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Simplification of antiretroviral therapy: comparative review of two-drug and three-drug regimens in HIV treatment

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Abstract

Combined antiretroviral therapies have revolutionized HIV management. Triple-drug regimens (3DR) have been the cornerstone of HIV treatment, which provide durable virologic suppression, reduce HIV-related morbidity and mortality, and improve immune reconstitution. However, 3DR are associated to long-term toxicities. In certain settings, two-drug regimens (2DR) present non-inferior virological efficacy compared to 3DR and may improve tolerability and adherence. In this review, we examine the efficacy, safety, and patient-centered outcomes of 3DR and 2DR, and the potential benefits of transitioning from triple to dual therapy regimens in people with HIV. We conducted a literature search on PubMed, EMBASE, and the Cochrane Library databases for studies published between January 2010 and June 2024. Overall data support the non-inferior efficacy of 2DR to 3DR in the management of HIV, with no evidence of an increased risk of subclinical failure with dual therapy. Switching from 3DR to 2DR may reduce the risk of drug interactions and toxicity. Within the 2DR, the long-acting therapies represent the most innovative dual therapy since they simplify the treatment by reducing from triple to dual therapy along shifting from daily pills to bi-monthly injections. Long-acting 2DR are effective, provide high levels of satisfaction, and improve adherence and quality of life.

Keywords

Antiretroviral therapy. HIV. Long-acting therapy. Treatment adherence. Virological suppression. Two-drug regimen. Triple-drug regimen.

Introduction

The advent of combination antiretroviral therapy (ART) in the mid-1990s marked a pivotal milestone in the management of HIV infection, revolutionizing the outlook from a once dire prognosis to a chronic, manageable condition[1]. Over decades, therapeutic strategies have evolved not only to achieve durable virologic suppression but also to mitigate treatment-related toxicities and optimize long-term outcomes[2]. Triple-drug ART regimens (3DR), typically combining

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two nucleoside reverse transcriptase inhibitors (NRTIs) with a third agent from the non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) classes, have been the cornerstone of HIV treatment initiation and maintenance[3]. These regimens have demonstrated robust efficacy in suppressing viral replication, reducing HIV-related morbidity and mortality, and improving immune reconstitution.

Despite their effectiveness, 3DR have potential drawbacks. Chief among these are long-term toxicity concerns[3], including metabolic abnormalities, such as dyslipidemia and insulin resistance[4,5]; renal dysfunction[6]; neuropsychiatric side effects[7]; cardiovascular events[8]; non-alcoholic fatty liver disease[9], as well as hepatic toxicity, accelerating aging, and other comorbidities[3,10,11]. All these toxicities are associated with different mechanisms, which include mitochondrial dysfunction, telomerase inhibition, genetic instability, immunoactivation, inflammation, and other biological interferences[12,13]. In response to these challenges, there has been growing interest in simplifying ART regimens by transitioning to dual-therapy approaches. The concept behind simplification is multifaceted: maintaining virologic suppression with fewer medications, thereby potentially reducing drug exposure and minimizing cumulative toxicity. Two-drug regimens (2DR) typically involve pairing an INSTI with either an NRTI or an NNRTI, capitalizing on potent antiretroviral agents with favorable safety profiles and reduced potential for drug-drug interactions.

The clinical rationale for dual therapy is supported by studies demonstrating non-inferiority in virologic efficacy compared with traditional triple therapy, along with potential benefits in terms of improved tolerability and adherence. Recent randomized controlled trials (RCTs) and observational cohort studies have evaluated various dual therapy combinations, assessing outcomes such as virologic suppression rates, immunologic recovery, and the emergence of resistance mutations[14-23].

In this narrative review, we comprehensively examine the evolving landscape of ART simplification, synthesizing current evidence on the efficacy, safety, and patient-centered outcomes associated with INSTI-based 3DR and 2DR, both oral and long-acting (LA) parenteral 2DR. Understanding the nuances and potential benefits of transitioning to dual therapy regimens is essential for optimizing care delivery and improving outcomes for individuals living with HIV.

Methods

This review employed a comprehensive literature search strategy to explore the comparative outcomes of INSTI-based two- and three-drug ART regimens in the management of HIV. The search was conducted using electronic databases, including PubMed, EMBASE, and the Cochrane Library, with a focus on studies published between January 2010 and June 2024. The search terms utilized variations of keywords such as “HIV”, “antiretroviral therapy”, “two-drug regimen”, “three-drug regimen”, “efficacy”, “safety”, “adherence”, and “clinical outcomes”. The inclusion criteria encompassed RCTs, observational studies, meta-analyses, and systematic reviews comparing two-drug and three-drug ART regimens in treatment-naive and treatment-experienced HIV-infected adults. In addition, searches were conducted in conference proceedings and abstract databases of major HIV-related conferences, such as the International AIDS Society conference, the European AIDS Clinical Society conference, and the Conference on Retroviruses and Opportunistic Infections. Studies were selected based on their relevance to the research question and the quality of evidence provided. Data extraction focused on key outcomes, including virological suppression (defined as HIV RNA < 50 copies/mL), immunological response, drug-related toxicity and adverse events, and emergence of drug resistance. Bias assessment and risk of confounding were considered in the interpretation of results. Data synthesis involved a narrative approach to summarize the findings across studies, with emphasis on methodological strengths and limitations.

Results

Efficacy

Several RCTs have compared the efficacy of INSTI-based 2DR and 3DR (Table 1). In general, similar efficacy has been observed with both approaches, although there are some specific situations where the evidence is less robust. In the context of ART-naïve participants, the GEMINI trials demonstrated non-inferiority of initiating ART with dolutegravir (DTG) + lamivudine (3TC) versus DTG + tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC). However, the 2DR was inferior to the 3DR in the subgroup of participants with CD4+ cell counts below 200 cells/μL and

Table 1. Compared efficacy of INSTI-based 2DR and 3DR, reported in RCTs

Study	Dual therapy	Triple therapy	Virological response Dual versus triple therapy	Non-virological response Dual versus triple therapy
ART-naïve patients				
GEMINI-1 and GEMINI-2[14]	DTG + 3TC (n = 719)	DTG + TDF + FTS (n = 722)	Pooled analysis: 91% versus 93% Adj dif−1.7 (95% CI−4.4-1.1) CD4 + ≤ 200 cells/μL: 79% versus 93%	Pooled analysis: 3% versus 2%
ART-treated patients: switching versus maintaining				
TANGO[15]	DTG + 3TC (n = 369)	TAF-based 3DR: TAF/FTC + PI, INSTI or NNRTI (n = 372)	93.2% versus 93.0% Adj dif 0.2 (95% CI−3.4-3.9)	0.3% versus 0.5% Adj dif−0.3 (95% CI−1.2-0.7)
SALSA[16]	DTG + 3TC (n = 246)	3-/4-ART*: 2 NRTI + INSTI, NNRTI or PI (n = 247)	94% versus 93% Adj dif 1.6 (95% CI−2.8-5.9)	0.4% versus 1.2% Adj dif−0.8 (95% CI−2.4-0.8)
DOLAM[18]	DTG + 3TC (n = 131)	Triple ART† (n = 134)		2% versus 1% Adj dif 0.8 (95% CI−3.3-5.2)
SWORD-1 and SWORD-2[17]	DTG + RPV (n = 516)	3DR‡ 2NRTIs + NNRTI, INSTI or PI (n = 512)	Pooled analysis: 94.7% versus 94.9% Adj dif−0.2 (95% CI−3.0-2.5)	Pooled analysis: < 1% versus 1% Adj dif−0.5 (95% CI−1.4-0.5)
ATLAS and FLAIR[27]	LA CAB + RPV (n = 591)	FLAIR study: DTG + ABC + 3TC ATLAS study: 2NRTI + NNRTI, INSTI or PI (n = 591)	93.1% versus 94.4% Adj dif−1.37 (95% CI−4.12-1.39)	1.9% versus 1.7% Adj dif 0.16 (95% CI−1.35-1.67)
ATLAS-2M[28]	CAB + RPV Q8W versus Q4W (n = 522; 523)		Week 152: 87.4% versus 85.9% Adj dif 1.5 (95% CI−2.6-5.6)	Week 152: 2.7% versus 1.0% Adj dif 1.7 (95% CI 0.1-3.3)
SOLAR[19]	CAB + RPV (n = 447)	BIC + FTC + TAF (n = 223)	90.2% versus 92.8%	1.1% versus 0.4% Adj dif 0.7 (95% CI−0.7-2.0)

The virological response is defined as < 50 copies of HIV-1 RNA/mL; non-virological response is defined as ≥ 50 copies of HIV-1 RNA/mL. Response data at week 48, except the ATLAS-2M study.
*INSTI in ≥ 30% of patients: DTG, EVG + COBI, BIC, RAL; NNRTI in ≥ 30% of patients: EFV; NRTI in ≥ 30% of patients: FTC, TDF, 3TC, TAF.
†3DR: EVG/COBI/FTC/TDF; EFV/FTC/TDF; FTC/RPV/TDF; DTG/ABC/3TC.
‡The most commonly reported PI at baseline was DRV/r; the most commonly reported INSTI at baseline was RAL; the most commonly reported NNTRI at baseline was EFV.
3TC: lamivudine; ABC: abacavir; Adj dif: adjusted difference; ART: antiretroviral therapy; BIC: bictegravir; CAB: cabotegravir; CAR: current antiretroviral regimen; COBI: cibicistat; DRV: darunvir; DTG: dolutegravir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; LA: long-acting; r: ritonavir-booster; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; RAL: raltegravir; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

did not show non-inferiority in the subgroup of participants with baseline HIV-1 RNA > 100,000 copies per mL[14]. Nevertheless, analysis at 144 weeks by baseline viral load showed similar results in both groups. In the CD4+ ≤ 200 cells/μL subgroup, the majority of virologic failures according to the snapshot were due to non-treatment-related reasons (such as loss of follow-up, withdrawn consent, or discontinuation because of non-treatment-related adverse events)[24]. The trials marked HIV-RNA > 500,000 copies/mL as an exclusion criterion, so the results should not be extrapolated to this population.

Recently, the DOLCE study demonstrated that dual therapy was non-inferior to triple therapy in a severely immunosuppressed population (CD4 < 200 cells/μL)[25]. In this phase IV randomized study, the proportion of participants achieving a viral load < 50 copies/mL at week 48 was similar between the dual therapy group (82.2%) and the triple therapy group (80.5%) with a post-hoc non-inferiority analysis confirming comparable efficacy (risk difference 1.7%; 90% CI −8.3 to 11.7%). The viral response was consistent across subgroups, including those with high baseline viral loads (> 500,000 copies/mL), and CD4 count increases were comparable between groups. Safety outcomes, including adverse events and immune reconstitution syndrome, were similar and aligned with known safety profiles. The DOLCE study has added information on the efficacy and the safety of dual therapy with DTG + 3TC, regardless of baseline CD4 counts and viral load[25].

Different RCTs have evaluated the efficacy of dual therapy with DTG + 3TC versus 3DR. The TANGO trial demonstrated non-inferiority of switching to DTG + 3TC versus maintaining tenofovir alafenamide (TAF)-based 3DR, with a proportion of participants with an HIV-1 RNA level ≥ 50 copies/mL at week 48 of 0.3% (1 of 369) after switching to DTG + 3TC versus 0.5% (2 of 372) for TAF-based regimens (adjusted treatment difference, −0.3 [95% confidence interval, −1.2-0.7])[26]. This efficacy was maintained until week 196[15]. The phase 3 SALSA study evaluated the efficacy of switching to DTG + 3TC compared with continuing various 3- or 4-drug antiretroviral regimens. Results were consistent with other RCTs such as TANGO, showing non-inferiority of 2DR. At week 48, 1 (0.4%) participant in the DTG + 3TC group and 3 (1.2%) in the current ART regimens group had HIV-1 RNA ≥ 50 copies/mL[16]. The phase 4 DOLAM study again demonstrated the efficacy of DTG + 3TC as a switch option for selected people with HIV (PWH) virologically suppressed with 3DR[18].

The SWORD study evaluated the switch from 3DR to DTG + rilpivirine (RPV), also showing the non-inferiority of this 2DR. At week 48, 95% of participants had viral loads below 50 copies per mL in each group (486 of 513 in the DTG + RPV group vs. 485 of 511 in the current ART regimen group)[17]. Analysis at 148 weeks showed maintained virologic suppression for a high proportion of participants[27].

Finally, the novel dual injectable therapy based on LA cabotegravir (CAB) + RPV has also been shown to be non-inferior to 3DR in the treatment switch scenario. In the phase 3 ATLAS and FLAIR studies, adults with virologic suppression were randomized to continue their current antiretroviral regimen or switch to the LA regimen of LA CAB + RPV. Non-inferiority criteria were met at week 48 for the primary (HIV-1 RNA ≥ 50 copies/mL) and key secondary (HIV-1 RNA < 50 copies/mL) efficacy endpoints. Seven individuals in each group (1.2%) developed confirmed virologic failure[28]. The ATLAS-2M trial evaluated the efficacy of LA CAB + RPV every 8 weeks (Q8W) versus every 4 weeks (Q4W). The Q8W strategy showed non-inferior efficacy. The effect was sustained long-term through 152 weeks, with 2.7% and 1.0% of participants with HIV-1 RNA ≥ 50 copies/mL with Q8W and Q4W, respectively (adjusted treatment difference of 1.7%; 95% CI 0.1-3.3%), meeting the non-inferiority threshold of 4%[29]. Finally, the SOLAR study compared LA CAB + RPV LA every 2 months with bictegravir (BIC) + FTC + TAF continued once daily for maintenance of HIV-1 virologic suppression. At month 12, LA CAB + RPV showed non-inferior efficacy (5 [1%] of 447 vs. 1 [< 1%] of 223 with HIV-1 RNA ≥ 50 copies/mL), with an adjusted treatment difference of 0.7 (95% CI −0.7-2.0)[19].

Real-world studies have also demonstrated the effectiveness and safety of dual therapies. DOLAVI real-life study reported, at week 48, a plasma viral load < 50 copies/mL in 86.3% of participants treated with DTG + 3TC by intention-to-treat (ITT) analysis and 98.7% by per-protocol (PP) analysis, and recorded 1.1% of virological failure (two consecutive viral load > 50 copies/mL)[30]. DTG-based 2DRs (combined with 3TC or RPV) as a switch strategy were associated with virological suppression rates of 96.9%, 97.4%, and 99.1% at weeks 24, 48, and 96, respectively, and 0.01% of virological failure over the 48-week study period[20]. TANDEM study also demonstrated the real-world effectiveness of DTG + 3TC in PWH-1 in test-and-treat settings or with high baseline viral loads[31]. DOLAMA real-life study demonstrated the effectiveness and safety of DTG + 3TC in virologically suppressed HIV-1 patients. At week 48, 82.4% of patients had viral load < 50 copies/mL using an ITT analysis, 96.7% according to PP analysis, and 3.3% of patients had virological failure[21]. The efficacy, durability, and tolerability of DTG + 3TC and DTG + RPV were also demonstrated in a real-world setting in Belgium. Through 48 weeks, the rate of virological suppression was 99.1% with DTG + 3TC and 96.2%

Table 2. Main toxicities of the antiretroviral drugs included in this review

Antiretroviral drug	Associated toxicities
Abacavir	Increased risk of ischemic heart disease in cohort studies
Tenofovir disoproxil fumarate	Renal impairment: Serum creatinine increase Proteinuria Glycosuria Hypophosphatemia Metabolic acidosis Decreased bone mineral density
Tenofovir alafenamide	Metabolic effects: Greater weight increase reported with TAF than with TDF Elevated blood lipid levels (TG, LDL, HDL, no change in TC: HDL ratio)
Dolutegravir	Neuropsychiatric symptoms: Depression Anxiety Insomnia Suicidal behavior
Bictegravir	Neuropsychiatric symptoms: Depression Anxiety Insomnia Suicidal behavior

HDL: high-density lipoprotein; LDL: low-density lipoprotein; TAF: tenofovir alafenamide; TC: total cholesterol; TDF: tenofovir disoproxil fumarate; TG: triglycerides.

with DTG + RPV[22]. Finally, the Rildo study showed that the switch from any antiretroviral regimen to RPV + DTG in a single-tablet regimen is a cost-effective, long-lasting, and robust strategy for HIV patients[23]. Likewise, the SPLASH program demonstrated high levels of viral suppression in patients with challenges adhering to oral ART[32], a large UK-based cohort study showed that robust approval processes and clinical protocols allowed on-time injections, leading to low rates of discontinuation and virological failure[33], and the CARES trial conducted in Africa demonstrated that LA therapy with CAB + RPV had non-inferior efficacy compared with oral therapy and presented a good safety profile[34].

Interactions

Although booster-free 3DRs do not have a high number of interactions, simplification of ART to 2DRs may lead to a reduction of them. In the current context, withdrawal of NRTIs such as TAF can reduce possible interactions with central nervous system drugs such as carbamazepine or phenytoin, and anti-infectives such as clarithromycin, rifampicin or itraconazole[3]. Intramuscular administration of CAB and RPV has the advantage of eliminating drug-drug interactions that occur at the gastrointestinal level due to changes in gastric pH (RPV needs a low pH for optimal absorption), chelation (CAB creates a complex with divalent cations, which hinders its absorption) or inhibition/induction of intestinal drug-metabolizing enzymes[3]. The use of illicit drugs to enhance sexual activity (chemsex) does not interact with 2DRs.

Drug toxicity

Because of improved life expectancy, PWH now uses ART for a much longer period, and the cumulative toxicity that can arise is not yet fully understood. Therefore, reducing the number of antiretroviral drugs has the potential to reduce cumulative toxicities.

Older NRTIs (such as zidovudine, didanosine, and stavudine) soon lost their competitiveness to less toxic NRTIs such as 3TC, FTC, abacavir (ABC), TDF, and recently TAF. However, toxicity issues remain a drawback for many of them (Table 2)[35]. Data suggest that

ABC may be associated with an increased risk of hyperlipidemia and cardiovascular events[8]. Although there is heterogeneity in the data, several published cohort studies and clinical trials support such an association, generally relating it to recent drug exposure, independently of traditional predisposing factors (Supplementary Table 1). Less controversy exists about the bone and renal tubular toxicity of TDF. TDF nephrotoxicity is caused by mitochondrial toxicity, which results in mitochondrial structural change and DNA damage and even may induce cellular apoptosis of the proximal tubular cells[6]. TDF can lead to renal impairment, with increases in serum creatinine, proteinuria, glycosuria, hypophosphatemia, and acute tubular necrosis[6]. In addition, TDF has been consistently associated with decreased bone mineral density[36]. In the previously mentioned GEMINI[14], TANGO[26], SALSA[16], and SWORD[17] trials, an improvement in renal and bone parameters was observed after the switch from TDF-based 3DR to 2DR.

Due to the association of TDF with proximal renal tubulopathy and loss of bone mineral density, TDF has been replaced with TAF in most ART guidelines[3]. However, there is growing concern about the potential metabolic side effects of TAF, such as weight gain or the lack of the lipid-lowering effect observed with TDF, especially when associated with integrase inhibitors[37], although the data is inconsistent concerning weight gain associated with TAF. In the ADVANCE clinical trial, participants receiving TAF + FTC had clinically and significantly greater weight gain than those receiving TDF + FTC. In the same way, the pooled analysis of eight Gilead Sciences-sponsored trials in ART-naïve participants found that TAF was associated with greater weight gain than ABC, TDF, or zidovudine, with mean weight gains at 96 weeks of 4.25 kg, 3.08 kg, 2.07 kg, and 0.39 kg, respectively[37]. This same study shows similar weight gain with the second-generation INSTIs DTG and BIC. Other observational studies, such as the one conducted on the Spanish CoRIS cohort, also found modest weight gain after switching from TDF to TAF[5]. The recent PASO-DOBLE trial has found significantly greater weight gain in participants initiating BIC + FTC + TAF than in those initiating DTG + 3TC[38]. However, other clinical trials have found no evidence of an effect of TAF on weight gain and seem to support the effect of TDF on attenuation of weight gain. In the GEMINI trials, the mean weight change after 96 weeks was 2.1 kg in those receiving DTG plus TDF + FTC compared to 3.1 kg in those receiving DTG plus 3TC group. Similarly, changes in lipid parameters generally favored DTG plus TDF + FTC[24]. In the SALSA trial, there was a significantly greater weight gain with the switch to DTG + 3TC compared to the continuation of the current 3DR (2.1 kg vs. 0.6 kg at week 48). This differential change in weight was driven by those who switched from a TDF-based regimen, with no significant differences observed in those who switched from TAF[16]. In the TANGO trial, there was no significant difference in mean weight gain after 144 weeks (2.2 kg in those who switched to DTG + 3TC and 1.7 kg in those who maintained TAF). However, in this trial, improvements in fasting lipids and fasting insulin were observed in participants who switched from a baseline-boosted 3DR to DTG + 3TC[26]. Recent analysis in the Swiss cohort observed a decrease in weight after the replacement of TAF with TDF, but not after switching to DTG + 3TC or LA CAB + RPV. However, an improvement in lipid parameters was observed with the switch to DTG + 3TC[4]. In the SWORD trial, switching to DTG + RPV did not affect serum concentrations of lipids, despite the withdrawal of TDF in a high percentage of participants[17]. Concerning LA CAB + RPV, the available data seem to indicate a neutral effect on metabolic parameters. In the SOLAR trial, the mean weight change was −0.40 kg in the LA CAB + RPV group and +0.05 kg in the BIC + FTC + TAF group, the difference being non-significant[19]. In addition, there were no significant changes in the proportion of participants with metabolic syndrome or insulin resistance between arms[39]. Finally, concerning metabolic toxicity, there is evidence that points to an association between the use of TAF and an increased risk of non-alcoholic fatty liver disease (NAFLD), whereas TDF would be associated with a lower risk of onset and progression of NAFLD[9]. However, TDF may produce hepatotoxicity and increase the risk of end-stage liver disease and hepatocellular carcinoma[10]. In this sense, RPV has been shown to decrease liver fibrosis and it has been postulated that it may represent an effective strategy for the management of chronic liver disease[40].

Neuropsychiatric toxicity is another major concern related to INSTIs, in both 3DR and 2DR. INSTIs, such as DTG and BIC, have been associated with neuropsychiatric symptoms including depression, anxiety, insomnia, and, in some cases, suicidal behavior[41]. The reported incidence of neuropsychiatric adverse events (NPAE) in DTG-treated patients leading to discontinuation is < 1% in RCTs and between 1% and 7% according to clinical cohorts[7]. In this regard, BIC appears similar to DTG[7]. Some risk factors associated

with an increased risk of discontinuing DTG-based regimens due to NPAE include being a woman, an age > 50 years, and treatment combinations with ABC[41]. In contrast, NPAE with CAB alone or with RPV is rare[7]. In dual therapy, such as the combination of DTG with 3TC or RPV, studies have shown discontinuation rates for toxicity similar to those for triple therapy, although with an adverse event profile that may be more manageable[42].

Subclinical failure: reservoir, inflammation, immune exhaustion

Different studies have compared 2DRs and 3DRs beyond the virological suppression in plasma defined in clinical trials. Analyses of blip rates and undetected plasma HIV-RNA have confirmed similar rates of virological suppression below the standard threshold of 50 copies/mL, in both oral[43] and LA intramuscular therapy[44]. Similar HIV-1 RNA decay kinetics in seminal plasma and rectal fluid between integrase inhibitor-based 3DRs and 2DRs have been reported. Moreover, there are studies suggesting a similar effect on viral suppression in the seminal and rectal compartments with the LA intramuscular formulations and the daily oral regimen[44]. In addition to viremia, other outcomes related to HIV control have been studied. The RUMBA study evaluated the impact of the switch from 3DR to 2DR on the viral reservoir, specifically on the intact HIV-1 reservoir and the active reservoir by HIV-1 transcription, and found no differences between the two treatment strategies[45]. Numerous studies have evaluated changes in inflammatory proteins predictive of mortality or non-AIDS events between 3DR and 2DR, with inconclusive results currently[46]. Some studies have found that maintenance of 3DR was associated with a more favorable long-term inflammatory profile than switching to 2DR. The AIR study reported differences in favor of 3DR in lower interleukin (IL)-6, high-sensitivity C-reactive protein, and D-dimer[47]. Conversely, the TANGO trial reported minimal changes in inflammatory biomarkers with slightly lower levels of IL-6 with 3DR at 144 weeks[43]. However, other randomized studies have not found concordant results with increased inflammation or immunoactivation in PWH receiving 2DR. In the SALSA study, changes in inflammatory biomarkers were generally small and similar between the DTG + 3TC and 3DR groups[16], whereas the DEBATE trial found no difference in IL-6 trajectories after 1 year of switch to DTG + 3TC versus BIC + FTC + TAF[48].

Posology and patient-reported outcomes

Intramuscular therapy with CAB + RPV is the first LA treatment approved for the management of HIV infection and has changed the paradigm of oral treatment. These therapies represent the most innovative dual therapy, simplifying the treatment in two ways, since they reduce the regimen from triple to dual therapy, and shift from the daily oral medication to the bi-monthly parenteral route. This has resulted in patient preferences gaining importance when prescribing ART. Several studies have reported the participant preference for LA CAB + RPV versus daily oral ART after 1 year of treatment. The SOLAR study showed higher satisfaction with treatment among participants in the LA group compared to those in the oral therapy group, with 90% reporting a preference for LA therapy[19]. Pooled data from the ATLAS and FLAIR trials show a 98% participant preference for monthly injectable therapy and significantly higher levels of treatment satisfaction over previous daily oral ART[28]. In addition, ATLAS-2M showed that every 8-week dosing was preferable to every 4-week dosing in those with experience with both regimens[29]. In the CARISEL study, most participants found injectable therapy less stigmatizing than daily oral therapy, 95% would recommend LA CAB + RPV to other PWH, and 99% reported preferring LA therapy to oral medication. The main reasons for this preference were related to discretion, convenience and not having to remember to take daily medication[49]. Similarly, the CUSTOMIZE study showed similar results, with 92% of participants reporting a preference for injectable therapy with CAB + RPV[50]. Real-life cohort studies have found similar results, as in the case of the CARLOS cohort where almost half of the participants reported challenges related to oral treatment (fear of disclosing their HIV status, anxiety about adherence requirements, daily reminders of their HIV status) and improved satisfaction after switching to LA therapy with CAB + RPV. Most patients showed adherence to their medical appointments, and 99% percent of participants preferred injectable therapy mainly due to convenience, adherence concerns, and pill fatigue[51]. The ILANA study also reported that participants preferred injections over oral therapy since injections were increasingly feasible, appropriate, and satisfactory, with 99% of injections given within the 7-day window[52]. The real-world JABS study associated LA cabotegravir plus rilpivirine with very high adherence, with 97.2% of injections administered within correct dosing windows

as clinic visits, as well as maintenance of virological suppression, safety, and treatment satisfaction. The results of this study are comparable to those in randomized clinical trials[53]. Moreover, physicians tended to agree, or strongly agreed, that LA therapeutics could improve adherence for all PWH (81% of physicians), and 76% of physicians viewed LA injectables as having the potential to address challenges such as pill burden, stigma, and drug/food interactions[54].

Conclusions

INSTI-based 2DR have shown non-inferior efficacy to 3DR in the management of HIV infection. The switch to these therapies is based on a potentially lower risk of drug interactions and toxicity. So far, there is no evidence that dual therapy is associated with an increased risk of subclinical failure in the short to medium term. These results position 2DR as a preferred strategy for HIV treatment, and similar to 3DR. Within the 2DR, the new LA therapies appear to be an effective and preferred strategy by most patients, given the additional benefits these therapies bring, such as improved convenience and drug adherence.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.M25000081. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Conflicts of interest

J. Martínez-Sanz declares having received personal honoraria from ViiV Healthcare, Janssen Cilag, Gilead Sciences and MSD, as part of the speaker's bureau or advisory board panels, and research grants from Gilead Sciences.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Menéndez-Arias L, Delgado R. Update and latest advances in antiretroviral therapy. Trends Pharmacol Sci. 2022;43:16-29.
2. Gibas KM, Kelly SG, Arribas JR, Cahn P, Orkin C, Daar ES, et al. Two-drug regimens for HIV treatment. Lancet HIV. 2022;9:e868-83.
3. European AIDS Clinical Society. EACS Guidelines version 11.1, October 2022. Available from: https://www.eacsociety.org/guidelines/guidelines-archive/
4. Damas J, Munting A, Fellay J, Haerry D, Marzolini C, Tarr PE, et al. Weight, anthropometric and metabolic changes after discontinuing antiretroviral therapy containing tenofovir alafenamide (TAF) in people with human immunodeficiency virus (HIV). Clin Infect Dis. 2024;79:990-8.
5. Martínez-Sanz J, Serrano-Villar S, Muriel A, García Fraile LJ, Orviz E, Mena de Cea Á, et al. Metabolic-related outcomes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in adults with HIV: a multicenter prospective cohort study. Clin Infect Dis. 2023;76:e652-60.
6. Venter WD, Fabian J, Feldman C. An overview of tenofovir and renal disease for the HIV-treating clinician. South Afr J HIV Med. 2018;19:817.
7. Senneker T, Tseng A. An update on neuropsychiatric adverse effects with second-generation integrase inhibitors and nonnucleoside reverse transcriptase inhibitors. Curr Opin HIV AIDS. 2021;16:309-20.
8. Jaschinski N, Greenberg L, Neesgaard B, Miró JM, Grabmeier-Pfistershammer K, Wandeler G, et al. Recent abacavir use and incident cardiovascular disease in contemporary-treated people with HIV. AIDS. 2023;37:467-75.
9. Riebensahm C, Berzigotti A, Surial B, Günthard HF, Tarr PE, Furrer H, et al. Factors associated with liver steatosis in people with human immunodeficiency virus on contemporary antiretroviral therapy. Open Forum Infect Dis. 2022;9:ofac538.
10. Ryom L, Lundgren JD, De Wit S, Kovari H, Reiss P, Law M, et al. Use of antiretroviral therapy and risk of end-stage liver disease and heaptocellular carcinoma in HIV-positive person. AIDS. 2016;30:1731-43.
11. Funderburg NT. Immunosenescence and HIV: Mutual Interactions? In: Growing Old with HIV: Co-morbidities & Ageing. 11th IAS Conference on HIV Science; 2021.
12. Roy U, Matthews A, Kamkwalala AR, Garg A, Rodrigo H, Clifford D, et al. Tenofovir Alafenamide is Associated with Shorter Telomere Length in People with HIV. Presented in the Conference on Retroviruses and Opportunistic Infections; 2022, abstract 625.
13. Schank M, Zhao J, Moorman JP, Yao ZQ. The impact of HIV- and ART-induced mitochondrial dysfunction in cellular senescence and aging. Cells. 2021;10:174.
14. Cahn P, Sierra Madero J, 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;393:143-55. Erratum in: Lancet. 2019;393:132.
15. De Wit S, Bonnet F, Osiyemi O, Bisshop F, Olalla J, Routy JP, et al. Durable efficacy of switching from a 3- or 4-drug tenofovir alafenamide-based regimen to the 2-drug regimen dolutegravir/lamivudine in the TANGO study through week 196. J Acquir Immune Defic Syndr. 2024;96:156-60.
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 human immunodeficiency virus 1 (HIV-1): week 48 results from the phase 3, noninferiority SALSA randomized trial. Clin Infect Dis. 2023;76:720-9.
17. Llibre JM, Hung CC, Brinson C, Castelli F, Girard PM, Kahl LP, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet. 2018;391:839-49. Erratum in: Lancet. 2018;391:2416.
18. Rojas J, de Lazzari E, Nregredo 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:e463-73.

19. Ramgopal MN, Castagna A, Cazanave C, Diaz-Brito V, Dretler R, Oka S, et al. Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial. Lancet HIV. 2023;10:e566-77.
20. Dueñas-Gutiérrez C, Buzón L, Pedrero-Tomé R, Iribarren JA, De Los Santos I, De la Fuente S, et al. Efficacy and safety of two-drug regimens with dolutegravir plus rilpivirine or lamivudine in HIV-1 virologically suppressed people living with HIV. Viruses. 2023;15:936.
21. Hidalgo-Tenorio C, Cortés LL, Gutiérrez A, Santos J, Omar M, Gálvez C, et al. DOLAMA study: effectiveness, safety and pharmacoeconomic analysis of dual therapy with dolutegravir and lamivudine in virologically suppressed HIV-1 patients. Medicine (Baltimore). 2019;98:e16813.
22. Nasreddine R, Yombi JC, Darcis G, Florence E, Allard SD, De Scheerder MA, et al. Efficacy, durability, and tolerability of dolutegravir/lamivudine and dolutegravir/rilpivirine for the treatment of HIV in a real-world setting in Belgium. HIV Med. 2023;24:267-78.
23. Hidalgo-Tenorio C, Vinuesa D, García-Vallecillos C, Muñoz-Medina L, Sequera S, Javier R, et al. Rildo: real-world multicenter study on the effectiveness and safety of single-tablet regimen of dolutegravir plus rilpivirine in treatment-experienced people living with HIV. Viruses. 2022;14:2626.
24. Cahn P, Sierra Madero J, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Three-year durable efficacy of dolutegravir plus lamivudine in antiretroviral therapy-naive adults with HIV-1 infection. AIDS. 2022;36:39-48.
25. Figueroa MI, Brites C, Cecchini D, Ramalho Teixeira Benvenuto A, Francos JL, Lacerda M, et al. Comparable efficacy and safety of dolutegravir/lamivudine to a three drug regimen amongst ARV naive people living with HIV with CD4 <200/mm^3: The DOLCE study. O24. Presented in HIV Drug Therapy Glasgow 2024. 10-13 november.
26. 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, non-inferiority TANGO study. Clin Infect Dis. 2020;71:1920-9.
27. Van Wyk J, Orkin C, Rubio R, Bogner J, Baker D, Khuong-Josses MA, et al. Brief report: durable suppression and low rate of virologic failure 3 years after switch to dolutegravir + rilpivirine 2-drug regimen: 148-week results from the SWORD-1 and SWORD-2 randomized clinical trials. J Acquir Immune Defic Syndr. 2020;85:325-30.
28. Rizzardini G, Overton ET, Orkin C, Swindells S, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting injectable cabotegravir + rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 ATLAS and FLAIR trials. J Acquir Immune Defic Syndr. 2020;85:498-506.
29. Overton ET, Richmond G, Rizzardini G, Thalme A, Girard PM, Wong A, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with human immunodeficiency virus 1 type 1 infection: 152-week results from ATLAS-2M, a randomized, open-label, phase 3b, noninferiority study. Clin Infect Dis. 2023;76:1646-54.
30. Hidalgo-Tenorio C, Pasquau J, Vinuesa D, Ferra S, Terrón A, SanJoaquín I, et al. DOLAVI real-life study of dolutegravir plus lamivudine in naive HIV-1 Patients (48 Weeks). Viruses. 2022;14:524.
31. Benson P, Kuretski J, Donovan C, Harper G, Merrill D, Metzner AA, et al. Real-world effectiveness of dolutegravir/lamivudine in people with HIV-1 in test-and-treat settings or with high baseline viral loads: TANDEM study subgroup analyses. Infect Dis Ther. 2024;13:875-89.
32. Hickey MD, Gistand N, Grochowski J, Mayorga-Munoz F, Imbert E, Szumowski JD, et al. 48-week viral suppression rates in people with HIV starting long-acting CAB/RPV with initial viremia. Clin Infect Dis. 2024 Oct 5:ciae500.
33. Ring K, Smuk M, Shongwe M, Okonta L, Mackie NE, Ayres S, et al. Multicentre service evaluation of injectable cabotegravir and rilpivirine delivery and outcomes across 12 UK clinics (SHARE LAI-net). HIV Med. 2024;25(10):1125-34.
34. Kityo C, Mambule IK, Musaazi J, Sokhela S, Mugerwa H, Ategeka G, et al. Switch to long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa (CARES): week 48 results from a randomised, multicentre, open-label, non-inferiority trial. Lancet Infect Dis. 2024;24(10):1083-92.
35. Pasquau J, Hidalgo-Tenorio C. Nuke-sparing regimens for the long-term care of HIV infection. AIDS Rev. 2015;17:220-30.
36. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: aids Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis. 2011;203:1791-801.
37. Sax PE, Erlandson KM, Lake JE, Mccomsey GA, Orkin C, Esser S, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020;71:1379-89.
38. Ryan P, Blanco JL, Masia M, Garcia-Fraile L, Crusells MJ, Domingo P, et al. OAB36. Non-inferior Efficacy and Less Weight Gain When Switching to DTG/3TC than when Switching to BIC/FTC/TAF in Virologically Suppressed People with HIV (PWH): The PASO-DOBLE (GeSIDA 11720) Randomized Clinical Trial. Co-morbidities: Beyond the Heart. AIDS; 2024. Available from: https://programme.aids2024.org/Abstract/Abstract/?abstractid=12253
39. Darrel HS, Antinori A, Eu B, Galindo MJ, Kinder C, Sweet D, et al. Weight and Metabolic Changes with Cabotegravir+Rilpivirine Long-acting or Bictegravir. Presented in the Conference on Retroviruses and Opportunistic Infections; 2023, abstract 146.
40. Moragrega AB, Gruevska A, Fuster-Martínez I, Benedicto AM, Tosca J, Montón C, et al. Anti-inflammatory and immunomodulating effects of rilpivirine: relevance for the therapeutics of chronic liver disease. Biomed Pharmacother. 2023;167:115537.
41. Pérez-Valero I, Corona D, Martínez N, López-Cavanillas M, Lluis C, Luque I. Real-world discontinuations due to neuropsychiatric symptoms in people living with HIV treated with second-generation integrase inhibitors: a systematic review. Expert Rev Anti Infect Ther. 2023;21:655-65.
42. Lagi F, Giacomelli A, Borghi V, Ciccullo A, Taramasso L, Madeddu G, et al. Efficacy and tolerability of dolutegravir/lamivudine versus dolutegravir/rilpivirine in switching from a three-drug regimen based on non-nucleoside reverse transcriptase inhibitors: a retrospective cohort study. J Med Virol. 2023;95:e29149.
43. 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 human immunodeficiency virus type 1: results through week 144 from the phase 3, noninferiority TANGO randomized trial. Clin Infect Dis. 2022;75:975-86.
44. Masiá M, Fernández-González M, Agulló V, Mascarell P, Padilla S, García-Abellán J, et al. Human immunodeficiency virus type 1 RNA levels in rectal and seminal compartments after switching to long-acting cabotegravir plus rilpivirine: a longitudinal study. Clin Infect Dis. 2023;76:e748-51.
45. De Scheerder MA, Degroote S, Delporte M, Kiselinova M, Trypsteen W, Vincke L, et al. In depth analysis of the HIV reservoir confirms effectiveness and safety of DTG/3TC in a phase 4 randomized controlled switch trial (RUMBA). J Infect Dis 2024 Sep 3:jiae405.
46. van Welzen BJ, Oomen PG, Hoepelman AI. Dual antiretroviral therapy-all quiet beneath the surface? Front Immunol. 2021;12:637910.
47. Serrano-Villar S, López-Huertas MR, Jiménez D, Galera C, Martínez-Sanz J, Moreno E, et al. Long-term changes of inflammatory biomarkers in individuals on suppressive three-drug or two-drug antiretroviral regimens. Front Immunol. 2022;13:848630.
48. 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;14:1279390.
49. Gutner CA, van der Valk M, Portilla J, Jeanmaire E, Belkhir L, Lutz T, et al. Patient participant perspectives on implementation of long-acting cabotegravir and rilpivirine: results from the cabotegravir and rilpivirine implementation study in european locations (CARISEL) study. J Int Assoc Provid AIDS Care. 2024;23:23259582241269837.
50. Garris CP, Czarnogorski M, Dalessandro M, D'Amico R, Nwafor T, Williams W, et al. Perspectives of people living with HIV-1 on implementation of long-acting cabotegravir plus rilpivirine in US healthcare settings: results from the CUSTOMIZE hybrid III implementation-effectiveness study. J Int AIDS Soc. 2022;25:e26006.
51. Scherzer J, Noe S, Jonsson-Oldenbüttel C, Wyen C, Esser S, Weinberg G, et al. Perceptions of Cabotegravir + Rilpivirine Long-Acting (CAB + RPV LA) from People Living with HIV (PLHIV) in the CARLOS Study. Poster EPE0863, 12th IAS Conference on HIV Science, Brisbane, Australia; 2023. Available from: https://www.natap.org/2023/IAS/IAS_10.htm.
52. Orkin CM, Haviland JS, Wong YL, Paparini S, Kasadha B, Hayes R, et al. Implementing LA cabotegravir(CAB)+rilpivirine(RPV) therapy in 6 UK clinics & in the community: ILANA. Presented in the Conference on Retroviruses and Opportunistic Infections; 2024, abstract 621.
53. John M, Williams L, Nolan G, Bonnett M, Castley A, Nolan D. Real-world use of long-acting cabotegravir and rilpivirine: 12-month results of the inJectable Antiretroviral therapy feasiBility Study (JABS). HIV Med. 2024;25(8):935-945.
54. Charlton R, Ambler W, Small M, Holbrook T, Hennessy F. Poster P165. Physician attitudes towards anti-retroviral therapy adherence and unmet treatment needs in people with HIV: a real-world survey in Europe and the United States. J Intern AIDS Soc. 2024;27(S6):e26370.