REVIEW

Two-drug maintenance therapy with dolutegravir/lamivudine in virologically suppressed HIV-1 patients: a systematic review and meta-analysis

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ABSTRACT

Background: The global burden of HIV remains significant, with approximately 39.9 million people living with the virus. Multi-drug antiretroviral therapy (ART) regimens can complicate treatment due to drug interactions, costs, and adherence issues. Dolutegravir (DTG) and Lamivudine (3TC) represent a promising two-drug regimen that may simplify therapy while maintaining efficacy.

Methods: We searched databases PubMed, Cochrane CENTRAL, Science Direct, and Google Scholar for randomized controlled trials (RCTs) assessing the safety and efficacy of switching to a dual therapy regimen of DTG and 3TC in HIV-1 seropositive adults. Primary outcomes included rates of virological suppression (HIV-1 RNA < 50 copies/mL) and virological failure.

Results: Five RCTs with 1,654 participants met the eligibility criteria. The rate of virological suppression (HIV-1 RNA < 50 copies/mL) was similar between those switching to DTG/3TC and those remaining on CAR (RR = 1.03, *P* = 0.11). No significant differences in virological failure rates or CD4+ cell counts were observed (RR = 0.56; *P* = 0.36; SMD = 0.08; *P* = 0.11). However, switching to DTG/3TC significantly improved the CD4+/CD8+ cell count ratio (SMD = -0.1; *P* = 0.04). Adverse event rates were comparable, with notable reductions in total and HDL cholesterol in the DTG/3TC group (SMD = -0.28; *P* = 0.03).

Conclusion: This analysis supports that switching to DTG/3TC is a viable option for maintaining virological suppression in adults with HIV, offering a simplified and effective approach to ART. Further research is needed to explore long-term effects and patient quality of life associated with two-drug regimens.

Keywords: HIV, virological suppression, DTG/3TC, CD4+/CD8+ ratio, adverse events.

Introduction

The global impact of Human Immunodeficiency Virus (HIV) remains substantial, with an estimated 39.9 million people affected by the virus worldwide as of 2023. Since the onset of the epidemic, an estimated 42.3 million individuals have succumbed to AIDS-related causes [1]. Despite considerable advancements in antiretroviral therapy (ART) that have significantly lowered HIV-related mortality, the virus remains a leading cause of death, particularly in low- and middle-income countries. The mortality burden is substantially higher among individuals who are not receiving ART or have developed resistance to the treatment. HIV is a retrovirus that attacks the immune system, gradually impairing its function by depleting CD4+ T cells. Antiretroviral therapy (ART) inhibits viral replication and restores immune function [2].

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The U.S. Department of Health and Human Services (HHS) recommends Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) as the preferred three-drug regimen (3DR) for HIV-1 patients, citing its high efficacy, strong resistance barrier, and favorable safety profile [3]. There is currently no commonly accepted four-drug regimen (4DR) in these guidelines. Managing HIV with multi-drug regimens remains difficult, particularly in patients with chronic conditions such as hepatitis, tuberculosis, hypertension, liver diseases, and so on, due to the risk of drug–drug interactions, high costs, toxicity, and adherence issues, which can increase the likelihood of treatment failure and resistance. The need for constant monitoring and specialized care increases the load on healthcare systems. Given the challenges inherent with multi-drug regimens, there is growing interest in two-drug regimens (2DRs) as a simpler but more effective alternative.

Dolutegravir (DTG) is a potent integrase strand transfer inhibitor (INSTI) that obstructs the integration of reverse-transcribed viral DNA into the host genome. Its high barrier to resistance supports its inclusion in 2DR [4]. This is particularly effective when paired with lamivudine (3TC), a well-tolerated nucleoside reverse transcriptase inhibitor (NRTI) that inhibits the reverse transcriptase enzyme [5]. This dual therapy (two-drug regimen, or 2DR) has been evaluated in several studies involving both ART-naïve patients (GEMINI 1-2) and those who are already virologically suppressed (TANGO and SALSA). In these large-scale randomized clinical trials, DTG/3TC demonstrated virological outcomes that were non-inferior to those of 3DR. Consequently, this dual regimen has been widely adopted in clinical practice [6-9].

Although previous meta-analyses have examined the efficacy of various two-drug regimens in HIV treatment, none have specifically evaluated the effectiveness of DTG/3TC compared to multi-drug approaches [10]. Therefore, this study seeks to enhance HIV care by evaluating the transition from 3DR or 4DR to DTG/3TC to better understand its long-term efficacy.

Methods

We performed a systematic review and meta-analysis according to the guidelines outlined by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Table S1) [11]. Institutional review board approval was unnecessary as the data were publicly available. The meta-analysis was registered on PROSPERO (CRD42024592574).

Data sources and search strategy

We performed an electronic search across databases including PubMed, Cochrane CENTRAL, ScienceDirect, and Google Scholar to identify randomized controlled trials (RCTs) that evaluated the safety and efficacy of transitioning DTG/3TC compared to continuing antiretroviral (CAR) therapy in virologically suppressed adults with HIV from database inception through 1st August 2024, with no restrictions on timeline or language. Keywords, along with Boolean operators such as OR and AND were used to create a comprehensive search strategy for each database (Table S2).

The following pre-defined inclusion criteria were used: [1] Randomized controlled trials (RCTs) that enrolled patients aged 18 years or older who were HIV-1 seropositive based on standard diagnostic methods and had been on their CAR therapy (which could include either a 3DR or 4DR regimen with two nucleoside or nucleotide reverse transcriptase inhibitors [NRTIs] combined with either a boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor [NNRTI], or an integrase inhibitor) for at least 6 months before participation. [2] Studies that compare clinical outcomes of patients switching from their current antiretroviral regimen to a dual therapy regimen consisting of dolutegravir and lamivudine. [3] Studies that evaluated at least one of the specified clinical outcomes. [4] Only RCTs were considered, while letters to the editor, reviews, and case reports were excluded.

Study selection

All articles identified through the systematic search were imported into EndNote Reference Manager [Version X7.5; Clarivate Analytics, Philadelphia, Pennsylvania, 2016] for screening, where duplicates were identified and removed. The remaining articles were then evaluated at the title and abstract level by two independent authors, followed by a full-text review to verify relevance. Any conflicts were resolved by mutual discussion with a third author.

Data extraction

Data from the selected studies were independently extracted by two authors using pre-defined collection forms. Data were extracted, including the name of the trials, year of publication, sample size, mean age of participants, percentage of males in the study population, patient demographics, follow-up duration, and outcome measures.

The primary outcomes included virological suppression (defined as the proportion of participants achieving HIV-1 RNA < 50 copies/ mL) and virological failure (defined as the proportion of participants achieving HIV-1 RNA > 50 copies/ mL) at week 48. The secondary outcomes included changes from baseline in CD4+ cell count, CD4+/CD8+ cell count ratio, the incidence of adverse events, levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TGL), and the cholesterol/TGL ratio.

Quality assessment

Two authors assessed the quality of the included trials. The Cochrane Risk of Bias tool was utilized to evaluate the risk of bias across each trial [12]. Trials were evaluated across the seven domains: random sequence generation, allocation concealment, participants and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting of outcome, and other potential biases. The quality assessment of each study

was classified as low, high, or unclear risk for each type of bias. If the two authors disagreed, a third author was approached to resolve the issue.

Statistical analysis

We performed statistical analysis using the Cochrane Review Manager software (RevMan version 5.4.1) with a random-effects model, applying risk ratio (RR) for dichotomous outcomes and standardized mean difference (SMD) for continuous outcomes. Pooled results were displayed using forest plots, and 95% confidence intervals (CIs) were reported alongside each effect estimate to indicate the precision of our findings. We evaluated heterogeneity across studies using Higgins I^2, considering values of I^2 between 25% and 50% as mild, 50% to 75% as moderate, and I^2 greater than 75% as severe [13]. We considered p-value < 0.05 as significant in all outcomes. Additionally, sensitivity analyses were performed to evaluate our results' robustness across each outcome.

Results

Study characteristics and baseline demographics

The initial search of the literature resulted in 1,841 potentially relevant articles. Five studies were included in this meta-analysis, after assessing these based on the pre-determined eligibility criteria, these studies collectively involved a total of 1,654 patients. The results of our literature search are summarized in the PRISMA flowchart (Figure 1). Table 1 and Table 2 show the study characteristics and baseline patient data.

Quality assessment

Each of the five studies included in our meta-analysis exhibited a low overall risk of bias. However, a common bias across all studies was the blinding of participants and personnel, suggesting a potential performance bias. Additionally, one study, named Rojas et al., exhibited selection bias due to inadequate allocation concealment (Figure S1 and S2) (Table S3).

Primary outcomes

Virological suppression (HIV-1 RNA < 50 copies/ML)

Pooled analysis across four studies (1,588 patients) showed a trend toward more virologic suppression with DTG/3TC, although it did not reach statistical significance (RR = 1.03, 95% CI: 0.99–1.07; $P = 0.11$, $I^2 = 25$) (Figure 2).

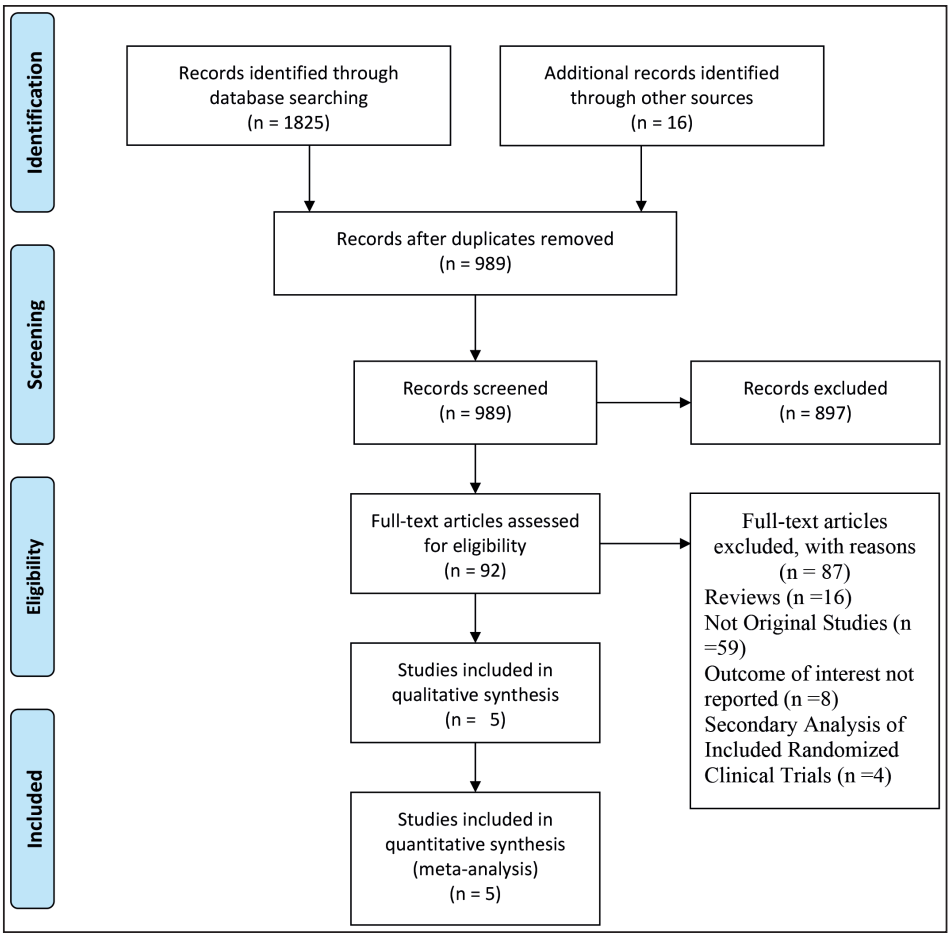

Figure 1. *PRISMA Flowchart detailing study selection.*

Table 1. *Study Characteristics Table.*

Trial Name	Type of Study	Sample Size (DTG/3TC)	Sample Size (Triple ART/CAR)	DTG/3TC Dosage (mg)	Follow-up (weeks)
DEBATE	Prospective RCT	33	33	50/300	48
SALSA	Non-inferiority Randomized Trial	246	247	50/300	52
TANGO	Non-inferiority Randomized Trial	369	372	50/300	148
DOLAM	RCT	131	134	50/300	48
ASPIRE	Pilot Randomized Trial	44	45	50/300	48

DTG: Dolutegravir, 3TC: Lamivudine, ART: Antiretroviral Therapy, CAR: Current Antiretroviral Regimen.

Secondary outcomes

Virological failure (HIV-1 RNA > 50 copies/ml)

Three trials reported data on virological failure. The pooled analysis, involving 1,444 patients, revealed no significant difference in virological failure rates for those who switched from CAR to DTG/3TC versus those who remained on CAR (RR = 0.56, 95% CI: 0.16, 1.94; P = 0.36, I^2 = 9%) (Figure 3).

Change from baseline in CD4+ cell count

All five studies, comprising 1,654 patients, assessed this outcome. The pooled analysis indicated no notable difference in the change from baseline in CD4+ cell count for patients who switched from CAR to DTG/3TC versus those who remained on CAR (SMD = 0.08, 95% CI: –0.02, 0.18; P = 0.11, I^2 = 0 (Figure 4).

Change from baseline in CD 4+/CD8+ cell count ratio

Pooled analysis across four studies (n = 1,565 patients) showed a notable difference in change from baseline in the CD4+/CD8+ cell count ratio for patients who switched from CAR to DTG/3TC versus those who remained on CAR (SMD = -0.11, 95% CI; –0.21, -0.01; P=0.04, I^2= 6%) (Figure 5).

Adverse events

Four studies reported the incidence of adverse events. In a pooled analysis of 1,588 patients, no notable difference was found in the incidence of adverse events among patients who switched from CAR to DTG/3TC (RR = 1.02, 95% CI = 0.96, 1.08; P = 0.60, I^2 = 0%) (Figure 6).

Total cholesterol

In the four studies that assessed total cholesterol levels, encompassing 1,588 patients, a significant difference was observed in total cholesterol for those who switched from CAR to DTG/3TC (SMD = -0.28, 95% CI: -0.53, -0.02; P = 0.03, I^2 = 82%) (Figure 7).

HDL cholesterol

Analysis of pooled data from three studies (n = 1,499 patients) showed a substantial reduction in HDL cholesterol in patients who switched from CAR to DTG/3TC (SMD = -0.25, 95% CI: -0.38, -0.11; P = 0.0004, I^2 = 41) (Figure 8).

LDL cholesterol

Combining data from four studies (n = 1,588 patients), the analysis exhibited no notable difference in LDL cholesterol in patients who switched from CAR to DTG/3TC (SMD = -0.20, 95% CI: -0.43, 0.03; P = 0.09, I^2 = 77%) (Figure 9).

TGL

Three studies, involving 1,323 patients showed no marked difference in triglyceride levels among patients who switched from CAR to DTG/3TC (SMD = -0.13, 95% CI: -0.34, 0.07; P = 0.21, I^2 = 63%) (Figure 10).

Cholesterol/TGL ratio

Among the 1,499 patients analyzed from three studies, the pooled data revealed no significant difference in the cholesterol/TGL ratio in patients who switched from CAR to DTG/3TC (SMD = -0.14, 95% CI: -0.43, 0.14; P = 0.33, I^2 = 86%) (Figure 11).

Emergent drug resistance

We examined the incidence of emergent drug-resistant mutations, particularly INSTI mutations, across the included studies. In the DEBATE trial, resistance outcomes were not reported as the study focused on immunological changes. In the ASPIRE trial, resistance testing was conducted in one participant with virologic failure at week 24, but no emergent RT or integrase resistance mutations were detected. In both the SALSA and TANGO trials, no participants met confirmed virologic withdrawal (CVW) criteria, and therefore, no resistance testing was performed, indicating no observed emergent resistance. The DOLAM trial reported mutations in two participants: one in the dual therapy group with Lys70Glu, Lys219Glu, Gly190Arg, and Met230Ile mutations detected in peripheral blood mononuclear cells, and another in the triple therapy group with Lys219Arg, Glu138Lys, and Met230Ile mutations detected in both plasma and peripheral blood mononuclear cells.

Sensitivity analysis

In the sensitivity analysis, excluding specific studies contributed to a marked reduction in heterogeneity for each outcome. For total cholesterol, excluding the SALSA study decreased the I^2 value from 82% to 60% (P =

Table 2. *Study baseline table.*

Study Name			SALSA	DEBATE	TANGO	DOLAM	ASPIRE
Clinical Trial Number			NCT04021290.	NCT04054089	NCT03446573	EudraCT 201500027435.	NCT02263326.
Sample Size	Participants		493	66	741	265	89
	D+L		246	33	369	131	44
	Triple ART/CAB		247	33	372	134	45
Age-yrs median (range)	D+L		45 (22–74)	48 (43, 57)	40.0 (20–74)	45 (37–53)	47 (38-54)
	Triple ART/CAR		45 (23–83)	55 (43, 60)	39.0 (18–73)	46 (39–51)	47 (38-54)
Gender	D+L	Male	138	29	344	111	39
		Female	108	4	25	20	5
	Triple ART/CAR	Male	163	28	339	116	40
		Female	84	5	33	18	5
Race	D+L	White	149	N/A	297	106	26
		Black	45	N/A	50	N/A	17
		Asian	31	N/A	13	N/A	N/A
		Others	21	6	9	25	1
	Triple ART/CAR	White	144	N/A	289	105	27
		Black	48	N/A	58	N/A	17
		Asian	39	N/A	13	N/A	N/A
		Others	16	3	12	29	1
CD4 cell count cells/micro lit median (range)	D+L		675 (154–2089)	734 (543, 971)	682 (133–1904)	700 (560–940)	680(498–927)
	Triple ART/CAR		668 (94–1954)	809 (648, 1,084)	720 (119–1810)	747 (551–891)	680(498–927)
CD4/CD8 ratio median(range)	D+L		N/A	1.0 (0.6, 1.3)	N/A	0·94 (0·70–1·34)	N/A
	Triple ART/CAR		N/A	1.1 (0.8, 1.3)	N/A	0·92 (0·75–1·08)	N/A
Third agent in previous therapy	D+L	INSTI	98	10	289	58	16
		EVG	24	4	243	25	N/A
		DTG	45	5	N/A	21	N/A
		RAL	6	1	N/A	12	N/A
		NNRTI	123	22	51	67	13
	Triple ART/CAR	INSTI	98	9	296	63	17
		EVG	27	3	249	23	N/A
		DTG	41	4	N/A	27	N/A
		RAL	4	2	N/A	13	N/A
		NNRTI	124	19	48	65	13
NRTI	D+L	3TC	96	8	N/A	38	38
		TDF	109	8	N/A	48	38
	Triple ART/CAR	3TC	***89***	9	N/A	35	39
		TDF	109	6	N/A	46	39
Weight-kg median (range)	D+L		73 (43–154)	78.0 (64.0, 85.0)	N/A	75 (67–83)	N/A
	Triple ART/CAR		75 (36–160)	76.0 (69.0, 87.0)	N/A	72 (67–79)	N/A
BMI-kg/m2 median (range)	D+L		25 (18–51)	24.7 (22.3, 29.1)	N/A	25 (23–27)	N/A
	Triple ART/CAR		26 (14–69)	25.5 (23.7, 29.2)	N/A	24 (23–27)	N/A
Any SAEs	D+L		10	N/A	57	3	0
	Triple ART/CAR		23	N/A	44	6	0
Drug related grade 2-5 AEs	D+L		14	N/A	21	29	4
	Triple ART/CAR		8	N/A	13	37	3

Age-yrs: Age in years, D+L: Dolutegravir + Lamivudine, Triple ART/CAR: Triple Antiretroviral Therapy/Combination Antiretroviral Regimen, CD4/CD8 ratio: Ratio of CD4 to CD8 cells, NRTI: Nucleoside Reverse Transcriptase Inhibitors, Weight-kg: Weight in kilograms, BMI-kg/m²: Body Mass Index in kilograms per square meter, SAEs: Serious Adverse Events, AEs: Adverse Events

0.008), indicating that this study contributed significantly to the initial variability. Similarly, for LDL cholesterol, removing the SALSA study reduced heterogeneity from 77% to 57% ($P = 0.008$), suggesting that this outcome's consistency improved after exclusion. For triglycerides, moderate initial heterogeneity ($I^2 = 63\%$) dropped to 0% ($P = 0.0004$) once the SALSA study was excluded, resulting in no residual heterogeneity. Lastly, for

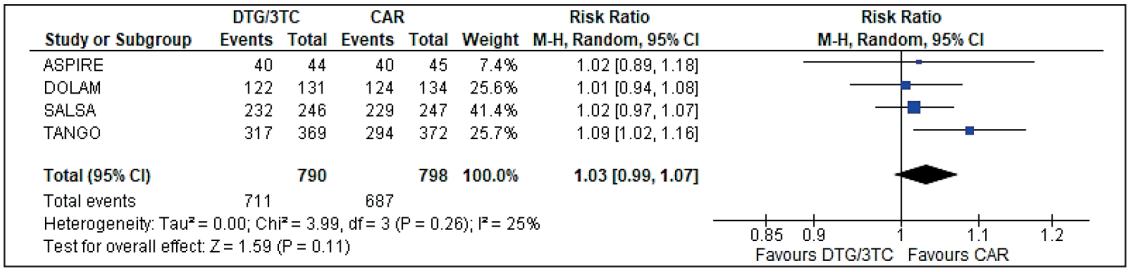

Figure 2. *Forest plot of participants achieving HIV-1 RNA < 50 copies/ml for DTG/3TC vs Triple ART/CAR.*

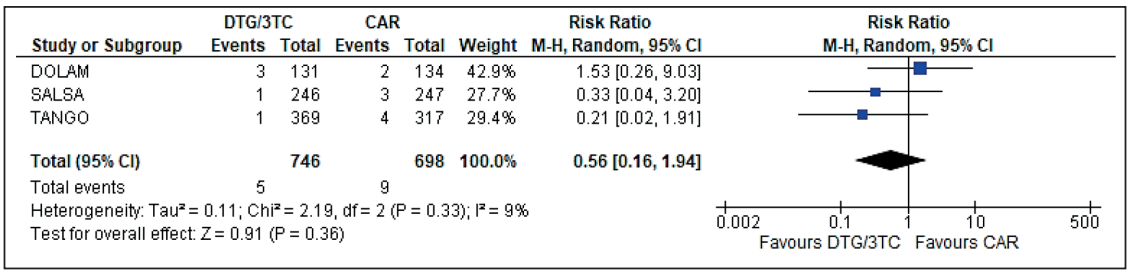

Figure 3. *Forest plot of participants with HIV-1 RNA > 50 copies/ml comparing DTG/3TC to Triple ART/CAR.*

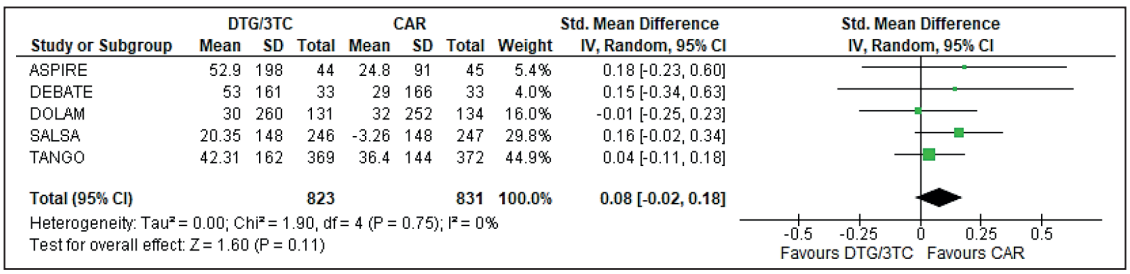

Figure 4. *Forest plot of change in CD4+ cell count from baseline, comparing DTG/3TC vs Triple ART/CAR.*

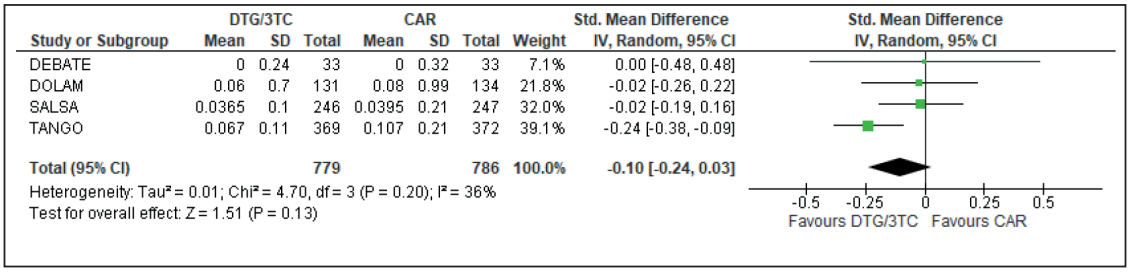

Figure 5. *Forest plot of change in CD4+/CD8+ ratio from baseline for DTG/3TC vs Triple ART/CAR.*

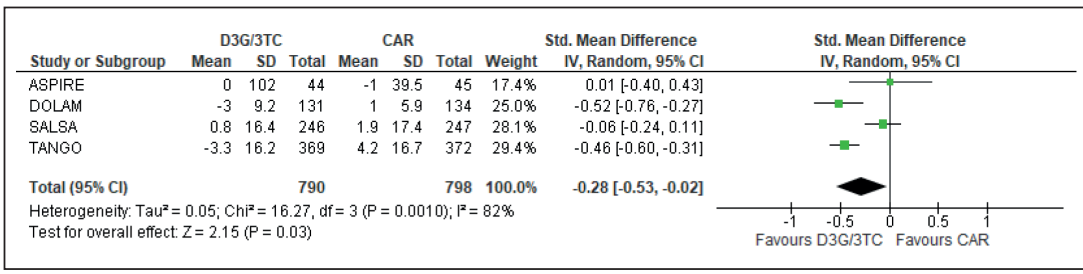

Figure 6. *Forest plot of adverse events comparing DTG/3TC and Triple ART/CAR.*

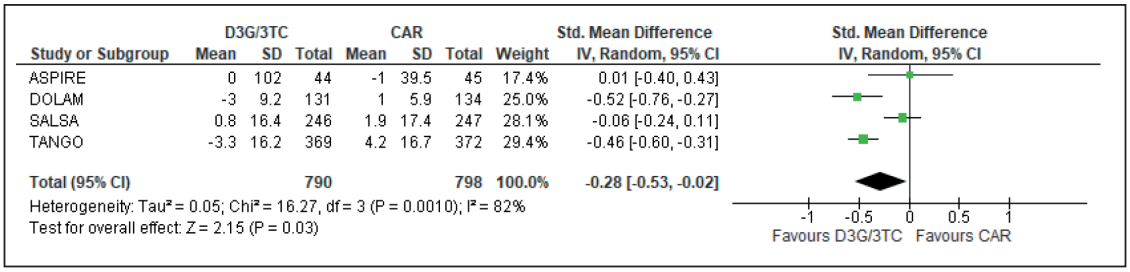

Figure 7. *Forest plot of total cholesterol changes between DTG/3TC and Triple ART/CAR.*

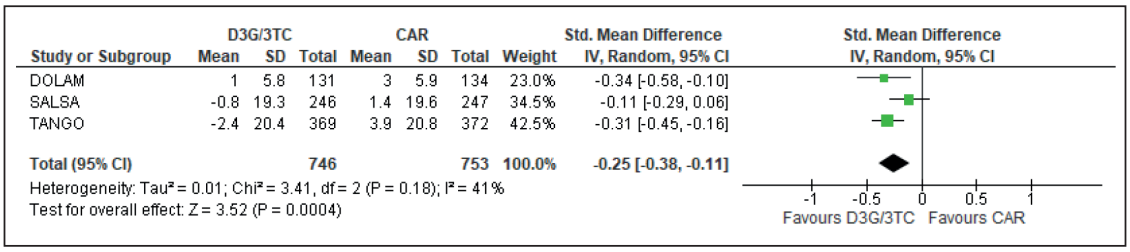

Figure 8. *Forest plot of HDL cholesterol changes for DTG/3TC vs Triple ART/CAR.*

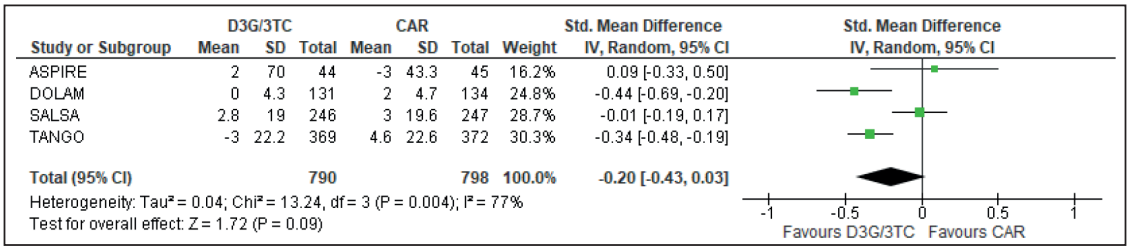

Figure 9. *Forest plot of LDL cholesterol changes comparing DTG/3TC and Triple ART/CAR.*

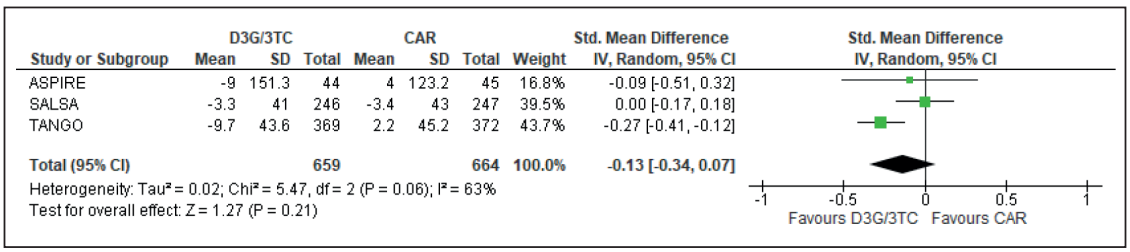

Figure 10. *Forest plot of triglyceride (TGL) changes between DTG/3TC and Triple ART/CAR.*

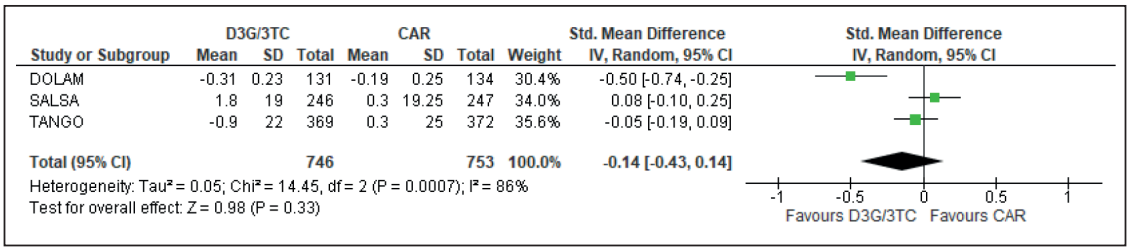

Figure 11. *Forest plot of cholesterol/TGL ratio changes comparing DTG/3TC vs Triple ART/CAR.*

the cholesterol/triglyceride (TGL) ratio, excluding the DOLAM study reduced the I² from 86% to 19% (P = 0.96), showing a significant decline in variability (Table 3).

Discussion

This meta-analysis of five studies examined the safety and efficacy of transitioning from a 3DR or 4DR antiretroviral regimen to a 2DR DTG/3TC combination[14-18]. Our

Table 3. *Sensitivity analysis for each outcome.*

Outcome	Study	I^2 Value Before S.A (%) / *P* Value	I^2 Value After S.A (%) / *P* Value
Total Cholesterol	SALSA	82% / 0.03	60% / 0.008
LDL Cholesterol	SALSA	77% / 0.09	57% / 0.008
Triglyceride	SALSA	63% / 0.21	0% / 0.0004
Cholesterol/TGL Ratio	DOLAM	86% / 0.33	19% / 0.96

findings indicate that employing DTG/3TC leads to similar virological suppression as CAR. There was no statistical difference between the two groups in terms of CD4+ cell count, CD4+/CD8+ cell count ratio, or virological failure. Adverse event rates were similar, though HDL cholesterol levels decreased in the DTG/3TC group. Overall, switching to DTG/3TC offers comparable virological suppression and safety to CAR.

DTG, an integrase strand transfer inhibitor (INSTI), significantly inhibits viral DNA integration into the host genome, inhibiting viral replication [19]. Meanwhile, 3TC, a nucleoside reverse transcriptase inhibitor (NRTI), inhibits the conversion of viral RNA to DNA, which is a critical stage in the HIV reproduction cycle. Together, these pathways provide strong inhibition of viral replication, resulting in better virological results in the early months of treatment [20]. We found that patients who switched to DTG/3TC exhibited comparable rates of virological suppression compared to those on CAR. This advantage can be attributed to the potent and complementary actions of DTG and 3TC. Specifically, DTG has shown efficacy against RAL- and EVG-resistant mutations such as Y143R, N155H, G140S/Q148H, T66I, and E92Q. In clinical trials, about 90% of patients using DTG saw their viral load drop below 50 copies per mL [21-23]. Resistance to DTG is much less common than to earlier drugs. Some resistance mutations, such as R263K, G118R, and N155H, can occur, but overall, DTG remains highly effective. Even when resistance develops, it is less severe than with earlier medicines, allowing DTG to remain effective in many situations, particularly when taken twice daily. However, certain complicated alterations, such as G140S and Q148H with additional mutations, can impair the drug's effectiveness, particularly in those who have failed previous HIV treatments [19]. INSTI resistance is a significant concern for DTG/3TC therapy. However, the likelihood of treatment emergent INSTI mutations was low in all the studies examined. Notably, no confirmed virologic withdrawal cases were reported in the SALSA and TANGO trials; hence, no resistance mutations were discovered. The ASPIRE trial observed no changes in RT or INSTI in one participant who had virologic failure. While the DOLAM study found resistance-associated mutations in two patients, these findings highlight the importance of monitoring resistance on an individual basis rather than assuming a general problem. These findings confirm earlier research indicating that DTG/3TC is a feasible option in virologically suppressed individuals with a low chance of resistance development.

These mechanisms allow DTG/ 3TC to achieve the same efficacy as those achieved by 3DRs or 4DRs. No significant differences were observed in virological failure rates between the DTG/3TC group and those remaining on their current regimen. Similarly, changes in CD4+ cell count and the CD4+/CD8+ cell count ratio did not differ significantly between the groups at either time point. This implies that immunological recovery and overall immune function associated with DTG/3TC are equivalent to those associated with existing regimens, implying that the transition does not significantly benefit or harm immune restoration. In terms of safety, the incidence of adverse events was comparable across the two groups, indicating that DTG/3TC has no additional safety concerns when compared to current regimens. However, a notable reduction in HDL cholesterol levels was observed in the DTG/3TC group, which highlights a change in lipid profile. The metabolic changes observed following the DTG/3TC switch may be due to the discontinuation of drugs with known metabolic side effects. However, it remains unclear whether DTG itself plays a role in lipid metabolism, necessitating further research to determine its direct effects. While overall lipid profile changes were minimal, a reduction in HDL cholesterol levels was observed in the DTG/3TC group. Given HDL's traditionally recognized role in cardiovascular health, this decline warrants further investigation to assess its potential long-term implications.

Antiretroviral medication may worsen comorbidities associated with aging, such as renal, hepatic, or cardiovascular disease; osteoporosis; and metabolic illnesses such as diabetes and dyslipidemia [24-26]. As a result, switching to 2DRs like DTG/3TC offers several advantages. For starters, the reduction in total medication exposure is a considerable benefit. Simplifying the regimen to fewer medications can lower the risk of long-term toxicities, which is especially useful for patients who will require lifelong antiretroviral therapy. The reduced number of pharmaceuticals also means fewer drug-drug interactions, which is beneficial for patients who require additional medications for comorbid conditions such as antihypertensives for hypertension, statins for hyperlipidemia, or anticoagulants for atrial fibrillation [27,28]. Fewer interactions lessen the burden of managing various medicines and the risk of harmful interactions. Furthermore, the greater tolerability associated with DTG/3TC leads to improved quality of life and adherence rates [29]. While DTG's genetic barrier adds to the prolonged efficacy of DTG/3TC, adherence remains an important component in long-term virological suppression. Suboptimal adherence can increase the chance of virological failure and resistance development, especially in patients who already have risk factors for poor adherence. Notably, the simplicity of

a two-drug regimen may improve adherence compared to more complex regimens, thus minimizing this risk. When performing a 2DR switch, it is important to consider the patient's HBV serostatus. Because 3TC has a lower genetic resistance to HBV, patients with untreated or active HBV co-infection may require additional HBV-active drugs to avoid reactivation. As a result, when considering a DTG/3TC transition, HBV status must be thoroughly screened and monitored. Furthermore, in resource-constrained settings where access to comprehensive HIV care may be limited, DTG/3TC is even more cost-effective. Fewer drugs lead to decreased treatment costs and resource consumption, making DTG/3TC a viable option in such cases [28].

Limitations

There are certain limitations to this meta-analysis. Variations in follow-up times and patient demographics among the included studies would have resulted in heterogeneity, influencing the overall results. Furthermore, relying on published data may introduce publication bias, while efforts were made to offset this through a thorough literature review. Furthermore, our trials used several types of antiretrovirals before switching to DTG/3TC, which could alter the reproducibility of our results.

Conclusions

This study confirms the efficacy and safety of transitioning from a 3DR or 4DR to a 2DR of DTG/3TC in virologically suppressed HIV-1 patients. This approach presents a promising strategy for simplifying HIV treatment while preserving virological suppression and reducing drug-related side effects. The efficiency of DTG/3TC, evidenced by their simple mode of action and validated by recent guidelines, highlights their potential as a preferred option in HIV therapy. Future research should look into the long-term effects of DTG/3TC and its applicability to a variety of patient types and circumstances.

List of Abbreviations

2DR	Two-Drug Regimen
3DR	Three-Drug Regimen
3TC	Lamivudine
4DR	Four-Drug Regimen
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
B/F/TAF	Bictegravir/Emtricitabine/Tenofovir Alafenamide
CCR5	C-C Chemokine Receptor Type 5
CD4+	Cluster of Differentiation 4-positive T cells
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
CXCR4	C-X-C Chemokine Receptor Type 4
DNA	Deoxyribonucleic Acid
DTG	Dolutegravir
HDL	High-Density Lipoprotein
I^2	Heterogeneity Statistic
INSTI	Integrase Strand Transfer Inhibitor
LDL	Low-Density Lipoprotein
Non-NRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
RR	Risk Ratio
SMD	Standardized Mean Difference
TGL	Triglycerides
WHO	World Health Organization

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Not applicable.

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Supplementary content (If any) is available online.

References

1. UNAIDS. Fact sheet 2024 - Latest global and regional HIV statistics on the status of the AIDS epidemic. 2024 [cited

2024 Sep 7]. Available from: https://www.unaids.org/en/resources/fact-sheet

2. Fanales-Belasio E, Raimondo M, Suligoi B, Buttò S. HIV virology and pathogenetic mechanisms of infection: a brief overview. Ann Ist Super Sanita. 2010;46(1):5–14. https://doi.org/10.4415/ANN_10_01_02

3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2024 Sep 12 [cited 2025 Mar 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK586306/

4. Brenner BG, Wainberg MA. Clinical benefit of dolutegravir in HIV-1 management related to the high genetic barrier to drug resistance. Virus Res. 2017;239:1–9. https://doi.org/10.1016/j.virusres.2017.03.002

5. Quercia R, Perno CF, Koteff J, Moore K, McCoig C, St Clair M, et al. Twenty-five years of lamivudine: current and future use for the treatment of HIV-1 infection. JAIDS. 2018;2025: Available from: http://www.jaids.com

6. Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019;393(10167):143–55. https://doi.org/10.1016/S0140-6736(18)32461-2

7. Maggiolo F, Gulminetti R, Pagnucco L, Digaetano M, Cervo A, Valenti D, et al. Long-term outcome of lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. BMC Infect Dis. 2022;22(1): https://doi.org/10.1186/s12879-022-07988-5

8. Van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla Sogorb J, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study. Clin Infect Dis. 2020;71(8):1920–9. https://doi.org/10.1093/cid/ciaa502

9. Llibre JM, Brites C, Cheng CY, Osiyemi O, Galera C, Hocqueloux L, et al. Efficacy and safety of switching to the 2-drug regimen dolutegravir/lamivudine versus continuing a 3- or 4-drug regimen for maintaining virologic suppression in adults living with HIV-1: week 48 results from the phase 3, noninferiority SALSA randomized trial. Clin Infect Dis. 2023;76(4):720–9. https://doi.org/10.1093/cid/ciac855

10. Achhra AC, Mwasakifwa G, Amin J, Boyd MA. Efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy: a systematic review and meta-analysis. Lancet HIV. 2016;3(8):e351–60. https://doi.org/10.1016/S2352-3018(16)30015-7

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:71. https://doi.org/10.1136/bmj.n71

12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:4898. https://doi.org/10.1136/bmj.l4898

13. Ottawa Hospital Research Institute [Internet]. [cited 2024 May 16]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

14. Cossarizza A, Cozzi-Lepri A, Mattioli M, Paolini A, Neroni A, De Biasi S, et al. Evaluating immunological and inflammatory changes of treatment-experienced people living with HIV switching from first-line triple cART regimens to DTG/3TC vs. B/F/TAF: the DEBATE trial. Front Immunol. 2023;14: https://doi.org/10.3389/fimmu.2023.10613634

15. Taiwo BO, Marconi VC, Berzins B, Moser CB, Nyaku AN, Fichtenbaum CJ, et al. Dolutegravir plus lamivudine maintains HIV-1 suppression through week 48 in a pilot randomized trial. Clin Infect Dis. 2018;66(11):1794–7. https://doi.org/10.1093/cid/ciy007

16. Llibre JM, Brites C, Cheng CY, Osiyemi O, Galera C, Hocqueloux L, et al. Efficacy and safety of switching to the 2-drug regimen dolutegravir/lamivudine versus continuing a 3- or 4-drug regimen for maintaining virologic suppression in adults living with HIV-1: week 48 results from the SALSA randomized trial. Clin Infect Dis. 2023;76(4):720–9. https://doi.org/10.1093/cid/ciac855

17. Osiyemi O, De Wit S, Ajana F, Bisshop F, Portilla J, Routy JP, et al. Efficacy and safety of switching to dolutegravir/lamivudine versus continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with HIV type 1: results through week 144 from the phase 3, noninferiority TANGO randomized trial. Clin Infect Dis. 2022;75(6):975–86. https://doi.org/10.1093/cid/ciac038

18. Rojas J, De Lazzari E, Negredo E, Domingo P, Tiraboschi J, Ribera E, et al. Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial. Lancet HIV. 2021;8(8):e463–73. https://doi.org/10.1016/S2352-3018(21)00117-3

19. Smith SJ, Zhao XZ, Passos DO, Lyumkis D, Burke TR, Hughes SH. Integrase strand transfer inhibitors are effective anti-HIV drugs. Viruses. 2021;13(2): https://doi.org/10.3390/v13020272

20. Audsley J, Giles M, Lewin SR. Lamivudine. In: Kucers' The Use of Antibiotics. 7th ed. 2024. 3729 p

21. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013;381(9868):735–43. https://doi.org/10.1016/S0140-6736(12)61853-4

22. Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS. 2013;27(11):1771–8. https://doi.org/10.1097/QAD.0b013e32836080e2

23. Van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis. 2012;12(2):111–8. https://doi.org/10.1016/S1473-3099(11)70353-0

24. Ofotokun I, Mcintosh E, Weitzmann MN. HIV: inflammation and bone. Curr HIV/AIDS Rep. 2012;9(1):16–25. https://doi.org/10.1007/s11904-011-0101-2

25. Cunha JD. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: old and new drugs. World J Virol. 2015;4(2):56. https://doi.org/10.5501/wjv.v4.i2.56

26. Salter ML, Lau B, Go VF, Mehta SH, Kirk GD. HIV infection, immune suppression, and uncontrolled viremia are associated with increased multimorbidity among aging injection drug users. Clin Infect Dis. 2011;53(12):1256–64. https://doi.org/10.1093/cid/cir447

27. Galizzi N, Poli A, Galli L, Muccini C, Mastrangelo A, Dell'Acqua R, et al. Retrospective study on the outcome of two-drug regimens based on dolutegravir plus one reverse transcriptase inhibitor in virologically-suppressed HIV-infected patients. Int J Antimicrob Agents. 2020;55(3): https://doi.org/10.1016/j.ijantimicag.2019.105835

28. Girouard MP, Sax PE, Parker RA, Taiwo B, Freedberg KA, Gulick RM, et al. The cost-effectiveness and budget impact of 2-drug dolutegravir-lamivudine regimens for the treatment of HIV infection in the United States. Clin Infect Dis. 2016;62(6):784. https://doi.org/10.1093/cid/civ999

29. Cabello-Ubeda A, De Quirós JCLB, Carbonero LM, Sanz J, Vergas J, Mena A, et al. 48-week effectiveness and tolerability of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral-naïve adults living with HIV: a multicenter real-life cohort. PLoS One. 2022;17(11):277685. https://doi.org/10.1371/journal.pone.0277685