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SYSTEMATIC REVIEW

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Comparison of the design and methodology of Phase 3 clinical trials of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) and dolutegravir-based dual therapy (DTG) in HIV: a systematic review of the literature

Santiago Grau[a], Jose Maria Miró[b,c], Julian Olalla[d], Juan C Alcalá[e], Antonio Castro[e], Dario Rubio-Rodríguez[f] and Carlos Rubio-Terrés[f]

[a]Pharmacy Department, Hospital Del Mar, Barcelona, Spain; [b]Department of Infectious Diseases, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain; [c]CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain; [d]Internal Medicine Department, Hospital Costa Del Sol, Marbella, Spain; [e]Gilead Sciences, Madrid, Spain; [f]Health Value, Madrid, Spain

ABSTRACT

Introduction: Current recommended antiretroviral regimens include a combination of two (dual; DT) or three (triple; TT) antiretroviral drugs. This study aims to determine whether the quality of evidence from clinical trials of dolutegravir (dolutegravir/lamivudine [DTG/3TC] or dolutegravir/rilpivirine [DTG/RPV]) is methodologically comparable to that of clinical trials conducted with bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF).

Areas covered: A systematic review of the medical literature was carried out in PubMed without date or language restrictions, following the PRISMA guidelines. All aspects of the methodological design of phase 3 randomized clinical trials (RCTs) of DT and TT, evaluated by the European Medicines Agency (registration trials), were reviewed. The quality of clinical trials was assessed using the Jadad scale.

Expert opinion: The search identified 5, 3 and 2 phase 3 RCTs with BIC/FTC/TAF, DTG/3TC and DTG/RPV, respectively, that met the inclusion criteria. The designs would not be comparable due to differences in pre-randomization losses, blinding, patient recruitment, as well as differences in methodological quality, with the average score of the RCTs conducted with BIC/FTC/TAF, DTG/3TC and DTG/RPV being 4.2 (high quality), 3.0 (medium quality) and 3.0 (medium quality), respectively. Due to methodological differences between the BIC/FTC/TAF, DTG/3TC and DTG/RPV RCTs, the results of these are not comparable.

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1. Introduction

In Spain, no significant impact of antiretroviral therapy (ART) on the progression of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) and mortality reduction was observed until 1996 with the combination of three or more drugs, including two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI) boosted or not with ritonavir [1–3]. Since then, ART has led to a steady reduction in AIDS cases [3] and associated mortality in Spain [4,5]. It is estimated that 151,400 people with HIV are currently living in Spain, that 87% of these (131,775) know their HIV status, that 97.3% of these are on treatment (128,216) and, finally, that 90.4% of these (115,900) have HIV viral suppression [4,5] with a consequent reduction in the transmission of the disease.

The 2021 infoAIDS glossary, published by the US Department of Health and Human Services, states that ART 'generally includes three antiretroviral drugs from at least two different classes of anti-HIV drugs.' [6] According to the GeSIDA/National AIDS Plan 2020 consensus document [7], 'the recommended guidelines for initial treatment of HIV-1 infection at present are a combination of two or three drugs.' All triple and dual regimens recommended as preferred by GeSIDA include an integrase inhibitor (INI) and at least one NRTI [7] (Table 1).

Clinical studies of dual therapy have not shown inferiority to standard (triple) therapy, being it of interest to analyze whether the quality of the clinical trials designs is equivalent or not. This study aims to review the available evidence to answer the following question: Can triple therapy (TT) with Bictegravir/Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) and dual therapy (DT) with Dolutegravir/Lamivudine (DTG/3TC) or Dolutegravir/Rilpivirine (DTG/RPV) be considered equivalent or comparable? The latter combination (DTG/RPV) of an INI with rilpivirine, an NNRTI (non-nucleoside reverse transcriptase inhibitor), is not among those currently recommended by GeSIDA as preferred for initial treatment [7] (Table 1). To answer these questions, systematic reviews of the available clinical studies of the three treatment regimens were conducted with respect to the following aspects: (i) Methodological quality of the scientific evidence: Is the design of the randomized clinical trials comparable?; and, consequently, (ii) Applicability in clinical practice: Are the efficacy results of BIC/FTC/TAF, DTG/3TC and DTG/RPV comparable?;

CONTACT Carlos Rubio-Terrés crubioterres@healthvalue.org Health Value, Madrid, Spain

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Article highlights

- Current recommended antiretroviral regimens include a combination of two (dual; DT) or three (triple; TT) antiretroviral drugs.
- A systematic review of the medical literature was carried out in PubMed to determine whether the quality of evidence from clinical trials of DT with dolutegravir (dolutegravir/lamivudine [DTG/3TC] or dolutegravir/rilpivirine [DTG/RPV]) based clinical trials is methodologically comparable to that of clinical trials conducted with TT with bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF).
- The search identified 5, 3 and 2 phase 3 RCTs with BIC/FTC/TAF, DTG/3TC and DTG/RPV, respectively, that met the inclusion criteria. The clinical trials designs would not be comparable due to differences in pre-randomisation losses, blinding and patient recruitment.
- Clinical trials would also not be comparable due to differences in methodological quality, with the average score of the RCTs conducted with BIC/FTC/TAF, DTG/3TC and DTG/RPV being 4.2 (high quality), 3.0 (medium quality) and 3.0 (medium quality), respectively.
- In conclusion, due to differences in methodolody and quality of evidence between the BIC/FTC/TAF, DTG/3TC and DTG/RPV RCTs, the results of these are not comparable.

Table 1. Preferred starting ART combinations recommended by GeSIDA [7].

Regimen	Abbreviation	Groups
Bictegravir/Emtricitabine/Tenofovir	BIC/FTC/TAF	INI/NRTI/NRTI
Dolutegravir/Abacavir/Lamivudine	DTG/ABC/3TC	INI/NRTI/NRTI
Dolutegravir/Emtricitabine/Tenofovir	DTG+FTC/TAF	INI/NRTI/NRTI
Dolutegravir/Lamivudine	DTG/3TC	INI/NRTI

INI: integrase inhibitors; NRTI: Nucleoside reverse transcriptase inhibitors.
This list does not include Dolutegravir/Rilpivirine (DTG/RPV), a combination of an INI with rilpivirine, an NNRTI (non-nucleoside reverse transcriptase inhibitor).

and (iii) Which of the compared schemes have higher methodological robustness according to the Jadad scale score?

2. Methods

2.1. Search strategy

The systematic reviews were conducted according to the recommendations of the PRISMA guidelines [8] and the methodology described above [9]. Three systematic reviews of articles available in PubMed were conducted, one on BIC/FTC/TAF, one on DTG/3TC and one on DTG/RPV.

The literature reviews were conducted in October 2021. There were no language or publication date limitations in the literature search. Two of the study's authors (DRR and CRT) reviewed the titles and abstracts from the database, assessing whether the studies met the following ***inclusion criteria***. Regarding patients: (i) Adults (≥18 years) with initial HIV-1 infection, previously untreated (naïve) and with a plasma HIV-1 RNA concentration greater than 500 copies per ml. Or: (ii) Adults (≥18 years) with HIV-1 infection that has resulted in virological suppression (switch) set at <50 HIV-1 RNA copies per ml for at least 3 months prior to measurement and in stable condition (no switch in treatment regimen in the last 3 months). With regard to the type of study, they should have been Phase 3 randomized clinical trials (RCTs) published as such with the combination of BIC/FTC/TAF, DTG/3TC or DTG/RPV. In addition, they should have been clinical trials assessed by the European Medicines Agency (EMA) in the regulatory dossier submitted for marketing authorization and therefore described in the product's label or, failing that, in the EMA assessment report [10–15] (in this way, the explanatory phase III clinical trials were analyzed, with a design considered adequate for obtaining the marketing license in the European Union). Finally, the primary objective of RCTs should be to assess the efficacy of treatment for HIV-1 infection.

Two study authors independently analyzed articles that met these inclusion criteria (DRR and CRT). Any discrepancies were resolved by consensus. The reference lists of these articles were also manually reviewed to identify other potential studies not identified in the internet search.

The ***search criteria*** in PubMed were as follows: (i) BIC/FTC/TAF: ('bictegravir'[Supplementary Concept] OR 'bictegravir'[All Fields]) AND ('emtricitabine tenofovir alafenamide'[Supplementary Concept] OR 'emtricitabine tenofovir alafenamide'[All Fields]); (ii) DTG/3TC: ('dolutegravir'[Supplementary Concept] OR 'dolutegravir'[All Fields]) AND ('lamivudine'[MeSH Terms] OR 'lamivudine'[All Fields] OR 'lamivudin'[All Fields]); and, finally, (iii) DTG/RPV: ('dolutegravir'[Supplementary Concept] OR 'dolutegravir'[All Fields]) AND ('rilpivirine'[MeSH Terms] OR 'rilpivirine'[All Fields]). The clinical trial protocols were also reviewed in the clinical trials web-based resource of the National Library of Medicine (NLM) and the National Institutes of Health (INH) of the United States of America (https://clinicaltrials.gov/).

As usual in systematic reviews [9], conference papers and posters were excluded. Phase 3b RCTs were also excluded because these studies are not part of the regulatory dossier submitted to the EMA for authorization of the new medicinal product but are generally used to expand the indications in certain populations or answer some questions not clarified in the registration RCTs.

2.2. Data extraction

The data extracted from the articles reviewed was as follows: (i) Numerical reference or acronym of the study; (ii) Description of study design: randomization, blinding, clinical trial phase, virological suppression criteria, whether intention-to-treat analysis was performed, week in which efficacy assessment was performed; (iii) Type of patients: non-pretreated or virologically suppressed; (iv) Treatment regimens: combination drugs; (v) Sample size of treated patients; (vi) Non-inferiority results; (vii) Virological suppression results. Data extraction was carried out by one author (DRR) and reviewed by another (CRT).

2.3. Assessment of the methodological quality of RCTs

The methodological quality of the RCTs was assessed using the modified Jadad scale [16,17], which uses the following criteria: (i) Is the study described as randomized? (ii) Was the method of randomization appropriate; (iii) Is the study described as double-blind; (iv) Are withdrawals and dropouts from the treatment described; (v) Are patient inclusion/exclusion criteria clearly described; (vi) Was the method of randomization inappropriate; and finally, (vii) Was the method of blinding inappropriate; Each affirmative answer to

questions (i) to (v) is worth 1 point. Each affirmative answer to questions (vi) and (vii) results in deducting 1 point. The highest possible quality corresponds to a score of 5. Scores of 4, 3 and 1–2 points are considered high, medium and low-quality RCTs, respectively [16,17].

Two authors independently carried out the modified Jadad scale assessment (DRR and CRT). Any discrepancies were resolved by consensus.

3. Results

3.1. Selected studies: treatment-naïve

3.1.1. BIC/FTC/TAF

In total, 26 bibliographic references were identified (19 in the systematic review and 7 from other sources). Of these, 11 references were selected (15 were excluded because, according to the abstracts, they did not meet the inclusion criteria), and 5 full articles were finally analyzed. The remaining 6 were excluded for the following reasons: 2 were RCTs with treatment switch in virological suppression [18,19], 3 were systematic reviews [20–22], and 1 was a meta-analysis [23]. The 5 selected articles (Supplementary Figure 1) were included in the systematic review. These articles correspond to two RCTs (Table 2): Study 1489, with two articles [24,25]; Study 1490, with two articles [26,27]; Aggregate data from both studies, with one article [19].

3.1.2. DTG/3TC

In total, 57 references were identified (44 in the systematic review and 13 from other sources; 3 duplicate references were eliminated). Of these 57 references, 18 were selected, and 9 full articles were analyzed. The remaining 9 were excluded for the following reasons: 4 were meta-analyses [28–31], 4 were systematic reviews or methodological analyses [32–35], and 1 was a cohort study [36]. Five articles were included in the systematic review, excluding the TANGO study as it involved a treatment switch (Supplementary Figure 2). These five articles correspond to two studies (Table 2), GEMINI 1 and GEMINI 2 [29,37–40].

3.2. Selected studies: treatment-experienced

3.2.1. BIC/FTC/TAF

In total, 28 bibliographic references were identified (19 in the systematic review and 9 from other sources). Of these 28 references, 13 were selected, and 3 full articles were analyzed. The remaining 10 were excluded for the following reasons: 5 were treatment-naïve RCTs [18,19], 3 were systematic reviews [20–22], and 1 was a meta-analysis [23]. Finally, one phase 3 RCT was excluded because the EMA did not evaluate it for marketing authorization [41]. The 3 selected articles (Supplementary Figure 3) were included in the systematic review. These three articles correspond to three RCTs [18,42,43]. (Table 3). One phase 3b RCT, limited to the subgroup of patients aged 65 years or older, was also excluded from the 28 references initially selected [44].

Table 2. Randomized clinical trials of BIC/FTC/TAF and DTG/3TC in naïve patients.

Treatment regimen	Study	Design	Treatments	N	Non-inferiority Mean (95%CI)	Virological suppression* 48 weeks	Virological suppression* 144 weeks	References
BIC/FTC/TAF	1489	RCT, DB, Phase 3 DB 144 weeks Virological suppression (<50 copies/ml HIV-1 RNA): • Non-inferiority (−12%) 144 weeks • Week 48 (PEE) • Week 96 (SEE) IT analysis with drug exposure	BIC/FTC/TAF DTG/ABC/3TC	314 315	−2.6% (−8.5%;3.4%) (144 weeks)	92.4% 93.3%	82% 84%	*Gallant, 2017 [24]* *Wohl, 2019 [25]* *Orkin, 2020 [19]*
	1490	RCT, DB, Phase 3 DB 144 weeks Virological suppression (<50 copies/ml HIV-1 RNA): • Non-inferiority (−12%) 144 weeks • Week 48 (PEE) • Week 96 (SEE) IT analysis with drug exposure	BIC/FTC/TAF DTG+FTC/TAF	320 325	−1.9% (−7.8%;3.9%) (144 weeks)	89% 93%	81% 84%	*Sax, 2017 [26]* *Stellbrink, 2019 [27]* *Orkin, 2020 [19]*
DTG/3TC	GEMINI 1 and 2	RCT, DB, Phase 3 DB 96 weeks Virological suppression (<50 copies/ml HIV-1 RNA): • Non-inferiority (−10%) 96 weeks • Week 48 (PEE) • Week 96 (SEE) • Week 144 (PS) IT analysis with drug exposure	DTG/3TC DTG+FTC/TDF	716 717	GEMINI 1 and 2: -3.4 (−6.7; 0.0007) (96 weeks) -1.8% (−5.8, 2.1) (144 weeks)	91% 93%	86% 89.5%	*Cahn, 2019 [37]* *Cahn, 2020a [38]* *Cahn, 2020b [39]* *Eron, 2020 [29]* *Cahn, 2022 [40]*

*Percentage of patients with <50 copies of HIV RNA per ml of plasma. BIC/FTC/TAF: Bictegravir/Emtricitabine/Tenofovir; DB: double-blind; DTG/3TC: Dolutegravir/Lamivudine; DTG/ABC/3TC: Dolutegravir/Abacavir/Lamivudine; DTG+FTC/TAF: Dolutegravir/Emtricitabine/ Tenofovir disoproxil fumarate; DTG+FTC/TDF: Dolutegravir/Emtricitabine/Tenofovir disoproxil fumarate; RCT, randomized clinical trial; IT, intention-to-treat; PEE, primary efficacy endpoint; SEE, secondary efficacy endpoint.

Table 3. Randomized clinical trials of BIC/FTC/TAF in virologically suppressed (switch) patients.

Treatment regimen	Study	Design	Treatments	N	Non-inferiority Mean (95%CI)	No virological suppression* 48 weeks	References
BIC/FTC/TAF	1844	Switch from: DTG/ABC/3TC RCT, DB, Phase 3 No virological suppression (≥50 copies/ml HIV-1 RNA): • Non-inferiority (−4%) • Week 48 (PEE)	BIC/FTC/TAF DTG/ABC/3TC	282 281	0.7% (−1.0%;2.8%)	1.1% 0.4%	*Molina, 2018 [42]*
	1878	Switch from: regimes with PI (DRV-ABC-3TC or ATC-ABC-3TC or DRV-FTC-TDF or ATC-FTC-TDF) RCT, unblinded, Phase 3 No virological suppression (≥50 copies/ml HIV-1 RNA): • Non-inferiority (−4%) • Week 48 (PEE)	BIC/FTC/TAF Regimes with PI	290 287	0.0% (−2.5%;2.5%)	2% 2%	*Daar, 2018 [43]*
	1961	Switch from: EVG/c/FTC/TAF, EVG/c/FTC/TDF, or ATV/r + FTC/TDF RCT, unblinded, Phase 3 No virological suppression (≥50 copies/ml HIV-1 RNA): • Non-inferiority (−4%) • Week 48 (PEE)	BIC/FTC/TAF Regimes with TAF or TDF	234 236 (Women only)	0.0% (−2.9%;2.9%)	1.7% 1.7%	*Kityo, 2019 [19]*

*Percentage of patients with ≥50 copies of HIV RNA in plasma. ATC-FTC-TDF: Atazanavir/ Emtricitabine/Tenofovir disoproxil fumarate; ATV/r+ FTC/TDF: Atazanavir/ Ritonavir+Emtricitabine/Tenofovir disoproxil fumarate; ATC-ABC-3TC: Atazanavir/Abacavir/Lamivudine; BIC/FTC/TAF: Bictegravir/Emtricitabine/Tenofovir; DB: double-blind; DRV-ABC-3TC: Darunavir/Abacavir/Lamivudine; DRV-FTC-TDF: Darunavir/Emtricitabine/Tenofovir disoproxil fumarate; DTG/ABC/3TC: Dolutegravir/ Abacavir/Lamivudine; RCT: randomized clinical trial; EVG/c/FTC/TAF: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir; EVG/c/FTC/TDF: Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir disoproxil fumarate; PI: protease inhibitors; PEE: primary efficacy endpoint.

3.2.2. DTG/3TC

In total, 61 references were identified (44 in the systematic review and 17 from other sources). Of these 61 references, 19 were selected, and 5 full articles were analyzed. The remaining 14 were excluded for the following reasons: 6 were observational studies [36,45–49], 4 were meta-analyses [28–31], and 4 were systematic reviews or methodological analyses [32–35,50]. After screening the five studies for eligibility, only the TANGO study [51] (Supplementary Figure 4) was included in the systematic review (Table 4).

3.2.3. DTG/RPV

In total, 168 bibliographic references were identified (166 in the systematic review and 2 from other sources). Of these 168 references, 31 were selected, and 10 full articles were analyzed. The remaining 21 were excluded for the following reasons: 13 were observational or non-randomized studies [49–62], and 8 were reviews [20,63–69]. Once the ten studies were analyzed for eligibility, three articles from the SWORD 1 and 2 clinical trials were included in the systematic review, with their supplements [70–72] (Table 4). Of the remaining seven articles, five were meta-analyses [31,73–76], and two were observational studies [77,78] (Supplementary Figure 5).

3.3. Is randomized clinical trial design with BIC/FTC/TAF, DTG/3TC and DTG/RPV comparable?

This question would be unnecessary if clinical trials directly comparing the efficacy and safety of BIC/FTC/TAF with DTG/3TC or DTG/RPV were available. However, as such studies are not available, the question must be raised whether indirect comparison (e.g. through a network meta-analysis) of RCTs conducted with one or the other regimen is warranted, for which purpose a comparison of the methodological designs of these RCTs has been carried out. If the designs were not comparable, if the patients included could be different, one would have to conclude that the efficacy and safety results of the two regimens would not be comparable.

3.3.1. Treatment-naïve: BIC/FTC/TAF vs DTG/3TC

This section analyses compares the design of RCTs with BIC/FTC/TAF (1489 and 1490) [19,24–27] and DTG/3TC (GEMINI 1 and 2) [29,37–40] in treatment-naïve HIV-infected patients (Table 2).

3.3.1.1. The comparator is different. Randomized controlled trials (RCTs) are widely accepted as the most rigorous research designs for evaluating the effects of health interventions. Random assignment of individuals to treatment groups increases the likelihood that the distribution of prognostic factors will be similar between groups and allows using blinding techniques, which are useful for obtaining an unbiased estimate of the endpoint [79,80].

One method of indirectly analyzing whether patient samples from two clinical trials can be comparable is to compare the effects obtained in the control groups, provided that the treatment of the controls is the same. This is the case, for example, when comparing two placebo-controlled studies. If the results are similar in the two placebo groups, this would back the comparability of the two clinical trials' patient samples (in terms of their prognostic factors). Unfortunately, this cannot be done in the present case, as the comparators in the

Table 4. Randomized clinical trials of DTG/3TC and DTG/RPV in virologically suppressed (switch) patients.

Treatment regimen	Study	Design	Treatments	N	Non-inferiority Mean (95%CI)	No virological suppression 48 weeks	References
DTG/3TC	TANGO	Switch from: TAF-based regime RCT, Unblinded, Phase 3 No virological suppression (≥50 copies/ml HIV-1 RNA): • Non-inferiority (−4%) • Week 48 (PEE)	DTG/3TC Regime with TAF	369 372	−0.3% (−1.2%; 0.7%)	0.3% 0.5%	*Van Wyk, 2020a [51]*
DTG/RPV	SWORD 1 and 2	Switch from: NNRTI (54%), PI (27%) and INI (20%) RCT, Unblinded, Phase 3 No virological suppression (≥50 copies/ml HIV-1 RNA): • Non-inferiority (−8%) • Week 48 (PEE) • Week 100 • Week 148	DTG/RPV Current ART	513 511	−0.2% (−3.0%; 2.5%) (48 weeks)	DTG/RPV: 3% (early switch) 2% (late switch) (148 weeks)	*Llibre, 2018 [71]* *Aboud, 2019 [72]* *Van Wyk, 2020 [73]*

DTG/3TC: Dolutegravir/Lamivudine; DTG/RPV: Dolutegravir/Rilpivirine; INI: integrase inhibitors: NNRTI, non-nucleoside reverse transcriptase inhibitor; PEEP, primary efficacy endpoint; TAF: Tenofovir; ART: antiretroviral treatment.

Table 5. Main methodological differences hindering comparability of clinical trials with BIC/FTC/TAF TT and DT with DTG/3TC and DTG/RPV.

Item	BIC/FTC/TAF	DTG/3TC	DTG/RPV	Impact of the methodological problem
Treatment-naïve				
Double-blind	YES	YES	Not applicable	If the answer is 'No,' the risk of biases (systematic errors) increases
Duration of blinding (weeks)	144	96[a]	Not applicable	If the duration is shorter, the risk of biases (systematic errors) increases
Pre-randomization losses	3.1%	7.3%	Not applicable	Pre-randomization losses reduce the external validity of the study
Treatment-experienced				
Double-blind	YES[b]	NO	NO	If the answer is 'No,' the risk of biases (systematic errors) increases
Inclusion of patients with liver diseases	YES	NO	NO	If patients with liver disease are excluded, there is a risk of recruiting patients with a better prognosis
Criteria for virological failure: Confirmed Virological Withdrawal (CVW)	NO	YES[c]	NO	Non-comparability of efficacy results

BIC/FTC/TAF: Bictegravir/Emtricitabine/Tenofovir; DT: dual therapy; DTG/3TC: Dolutegravir/Lamivudine; DTG/RPV: Dolutegravir/Rilpivirine; TT: triple therapy.
(a) Applicable to the third-year analysis (secondary analysis). (b) In the 1844 study, not in the 1878 and 1961 studies. (c) A snapshot assessment of virological failure is also performed in the TANGO study.

TT and DT clinical trials are different: DTG/ABC/3TC or DTG +FTC/TAF and DTG+FTC/TDF, respectively.

3.3.1.2. The duration of blinding is different. According to the EMA guideline on the statistical design of clinical trials, 'blinding aims to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that knowledge of the treatment may have on the recruitment and allocation of subjects, their subsequent care, subjects' attitudes to treatments, the assessment of endpoints, the handling of drop-outs, the exclusion of data from the analysis, etc. The fundamental objective is to avoid identification of treatments until all opportunities for bias have passed' [81].

According to the classic paper by Hulley and Cummings [82], masking 'does not prevent overall bias from appearing in measurements, but it can eliminate differential biases that affect one study group more than another.' Double-blind masking ensures that, if biases exist, they affect both groups equally.

The duration of masking (double-blind) was longer with BIC/FTC/TAF (144 weeks) than with DTG/3TC (96 weeks). Could this difference increase the risk of bias and compromise the comparability of the results of clinical trials of both regimens? This could indeed be the case for the following reasons.

The DTG/3TC comparator was DTG+FTC/TDF, containing tenofovir disoproxil fumarate (TDF). It is well known that TDF can cause renal toxicity [83] and bone toxicity. In contrast, with tenofovir alafenamide (TAF), present in BIC/FTC/TAF, renal effects are much lower than with TDF at 48 weeks of treatment in ART-naïve patients (RR: 0.31; CI 95% CI: 0.18–0.55; $p < 0.05$) [83]. However, in another meta-analysis of treatment-experienced or treatment-naïve patients, no significant differences in renal toxicity were observed between unboosted TDF and TAF [84]. The question arises: Is there a possibility that in the GEMINI 1 and 2 studies, once treatment blinding was removed, some investigators might consciously or unconsciously [79,80,85] switch the treatment of the control group due to the possibility of renal and bone toxicity with TDF? Could there be more drop-outs with the DT due to early

unblinding? These possibilities of outcome assessment bias due to possible preconceptions of the investigators [80,86] in the DT study could compromise the comparability of the TT and DT clinical trials, especially considering that the double-blinding was broken in the DT clinical trial at 96 weeks. In contrast, in the TT study, it was done at 144 weeks of treatment.

Although the hypotheses put forward above would be plausible, the data from the TT and DT studies does not support the possibility that the duration of blinding has had a real impact on the drop-out rates of both treatment regimens [19,38,39].

3.3.1.3. Different patient losses prior to randomization.

The results obtained in a clinical trial are useful to the extent that they can be extrapolated to a larger population of patients, which the sample is intended to represent [87], the so-called external validity of the study [80]. Pre-randomization losses refer to eligible patients who, usually by their own or the investigator's choice or for other reasons, do not participate in the trial [88]. Pre-randomization losses diminish the external validity of studies, as questions arise as to whether non-randomized patients in the sampling population may differ in any prognostic factors from randomized patients [80]. Therefore, it is advisable to know the characteristics of the lost patients before randomization since if they differ from the characteristics of the subjects included in the clinical trial, it will not be possible to generalize the results of the trial [88].

In the BIC/FTC/TAF RCTs (1489 and 1490), pre-randomization losses occurred in 42 of 1,330 eligible patients (3.1%) [24,26]. In the DTG/3TC RCTs (GEMINI 1 and 2), pre-randomization losses occurred in 112 of 1,537 eligible patients (7.3%) (of 553 patients stated as ineligible, 437 did not meet the inclusion/exclusion criteria) [29,37]. Thus, pre-randomization losses were 4.2% higher in absolute terms in the DTG/3TC studies than in the BIC/FTC/TAF studies. On the other hand, results from studies with losses of more than 20% (this is not the case) are considered subject to a high risk of bias [89,90].

Another important aspect concerns the exclusion of patients prior to randomization, with only one criterion: the investigator's decision. In this respect, the investigator decided to exclude 50 patients (44.6%) in the GEMINI 1 and 2 studies of DTG/3TC [37] of the 112 eligible patients no randomized and did not give any other reasons. However, in the BIC/FTC/TAF study articles, 1489 and 1490 [24,26], only 2 patients per trial were excluded for this reason, with a total pre-randomization loss of 2.1%. In this regard, it is important to note that it is unknown whether there were different recruitment policies among the studies compared, which could make the comparability of the studies more debatable.

In addition, a substantial difference was observed for patients excluded due to preexisting viral mutations. In the DTG/3TC studies [37], 246 patients out of 1,974 evaluated were excluded (12.5%), while in the BIC/FTC/TAF studies [24,26] only 3 patients out of 1,481 (0.2%) were excluded for this reason. This difference is explained because the BIC/FTC/TAF studies only excluded patients if there was primary resistance to FTC or TAF, while the DTG/3TC studies also excluded those with PI and non-nucleoside resistance.

Of this data, it is noteworthy that pre-randomization losses were 4.2% higher in absolute terms in the DTG/3TC studies (GEMINI 1 and 2) than in the BIC/FTC/TAF studies (1489 and 1490). This means that ***in the DTG/3TC clinical trials, there may have been an hyper-selection of patients compared to the BIC/FTC/TAF studies. Consequently, the external validity of DTG/3TC clinical studies might be lower than that of BIC/FTC/TAF clinical studies.***

3.1.1.4. Other differences in patient inclusion and exclusion criteria.

In some of the DTG/3TC studies, there was an upper limit of plasma viral load for case inclusion (<500,000 copies/ml) (GEMINI 1 and 2) that would exclude both primo-infected and very advanced patients. On the other hand, the 1961 BIC/FTC/TAF [18] study only included women, so its results would not apply to men.

3.3.2. Treatment-experienced (treatment switch): BIC/FTC/TAF vs DTG/3TC

This section analyses and compares the design of RCTs with BIC/FTC/TAF (1844, 1878, 1961) [18,42,43] and with DTG/3TC (TANGO) [51] in previously treated adult patients with virological suppression (plasma HIV-1 RNA <50 copies in ml of plasma HIV-1 RNA), who switched to a new treatment (BIC/FTC/TAF or DTG/3TC) (Tables 3 and 4).

3.3.2.1. Differences in blinding.

As mentioned above, double-blind blinding ensures that they affect both groups equally if biases exist. In general, it can be argued that the greater the blinding of a clinical trial, the lower the risk of bias should be [91]. In the case of BIC/FTC/TAF, one RCT (1844) is available, which was double-blind [42]. In contrast, the TANGO study of DTG/3TC was not blinded. Consequently, ***theoretically, the presence of bias would be more likely in unblinded studies (both DTG/3TC and BIC/FTC/TAF) than in double-blinded mask studies of BIC/FTC/TAF***.

3.3.2.2. Differences in patients' baseline factors.

Some of the patient inclusion criteria, prognostic factors for disease progression, differed in the TT and DT clinical trials.

3.3.2.2.1. Different treatment-experienced. The TANGO study with DTG/3TC included only patients treated first-line, i.e. with a single pre-treatment, with undetectable levels six months prior to screening [51]. However, the BIC/FTC/TAF studies [18,42,43] allowed the inclusion of patients who had had one or more previous treatments (not linked to loss of efficacy), so patients included in the BIC/FTC/TAF studies may have a worse prognosis than patients in the DTG/3TC studies. However, the clinical trial articles do not report the number of previous ARTs, so the possible difference in the prognosis of patients with one or the other scheme cannot be confirmed or ruled out. In particular, the 1961 study with BIC/FTC/TAF [18] included treatment-naïve patients from other studies, who would be treated first-line, and study 1844 [42] allowed the inclusion of patients due to a treatment switch.

3.3.2.2.2. Differences in the pre-treatment duration. Patients had no previous treatment of more than three years in the TANGO study. However, for example, in the 1878 study, the patients included had been pre-treated for between 5.4 and 5.5 years. In study 1844 [42], the duration of pre-treatment was 1.1 years. This is another difference in prognostic factors that should be considered.

3.3.2.2.3. Differences in the exclusion of patients with isolated transient virological rebound (blips). Blips are defined as plasma viral load values between 50 and 1,000 copies/ml HIV-1 RNA, with pre- and post-load values <50 copies/ml [92]. In the TANGO study with DTG/3TC [51], participants with any plasma HIV-1 RNA measurement ≥50 copies/ml in the 6 months prior to inclusion; ≥2 measurements ≥50 copies/ml or any measurement >200 copies/ml during the 6 and 12 months of screening; or a prior regimen switch due to virologic failure (plasma HIV-1 RNA ≥400 copies/ml) were ineligible. However, clinical studies with BIC/FTC/TAF [18,42,43] did not exclude patients with blips.

3.3.2.2.4. Differences in patient inclusion according to time of undetectability prior to screening. There are differences in the inclusion criteria across studies regarding the requirement to demonstrate virological suppression, using measurement of plasma HIV-1 RNA ≥50 copies/ml prior to inclusion. While all of them required undetectability (<50) at study entry, the TANGO study excluded patients with any viral load >200 copies/ml in the previous 12 months, two or more viral loads >50 in the previous 12 months or any viral load >50 in the previous 6 months. Also, in study 1878, the inclusion criterion was to be undetectable (<50) in the 6 months prior to inclusion, although patients who had blips in this time period were allowed to be included. These criteria tend to be looser and more inclusive in the rest of the BIC/FTC/TAF studies. Thus, in studies 1844 and 1961, the inclusion criterion was to be undetectable in the 3 months prior to inclusion, with previous blips allowed, depending on the protocol.

3.3.2.3. Differences in the performance of the resistance test. In the BIC/FTC/TAF studies [42,43], the HIV mutation resistance test was confirmed by a second sample, taken 2–3 weeks after the first sample indicated VF. However, in the TANGO [51] study, resistance was defined in the first sample. According to White et al. [93], only 51% of the total resistances observed in the confirmed VF would be detected in the sample taken at the first VF [7]. In addition, it is common to perform the resistance test on the second confirmatory sample, particularly if the viral load of the first sample is not higher than 400 copies/ml. Consequently, ***the different criteria used to determine treatment resistance hinder comparing results obtained with BIC/FTC/TAF and DTG/3TC***.

3.3.3. Treatment-experienced (treatment switch): BIC/FTC/TAF vs DTG/RPV

3.3.3.1. Differences in blinding. In the SWORD 1 and 2 studies, random allocation of treatments was not blinded. Consequently, the ***bias would, theoretically, be more likely in unblinded studies with DTG/RPV than in double-blinded studies with BIC/FTC/TAF***.

3.4. Methodological quality of clinical trials (Jadad scale)

As shown in Figure 1, with BIC/FTC/TAF, three clinical trials obtained the maximum score (5 points; high quality), and two were of medium quality (3 points). Regarding the clinical trials conducted with DTG/3TC, one was of high quality (4 points), and one was of low quality (2 points). Finally, the clinical trials conducted with DTG/RPV were of medium quality (3 points). On average, the BIC/FTC/TAF, DTG/3TC, and DTG/RPV clinical trials scored 4.3 (high quality), 3.0 (medium quality) and 3.0 (medium quality), respectively. According to the modified Jadad scale, RCTs conducted with BIC/FTC/TAF would provide a more robust level of evidence than RCTs conducted with DTG/3TC and DTG/RPV.

4. Conclusions

The methodological differences between the BIC/FTC/TAF, DTG/3TC and DTG/RPV RCTs entail differences in the likelihood of bias and the external validity of their results, so they are not

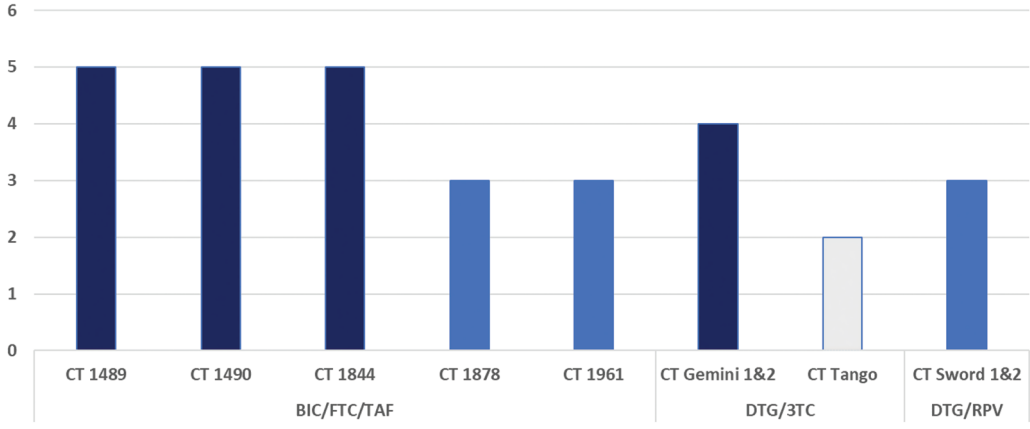

Figure 1. Quality of clinical trials conducted with BIC/FTC/TAF, DTG/3TC and DTG/RPV, according to the Jadad scale, with a score between 0 (lowest quality) and 5 (highest quality). Low quality: 0–2 points; Medium quality: 3 points; High quality: 4–5 points [16,17].

BIC/FTC/TAF: Bictegravir/Emtricitabine/Tenofovir; DTG/3TC: Dolutegravir/Lamivudine; DTG/RPV: Dolutegravir/Rilpivirine. CT: clinical trial.

comparable with the methodological quality and robustness of evidence of the BIC/FTC/TAF RCTs being higher. Consequently, based on the available data, the equivalence of BIC/FTC/TAF and DTG/3TC or DTG/RPV in treating HIV/AIDS patients cannot be confirmed. Therefore, to determine whether there are real differences in efficacy between BIC/FTC/TAF and DTG/3TC or DTG/RPV, RCTs directly comparing the two treatment regimens in HIV/AIDS patients would be necessary.

5. Expert opinion

The Overall, it is problematic to compare the efficacy of the three HIV treatment regimens (BIC/FTC/TAF, DTG/3TC and DTG/RPV) because no RCTs directly comparing them are available. In these circumstances, indirect comparison can only be made through two approaches: by analyzing the comparability of the RCT design and the characteristics of the patients included or by comparing efficacy through meta-analyses of indirect comparisons. In this paper, we have opted for the first option, which, in any case, should be a compulsory exercise before carrying out a meta-analysis of indirect comparisons.

The designs of the different RCTs of BIC/FTC/TAF, DTG/3TC and DTG/RPV would not be comparable due to differences in pre-randomization losses, blinding, and patient recruitment (Table 5), as well as variability in methodological quality analyzed using the Jadad scale. This disparity entails differences in the likelihood of bias, the external validity of study results and, ultimately, low comparability.

A significant number of ***systematic reviews and meta-analyses*** have been identified in the literature review: (i) With BIC/FTC/TAF, 3 reviews [20–22] and 1 metaanalysis [23]; (ii) With DTG/3TC, 3 reviews [33–35], 2 pooled analyses [29,30] and 3 metaanalyses [28,31,94]; (iii) With DTG/RPV, 5 meta-analyses [31,73–76].

Regarding the ***comparison of BIC/FTC/TAF*** and ***DTG/3TC***, most of the reviews (systematic or literature) are monographs of BIC/FTC/TAF [20–22] and DTG/3TC [35], merely descriptive, and do not perform a comparative analysis of the two. In contrast, the Spanish article by Cadiñanos et al. [33] provides a literature review of the risks and benefits of reducing the number of drugs to treat HIV-1 infection. Similarly, the study by Cento et al. [34] also partially compares TT and DT. Although this is not a systematic review but rather a literature review, the study by Cadiñanos et al. [33] is of particular interest because, although it is an expert opinion, it attempts to answer the questions raised in this review. They cite the potential benefits of DT over TT, in particular aspects such as toxicity, adherence to treatment and monitoring costs. They also suggest that DT may have reduced efficacy in achieving or maintaining virological suppression, increased residual viremia and mutation-associated resistance or ineffectiveness in HBV co-infection. In the specific case of DT with DTG/3TC, they do not recommend its use in treatment-naïve patients with HBV co-infection, as well as in patients with an HIV-1 viral load greater than 500,000 copies per ml or a CD4 cell count of less than 200 cells/mm^{3,} or in patients with mutational resistance to DTG/3TC (exclusion criteria) [33]. In patients with viral suppression, who change ART, it is also not recommended in HBV co-infection and the case of resistance mutation to any components of the regimen. These recommendations are based on expert opinion, which, it must be remembered, is always based on the lowest level of evidence [95]. In fact, expert opinion is generally called upon precisely when the available evidence is considered insufficient [96]. For this reason, meta-analyses of RCTs, which quantify the differences between treatments and have the highest level of evidence, are of the most interest [97].

In this regard, the ARCA [98] cohort analyzed factors associated with treatment discontinuation and virological failure in DTs based on lamivudine and an INI or PI/p. The factors with which a statistically significant association or trend was found were the presence of HBsAg, low GSS (genotypic sensitivity score) and the presence of the M184V mutation in those patients with less than three years of virological suppression. In the same vein, data has recently been reported from the European LAMRES [99] cohort reporting a significantly higher probability of VF with DTG/3TC in those individuals in whom the M184VA mutation was detected ≤5 years prior to the switch to this DT compared to those individuals in whom the M184V mutation was detected more than five years prior to the switch to DTG/3TC.

Based on the available reviews and meta-analyses, it can be concluded that: (i) The DTG/3TC regimen would not be appropriate for certain patients (with HBV co-infection, as well as in patients with an HIV-1 viral load greater than 500,000 copies per ml, CD4 cell count less than 200 cells/mm^{3,} or in patients with mutation resistance to DTG/3TC) [33]; and (ii) A network meta-analysis [28] found no statistically significant difference between DTG/3TC and BIC/FTC/TAF for viral suppression at 48 weeks, with a mean difference of −0.9% (95%CI −7.9%; 6.1%). CD4+ results at 48 weeks were similar for all regimens analyzed.

Regarding comparing ***BIC/FTC/TAF*** and ***DTG/RPV***, several studies were reviewed that could include data in this respect. The meta-analysis by Achhra et al., published in 2016, made an overall comparison of TT and DT [73] but did not include DT with DTG/RPV because the SWORD 1 and 2 studies were ongoing at the time. The meta-analysis by Nickel et al. was conducted for DTG regimens in non-pretreated patients and therefore did not analyze the SWORD 1 and 2 studies in pre-treated patients [74]. The meta-analysis by Punekar et al. compared ART with DTG/3TC and DTG/RPV [31]. Finally, the meta-analysis by Zhang et al. compared different TT but not against DT [76]. In conclusion, the published meta-analyses do not provide data of interest in comparing BICT/FTC/TAF and DTG/RPV.

Recently, the results of a retrospective analysis of the VACH [100] cohort have been published. The authors compare the persistence of TT, including an integrase inhibitor (INI) and DT with DTG or a protease inhibitor (PI) in previously treated HIV patients. According to these results, time to discontinuation and the probability of remaining without virological failure are significantly higher in patients who received TT than those who received DT, with no difference in toxicity.

The ***safety*** of the treatments compared has not been an objective of this paper. However, it is of interest to note that the network meta-analysis by Radford et al [28] showed no statistically significant differences after one year of follow-up between TT and DT, with tolerability odds ratios associated with DTG/3TC versus BIC/FTC/TAF treatment of 0.78 (95%CI 0.39, 1.53) for all adverse effects, 0.86 (95%CI 0.34, 2.10) for

serious adverse effects and 0.93 (95%CI 0.55, 1.60) for treatment regimen-associated adverse effects.

This systematic review has several strengths and limitations. Among the strengths, it should be noted that it has been carried out using the PRISMA guidelines [101], which include the main items to be considered for publishing a systematic review in a medical journal. In addition, no language limitations were considered, avoiding possible associated biases [9]. A possible strength is that it only includes full studies (articles), not posters presented at conferences. The reasons for excluding posters from conference papers were as follows: (i) they do not include all relevant study information; (ii) they often include preliminary results, not final results, of studies; and (iii) because they are incomplete publications, no reliable assessment of study quality can be made [9].

The efficacy and safety of TT with BIC/FTC/TAF and DT with DTG/3TC have been compared [28], and it was concluded that there would be no statistically significant difference between the two regimens concerning viral suppression at 48 weeks. This has led to the addition of DT within the treatment paradigm for HIV/AIDS patients [102]. However, as demonstrated in this paper, the methodological differences in the BIC/FTC/TAF and DTG/3TC RCTs would not allow for a meta-analysis of indirect comparisons. Furthermore, the methodological differences lead to a result confirming non-comparability. According to the Jadad scale, the methodological quality and robustness of evidence of RCTs conducted with BIC/FTC/TAF TT would be superior to that of RCTs conducted with DT with DTG/3TC and DTG/RPV.

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