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

José L. Blanco-Arévalo[1], Miguel García-Deltoro[2], Miguel Torralba[3], Manuel Vélez-Díaz-Pallarés[4], Antonio Castro[5], Darío Rubio-Rodríguez[6], and Carlos Rubio-Terrés[6]*

[1]Infectious Diseases and AIDS Unit, Hospital Clinic, Barcelona; [2]Infectious Diseases Unit, Hospital General Universitario de Valencia, Valencia; [3]Internal Medicine Department, Hospital Universitario de Guadalajara, IDISCAM, Guadalajara; [4]Department of Pharmacy, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid; [5]Gilead Sciences SL, Madrid; [6]Health Value SL, Madrid. Spain

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[1]. 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[2] and could become a significant public health trait[3]. The WHO recommends that countries should conduct regular national surveil-

***Correspondence to:**
Darío Rubio-Rodríguez
E-mail: drubiorodriguez@healthvalue.org

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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[2].

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%[2]. Primary resistance to NNRTIs was up to 3 times more common than secondary resistance[2]. 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[2]. In a study conducted in Canada between 2007 and 2011, the monthly cost per patient with resistance was estimated at 1291 Canadian dollars[4].

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[5]. 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[6,7] and by the AIDS Research Network (RIS) in 2020[8].

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[9,10]. In addition, the preferred reporting items for systematic reviews and meta-analyses guidelines[11-13] 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 ≥ 50 or 200 copies/ml of HIV-1 RNA[14-17]. 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[18,19]. In addition, systematic reviews

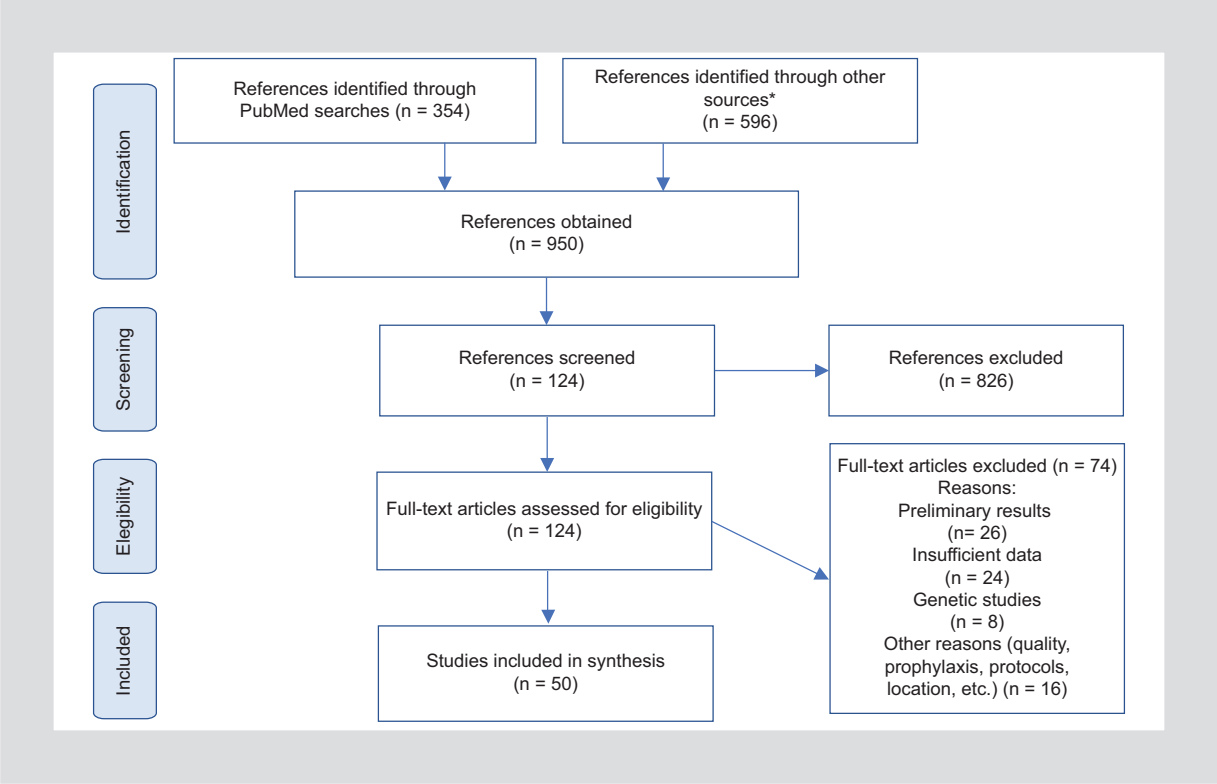

Figure 1. *Flowchart of the bibliographic searches carried out. *Removing duplicates from PubMed.*

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[20] and the Newcastle-Ottawa Quality Assessment Form for Cohort Studies[21] 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[22] and (ii) the MINORS score for observational studies[23].

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
Dolutegravir									
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/3TCDTG/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†
Bictegravir									
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 BIC/FTC/TAF	5 years	1.4%	0.0%	Low*
Cabotegravir									
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: rilpivirine; 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/ MR/VS	Subsequent ART	VF‡	MR	ROB
Dolutegravir											
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, DTG/RPV	1.1%	0.3%	High†
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	3.7%	0.0%	-
Marcelin, 2023	NA	France	Cohort, retrospective	1,432	3 years	Standard ART	1 or 2 VF	DTG/ABC/3TC	8.1%	0.6%	High†
Marcelin, 2023	NA	France	Cohort, retrospective	452	3 years	Standard ART	1 or 2 VF	DTG/3TC	6.0%	0.9%	High†
Bictegravir											
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 DTG/FTC/TDF	INI resistance	BIC/FTC/TAF	NA	0.0%	Low
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	1,825 182	48-180 weeks	Standard ART	VS M184V/I	BIC/FTC/TAF	NA	0.0%	
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*
Cabotegravir											
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% CAB: 0.3%	High†
Overton, 2023	NA	Multinational	RCT-NM	522 523	152 weeks	Standard ART	VS	CAB/RPV (4 weeks) CAB/RPV (8 weeks)	0.4% 2.3%	1.9% 1.5%	Low*

(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/ MR/VS	Subsequent ART	VF‡	MR	ROB
Deschanvres, 2023	NA	France	Cohort, retrospective	1,134	28 weeks	Standard ART	VS	CAB/RPV	1.2%	0.4%	High†
Jongen, 2023	NA	Netherlands	Case-control	588	42 weeks	Standard ART	No VF	CAB/RPV	0.9%	0.3%	Low†
Ramgopal, 2023	NA	Multinational	RCT-NM	447	12 weeks	BIC/FTC/TAF	VS	CAB/RPV	0.4%	NA	Low*
Sinclair, 2023	NA	USA	Cohort, prospective	189	6 weeks	Standard ART	-	CAB/RPV	2.1%	1.1%	High†

3TC: lamivudine; ABC: abacavir; ART: antiretroviral treatment; BIC: bictegravir; CAB: cabotegravir; DB: double-blind; DTG: dolutegravir; FTC: emtricitabine; INI: integrase inhibitors; MA: meta-analysis; 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: virological failure; VS: viral suppression. general, > 50-200 copies/ml RNA of HIV-1.
*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.

Results in ART-naïve patients

DTG

VF

VF was analyzed in five studies of ART with DTG, two double-blind, randomized clinical trials (RCTs)[24,25] and three retrospective cohort studies[26-28]. 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[24,26-31], with RM (0.3%) observed only in the observational study signed by De Salazar et al.[31], 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[32] and a multinational double-blind RCT[33], respectively. The second study, by Sax et al.[33], 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[25,32,34]. RMs were not described for BIC (Fig. 2 and Table 1).

CAB

VF

VF data from three RCTs of ART with CAB were analyzed[25,35,36]. VF ranged from 1.2% in the study by Cutrell et al.[35] with 1039 patients and 48 weeks of duration and 9% in the study by Sutton et al.[36] 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									
Messiaen, 2013	2012	-	MA	NA	DTG/ABC/3TCDTG/TDF/FTC	24-48 weeks	NA	0.0%	-
Lepik, 2018	2014	Canada	Cohort, retrospective	392	DTG/ABC/3TCDTG/TDF/FTC	48 weeks	NA	1.3%	High†
Tzou, 2020	2019	Multinational	Database	2,450	NA	NA	NA	6.2% from MR to INI	High†
Torres, 2022	2007-19	Spain	Cohort, retrospective	134	ART with DTG	NA	3.7%	NA	High†
Andreatta, 2023	ND	Multinational	5 CT Review	1,316	DTG + 2 NRTI	48	1.8%	NA	-
						96	3.3%	NA	
						144	3.5%	NA	
Bictegravir									
Torralba, 2023	2019-22	Spain	Cohort, retrospective	505	BIC/FTC/TAF	NA	0.6%	NA	High†
Andreatta, 2023	NA	Multinational	5 CT Review	1,306	BIC/FTC/TAF	48	1.5%	NA	-
						96	1.5%	NA	
						144	1.4%	NA	
Cabotegravir									
Scheibe, 2022	1997-2021	Poland	Cohort, retrospective	942 275	CAB/RPV	NA	NA	Without previous ART: 1.3% 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: ribonucleic acid; ROB: Risk of bias; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: 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).

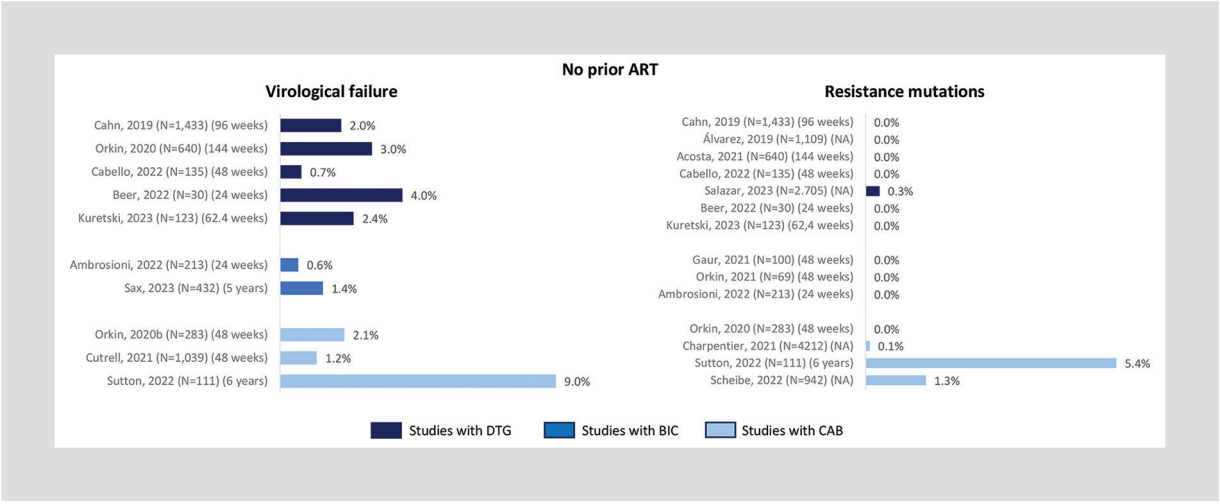

Figure 2. *Virological failure (VF) and HIV-1 resistance mutations (RM) associated with drug treatment. Patients without prior ART. For each study, the following data are indicated: name of the first author, year of publication, number of patients in the study, duration of ART, and percentage of VF or 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[36-38] of four studies of ART with CAB[25,36-38], ranging from 0.1% in the retrospective cohort study conducted in France with a sample of 4,212 patients[37] to 5.4% in the study by Sutton et al.[36] 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[39] reported previous resistance, and one[40] reported previous VF.

VF

The VF of ART with DTG was reviewed in four studies: one RCT[41], two retrospective cohort studies[40,42], and one meta-analysis of RCTs and observational studies[39]. According to these studies, the VF rate ranged from 0%[39,41] to 8.1% in a retrospective cohort study with 1432 patients followed for 3 years[40]; 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[41,43,44] and two retrospective cohort studies[40,42]. The RM rate ranged from 0%[41] to 1.9%[44]. 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[41,45,46]. In the other studies, patients had prior virological suppression (VS).

VF

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

Resistance mutations

RMs did not occur in any of the 13 studies[34,41,45-49,51,52,54,55], 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[46] 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[56].

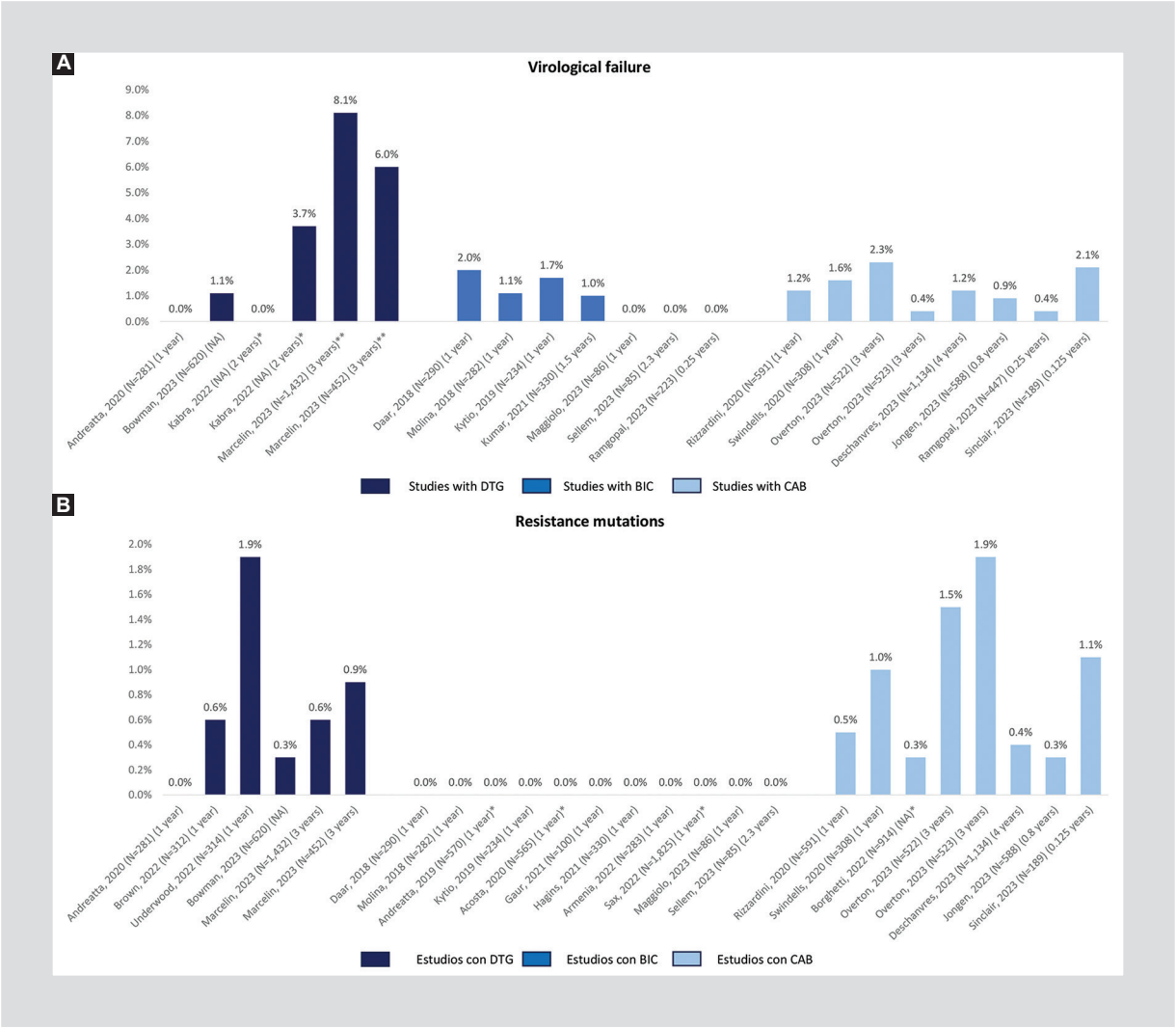

Figure 3. A: *virological failure (VF) associated with pharmacological treatment. Patients with prior ART. For each study, the following data are indicated: Name of the first author, year of publication, number of patients in the study, duration of ART, and percentage of VF.* **B:** *HIV-1 resistance 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[53,57-62], ranging from 0.4%[53,59] to 2.3%[59]. In the latter case, the study had duration of 3 years (Fig. 3A and Table 2).

Resistance mutations

Seven studies were analyzed[56-62], with RM rates ranging from 0.3%[56,61] to 1.9%[59] (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[63,64] and 0.6-1.5% with BIC[64,65] (Table 3).

Resistance mutations

RMs with DTG, in ART non-naïve and naïve patients, were 0%[66], 1.3%[67], or 6.2% at INIs[68].

Results for all the latest INIs as a whole

In a European cross-sectional study[69], in 1,950 ART-naïve patients, a 4% RM to INI set (DTG, EVG, and RAL) was observed. A prospective cohort study[70] 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[71] in 855 French ART-naïve patients observed an emerging RM rate of 4.2-6.5%. Finally, a meta-analysis published in 2021[72], 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[31]. No RMs were observed with BIC. They were with CAB, reaching 5.4%[36]. 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[40]. 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[40]. 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[73].

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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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.

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