without statistical difference significant, and patients were under triple therapy for a median of 246.98 ± 176.12 weeks before simplification. The table also highlights that patients on dual therapy had a higher average age compared to those on triple therapy, supporting the indication of simplification in Brazil to reduce toxicity or prevent it in older patients. This is noteworthy as there is no reduction in the number of pills with simplification. Additionally, a statistically significant difference is observed when comparing therapy duration in weeks, given that the use of dual therapy, according to the Brazilian consensus, is relatively recent.

A recent cross-sectional multicentre study in HIV testing services in Brazil and Peru (15 cities), to detect recent infection, evidenced that from 31-Jan-2021 to 29-May-2022, 4.586 (66.5%) individuals participated in Brazil, and overall, 5946 (86.2%) were cisgender men, 751 (10.9%) transgender women and 202 (2.9%) non-binary/gender diverse [29]. This finding corroborates the higher number of men than women in our study. The lower average age of patients on triple therapy compared to double therapy can also be explained by the late simplification of therapy in the country, since this tends to occur when the patient is at greater risk of kidney or bone disease due to tenofovir. A study showed that "Experienced ageing" patients typically had one or more comorbidities (62.1%) and were receiving at least one comedication (71%). Central Nervous System (CNS) agents (prescribed in 44.6% of the "experienced ageing" patients) and antilipidaemics (in 44.2%) were the most frequently prescribed comedications. INSTIs were used in 23% of the population and were used significantly more often in patients with comorbidities and coprescriptions [30].

There was a statistical difference detected between the time patients used dual and triple therapy. As the recommended therapy in the country to date is triple therapy, the majority of patients are on combined therapy with three medications. The possibility of using simplified therapy with two medications was only allowed in the country on a technical note in 2021 [31].

Analyzes of immunological and virological data – Efficacy Dual *vs.* Triple Therapy

Table 3 analyzes the immunological and virological data of the patients. A statistically significant higher viral suppression (viral load below 20 copies) was observed in patients on dual therapy compared to triple therapy. In Table 4, we stratified viral suppression by the number of copies, and dual therapy consistently maintained a better response, including a response below 200 copies with 97.2% efficacy. There was also a higher percentage of patients on dual therapy with CD4 counts greater than 250 cells/mm³ but not exceeding 350 cells/mm³ compared to triple therapy. This could be related to a potential higher adherence to dual therapy compared to triple therapy, directly impacting greater immunological recovery and viral suppression. However, there is a statistically significant higher percentage of patients with a higher CD4/CD8 ratio using triple therapy compared to dual therapy. When evaluating the CD4/CD8 ratio above 1, this statistical difference

Table 2: Demographic Characteristics and Therapy Duration of the Study Population.

		Regimen ARV		
Sex	**Total**	**Dual**	**Triple**	***p* - value**
Female	238 (24.5%)	132 (25.3%)	106(23.6%)	0.520
Male	733 (75.5%)	389 (74.7%)	344(76.4%)	
Age	47.39 ± 13.59	51.55 ± 12.33*	42.58 ± 13.41	< 0.001
Duration of actual TARV	115.17 ± 112.63	70.16 ± 47.45	167.29 ± 140.43*	< 0.001

**p* < 0.05, Fisher's exact test or Pearson's chi-square test (n, %) or Student's t-test (mean ± SD).

Table 3: Virological and immunological responses of the patients in the study.

		Regimen ARV		
	Total	**Dual (N = 521)**	**Triple (N = 450)**	***p* - value**
Suppressed Viral load	18033 ± 173712	409 ± 3802	32700 ± 234220	0.009
Yes	639(81.3%)	322(90.2%)*	317(73.9%)	<0.001
No	147(18.7%)	35(9.8%)	112(26.1%)*	
CD4 absolute value	558.26 ± 366.87	525.85 ± 286.45	565.93 ± 383.37	0.355
CD4 count cells/mm³				
<250	86(18.5%)	10(11.2%)	76(20.2%)*	0.049
≥250	379(81.5%)	79(88.8%)*	300(79.8%)	
CD4 count cells/mm³				
<350	140(30.1%)	24(27.0%)	116(30.9%)	0.473
≥ 350	325(69.9%)	65(73.0%)	260(69.1%)	
Relation CD4/CD8	0.64 ± 0.45	0.53 ± 0.30	0.67 ± 0.47	0.012
<1	371(80.8%)	79(94.0%)	292(77.9%)	0.001
≥1	88(19.2%)	5(6.0%)	83(22.1%)	
CD8 absolute value	985.78 ± 547.11	1111.42 ± 550.55	956.29 ± 542.83	0.017
Relation CD4/CD8				
Duration between Simplification and last exam	54.93 ± 157.16	5.97 ± 165.53	96.35 ± 136.83	<0.001

**p* < 0.05, Fisher's exact test or Pearson's chi-square test (n, %) or Student's t-test (mean ± SD).

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Table 4: Virological stratified response of the patients in the study.

	Regimen ARV		
Viral load copies	Dual (N = 357)	Triple (N = 429)	*p* - value
< 20	322 (90.2%)	317 (73.9%)	< 0.001
<50	341 (95.5%)	350 (81.6%)	
<200	347 (97.2%)	375 (87.4%)	
> 200	10 (2.8%)	54 (12.6%)	

also persists in favor of triple therapy. These findings may be related to better inflammatory control in patients using triple therapy, but further investigation with inflammatory markers would be necessary. Considering that there is a higher likelihood of older patients and those with comorbidities in the dual therapy group, there is also a higher probability of an inflammatory response. The quantity of CD8 is higher in dual therapy; however, patients who underwent CD4 and CD8 testing have older tests than those on dual therapy, following the recommendations of the Brazilian Guideline.

Following long-term therapy, patients generally present with significant CD4 T-cell recovery in contrast to persistently elevated CD8 T-cell counts, leading to a partial restoration of the CD4:CD8 ratio. A low CD4:CD8 ratio has been associated with aging and acts as a predictor of mortality in the general population. This ratio may represent the combined effects of inflammation and immunological changes termed "inflammaging". Although the mechanisms underlying partial correction of the CD4:CD8 ratio and persistently elevated CD8 T cell counts in long-term treated patients remain poorly understood, recent evidence suggests that patients with optimal CD4 T cell recovery and low CD4:CD8 ratios still have increased immune activation, an immunosenescent phenotype, and are at increased risk of non-AIDS morbidity and mortality. The CD4:CD8 ratio can contribute to the immunologic evaluation of treated patients in long-term follow-up and can be used to monitor both immune dysfunction and viral reservoir size in immune-based clinical trials [32]. A study evidenced that a CD4:CD8 ratio increase is observed during suppressive dual regimens, and its extent is related to baseline values and previous HIV-related factors [33]. Another author reported that earlier and more intense CD4:CD8 ratio recovery was observed in patients with higher physical activity in the two-year follow-up (p = 0.049), [34]. A key feature of HIV infection is the expression of multiple proinflammatory cytokines. Expressed as soluble factors or membrane-bound molecules, proinflammatory cytokines regulate both HIV replication and T-cell apoptosis. Proinflammatory cytokines play a key role in the HIV life cycle, particularly at the transcriptional level, favoring the ability of HIV to establish latent reservoirs. In addition, proinflammatory cytokines are involved in the apoptosis of both CD4+ T cells and CD8+ T cells, leading to immune suppression. Furthermore, several HIV proteins such as Nef, Tat, and Vpr hijack proinflammatory cytokine signaling, further highlighting the potential importance of inflammation in HIV pathogenesis. *In vivo*, chronic inflammatory conditions have been correlated with increased viremia and accelerated disease progression. Understanding the role of inflammation in HIV infection may lead to new therapeutic strategies that could ultimately enhance immune recovery and limit viral reservoir formation in HIV-infected patients [35].

A study demonstrated that switching to a dual ART regimen based on lamivudine + dolutegravir maintains virologic efficacy until week 24 and is associated with slight improvements in immunologic and metabolic status. The strategy allows the free use of concomitant medications for associated pathologies. Dual therapy is less expensive in economic terms [36]. A Swiss study evidenced that de-escalation to dolutegravir/FTC or dolutegravir/3TC is possible in the majority of patients virologically suppressed on triple ART, and may effectively address patient and physician concerns about long-term safety and cost of ART [37]. Comparing the viral decay seen in the pilot ACTG A5353 study with the decay observed with dolutegravir plus two NRTIs in the SPRING-1 and SINGLE studies, while also exploring the impact of baseline viral load concluded that viral decay with dolutegravir/lamivudine was comparable to viral decay with dolutegravir-based triple therapy, even in individuals with higher pretreatment VL (> 100000 copies/mL) [38].

Discussion

In recent years, there has been a growing focus on simplifying HIV treatment regimens in order to improve adherence and outcomes for individuals living with HIV. One strategy that has gained attention is the use of lamivudine and dolutegravir as a simplified therapy combination. Lamivudine and dolutegravir, when used in combination, have shown promising results in achieving durable and lifelong suppression of HIV replication, which is crucial in managing the disease as a chronic condition. By simplifying the regimen to lamivudine and dolutegravir, patients can potentially experience fewer adverse events compared to other regimens. Research studies have demonstrated the effectiveness and safety of lamivudine and dolutegravir therapy in managing HIV. One of the key advantages of this combination is its ability to reduce pill burden, as it involves taking only two medications instead of the more complex regimens that may require multiple pills at different times throughout the day. This simplified approach not only improves adherence but also reduces the likelihood of missed doses, contributing to better long-term viral suppression [39].

Furthermore, the potential cost savings associated with a simplified regimen could have significant implications for healthcare systems and patients alike. As healthcare providers continue to explore and promote simplified treatment options, the use of lamivudine and dolutegravir therapy represents a promising advancement in HIV care.

The findings of patients who simplified to dual therapy suggest its use in Brazil's older population, primarily due to the renal and bone toxicity associated with tenofovir [40,41]. The alternative for triple therapy would involve the use of zidovudine, which causes significant metabolic toxicity along with lipodystrophy [42,43], or abacavir, which has been correlated with cardiovascular events [44]. Therefore, considering the toxicity associated with triple therapy, simplifying to dual therapy appears to be the better option for patients. Switching to a two-drug regimen is a viable option for individuals with HIV who have achieved virological

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suppression. Some clinicians, even in the absence of evident contraindications to triple therapy, contemplate the potential benefits of reducing lifetime antiretroviral exposure through a two-drug regimen, provided it does not compromise virological outcomes or safety, and prevent side effects and toxicity in the future. Additional factors prompting a switch to a two-drug regimen may include payer or insurance restrictions, cost considerations, pill size, drug-drug interactions, and drug intolerance [45].

Several switch studies have been conducted in virologically suppressed patients, as combinations of dolutegravir plus lamivudine, dolutegravir plus rilpivirine, boosted darunavir or atazanavir plus lamivudine, and long-acting cabotegravir plus long-acting rilpivirine. The European AIDS Clinical Society also considers boosted darunavir plus rilpivirine or dolutegravir as potential two-drug regimens for individuals with HIV who have experience with antiretroviral therapy. An important benefit of antiretroviral therapy is preventing HIV transmission, which does not occur in serodifferent sexual partners when the viral load is suppressed to less than 200 copies per mL [46].

The present study demonstrated greater virological suppression with dual therapy in real-life settings, including a response below 200 copies with 97.2% efficacy. providing support for this option in patients requiring therapy simplification with safety. The combination of dolutegravir plus lamivudine presents advantages as the absence of specific food and calorie requirements associated with dolutegravir plus rilpivirine, as well as the metabolic and drug interaction concerns linked to boosted darunavir. Numerous studies have consistently demonstrated the efficacy and safety of dolutegravir plus lamivudine when employed as a switch strategy for individuals with HIV who have not experienced previous treatment failure or developed resistance. In the most extensive trials, spanning up to week 144 in TANGO23 and week 48 in SALSA21, no participants experienced virological failure. Additionally, participants in the groups receiving dolutegravir plus lamivudine in ASPIRE, TANGO, DOLAM, or SALSA showed no development of resistance-associated mutations to INSTIs or reverse transcriptase inhibitors [47-49].

Conclusion

The current study suggests a highly effective response to dual therapy compared to triple therapy in people living with HIV/AIDS (PLWHA) in real-life settings, supporting therapy simplification as a sustainable option to maintain virological suppression in patients experiencing toxicity or comorbidities that may impact their future survival and quality of life. Long-term studies can provide further support and should be continued, particularly concerning the inflammatory evaluation of dual therapy, given the findings indicating a poorer response in the CD4/CD8 ratio.

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