

# HIV-1 resistance and virological failure to treatment with the integrase inhibitors bictegravir, cabotegravir, and dolutegravir: a systematic literature review

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## Abstract

*We describe and analyze resistance-associated mutations (RM) and virological failures (VF) on antiretroviral therapy using the latest approved integrase inhibitors (INIs) dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB), together with their companion drugs in fixed-dose formulations: BIC/emtricitabine/tenofovir; CAB/rilpivirine; DTG/abacavir/lamivudine; DTG/emtricitabine/tenofovir; and DTG/lamivudine. Systematic literature searches were conducted in PubMed and other electronic databases for clinical studies published between January 2010 and May 2023, according to preferred reporting items for systematic reviews and meta-analyses guidelines (PRISMA), which analyzed VFs and RMs of INIs. Fifty clinical studies were included in the synthesis. VF in antiretroviral treatment (ART)-naïve patients occurred in 0.7-4.0%, 0.6-1.4%, and 0.6-9.0% of patients treated with DTG, BIC, and CAB, respectively. VF was reported in patients with previous ART in 0-8.1%, 0-2.0%, and 0.4-2.3% of those treated with DTG, BIC, and CAB, respectively. RMs were detected in ART-naïve patients in only one study with DTG (0.3%), none of the studies with BIC, and three of the studies with CAB (0.1-5.4%). In ART-experienced patients, RMs were detected in 0-1.9% of DTG-treated patients. No cases of RM were detected in the 11 BIC studies reviewed. In the case of CAB, RMs were detected in eight studies, ranging from 0.3% to 1.9% of patients. In conclusion, RM rates in the studies reviewed were generally low using the latest INIs. This review identified BIC as the INI with the lowest number of observed VF and lack of RM.*

## Keywords

**HIV-1 resistance. Virological failure. Integrase inhibitors. Bictegravir. Cabotegravir. Dolutegravir.**

## Introduction

According to the World Health Organization (WHO), 29.8 million people received antiretroviral treatment (ART) worldwide in 2022<sup>1</sup>. HIV resistance to ART is due to mutations or changes in the viral genome, which

lead to decreased sensitivity of HIV to one or more drugs. Such resistance could jeopardize the efficacy of antiretroviral drugs in reducing HIV transmission and associated morbidity and mortality<sup>2</sup> and could become a significant public health trait<sup>3</sup>. The WHO recommends that countries should conduct regular national surveil-

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lance studies on HIV resistance to ART in different populations, including adults, children, and adolescents, in both previously untreated and pre-treated patients<sup>2</sup>.

For non-nucleoside reverse transcriptase inhibitors (NNRTIs), in 21 of the 30 studies reported to the WHO, resistance to nevirapine (NVP) or efavirenz (EFV) in ART-naïve subjects reached levels above 10%<sup>2</sup>. Primary resistance to NNRTIs was up to 3 times more common than secondary resistance<sup>2</sup>. With respect to nucleoside analogs, nearly half of children born to HIV-infected mothers who had received ART had resistance to one or more NRTIs<sup>2</sup>. In a study conducted in Canada between 2007 and 2011, the monthly cost per patient with resistance was estimated at 1291 Canadian dollars<sup>4</sup>.

The risk of death is estimated to be higher in patients with HIV drug resistance (odds ratio: 4.25, confidence interval 95%: 2.10-8.62) compared to drug-sensitive patients<sup>5</sup>. Given the magnitude of the problem, several recommendations on managing HIV resistance to ART have been published in Spain, both by the AIDS Study Group/AIDS Education Group (GeSIDA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) in 2018<sup>6,7</sup> and by the AIDS Research Network (RIS) in 2020<sup>8</sup>.

This study aims to describe and analyze resistance-associated mutations (RM) and virological failures (VF) using the latest integrase inhibitors (INIs) bictegravir (BIC), dolutegravir (DTG), and cabotegravir (CAB), along with their companion drugs in fixed-dose formulations: BIC/emtricitabine/tenofovir; CAB/rilpivirine; DTG/abacavir/lamivudine; DTG/emtricitabine/tenofovir; and DTG/lamivudine. A secondary analysis was also conducted on the economic impact of VFs associated with HIV-1 RMs on ART.

## Methods

### General methods and definitions

We followed the general methodology described in two previously published systematic reviews<sup>9,10</sup>. In addition, the preferred reporting items for systematic reviews and meta-analyses guidelines<sup>11-13</sup> were used. The methodology and results of the systematic review were reviewed and validated by a panel of hospital clinical experts (co-authors of this work) composed of two infectious disease specialists (JLBA, MGD), a specialist in internal medicine (MT), and a hospital pharmacist (MVDP).

Plasma HIV viral load (PVL), expressed as RNA copy number per milliliter, is the main parameter for ART monitoring. VF is considered present when the viral load is  $\geq 50$  or 200 copies/ml of HIV-1 RNA<sup>14-17</sup>. RM is one of the factors that can determine VF.

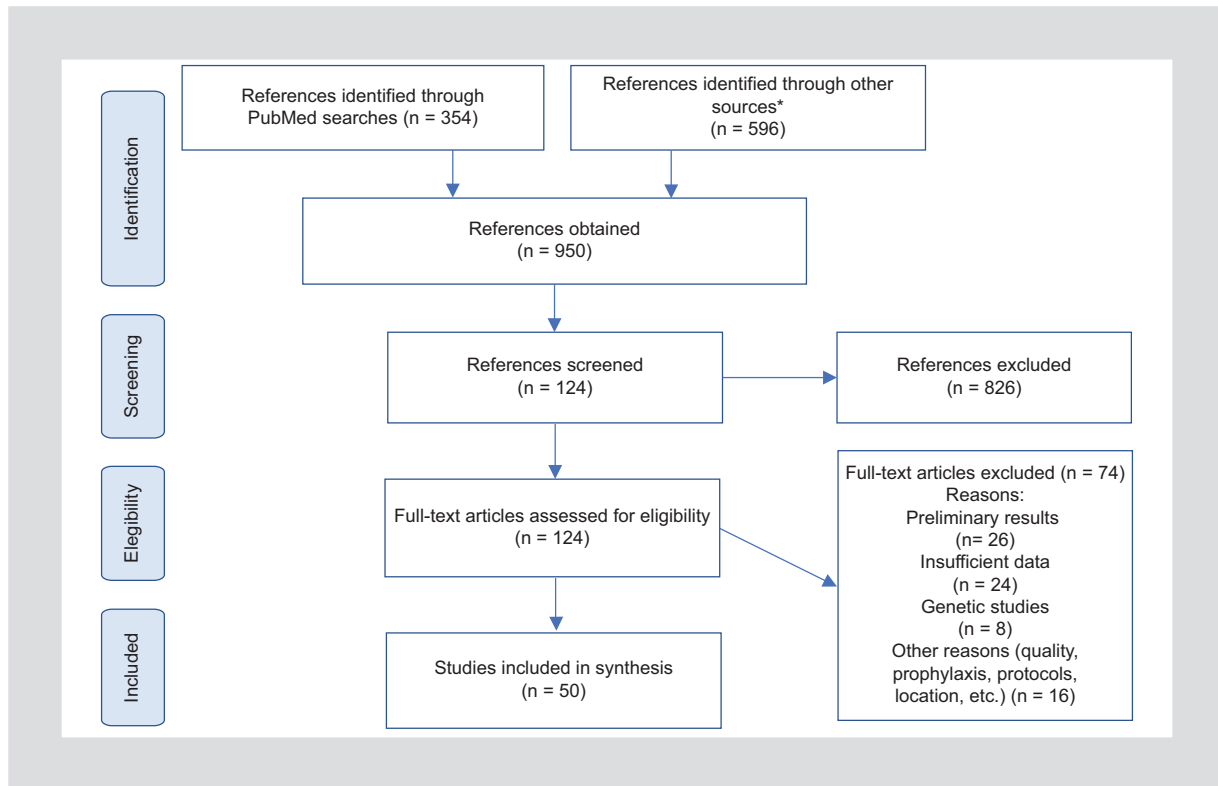
### Search strategy

A systematic literature review was conducted through an Internet search of the databases PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), OVID (<https://ovidsp.ovid.com/>), Cochrane Library (<https://www.cochranelibrary.com/>), LILACS (<https://lilacs.bvsalud.org/es/>), UNAIDS publications (<https://www.unaids.org/en/resources/publications/all>), and Google Scholar (<https://scholar.google.es/>). The search was stratified as follows: first, a main search was conducted in PubMed, and then, references not identified in the main search were selected using other sources. The searches were conducted without language limitations and, according to the expert panel's opinion, between January 2010 and May 2023. The search strategies used, the references obtained, and those excluded are presented in supplement 1.

### Study inclusion and exclusion criteria

Titles and abstracts obtained from databases and other sources were reviewed by two investigators (in case of discrepancy, a third investigator decided), who assessed whether the studies met the following inclusion criteria:

- Full text of the available article, as well as short papers or pre-publications presented at conferences in poster form that had the necessary information on the description of VF or RM along with treatment modality;
- Randomized controlled clinical trials or observational studies in which VF or RM using any of the latest INIs were described (BIC, CAB, and DTG, along with their companion drugs using as fixed-dose formulations: BIC/emtricitabine/tenofovir; CAB/rilpivirine; DTG/abacavir/lamivudine; DTG/emtricitabine/tenofovir; and DTG/lamivudine. Data from observational studies should come from developed countries, with a human development index (HDI) equal to or  $> 0.800$  (very high HDI according to the UN) and located in countries or political entities with comparable health systems and similar socioeconomic status to those of the European Union<sup>18,19</sup>. In addition, systematic reviews



**Figure 1.** Flowchart of the bibliographic searches carried out. \*Removing duplicates from PubMed.

and meta-analyses were reviewed to identify clinical studies described therein. The HDI restriction only applied to observational studies, and not to clinical trials, meta-analyses, or systematic reviews;

- Studies that examined the frequency, prevalence, or incidence of VF or RMs to ART, as defined in clinical studies;
- Studies that analyzed the economic impact associated with the management of VF associated with HIV-1 RMs to ART. If no relevant studies were obtained on the economic impact, a survey of the four clinical expert's cosigning this article should be undertaken to estimate the use of resources associated with the proper managing of RMs.

Only studies of sufficient quality were included in the systematic review, according to the Jadad guidelines for clinical trials<sup>20</sup> and the Newcastle-Ottawa Quality Assessment Form for Cohort Studies<sup>21</sup> for observational studies, to exclude studies of low quality (< 3 points for clinical trials) or poor quality (< 6 points for observational studies).

The risk of bias (ROB) of the studies included in the systematic review was evaluated using two instruments: (i) the ROB 2 score for clinical trials<sup>22</sup> and (ii) the MINORS score for observational studies<sup>23</sup>.

## Results

### Bibliographic search

The flow chart for the selection of references is presented in figure 1. A total of 950 references were obtained, of which 124 were initially selected. Finally, 74 references were excluded (Supplement 2), so the synthesis was limited to 50 references (Supplement 3). The reasons for exclusion of studies are specified in both figure 1 and table S5 of supplement 1.

### Data extracted and main findings

All major data extracted from the chosen articles are recorded in tables 1-3. All selected studies were of moderate or high quality (data not shown). The ROB was, logically, higher in observational studies than in clinical trials.

**Table 1. VF and HIV-1 mutations resistance (MR) associated with drug treatment. Patients without previous ART. For each study, the following data are indicated: name of the first author, year of publication, number of patients in the study, duration of ART, and percentage of VF or MR**

| Author                     | Study year  | Countries     | Design                | n     | ART                        | Duration  | VF†  | MR   | ROB   |
|----------------------------|-------------|---------------|-----------------------|-------|----------------------------|-----------|------|------|-------|
| <b>Dolutegravir</b>        |             |               |                       |       |                            |           |      |      |       |
| Cahn et al., 2019          | 2017        | Multinational | RCT-DB                | 1,433 | DTG/3TC DTG/FTC/TDF        | 96 weeks  | 2.0% | 0.0% | Low*  |
| Álvarez, 2019              | 2017        | Spain         | Cohort, retrospective | 1,109 | ART with DTG               | NA        | NA   | 0.0% | Low†  |
| Orkin et al., 2020         | NA          | Multinational | RCT-DB                | 640   | DTG/ABC/3TC DTG/FTC/TAF    | 144 weeks | 3.0% | NA   | Low*  |
| Acosta et al., 2021        | NA          | Multinational | 2 RCT-DB              | 640   | DTG/ABC/3TC DTG/FTC/TAF    | 144 weeks | NA   | 0.0% | Low*  |
| Cabello-Ubeda et al., 2022 | Before 2020 | Spain         | Cohort, retrospective | 135   | DTG/3TC                    | 48 weeks  | 0.7% | 0.0% | High† |
| Beer et al., 2022          | 2018-20     | Germany       | Cohort, prospective   | 30    | DTG/3TC                    | 24 weeks  | 4.0% | 0.0% | Low†  |
| Kuretski et al., 2023      | NA          | USA           | Cohort, retrospective | 123   | DTG/3TC                    | 1.3 years | 2.4% | 0.0% | Low†  |
| De Salazar et al., 2023    | 2021        | Multinational | Cohort, retrospective | 2,705 | ART con DTG                | NA        | NA   | 0.3% | High† |
| <b>Bictegravir</b>         |             |               |                       |       |                            |           |      |      |       |
| Gaur et al., 2021          | NA          | Multinational | Cohort                | 100   | BIC/FTC/TAF                | 48 weeks  | NA   | 0.0% | High† |
| Orkin et al., 2021         | NA          | Multinational | 5 CT review           | 69    | BIC/FTC/TAF                | 48 weeks  | NA   | 0.0% | -     |
| Ambrosioni et al., 2022    | NA          | Spain         | Cohort, retrospective | 213   | BIC/FTC/TAF                | 24 weeks  | 0.6% | 0.0% | Low*  |
| Sax et al., 2023           | NA          | Multinational | 2 RCT-DB              | 432   | BIC/ABC/3TC<br>BIC/FTC/TAF | 5 years   | 1.4% | 0.0% | Low*  |
| <b>Cabotegravir</b>        |             |               |                       |       |                            |           |      |      |       |
| Orkin et al., 2020         | 2016-18     | Multinational | RCT-DB                | 283   | CAB/RPV                    | 48 weeks  | 2.1% | 0.0% | Low*  |
| Charpentier et al., 2021   | 2010-20     | France        | Cohort, retrospective | 4,212 | CAB/RPV                    | 48 weeks  | NA   | 0.1% | High† |
| Cutrell et al., 2021       | NA          | Multinational | RCT reanalysis        | 1,039 | CAB/RPV                    | 48 weeks  | 1.2% | NA   | Low*  |
| Scheibe et al., 2022       | 1997-2021   | Poland        | Cohort, retrospective | 942   | CAB/RPV                    | NA        | NA   | 1.3% | High† |
| Sutton et al., 2022        | NA          | Multinational | RCT-SB                | 111   | CAB/NRTI                   | 6 years   | 9.0% | 5.4% | Low*  |

3TC: lamivudine; ABC: abacavir; ART: antiretroviral treatment; BIC: bictegravir; CAB: cabotegravir; CT: clinical trials; DB: double-blind; DTG: dolutegravir; FTC: emtricitabine; MR: mutations resistance; N: sample size; NA: data not available or not found in the publication; NRTI: nucleoside analog reverse transcriptase inhibitors; RCT: randomized clinical trial; RNA: ribonucleic acid; ROB: Risk of bias; RPV: raltegravir; SB: single blind; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; USA: United States of America; VF: virological failure.

\*ROB 2 score: some ROB concern about the open-label or not masked design (in the initial phase or in the extension phase).

†MINORS score: low ROB (score: 16 for non-comparative studies and 24 for comparative studies), high ROB (score: < 16 for non-comparative studies and < 24 for comparative studies).

‡In general, > 50-200 copies/ml RNA of HIV-1.

**Table 2.** VF and HIV-1 mutations resistance (MR) associated with drug treatment. Patients with previous ART. For each study, the following data are indicated: name of the first author, year of publication, year in which it was made, countries where it was made, study design, number of patients included, duration of ART, previous ART, VF previous data, MR or VS, subsequent ART being analyzed and percentage of VF or MR

| Author              | Study year | Countries     | Design                | n     | Duration     | Previous ART | Previous VF/<br>MR/VS         | Subsequent ART    | VF†  | MR                      | ROB   |
|---------------------|------------|---------------|-----------------------|-------|--------------|--------------|-------------------------------|-------------------|------|-------------------------|-------|
| <b>Dolutegravir</b> |            |               |                       |       |              |              |                               |                   |      |                         |       |
| Andreatta, 2019     | NA         | Multinational | 1 RCT-NM/ 1 RCT-DB    | 281   | 48 weeks     | DTG/ABC/3TC  | -                             | DTG/ABC/3TC       | 0.0% | 0.0%                    | Low*  |
| Brown, 2022         | NA         | Multinational | RCT-NM                | 312   | 48 weeks     | NRTI/ NNRTI  | -                             | DTG+2NARTI        | NA   | 0.6%                    | Low*  |
| Underwood, 2022     | 2017       | USA           | RCT-NM                | 314   | 48 weeks     | Standard ART | -                             | DTG+2NARTI        | NA   | 1.9%                    | Low*  |
| Bowman, 2023        | 2021       | U. Kingdom    | Cohort, retrospective | 620   | NA           | Standard ART | -                             | DTG/3TC,          | 1.1% | 0.3%                    | High† |
|                     |            |               |                       |       |              |              |                               | DTG/RPV           |      |                         |       |
| Kabra, 2022         | 2013-2022  | -             | MA (RCT)              | 186   | 96 weeks     | Standard ART | M184V/I                       | DTG/3TC           | 0.0% | 0.0%                    | -     |
| Kabra, 2022         | 2013-2022  | -             | MA (RWE)              | 186   | 96 weeks     | Standard ART | M184V/I                       | DTG/3TC           | 0.0% | 0.0%                    | -     |
| Marcellin, 2023     | NA         | France        | Cohort, retrospective | 1,432 | 3 years      | Standard ART | 1 or 2 VF                     | DTG/ABC/3TC       | 8.1% | 0.6%                    | High† |
| Marcellin, 2023     | NA         | France        | Cohort, retrospective | 452   | 3 years      | Standard ART | 1 or 2 VF                     | DTG/3TC           | 6.0% | 0.9%                    | High† |
| <b>Bictegravir</b>  |            |               |                       |       |              |              |                               |                   |      |                         |       |
| Daar, 2018          | 2016       | Multinational | RCT-NM                | 290   | 48 weeks     | PI           | VS                            | BIC/FTC/TAF       | 2.0% | 0.0%                    | Low*  |
| Molina, 2018        | 2016       | Multinational | RCT-DB                | 282   | 48 weeks     | DTG/FTC/TAF  | VS                            | BIC/FTC/TAF       | 1.1% | 0.0%                    | Low*  |
| Andreatta, 2019     | NA         | Multinational | RCT-NM                | 570   | 48 weeks     | DTG/ABC/3TC  | Previous MR                   | BIC/FTC/TAF       | NA   | 0.0%                    | Low*  |
| Kityo, 2019         | NA         | Multinational | RCT-NM                | 234   | 48 weeks     | Standard ART | VS                            | BIC/FTC/TAF       | 1.7% | 0.0%                    | Low*  |
| Acosta et al., 2020 | NA         | Multinational | RCT-DB                | 565   | 48 weeks     | DTG/FTC/TAF  | INI resistance                | BIC/FTC/TAF       | NA   | 0.0%                    | Low   |
|                     |            |               |                       |       |              | DTG/FTC/TDF  |                               |                   |      |                         |       |
| Gaur, 2021          | NA         | Multinational | Cohort, prospective   | 100   | 48 weeks     | Standard ART | VS                            | BIC/FTC/TAF       | NA   | 0.0%                    | High† |
| Hagins, 2021        | 2018       | USA           | RCT-NM                | 330   | 24 weeks     | Standard ART | VS                            | BIC/FTC/TAF       | NA   | 0.0%                    | Low*  |
| Kumar, 2021         | NA         | USA           | RCT-NM                | 330   | 72 weeks     | Standard ART | VS                            | BIC/FTC/TAF       | 1.0% | 0.0%                    | Low*  |
| Armenia, 2022       | NA         | Italy         | Cohort, retrospective | 283   | 48 weeks     | Standard ART | VS                            | BIC/FTC/TAF       | NA   | 0.0%                    | -     |
| Sax et al., 2022    | NA         | Multinational | Review 6 studies      | 1,825 | 48-180 weeks | Standard ART | VS M184V/I                    | BIC/FTC/TAF       | NA   | 0.0%                    |       |
|                     |            |               |                       | 182   |              |              |                               |                   |      |                         |       |
| Maggiolo, 2023      | NA         | Multinational | Cohort, prospective   | 86    | 96 weeks     | Standard ART | VS                            | BIC/FTC/TAF       | 0.0% | 0.0%                    | High† |
| Sellem, 2023        | 2020       | France        | Cohort, retrospective | 85    | 48 weeks     | Standard ART | VS                            | BIC/FTC/TAF       | 0.0% | 0.0%                    | High† |
| Ramgopal, 2023      | NA         | Multinational | RCT-NM                | 223   | 12 weeks     | BIC/FTC/TAF  | VS                            | BIC/FTC/TAF       | NA   | 0.0%                    | Low*  |
| <b>Cabotegravir</b> |            |               |                       |       |              |              |                               |                   |      |                         |       |
| Rizzardini, 2020    | NA         | Multinational | RCT-NM                | 591   | 48 weeks     | Standard ART | VS                            | CAB/RPV           | 1.2% | 0.5%                    | Low*  |
| Swindells, 2020     | NA         | Multinational | RCT-NM                | 308   | 48 weeks     | Standard ART | VS                            | CAB/RPV           | 1.6% | 1.0%                    | Low*  |
| Borghetti, 2022     | NA         | Italy         | Transversal           | 896   | NA           | Standard ART | ≥ 1 genotypic resistance y VS | CAB/RPV           | NA   | RPV: 17.9%<br>CAB: 0.3% | High† |
| Overton, 2023       | NA         | Multinational | RCT-NM                | 522   | 152 weeks    | Standard ART | VS                            | CAB/RPV (4 weeks) | 0.4% | 1.9%                    | Low*  |
|                     |            |               |                       | 523   |              |              |                               | CAB/RPV (8 weeks) | 2.3% | 1.5%                    |       |

(Continues)

**Table 2. VF and HIV-1 mutations resistance (MR) associated with drug treatment. Patients with previous ART. For each study, the following data are indicated: name of the first author, year of publication, year in which it was made, countries where it was made, study design, number of patients included, duration of ART, previous ART, VF previous data, MR or VS, subsequent ART being analyzed and percentage of VF or MR (continued)**

| Author            | Study year | Countries     | Design                | n     | Duration | Previous ART | Previous VF/<br>MR/VS | Subsequent ART | VF <sup>†</sup> | MR   | ROB               |
|-------------------|------------|---------------|-----------------------|-------|----------|--------------|-----------------------|----------------|-----------------|------|-------------------|
| Deschanvres, 2023 | NA         | France        | Cohort, retrospective | 1,134 | 28 weeks | Standard ART | VS                    | CAB/RPV        | 1.2%            | 0.4% | High <sup>†</sup> |
| Jongen, 2023      | NA         | Netherlands   | Case-control          | 588   | 42 weeks | Standard ART | No VF                 | CAB/RPV        | 0.9%            | 0.3% | Low <sup>†</sup>  |
| Ramgopal, 2023    | NA         | Multinational | RCT-NM                | 447   | 12 weeks | BIC/FTC/TAF  | VS                    | CAB/RPV        | 0.4%            | NA   | Low <sup>*</sup>  |
| Sinclair, 2023    | NA         | USA           | Cohort, prospective   | 189   | 6 weeks  | Standard ART | -                     | CAB/RPV        | 2.1%            | 1.1% | High <sup>†</sup> |

3TC: lamivudine; ABC: abacavir; ART: antiretroviral treatment; BIC: bictegravir; DB: double-blind; DTG: dolutegravir; FTC: emtricitabine; INI: integrase inhibitors; MR: resistance mutations; N: sample size; NA: data not available or not found in the publication; NRTI: nucleoside analog reverse transcriptase inhibitors; NM: not masked; NNRTI: no nucleoside analog reverse transcriptase inhibitors; RCT: randomized clinical trial; ROB: Risk of bias; RNA: ribonucleic acid; RPV: rilpivirine; RWE: real world evidence; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; USA: United States of America; VF: viral suppression, general, > 50-200 copies/ml RNA of HIV-1.  
<sup>\*</sup>ROB 2 score: some ROB concern about the open-label or not masked design (in the initial phase or in the extension phase).  
<sup>†</sup>MINORS score: low ROB (score: 16 for non-comparative studies and 24 for comparative studies), high ROB (score: < 16 for non-comparative studies and < 24 for comparative studies).  
<sup>‡</sup>In general, > 50-200 copies/ml RNA of HIV-1.

## Results in ART-naïve patients

### DTG

#### VF

VF was analyzed in five studies of ART with DTG, two double-blind, randomized clinical trials (RCTs)<sup>24,25</sup> and three retrospective cohort studies<sup>26-28</sup>. In the two RCTs, the studies with the largest sample sizes (1433 and 1109 patients, respectively), the VF rate was 2% and 3%, the latter for 144 weeks of treatment. In observational, small sample size studies (< 150 patients) conducted in Spain, Germany, and the United States, the VF rate ranged from 0.7% (Spain) to 4% (Germany) (Fig. 2 and Table 1).

### Resistance mutations

Regarding resistance mutations (RM), seven studies of ART with DTG were reviewed<sup>24,26-31</sup>, with RM (0.3%) observed only in the observational study signed by De Salazar et al.<sup>31</sup>, including 2705 patients (Fig. 2 and Table 1).

### BIC

#### VF

VF has been reported in 0.6% and 1.4% of patients in two studies on ART with BIC, a retrospective cohort study<sup>32</sup> and a multinational double-blind RCT<sup>33</sup>, respectively. The second study, by Sax et al.<sup>33</sup>, had a duration of 5 years (Fig. 2 and Table 1).

### Resistance mutations

RM were not described in any of the identified ART studies with BIC<sup>25,32,34</sup>. RMs were not described for BIC (Fig. 2 and Table 1).

### CAB

#### VF

VF data from three RCTs of ART with CAB were analyzed<sup>25,35,36</sup>. VF ranged from 1.2% in the study by Cutrell et al.<sup>35</sup> with 1039 patients and 48 weeks of duration and 9% in the study by Sutton et al.<sup>36</sup> with 111 patients treated for up to 6 years (Fig. 2 and Table 1).

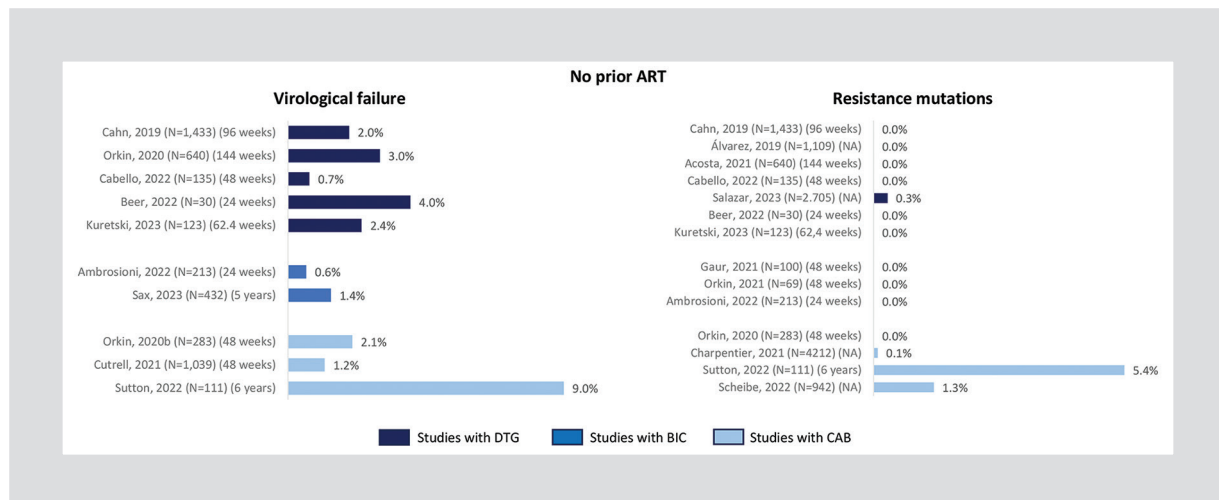
**Table 3. VF and HIV-1 mutations resistance (MR) associated with drug treatment. Patients with and without prior ART. For each study, the following data are indicated: name of the first author, year of publication, year in which it was made, countries where it was made, study design, number of patients included, duration of ART, previous ART, VF previous data, MR or VS, subsequent ART being analyzed, and percentage of VF or MR**

| Author                                                                                         | Study year | Countries     | Design                | N     | ART                | Duration    | VF*  | MR                                                     | ROB   |
|------------------------------------------------------------------------------------------------|------------|---------------|-----------------------|-------|--------------------|-------------|------|--------------------------------------------------------|-------|
| Dolutegravir<br>Messiaen, 2013<br>Lepik, 2018<br>Tzou, 2020<br>Torres, 2022<br>Andreatta, 2023 | 2012       | -             | MA                    | NA    | DTG/ABC/3TCDTG/FTC | 24-48 weeks | NA   | 0.0%                                                   | -     |
|                                                                                                | 2014       | Canada        | Cohort, retrospective | 392   | DTG/ABC/3TCDTG/FTC | 48 weeks    | NA   | 1.3%                                                   | High† |
|                                                                                                | 2019       | Multinational | Database              | 2,450 | NA                 | NA          | NA   | 6.2% from MR to INI                                    | High† |
|                                                                                                | 2007-19    | Spain         | Cohort, retrospective | 134   | ART with DTG       | NA          | 3.7% | NA                                                     | High† |
|                                                                                                | ND         | Multinational | 5 CT Review           | 1,316 | DTG + 2 NRTI       | 48          | 1.8% | NA                                                     | -     |
| Bictegravir<br>Torralba, 2023<br>Andreatta, 2023                                               | NA         | Spain         | 5 CT Review           | 1,306 | BIC/FTC/TAF        | 96          | 3.3% | NA                                                     | -     |
|                                                                                                | 2019-22    | Multinational | Cohort, retrospective | 505   | BIC/FTC/TAF        | 144         | 3.5% | NA                                                     | High† |
|                                                                                                | NA         | Spain         | 5 CT Review           | 1,306 | BIC/FTC/TAF        | 48          | 0.6% | NA                                                     | -     |
|                                                                                                | NA         | Multinational | 5 CT Review           | 1,306 | BIC/FTC/TAF        | 96          | 1.5% | NA                                                     | -     |
| Cabotegravir<br>Scheib, 2022                                                                   | 1997-2021  | Poland        | Cohort, retrospective | 942   | CAB/RPV            | NA          | NA   | Without previous ART: 1.3%<br>With previous ART: 14.5% | High† |
|                                                                                                | 2021       | Poland        | Cohort, retrospective | 275   | CAB/RPV            | NA          | NA   | Without previous ART: 1.3%<br>With previous ART: 14.5% | High† |

3TC: lamivudine; ABC: abacavir; ART: antiretroviral treatment; BIC: bictegravir; CAB: cabotegravir; CT: clinical trials; DTG: dolutegravir; FTC: emtricitabine; INI: integrase inhibitors; MA: meta-analysis; N: sample size; NA: data not available or not found in the publication; NRTI: nucleoside analog reverse transcriptase inhibitors; MR: resistance mutations; RNA: resistance mutations; ROB: Risk of bias; RPV: rilpivirine; TAF: tenofovir disoproxil fumarate; VF: virological failure.

\*In general, > 50-200 copies/ml RNA of HIV-1.

†MINORS score: low ROB (score: 16 for non-comparative studies and 24 for comparative studies), high ROB (score: < 16 for non-comparative studies and < 24 for comparative studies).



**Figure 2.** Virological failure (VF) and HIV-1 resistance mutations (RM) associated with drug treatment. Patients without prior ART. For each study, the following data are indicated: name of the first author, year of publication, number of patients in the study, duration of ART, and percentage of VF or MR. ART: antiretroviral treatment; BIC: bictegravir ART studies; CAB: cabotegravir ART studies; DTG: studies of ART with dolutegravir; N: sample size; NA: data not available or not found in the publication; RM: resistance mutations; VF: virological failure.

## Resistance mutations

RMs were observed in three<sup>36-38</sup> of four studies of ART with CAB<sup>25,36-38</sup>, ranging from 0.1% in the retrospective cohort study conducted in France with a sample of 4,212 patients<sup>37</sup> to 5.4% in the study by Sutton et al.<sup>36</sup> with a small sample size treated for up to 6 years (Fig. 2 and Table 1).

## Results in ART non-naïve patients

### DTG

Of the six studies reviewed, one study<sup>39</sup> reported previous resistance, and one<sup>40</sup> reported previous VF.

### VF

The VF of ART with DTG was reviewed in four studies: one RCT<sup>41</sup>, two retrospective cohort studies<sup>40,42</sup>, and one meta-analysis of RCTs and observational studies<sup>39</sup>. According to these studies, the VF rate ranged from 0%<sup>39,41</sup> to 8.1% in a retrospective cohort study with 1432 patients followed for 3 years<sup>40</sup>; the latter cohort included patients with one or two previous VF (Fig. 3A and Table 2).

## Resistance mutations

RMs associated with ART with DTG were analyzed in five studies: three RCTs<sup>41,43,44</sup> and two retrospective cohort

studies<sup>40,42</sup>. The RM rate ranged from 0%<sup>41</sup> to 1.9%<sup>44</sup>. According to the study with the largest sample size (n = 1432) and duration (3 years), the rate of RM was 0.6% in patients with 1 or 2 previous VFs (Fig. 3B and Table 2).

### BIC

Of the 13 studies reviewed, previous resistance was described in three<sup>41,45,46</sup>. In the other studies, patients had prior virological suppression (VS).

### VF

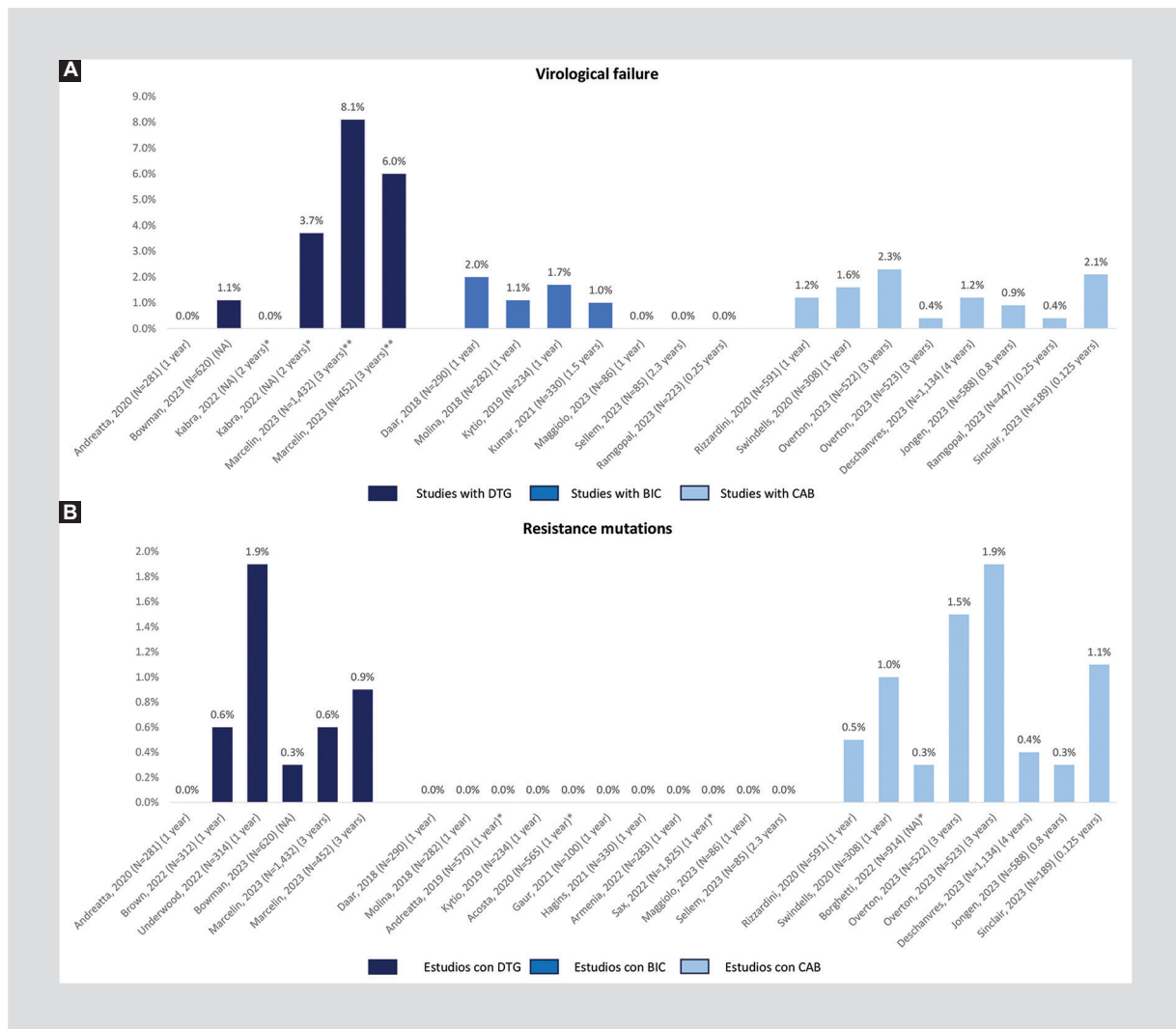
Seven studies<sup>47-53</sup> were analyzed, in which VF rates ranged from 0%<sup>50-53</sup> to 2.0%<sup>47</sup> (Fig. 3A and Table 2).

## Resistance mutations

RMs did not occur in any of the 13 studies<sup>34,41,45-49,51,52,54,55</sup>, reviewed, most of which included virologically suppressed patients. The duration of the studies ranged from 1 to 2.3 years. Of note is the review of six clinical studies<sup>46</sup> that included 1,852 patients with VS, 182 with the M184V/I mutation, with 0% RM. (Fig. 3B and Table 2).

### CAB

Of the eight studies analyzed, one described previous resistance<sup>56</sup>.



**Figure 3. A: virological failure (VF) associated with pharmacological treatment. Patients with prior ART. For each study, the following data are indicated: Name of the first author, year of publication, number of patients in the study, duration of ART, and percentage of VF. B: HIV-1 resistance mutations (RM) associated with drug treatment. Patients with prior ART. For each study, the following data are indicated: name of the first author, year of publication, number of patients in the study, duration of ART, and percentage of RM. ART: antiretroviral treatment; BIC: bictegravir ART studies; CAB: cabotegravir ART studies; DTG: studies of ART with dolutegravir; N: sample size; NA: data not available or not found in the publication; VF: virological failure.**

\*With previous mutation.

\*\*With prior virological failure.

## VF

Seven studies looking at VF with ART with CAB were reviewed<sup>53,57-62</sup>, ranging from 0.4%<sup>53,59</sup> to 2.3%<sup>59</sup>. In the latter case, the study had duration of 3 years (Fig. 3A and Table 2).

## Resistance mutations

Seven studies were analyzed<sup>56-62</sup>, with RM rates ranging from 0.3%<sup>56,61</sup> to 1.9%<sup>59</sup> (Fig. 3B and Table 2).

## Results in ART non-naïve and naïve patients

### VF

VF, regardless of whether the patient had previous ART, was 1.8-3.7% with DTG<sup>63,64</sup> and 0.6-1.5% with BIC<sup>64,65</sup> (Table 3).

### Resistance mutations

RMs with DTG, in ART non-naïve and naïve patients, were 0%<sup>66</sup>, 1.3%<sup>67</sup>, or 6.2% at INIs<sup>68</sup>.

## Results for all the latest INIs as a whole

In a European cross-sectional study<sup>69</sup>, in 1,950 ART-naïve patients, a 4% RM to INI set (DTG, EVG, and RAL) was observed. A prospective cohort study<sup>70</sup> collected data from 3682 pre-treated patients (some with RM) from the USA, with RM observed in 2% of patients treated with INI. A retrospective cohort study<sup>71</sup> in 855 French ART-naïve patients observed an emerging RM rate of 4.2-6.5%. Finally, a meta-analysis published in 2021<sup>72</sup>, which included 1249 ART-naïve patients, found RMs to INIs in 0.3% of patients.

## Estimating the economic impact of GMs

Due to the shortage of studies on the economic impact of RMs (Supplement 4 and Table S6), a survey was conducted by the four clinical experts cosigning this article, resulting in an estimate of the resource use associated with RM management (Supplement 4 and Table S7).

## Discussion

According to this systematic review, the rates of RM in the analyzed studies published between 2013 and 2023 were generally low. In ART-naïve patients, no RMs were observed with DTG, except for an observational study of 2705 patients, in which RMs were described in 0.3% of patients<sup>31</sup>. No RMs were observed with BIC. They were with CAB, reaching 5.4%<sup>36</sup>. In pre-treated patients, RMs with DTG were not observed or were 0.6-0.9% in the most extensive observational study, which included patients with 1 or 2 VF<sup>40</sup>. RMs were neither observed with BIC. With CAB, RMs were described in most studies, ranging from 0.3% to 1.9%.

Regarding VFs, in ART-naïve patients, they have been described with DTG (0.7-4.0%), BIC (0.6-1.4%), and CAB (1.2-9.0%). Pre-treatment VFs had 0% DTG with no prior resistance and reached 8.1% of patients with 1 or 2 prior VFs<sup>40</sup>. With BIC, it ranged from 0% to 2.0%. With CAB, it ranged from 0.4% to 2.3%.

These results should be considered in light of the possible strengths and weaknesses of the study itself. Regarding strengths, the inclusion criteria were broad, and four clinicians with expertise in managing HIV patients validated the study protocol. Furthermore, these results are in line with those described in a recent WHO report on HIV RM, according to which resistance to DTG ranges from 3.9% to 8.6% and may reach up to 19.6% in pre-treated patients<sup>73</sup>.

Regarding the weaknesses of the study, it should be noted that the VF and RM data were obtained from studies with heterogeneous methodology, both in terms of their design (RCTs, observational studies, meta-analyses) and the fact that the data of interest (VF and RM) were occasionally secondary or tertiary objectives and that they were limited to countries with an HDI equal to or > 0.800. Hence, results cannot be extrapolated to other settings. Other possible reasons for discrepancies between study results may be related to differences in patient's characteristics, although in the present analysis, we have discriminated between ART-naïve patients, pre-treated patients without prior failure or resistance, and those pre-treated with prior failure or resistance. In addition, differences in the resistance tests used, criteria for defining VF according to PVL (> 50, > 200, > 500 copies/ml HIV-1 RNA, first or second confirmation), in the follow-up time (which ranged from 24 weeks to 6 years) or in the time to access different drugs could all have influenced the comparisons. It is essential to remember that no matter how extensive and detailed the literature searches are, there is no absolute certainty that all published studies were equally suitable for this synthesis.

## Conclusion

In this systematic review, not all the latest INIs seem to have the same efficacy or effectiveness, given the higher prevalence of VF under DTG and CAB in both ART-naïve and pre-treated patients compared to BIC. Similarly, the greater barrier to resistance was observed with BIC. However, it should be noted that in some studies with this drug, the follow-up was shorter, which could contribute to the lack of emergence of resistance mutations.

## Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.24000011. 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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This study was sponsored by Gilead Sciences SL, Madrid, Spain.

## Conflicts of interest

D. Rubio-Rodríguez is a senior consultant of Health Value, a company that has received fees in relation to the present study. C. Rubio-Terrés is director of Health Value SL, a company that has received fees in relation to the present study. A. Castro is an employee of Gilead Sciences Spain. M. Torralba has carried out consulting work for Gilead Sciences and ViiV Healthcare; he has also received fees for presentations for Gilead Sciences, Johnson and Johnson Innovative medicine, and ViiV Healthcare. M. García Deltoro has carried out consulting work for Gilead Sciences, ViiV Healthcare, Johnson and Johnson, and Merck Sharp and Dohme; he has also received fees for investigations and presentations for Gilead Sciences, Johnson and Johnson, ViiV Healthcare, and Merck Sharp and Dohme.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

## References

1. OMS. Organización Mundial de la Salud. Hoja Informativa 2023. Estadísticas Mundiales Sobre el VIH. ONUSIDA; 2023. Available from: [https://www.unaids.org/sites/default/files/media\\_asset/unaids\\_factsheet\\_es.pdf](https://www.unaids.org/sites/default/files/media_asset/unaids_factsheet_es.pdf) [Last accessed on 2023 Oct 02].
2. OMS. Organización Mundial de la Salud. Farmacorresistencia del VIH; 2021. Available from: <https://www.who.int/es/news-room/fact-sheets/detail/hiv-drug-resistance> [Last accessed on 2023 Mar 30].
3. Melku M, Gesesew HA, Ward PR. Magnitude and predictors of HIV-Drug resistance in Africa: a protocol for systematic review and meta-analysis. *PLoS One*. 2022;17:e0267159.
4. Krentz HB, Ko K, Beckthold B, Gill MJ. The cost of antiretroviral drug resistance in HIV-positive patients. *Antivir Ther*. 2014;19:341-8.
5. Zhang T, Liao L, Shao Y, Feng Y, Ruan Y, Xing H. Relationship between drug resistance and death in HIV-Infected patients receiving antiretroviral therapy - 7 PLADs, China, 2010-2019. *China CDC Wkly*. 2021;3:291-7.
6. Grupo de Educación en SIDA (GeSIDA) de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Documento sobre la Utilidad Clínica de Las Resistencias A Antirretrovirales. GeSIDA; 2018. Available from: [https://gesida-seimc.org/wp-content/uploads/2019/03/14\\_documento\\_sobre\\_utilidad\\_clinica\\_resistencias\\_a\\_antirretrovirales.pdf](https://gesida-seimc.org/wp-content/uploads/2019/03/14_documento_sobre_utilidad_clinica_resistencias_a_antirretrovirales.pdf) [Last accessed on 2023 Apr 24].
7. Documento de Consenso de GeSIDA/Plan Nacional sobre el Sida Respecto al Tratamiento Antirretroviral en Adultos Infectados por el Virus de la Inmunodeficiencia Humana. Panel de Expertos de GeSIDA y Plan Nacional sobre el Sida; 2023. Available from: [https://gesida-seimc.org/wp-content/uploads/2023/02/guia\\_modificada\\_documento\\_de\\_consenso\\_de\\_gesidaplannacional\\_sobre\\_el\\_sida\\_respecto\\_al\\_tratamiento\\_antirretroviral\\_en\\_adultos\\_infectados\\_por\\_el\\_virus\\_de\\_la\\_inmunodeficiencia\\_humana.pdf](https://gesida-seimc.org/wp-content/uploads/2023/02/guia_modificada_documento_de_consenso_de_gesidaplannacional_sobre_el_sida_respecto_al_tratamiento_antirretroviral_en_adultos_infectados_por_el_virus_de_la_inmunodeficiencia_humana.pdf) [Last accessed on 2023 Jun 23].
8. Guía de Resistencias a los Antirretrovirales. Red de Investigación en SIDA (RIS). RD16/0025; 2020. Available from: <https://www.redris.es/blog/-blogs/guia-de-resistencias-a-los-antirretrovirales-de-la-ris-actualizacion-2020> [Last accessed on 2023 Jun 23].
9. Rubio-Rodríguez D, De Diego Blanco S, Pérez M, Rubio-Terrés C. Cost-effectiveness of drug treatments for advanced melanoma: a systematic literature review. *Pharmacoeconomics*. 2017;35:879-93.
10. Grau S, Miró JM, Olalla J, Alcalá JC, Castro A, Rubio-Rodríguez D, et al. Comparison of the design and methodology of phase 3 clinical trials of bicittegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) and dolutegravir-based dual therapy (DTG) in HIV: a systematic review of the literature. *Expert Rev Anti Infect Ther*. 2023;21:65-76.
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-9, W64.
13. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.
14. ASHM. Virological Failure; 2019. Available from: <https://hivmanagement.ashm.org.au/long-term-management-of-antiretroviral-therapy/virological-failure> [Last accessed on 2024 Feb 24].
15. Gandhi RT, Bedimo R, Hoy JF, Landovitz RJ, Smith DM, Eaton EF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the international antiviral society-USA panel. *JAMA*. 2023;329:63-84.
16. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available from: <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/virologic-failure> [Last accessed on 2023 Mar 02].
17. Panel de Expertos de GeSIDA y de la División de Control de VIH, ITS, Hepatitis Virales y Tuberculosis del Ministerio de Sanidad. Documento de Consenso de GeSIDA/División de Control de VIH, ITS, Hepatitis Virales y Tuberculosis del Ministerio de Sanidad Respecto al Tratamiento Antirretroviral en Adultos Infectados por el Virus de la Inmunodeficiencia humana; 2023. Available from: [https://gesida-seimc.org/wp-content/uploads/2023/06/guia\\_tar\\_v12.pdf](https://gesida-seimc.org/wp-content/uploads/2023/06/guia_tar_v12.pdf) [Last accessed on 2023 Nov 10].
18. First World Countries; 2023. Available from: <https://worldpopulationreview.com/country-rankings/first-world-countries> [Last accessed on 2023 Aug 29].
19. Human Development Index (HDI) by Country 2023. Available from: <https://worldpopulationreview.com/country-rankings/hdi-by-country> [Last accessed on 2023 Aug 29].
20. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
21. Newcastle-Ottawa Quality Assessment Scale. Available from: [https://www.ohri.ca/programs/clinical\\_epidemiology/nosgen.pdf](https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf) [Last accessed on 2024 Mar 02].
22. Risk of Bias 2 (RoB 2) Tool. Cochrane Methods. Available from: <https://methods.cochrane.org/risk-bias-2> [Last accessed on 2024 Apr 28].
23. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003;73:712-6.
24. 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-naïve 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.
25. Orkin C, DeJesus E, Sax PE, Arribas JR, Gupta SK, Martorell C, et al. Fixed-dose combination bicittegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV*. 2020;7:e389-400.
26. Cabello-Ubeda A, de Quirós JC, Martín Carbonero L, Sanz J, Vergas J, Mena Á, et al. 48-Week effectiveness and tolerability of dolutegravir (DTG) + lamivudine (3TC) in antiretroviral-naïve adults living with HIV: a multicenter real-life cohort. *PLoS One*. 2022;17:e0277606.

27. Beer D, Scherzer J, Noe S, Scholten S, Wyen C, Postel N, et al. 2-Year Outcomes of Dolutegravir (DTG) and Lamivudine (3TC) in Art-Naïve and Pre-treated People Living with HIV in Germany: real-world Data from the German URBAN Cohort. HIV Drug Therapy Glasgow. Scotland: Virtual and Glasgow; 2022. Available from: <https://viivexchange.com/content/dam/cf-viiv/viivexchange/medical/files/p14-hiv-glasgow-2022-beer-urban-poster-p117-merged.pdf> [Last accessed on 2023 Nov 08].
28. Kuretski J, Donovan C, Harper G, Merrill D, Mycock K, Oglesby A, et al. Real-world Treatment Experience of Treatment-naïve People Living with HIV who Initiated Treatment with Single-tablet Dolutegravir/Lamivudine in a Test and Treat Setting in the United States. IDWeek, Virtual and Washington, DC; 2022. Available from: [https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/ea58ece8-e706-4777-b8f8-eebe4eaa4b79/ea58ece8-e706-4777-b8f8-eebe4eaa4b79-viewable\\_rendition\\_v.pdf?medcommid=ref--all-004495](https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/ea58ece8-e706-4777-b8f8-eebe4eaa4b79/ea58ece8-e706-4777-b8f8-eebe4eaa4b79-viewable_rendition_v.pdf?medcommid=ref--all-004495) [Last accessed on 2023 Nov 08].
29. Alvarez M, Casas P, de Salazar A, Chueca N, Guerrero-Beltran C, Rodríguez C, et al. Surveillance of transmitted drug resistance to integrase inhibitors in Spain: implications for clinical practice. *J Antimicrob Chemother.* 2019;74:1693-700.
30. Acosta RK, Chen GQ, Chang S, Martin R, Wang X, Huang H, et al. Three-year study of pre-existing drug resistance substitutions and efficacy of bictegravir/emtricitabine/tenofovir alafenamide in HIV-1 treatment-naïve participants. *J Antimicrob Chemother.* 2021;76:2153-7.
31. De Salazar A, Viñuela L, Fuentes A, Teyssou E, Charpentier C, Lambert-Niclot S, et al. Transmitted drug resistance to integrase-based first-line human immunodeficiency virus antiretroviral regimens in Mediterranean Europe. *Clin Infect Dis.* 2023;76:1628-35.
32. Ambrosioni J, Rojas Liévano J, Berrocal L, Inciarte A, de la Mora L, González-Cordón A, et al. Real-life experience with bictegravir/emtricitabine/tenofovir alafenamide in a large reference clinical centre. *J Antimicrob Chemother.* 2022;77:1133-9.
33. Sax PE, Arribas JR, Orkin C, Lazzarin A, Pozniak A, DeJesus E, et al. Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials. *eClinicalMedicine.* 2023;59:101991.
34. Gaur AH, Cotton MF, Rodriguez CA, McGrath EJ, Helström E, Liberty A, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide in adolescents and children with HIV: week 48 results of a single-arm, open-label, multicentre, phase 2/3 trial. *Lancet Child Adolesc Health.* 2021;5:642-51.
35. Cutrell AG, Schapiro JM, Perno CF, Kuritzkes DR, Quercia R, Patel P, et al. Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis. *AIDS.* 2021;35:1333-42.
36. Sutton KC, De Vente J, Leblanc R, DeJesus E, Smith G, Mills A, et al. Long-term efficacy, safety, and durability of cabotegravir and rilpivirine as 2-drug oral maintenance therapy after 6 years of study. *Open Forum Infect Dis.* 2022;9:ofac067.
37. Charpentier C, Storto A, Soulié C, Ferré VM, Wirten M, Joly V, et al. Prevalence of genotypic baseline risk factors for cabotegravir + rilpivirine failure among ARV-naïve patients. *J Antimicrob Chemother.* 2021;76:2983-7.
38. Scheibe K, Urbańska A, Serwin K, Parczewski M. Frequency of genotypic factors possibly associated with cabotegravir/rilpivirine failure in antiretroviral treatment-naïve and -experienced HIV-1 infected population. *Infect Genet Evol.* 2022;104:105358.
39. Kabra M, Barber TJ, Allavena C, Marcelin AG, Di Giambenedetto S, Pasquau J, et al. Effectiveness of Dolutegravir + Lamivudine in Real-world Studies in People with HIV-1 With M184V/I Mutations: A Systematic Review and Meta-analysis. *HIV Drug Therapy Glasgow. Scotland: Virtual and Glasgow; 2022.* Available from: [https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/88dd2fc6-0def-4139-a43a-6b0a0e543c9a/88dd2fc6-0def-4139-a43a-6b0a0e543c9a-viewable\\_rendition\\_v.pdf?medcommid=ref--all-4647](https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/88dd2fc6-0def-4139-a43a-6b0a0e543c9a/88dd2fc6-0def-4139-a43a-6b0a0e543c9a-viewable_rendition_v.pdf?medcommid=ref--all-4647) [Last accessed on 2023 Nov 08].
40. Marcelin AG, Soulié C, Wirten M, Charpentier C, Descamps D, Calvez V, et al. 3-Year Analysis of Emergent Resistance-Associated Mutations at First- or Second-line HIV-1 Virologic Failure with Second Generation INSTIs in 2- and 3-Drug Regimens (Virostar Study). 19<sup>th</sup> European AIDS Conference, Warsaw, Poland; 2023. Available from: <https://eacs2023.abstractserver.com/program/#/details/presentations/950> [Last accessed on 2023 Nov 30].
41. Andreatta K, Willkom M, Martin R, Chang S, Wei L, Liu H, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184V/I. *J Antimicrob Chemother.* 2019;74:3555-64.
42. Bowman C, Ambrose A, Kanitkar T, Flores K, Simoes P, Hart J, et al. Real world use of dolutegravir two drug regimens. *AIDS.* 2023;37:785-8.
43. Brown D, Kaplan R, Losso M, et al. Efficacy of second-line dolutegravir plus 2 nucleoside reverse transcriptase inhibitors by baseline nucleoside reverse transcriptase inhibitor resistance and nucleoside reverse transcriptase inhibitor use in the DAWNING study. *Antiviral Therapy.* 2022;27(2). doi:10.1177/13596535221077487
44. Underwood M, Horton J, Nangle K, Hopking J, Smith K, Aboud M, et al. Integrase inhibitor resistance mechanisms and structural characteristics in antiretroviral therapy-experienced, integrase inhibitor-naïve adults with HIV-1 infection treated with dolutegravir plus two nucleoside reverse transcriptase inhibitors in the DAWNING study. *Antimicrob Agents Chemother.* 2022;66:e0164321.
45. Acosta RK, Willkom M, Andreatta K, Liu H, Martin R, Parvanga A, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) from dolutegravir (DTG)+F/TAF or DTG+F/tenofovir disoproxil fumarate (TDF) in the presence of pre-existing NRTI resistance. *J Acquir Immune Defic Syndr.* 2020;85:363-71.
46. Sax PE, Andreatta K, Molina JM, Daar ES, Hagins D, Acosta R, et al. High efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in people with suppressed HIV and preexisting M184V/I. *AIDS.* 2022;36:1511-20.
47. Daar ES, DeJesus E, Ruane P, Crofoot G, Oguchi G, Creticos C, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV.* 2018;5:e347-56.
48. Molina JM, Ward D, Brar I, Mills A, Stellbrink HJ, López-Cortés L, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV.* 2018;5:e357-65.
49. Kityo C, Hagins D, Koenig E, Avihingsanon A, Chetchotisakd P, Supparatpinyo K, et al. Switching to Fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) in virologically suppressed HIV-1 infected women: a randomized, open-label, multicenter, active-controlled, phase 3, noninferiority trial. *J Acquir Immune Defic Syndr.* 2019;82:321-8.
50. Kumar P, Stephens JL, Wurapa AK, Brar I, Burton MJ, Applin S, et al. Week 72 Outcomes and COVID-19 Impact from the BRAAVE 2020 Study: A Randomized Switch to B/F/TAF in Black American Adults With HIV. In: 11<sup>th</sup> IAS Conference on HIV Science. 2021. Available from: [https://www.natap.org/2021/ias/ias\\_16.htm](https://www.natap.org/2021/ias/ias_16.htm) [Last accessed on 2023 Nov 07].
51. Maggiolo F, Rizzardini G, Molina JM, Pulido F, De Wit S, Vandekerckhove L, et al. Bictegravir/emtricitabine/tenofovir alafenamide in older individuals with HIV: results of a 96-week, phase 3b, open-label, switch trial in virologically suppressed people ≥65 years of age. *HIV Med.* 2023;24:27-36.
52. Sellem B, Abdi B, Lê M, Tubiana R, Valantin MA, Seang S, et al. Intermit-tent bictegravir/emtricitabine/tenofovir alafenamide treatment maintains high level of viral suppression in virally suppressed people living with HIV. *J Pers Med.* 2023;13:583.
53. Ramgopal MN, Castagna A, Cazanave C, Diaz-Brito V, Dretler R, Oka S, et al. SOLAR (Switch Onto Long-acting Regimen) 12-Month Results - Randomized Switch Trial of CAB + RPV LA vs Oral BIC/FTC/TAF, Abstract 191. Seattle, Washington: Conference on Retroviruses and Opportunistic Infections; 2023. Available from: [https://www.natap.org/2023/croi/croi\\_207.htm](https://www.natap.org/2023/croi/croi_207.htm) [Last accessed 2023 Nov 08].
54. Hagins D, Kumar P, Saag M, Wurapa AK, Brar I, Berger D, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide in black americans with HIV-1: a randomized phase 3b, multicenter, open-label study. *J Acquir Immune Defic Syndr.* 2021;88:86-95.
55. Armenia D, Forbici F, Bertoli A, Berno G, Malagnino V, Gagliardini R, et al. Bictegravir/emtricitabine/tenofovir alafenamide ensures high rates of virological suppression maintenance despite previous resistance in PLWH who optimize treatment in clinical practice. *J Glob Antimicrob Resist.* 2022;30:326-34.
56. Borghetti A, Farinacci D, Ciccullo A, Dusina A, Moschese D, Iannone V, et al. Are we ready for long-acting? A feasibility evaluation of long-acting cabotegravir-rilpivirine in clinical practice. *J Med Virol.* 2022;94:4970-4.
57. 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.
58. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med.* 2020;382:1112-23.
59. 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.
60. Deschanvres C, Allavena C, Palich R, Rey D, Cheret A, Zaegel-Faucher, et al. Cabotegravir-Rilpivirine Long Acting: Data in Real Life Setting in a French Cohort. In: 19<sup>th</sup> European AIDS Conference. Warsaw, Poland; 2023. Available from: [https://www.natap.org/2023/eacs/eacs\\_59.htm](https://www.natap.org/2023/eacs/eacs_59.htm) [Last accessed on 2023 Nov 30].

61. Jongen V. Effectiveness of LA Injectable Cabotegravir + Rilpivirine for the Treatment of HIV-1: Results from the Dutch Athena National Observation Cohort. In: 19<sup>th</sup> European AIDS Conference. Warsaw, Poland; 2023. Available from: [https://www.natap.org/2023/eacs/eacs\\_69.htm](https://www.natap.org/2023/eacs/eacs_69.htm) [Last accessed on 2023 Nov 30].
62. Sinclair G, Sension M, Dretler A, Schenneider S, Schubert C, Merrill D, et al. Clinical Outcomes at Month 6 After Initiation of Cabotegravir and Rilpivirine Long-Acting (CAB+RPV LA) in an Observational Real-World Study (BEYOND). ID Week, Boston, MA. Available from: [https://www.natap.org/2023/idweek/idweek\\_41.htm](https://www.natap.org/2023/idweek/idweek_41.htm) [Last accessed on 2023 Nov 30].
63. Torres-Fernandez D, de Ory SJ, Fortuny C, Sainz T, Falcón D, Bernal E, et al. Integrase inhibitors in children and adolescents: clinical use and resistance. *J Antimicrob Chemother.* 2022;77:2784-92.
64. Andreatta K, Sax PE, Wohl D, D'Antoni ML, Huang H, Hindman J, et al. Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) Versus Dolutegravir (DTG)-Based 3-Drug Regimens in Adults with HIV Who Have Suboptimal Antiretroviral Adherence. Available from: [https://www.askgileadmedical.com/docs/conference/andreatta\\_efficacy%20of%20bictegraviremtricitabinetenofovir%20alafenamide%20\(bftaf\)%20versus%20dolutegravir%20\(dtg\)-based%203-drug%20regimensefficacy%20of%20bictegravir/emtricitabinetenofovir%20alafenamide%20\(bftaf\)%20@pdf](https://www.askgileadmedical.com/docs/conference/andreatta_efficacy%20of%20bictegraviremtricitabinetenofovir%20alafenamide%20(bftaf)%20versus%20dolutegravir%20(dtg)-based%203-drug%20regimensefficacy%20of%20bictegravir/emtricitabinetenofovir%20alafenamide%20(bftaf)%20@pdf) [Last accessed on 2023 Nov 30].
65. Torralba M, Rodríguez G, González Gasca FJ, Cuadra F, Barberá J, Geijo P, et al. Bictegravir/emtricitabine/tenofovir alafenamide in a multicentre cohort: real-life experience from Spain. *Ann Pharmacother.* 2023;58:140-7.
66. Messiaen P, Wensing AM, Fun A, Nijhuis M, Brusselaers N, Vandekerckhove L. Clinical use of HIV integrase inhibitors: a systematic review and meta-analysis. *PLoS One.* 2013;8:e52562.
67. Lepik KJ, Harrigan PR, Yip B, Wang L, Robbins MA, Zhang WW, et al. Emergent drug resistance with integrase strand transfer inhibitor-based regimens. *AIDS.* 2017;31:1425-34.
68. Tzou PL, Rhee SY, Descamps D, Clutter DS, Hare B, Mor O, et al. Integrase strand transfer inhibitor (INSTI)-resistance mutations for the surveillance of transmitted HIV-1 drug resistance. *J Antimicrob Chemother.* 2020;75:170-82.
69. Casadellà M, van Ham PM, Noguera-Julian M, van Kessel A, Pou C, Hofstra LM, et al. Primary resistance to integrase strand-transfer inhibitors in Europe. *J Antimicrob Chemother.* 2015;70:2885-8.
70. Davy-Mendez T, Eron JJ, Brunet L, Zakharova O, Dennis AM, Napravnik S. New antiretroviral agent use affects prevalence of HIV drug resistance in clinical care populations. *AIDS.* 2018;32:2593-603.
71. Visseaux B, Assoumou L, Mahjoub N, Grude M, Traub MA, Raymond S, et al. Surveillance of HIV-1 primary infections in France from 2014 to 2016: toward stable resistance, but higher diversity, clustering and virulence? *J Antimicrob Chemother.* 2020;75:183-93.
72. Guo C, Wu Y, Zhang Y, Liu X, Li A, Gao M, et al. Transmitted drug resistance in antiretroviral therapy-naïve persons with acute/early/primary HIV infection: a systematic review and meta-analysis. *Front Pharmacol.* 2021;12:718763.
73. WHO. HIV Drug Resistance. Brief Report 2024. Available from: <https://iris.who.int/bitstream/handle/10665/376039/9789240086319-eng.pdf?sequence=1> [Last accessed on 2024 Mar 02].