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REVIEW

Clinical Outcomes of Integrase Strand Transfer Inhibitors Containing Antiretroviral Therapy in HIV-2: A Narrative Review

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ABSTRACT

The human immunodeficiency virus type 2 (HIV-2) is a particular subtype of HIV, which is endemic in West Africa and is characterized by a more indolent course than HIV-1. As people living with HIV-2 (PWH-2) are at risk for the development of acquired immunodeficiency syndrome and can transmit the virus, antiretroviral therapy is usually indicated. However, the optimal treatment of HIV-2 is unknown and historically the protease inhibitors (PIs) were a regular part of therapy. Nowadays, the use of integrase strand transfer inhibitors (INSTIs) in HIV-2 is increasing but the evidence supporting this approach is limited. In this narrative review, we outline the clinical data on the use of INSTI-containing antiretroviral therapy in HIV-2. We found that in the setting of treatment-naïve PWH-2, the use of INSTIs is successful, but also noted large heterogeneity in reported outcomes and that most cohorts are small with limited follow-up time. There is a lack of studies comparing the efficacy of INSTIs to other first-line options. For treatment-experienced PWH-2, the efficacy of INSTI is highly variable.

Keywords: HIV-2; Integrase strand transfer inhibitors; Efficacy; Antiretroviral therapy

Key Summary Points

The optimal antiretroviral therapy for HIV-2 infection still needs to be defined.

For treatment-naïve PWH-2, INSTI-containing antiretroviral therapy is associated with excellent virological outcomes, but a moderate immunological response. For treatment-experienced PWH-2, treatment outcomes are highly variable.

In general, all studies describing the efficacy of INSTI-containing antiretroviral therapy in HIV-2 are small and have a limited follow-up time.

So far, there are no peer-reviewed studies that compare treatment outcomes between INSTI and PI-based therapies.

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INTRODUCTION

The human immunodeficiency virus type 2 (HIV-2) is a particular subtype of HIV, which is endemic in West Africa and is characterized by a longer asymptomatic period, a slower decline in $CD4^+$ cell count and lower plasma viral loads compared to infection with HIV type 1 [1, 2]. In addition, a significant percentage of those with HIV-2 infection does not have a detectable HIV-2 viremia [3]. Despite the slower rate of disease progression, the majority of people living with HIV-2 (PWH-2) will eventually develop acquired immunodeficiency syndrome (AIDS), resulting in morbidity and mortality [4, 5]. For that reason, most guidelines suggest the initiation of combination antiretroviral therapy (cART) in all PWH-2, regardless of the $CD4^+$ cell counts and/or viral load (VL) [6, 7].

However, the treatment options for HIV-2-infection are limited, as a significant proportion of the current antiretroviral drugs is not or only partially active against HIV-2. For example, HIV-2 is naturally resistant to all non-nucleoside reverse transcriptase inhibitors and fusion inhibitors [8, 9] and reduced susceptibility was reported for the early generation protease inhibitors (PIs) [10].

For that reason, early HIV-2 treatment guidelines recommended starting people with HIV-2 on a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with a ritonavir-boosted PI, preferably lopinavir (LPV) or darunavir (DRV) [11]. This approach was mainly based on in vitro data and observational studies; a systematic review in 2014 concluded that the quality of evidence of for PI-based cART is limited and reported suboptimal clinical and immuno-virological outcomes [12]. More recently, the integrase strand transfer inhibitors (INSTI) have acquired a prominent position in the guidelines for HIV-2 management and their use have increased over time [13]. However, the evidence supporting these recommendations is limited.

In this narrative review, we will provide an overview on the current available clinical evidence on the use of INSTI in the management of HIV-2 infection. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

HIV-2 Treatment Goals and Guidelines

The main treatment goals in HIV-2 are generally in line with those of HIV-1: healthcare providers strive for a durable suppression of the HIV-2 VL, immune reconstitution and prevention of HIV-related morbidity and mortality. However, as a significant percentage of PWH-2 does not display a detectable viremia at baseline, the virological goal is generally defined as 'achieving and/or maintaining virological suppression' and the degree of immunological recovery is also used to define treatment success in HIV-2.

As mentioned in the Introduction, INSTIs are now listed among the first-line options in several guidelines on the management of HIV-2. The United States Department of Health and Human Services recommends initiating cART in all persons directly or soon after HIV-2 diagnosis in order to prevent disease progression and further transmission, preferring a regimen containing one INSTI plus two NRTIs with no preference for a specific INSTI [7]. An alternative regimen would include two NRTIs with a ritonavir boosted (/r) PI, either DRV or LPV. In the guidelines of the European AIDS Clinical Society, there are no separate recommendations for HIV-2 [14].

The most comprehensive HIV-2 treatment guideline has been published by the British HIV Association (BHIVA) [13]. They *suggest* that all people with HIV-2 should start cART and *recommend* treatment initiation for certain clinical characteristics such as in the case of HIV-1/HIV-2 dual infection, advanced immunodeficiency, or a detectable HIV-2 viremia. Treatment combinations should preferably consist of tenofovir disoproxil (TDF) with emtricitabine (FTC) (grade IC recommendation) or tenofovir alafenamide (TAF) with FTC as alternative (grade 2C). Abacavir (ABC) with lamivudine (3TC) is suggested as an alternative NRTI backbone in case of reasons to avoid tenofovir-containing cART. The recommended third agent is either the INSTI dolutegravir (DTG) or PI DRV/r, with an equal grade of

recommendation (1C). Alternative options that are suggested are the INSTIs bictegravir (BIC), raltegravir (RAL), or cobicistat-boosted elvitegravir (EVG/c). The use of LPV/r should be limited to those that cannot tolerate the first-line options and when there are clinical reasons to avoid an alternative INSTI-based combination.

In addition to guidance on preferred antiretrovirals, the BHIVA guideline also makes recommendations on optimal dosing. For both first-line options, DTG- and DRV-based cART, the authors recommend twice daily dosing—especially in those with detectable HIV-2 viremia: DTG 50 mg b.i.d. and DRV 600 mg b.i.d. plus ritonavir 100 mg b.i.d. The reason for this approach is the risk of resistance development, which could further limit the already small number of treatment options in HIV-2. For RAL, it is recommended to use the two daily dosing regimens (400 mg b.i.d.), but a higher dosage is not explicitly mentioned in the guidelines. As BIC (50 mg q.d.) and EVG/c (150/150 mg q.d.) are only available as part of single-tablet regimens (STR), it is not possible to adjust the INSTI dose, which is considered to be a disadvantage according to the guidelines [13].

In Vitro Evidence for the Use of INSTIs in HIV-2

Several groups studied the in vitro activity of the available INSTIs against HIV-2, in both wild-type and strains with acquired resistance mutations. One of the first studies evaluating the phenotypic susceptibility of HIV-2 to INSTI was published in 2008 and analyzed the activity of RAL and EVG in 14 isolates [15]. Despite the fact that HIV-2 subtype displays a 40% heterogeneity compared to HIV-1 in the integrase genes, the phenotypic susceptibility of the HIV-2 isolates for RAL and EVG was similar to that of HIV-1. This paper was the first in vitro evidence for the activity of INSTI against HIV-2 and these findings gave rise to the use of INSTI in clinical practice in this specific population. These findings for RAL were later confirmed in several other studies [16–18]. In the subsequent years, data on the susceptibility for DTG [19, 20] and BIC [21–23] emerged, suggesting that these INSTIs are also feasible treatment options for HIV-2 wild-type; this also applies for cabotegravir [24]. In addition, some studies evaluated the susceptibility for DTG and BIC in HIV-2 strains with resistance mutations in the integrase domain. Although dolutegravir remained a valuable option in this population, the impact of certain integrase substitutions on in vitro susceptibility tend to be more profound in HIV-2 than in HIV-1 [20]. An analysis from the University of Washington—Dakar HIV-2 study group showed that the head-to-head antiviral activity (defined as the half maximal effective concentrations (EC50)) of BIC, DTG and cabotegravir against HIV-2 isolates is similar for the different INSTIs [21].

Clinical Outcomes of Integrase Inhibitors in HIV-2

Literature Search

In order to assess the clinical outcomes of integrase inhibitors in HIV-2, we performed a literature search for the following databases from January 1, 2004, until December 1, 2023: MEDLINE (accessed by PubMed), EMBASE and ClinicalTrials.gov. The search string can be found in Table 1. Studies eligible for inclusion were all reports that reported on clinical outcomes—defined as CD4+cell and/or HIV-2 viral load response—in PWH with HIV-2 mono-infection or HIV-1/HIV-2 dual infection; case reports/series, cohort studies, and clinical trials were all eligible, including non-peer-reviewed conference presentations. Articles were independently screened for eligibility by the two authors (WB and BW) based on title and abstract review. The authors also reviewed the full-text articles and determined final inclusion in the review. In case two reports described the same population, the most comprehensive description was used. Data from the included studies were extracted separately by WB and BW who were blinded to each other's work. Extracted data were then compared for agreement and reconciled though group consensus. In case of disparities the supervisor (BW) decided on inclusion. Data extraction included study characteristics and outcomes.

Overall, we found 519 articles of interest; after removing the duplicates, screening title/abstract

Table 1 Search strings

Search string for PubMed
("hiv-2"[MeSH Terms] OR "hiv-2" [All Fields] OR "human immunodeficiency virus type 2" [All Fields]) AND ("Integrase Inhibitors" [MeSH Terms] OR "HIV Integrase Inhibitors" [MeSH Terms] OR "Integrase Inhibitors" [All Fields] OR ("integrase" [All Fields] AND "inhibitors" [All Fields]) OR "INSTI" [All Fields] OR "integrase strand transfer inhibitor" [all fields] OR ("Raltegravir Potassium" [MeSH Terms] OR "Raltegravir" [All Fields] OR "Dolutegravir" [All Fields] OR "elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate drug combination" [MeSH Terms] OR "Elvitegravir" [All Fields] OR "Bictegravir" [All Fields] OR "Biktarvy" [All Fields] OR "Cabotegravir" [All Fields]))
Search string for Embase
('human immunodeficiency virus 2' OR 'hiv-2' OR 'hiv2' OR 'human immunodeficiency virus type 2') AND ('integrase inhibitor' OR 'integrase inhibitor' OR ('integrase' AND 'inhibitor*') OR 'INSTI' OR 'integrase strand transfer inhibitor' OR 'raltegravir' OR 'dolutegravir' OR 'elvitegravir' OR 'elvitegravir' OR 'cobicistat plus elvitegravir plus emtricitabine plus tenofovir dixoproxil' OR 'bictegravir' OR 'biktarvy' OR 'bictegravir plus emtricitabine plus tenofovir alafenamide' OR 'cabotegravir')*

and eventually the full text, we identified 25 reports on clinical outcomes – either virological or immunological—in patients with HIV-2 or HIV-1/HIV-2 dual infections using a registered INSTI as part of the antiretroviral regimen [25–49]. During the review process, we noted that the INSTI treatment outcomes for several PWH-2 were described in multiple papers: the cases described by both Salgado et al. [28] and Treviño et al. [36] are likely to be part of the larger observational cohort based on a national registry [46]. Secondly, the person with an HIV-1/2 dual infection described in the paper of Cardoso et al. [39] was probably also part of the cohort described by Sequeira et al. [43]—as the authors are from the same center. These three reports were not used in the further analysis. In addition, overlap in the populations described in two Portuguese cohorts cannot be excluded [40, 43], but as the authors are from different centers and the data seem to be collected in different time periods, we decided to consider the treatment courses as unique. In addition, some PWH-2 are likely to be described multiple times with different treatment courses. Descamps et al. describes treatment outcomes to DTG in those with a history of virological failure on RAL [42], while these individuals are probably also part of the cohort described by Charpentier et al. [41]. In addition, some of the treatment-experienced individuals included in the study of Joly et al. [48] are likely to be part of three earlier French papers [41, 42, 45].

General Characteristics

The majority of the 22 unique included reports were case studies: only nine studies included more than ten participants. The highest level of evidence is provided by three single-arm clinical trials; there are no comparator trials available. Due to the overlap mentioned above, it is not possible to assess the exact number of unique individuals and treatment courses. Therefore, we are not able to provide a summary on the general demographic, biochemical, and clinical characteristics, but these are displayed per included study (Table 2).

After excluding the treatment courses, which are assumed to be described multiple times in different reports, the total estimated number of treatment courses is 319, with half of these courses being in treatment-experienced individuals. Most treatment regimens included RAL ($n=132$), followed by DTG ($n=125$). In three papers, the efficacy of a once-daily fixed-dose combination containing EVG was evaluated [34, 44, 46] and one study describes the outcomes in 24 PWH-2 receiving BIC/TAF/FTC [48]. In treatment-naïve patients, INSTI treatment was always initiated along a combination of two NRTIs, mostly TDF/FTC. Treatment-experienced patients received more heterogeneous regimens, but most common combinations consisted of two NRTIs and a PI plus INSTI. One paper describes the virological outcomes in two patients with an unorthodox backbone consisting of zidovudine (AZT) and foscarnet [35]. The median CD4 cell count at INSTI

Table 2 Demographical, immunological, and clinical characteristics of patients initiating INSTI treatment

Author, year	Country	Design	Sample size	Population	Age	Sex	Treatment naive?	INSTI	Backbone treatment	Time of measurement(s)*	CD4 count at baseline (cells/mm^3)	CD4 count after INSTI initiation (cells/mm^3)	Delta of CD4 count (cells/mm^3) **	VL at baseline (copies/ml)	VL after INSTI initiation (copies/ml)
Damond, 2008 [25]	Mali	Case series	2	HIV-2 ($n = 2$)	A) 56 B) 46	A) Male B) Female	No	RAL	A) 3TC + ABC + DRV/r B) TDF + ABC + DRV/r	1, 3, 6 months	A) 27 B) 24	M1: 248 (A), 27 (B) M3: 420 (A), 105 (B) M6: 345 (A), 102 (B)	M1: + 221(A), + 3 (B) M3: + 393 (A), + 81 (B) M6: + 318 (A), + 78 (B)	A) 6517 B) 8445	M1: 217 (A), und (B) M3: und (A), und (B) M6: und (A), und (B)
Garrett, 2008 [26]	Ivory Coast	Case report	1	HIV-2 ($n = 1$)	41	Male	No	RAL	AZT + ABC + DRV/r	2, 4 months	80	M4: 250	+ 170	55,400	M2: < 100 M4: 5900
Roquebert, 2008 [27]	Mali	Case report	1	HIV-2 ($n = 1$)	59	Male	No	RAL	DRV/r	1, 4 months	56	M1: 244 M4: 204	M1: + 188 M4: + 148	33,820	M1: 18,000 M4: 71,360
Salgado, 2009 [28]	Spain	Case report	1	HIV-2 ($n = 1$)	20	Male	No	RAL	ddI + DRV/r + maraviroc	8 months	50	40	− 10	5012	502
Armstrong-James, 2010 [29]	West Africa	Case report	1	HIV-2 ($n = 1$)	48	Male	No	RAL	TDF + FTC + TPV/r + maraviroc	3, 11 months	35	M3: 135 M11: 97	M3: + 100 M11: + 62	42,000	M3: und M11: 73,740
Burger, 2010 [30]	A) Cape Verdian B) Mozambique	Case series	2	Dual ($n = 1$) HIV-2 ($n = 1$)	A) 47 B) 41	A) Male B) Male	Yes	RAL	TDF + FTC	A) 3 months B) NR	A) 110 B) 40	NR	NR	A) 40,000, < 50 (HIV-1, HIV-2) B) 1280	A) 105, < 50 (HIV-1, HIV-2) B) NR
Francisci, 2011 [31]	Ivory Coast	Case report	1	HIV-2 ($n = 1$)	42	Male	No	RAL	TDF + 3TC	5 months	211	345	+ 134	14,487	und

Table 2 continued

Author, year	Country	Design	Sample size	Population	Age	Sex	Treatment naive?	INSTI	Backbone treatment	Time of measurement(s)*	CD4 count at baseline (cells/mm^3)	CD4 count after INSTI initiation (cells/mm^3)	Delta of CD4 count (cells/mm^3) **	VL at baseline (copies/ml)	VL after INSTI initiation (copies/ml)
Wandeler, 2011 [32]	Togo	Case report	1	HIV-2 ($n=1$)	55	Male	No	RAL	TDF + FTC + LPV/r	2 years	120	> 200	+ 80	25,119	und
Peterson, 2012 [33]	A) West Africa B) Senegal C) West Africa D) Ghana E) Belgium	Case series	5	HIV-2 ($n=5$)	A) 55 B) 50 C) 58 D) 41 E) 33	A) Female B) Male C) Female D) Female E) Female	A) No B) No C) No D) No E) Yes	RAL	A) AZT + 3TC + DRV/r B) TDF + FTC + DRV/r C) AZT + TDF + 3TC + DRV/r D) AZT + ABC + 3TC + SQV/r E) TDF + FTC	A) 1 year B) 2 years C) 3.5 years D) 2 years E) 2 years	A) 282 B) 55 C) 42 D) 53 E) 180	A) 428 B) 293 C) 321 D) 365 E) 295	A) + 146 B) + 238 C) + 279 D) + 321 E) + 155	A) 61,000 B) > 2000 C) 136,300 D) 1560 E) 331	A) und B) und C) 55 D) 50 E) und
Zheng, 2014 [34]	Ivory Coast	Case report	1	HIV-2 ($n=1$)	57	Male	Yes	EVG	TDF + FTC + Cobicistat (Stribild)	1, 8 months	386	M1: 466 M8: 450	M1: + 80 M8: + 64	1975	M1: und M8: und
Delory, 2015 [35]	France	Case series	2	HIV-2 ($n=2$)	A) 46 B) 51	A) Male B) Male	No	DTG	AZT + Foscarnet	11 months	A) 37 B) 199	A) 60 B) 620	A) + 23 B) + 421	A) 3981 B) 15,849	A) 2512 B) 1259
Treviño, 2015 [36]	Spain	2 cases from a retrospective OS	2	HIV-2 ($n=2$)	NR	NR	No	DTG	TDF + FTC	12 months	A) 124 B) 12	A) 207 B) 72	A) + 83 B) + 60	A) 7943 B) 50,119	A) und B) 5012
Ceia, 2019 [37]	Portugal	Case report	1	Dual ($n=1$)	46	Male	No	DTG	TDF + FTC + DRV/r	12 months	89	329	+ 240	5320	und
Tchounga, 2020 [39]	Ivory Coast	2 cases from a prospective OS	2	HIV-2 ($n=2$)	A) 33 B) 50	A) Male B) Male	No	RAL	TDF + 3TC + DRV/r	5 years	A) 141 B) 425	A) 214 B) 69	A) + 73 B) -365	A) 33,287 B) 8790	A) und B) und
Cardoso, 2021 [39]	Guinea	Case report	1	Dual ($n=1$)	54	Male	No	DTG	TAF + maraviroc	11 months	245	374	+ 129	754	und

Table 2 continued

Author, year	Country	Design	Sample size	Population	Age (median)	% Male	Treatment naive?	INSTI	Backbone treatment	Time of measurement(s)* (months)	Median CD4 count at baseline (cells/mm^3)	Median CD4 count after INSTI initiation (cells/mm^3)	Delta of CD4 count (cells/mm^3) **	Median VL at baseline (copies/ml)	Median VL after INSTI initiation (copies/ml)
Doroana, 2010 [40]	Portugal	Retrospective OS	20	HIV-2 ($n=20$)	53	50%	No	RAL	OBT	6, 11	120	M6: 190 M12: 180	M6: + 70 M11: + 60	10/20: und 10/20: > 50	M6: 17/20 und, 3/20 > 50 M11: 16/20 und, 4/20 > 50
Charpentier, 2011 [41]	France	Retrospective OS	7	HIV-2 ($n=7$)	NR	NR	No	RAL	1/2/3 NRTIs + DRV/r	3, 8	48	NR	NR	19,055	M3: 5/7 und M8: 7/7 rebounded
Descamps, 2015 [42]	France	Prospective OS	13	HIV-2 ($n=13$)	51	77%	No	DTG	OBT	3, 6	100	M3: 158 M6: 166	M3: + 58 M6: + 66	9544	M3: 6/13: und, 7/13: 1450 M6: 4/12: und, 7/12: 4395
Sequeira, 2016 [43]	Portugal	Retrospective OS	39	HIV-2 ($n=39$)	47	38%	14/39: Yes 25/39: No	31/39: RAL 8/39: DTG	OBT	3, 6, 9	316	M3: 362 M6: 506 M9: 516	M3: + 46 M6: + 190 M9: + 200	NR	M3: 36/39 und M6: 38/39 und M9: 37/39 und
Ba, 2018 [44]	Senegal	1-arm, open-label, phase-4 clinical trial	30	HIV-2 ($n=30$)	49	20%	Yes	EVG	TDF + FTC + cobicistat (Stribild)	11	408	569	+ 161	8/30: und 7/30: < 10 15/30: 41	27/30: < 50 1/30: > 50
Matheron, 2018 [45]	France	1-arm, open-label, phase-2 clinical trial	30	HIV-2 ($n=30$)	49	33%	Yes	RAL	TDF + FTC	11	436	523	+ 87	10/30 und 20/30 316	27/28: und 1/28: 1995

Table 2 continued

Author, year	Country	Design	Sample size	Population	Age (median)	% Male	Treatment naive?	INSTI	Backbone treatment	Time of measurement(s)* (months)	Median CD4 count at baseline (cells/mm^3)	Median CD4 count after INSTI initiation (cells/mm^3)	Delta of CD4 count (cells/mm^3) **	Median VL at baseline (copies/ml)	Median VL after INSTI initiation (copies/ml)
Requena, 2019 [46]	Spain	Retrospective OS	44	Dual ($n=5$) HIV-2 ($n=39$)	43	74%	18/44: Yes 26/44: No	TN: 9/18: RAL 6/18: EVG 3/18: DTG TE: 19/26: RAL 1/26: EVG 6/26: DTG	TN: TDF + FTC/3TC TE: two NRTIs, 13/26 + PI	TN: 12 TE: 13 (Median)	TN: 264 TE: 194	TN: 346 TE: 320	TN: + 82 TE: + 126	TN: 3981 TE: 5012	TN: 16/18 und TE: 13/26 und
Pujari, 2020 [47]	West India	Retrospective OS	62	Dual ($n=10$) HIV-2 ($n=52$)	53	77%	12/62: Yes 50/62: No	DTG	TN + TE: OBT TE: LPV/r or RAL is replaced by DTG	6, 12, 18	TN: 414 TE: 614	(TN, TE) M6: 612, 620 M12: 719, 684 M18: 686, 663	(TN, TE) M6: + 198, + 6 M12: + 305, + 70 M18: + 272, + 49	TN: NR TE: 24/62 und, 38/62 NR	TN: NR TE: 21/24 und
Joly, 2023 [48]	France	Retrospective OS	24	HIV-2 ($n=24$)	58	42%	5/24: Yes 19/24: No	BIC	TAF + FTC	28	580	615	+ 35	21/24: und 3/24: 94	24/24: und
Pacheco, 2023 [49]	Portugal	1-arm, open-label, phase-2 clinical trial	30	HIV-2 ($n=30$)	54	0.27	Yes	DTG	ABC + 3TC or TDF + FTC	11	438	534	+ 96	13/30: und 17/30: 403	M11: 27/30 und

3TC lamivudine, *ABC* abacavir, *AZT* zidovudine, *BIC* bictegravir, *ddI* didanosine, *DRV* darunavir, *DTG* dolutegravir, *EVG* elvitegravir, *FTC* emtricitabine, *LPV* lopinavir, *NR* not reported, *NRTI* nucleoside reverse transcriptase inhibitor, *OBT* optimized background therapy, *OS* observational study, *PI* protease inhibitor, *RAL* raltegravir, *r* ritonavir, *SQV* saquinavir, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate, *TE* treatment-experienced, *TN* treatment-naive, *TPV* tipranavir, *und* undetectable, *VL* viral load

*After INSTI initiation

**If multiple time measurements, latest time point was used

initiation, when accounted for all included cases, was above 250 cells/mm^3. Almost all included studies reported HIV-2 RNA viral load at baseline for at least a part of the included population; only one study, accounting for 39 PWH-2, did not report baseline VL [43]. For 86 treatment courses (27% of total), the HIV-2 VL was undetectable upon treatment initiation. Virological suppression at the end of follow-up was reported in the majority of the treatment courses (61.4% (196/319)). In general, virological treatment outcomes were better in treatment-naïve PWH-2 compared those who are treatment-experienced. However, as treatment outcomes were inconsistently reported in the included studies, we are not able to reliably quantify this difference.

Case Reports and Series

As mentioned earlier, 16 papers included less than ten patients, who were mostly treatment-experienced. RAL was the most commonly used INSTI (n=24 (77%)), followed by DTG (n=6 (19%) and EVG (n=1 (3%); all were followed for at least 4 months with a maximum follow-up time up to 5 years. The vast majority of the included PWH-2 were treatment experienced (27/31 (87.1%)); all treatment experienced were switched to INSTI-containing cART because of earlier virological failure. At baseline, virtually all (30/31 (97%) had a detectable HIV-2 VL and at the end of follow-up only a minority (13/31 (41.9%) achieved an undetectable VL; the degree of immunological recovery was variable, ranging from a decline of 365 cells/mm^3 to an increase of 421 cells/mm^3. It should be noted that the numbers are strongly influenced by the study of Charpentier et al., who selected seven heavily pre-treated HIV-2-infected patients failing on RAL-containing cART from the French HIV-2 National AIDS Research Agency—Emerging Infectious Diseases (ANRS) cohort CO5, for the purpose of genotypic analysis [41]. Excluding this paper would have yielded virological suppression in 54%.

Observational Studies

There are six publications describing larger observational cohorts. Two reports originate from Portugal and were only published as a congress abstract, making complete data extraction difficult. These studies, including 20 and 39 participants, mainly focused on treatment-experienced patients and reported that a total of 80–95% of the participants achieve virological suppression after the initiation of an INSTI [40, 43]. Due to limited reporting in the included studies, we were not able to assess differences in outcomes between treatment-naïve and treatment-experienced individuals. One of the four remaining observational cohorts is a French study that evaluates the efficacy of twice-daily DTG 50 mg after failure on a RAL-containing regimen in 13 PWH-2 [42]. In this heavily treatment-experienced population, with a median of 16 previous antiretroviral regimens, an optimized background regimen was initiated in combination with DTG. At month 6, virological suppression was achieved in four of the 12 (33%) remaining study participants. Virological non-response was only observed in those bearing a N155H (n=4) or Q148R/K (n=2) mutation at baseline. With respect to immunological parameters, there was an increase of 67 CD4+cells/mm^3. There were no data reported on the outcomes beyond 6 months.

In a relatively large Spanish retrospective cohort (n=44), all PWH-2 treated on INSTIs were analyzed for immunological and virological success [46]. RAL was the most commonly used INSTI in this cohort (n=28), followed by DTG (n=9) and EVG (n=7)—dosing was not mentioned in the manuscript. The analysis included 18 treatment-naïve participants; after a median of follow-up of 13 months 88.9% achieved/maintained an undetectable VL and a median increase of 82 CD4+cells/mm^3 (range, 13–272). Of the remaining 26 treatment-experienced PWH-2, an undetectable HIV-2 VL was achieved/maintained in 65.4% of the population (n=17), but relapse occurred in four individuals during follow-up. The median CD4 cell count increase in this population was 126 cells/mm^3. Eventually, virological failure was recognized in 15 individuals (two being treatment-naïve and 13 treatment-experienced) and 12 developed INSTI-associated resistance mutations (mainly N155H, Q148H/R, and Y143C/G).

The largest retrospective observational study evaluating the clinical efficacy of once daily DTG in HIV-2, was conducted in West India, including 62 PWH-2: 12 treatment-naïve and 50 treatment-experienced [47]. Virological and immunological outcomes were reported at 6, 12, and 18 months after the initiation of DTG-containing cART. During follow-up, virological suppression—defined as an HIV-2 RNA < 100 copies/ml—was achieved/maintained in 89.6% of the treatment-experienced and 85.7% of the treatment-naïve participants. The median increase in CD4 cell count after 12 months was 70 cells/mm^3 and 305 cells/mm^3, respectively. Despite being the largest cohort so far, these findings are difficult to interpret due to significant limitations in the data collection and reporting. Most importantly, it is unclear in how many of the PWH-2 HIV-2 VL measurement was actually performed—putting the reported virological response rates at risk for bias. Although a median duration on DTG-based treatment was reported to be 21 months for all individuals, there was a CD4 cell count available in only 29% of the participants at 18 months (16.7% for treatment-naïve ($n = 2$) and 32% for treatment-experienced ($n = 16$)).

The only study describing the virological and immunological outcomes for PWH-2 receiving BIC—as part of a fixed-dose tablet together with tenofovir alafenamide and emtricitabine (BIC/FTC/TAF) – was presented at the 31st Conference on Retroviruses and Opportunistic infections [48]. This retrospective, non-comparative study included 24 PWH-2, of whom five were treatment-naïve and 19 treatment-experienced. Of the treatment-experienced, all had an undetectable HIV-2 VL at baseline and the majority (74%) received INSTI-based cART in past. A particular strength of this study is the long follow-up time, with a median duration of BIC/FTC/TAF treatment of 27.8 months (interquartile range, 16.4–36.2). During treatment, all achieved/maintained a HIV-2 VL < 40 copies/ml; the mean CD4 cell count increase was 54 cells/mm^3 for the total population and 106 for the treatment-naïve subgroup. One participant discontinued the regimen. These findings support the use of BIC/FTC/TAF as a treatment option in both treatment-naïve and treatment-experienced PWH.

Clinical Trials

So far, three single-arm, open-label clinical trials that evaluated the effect of INSTI (RAL, EVG/c and DTG) for treatment efficacy and safety in treatment-naïve PWH-2 have been published. In general, the virological outcomes in these studies were excellent but the immunological recovery was moderate.

The first of these studies was performed in Senegal and evaluated the effectiveness of a single-tablet regimen of EVG/c/FTC/TDF for the treatment of HIV-2 [44]. HIV-2-infected, antiretroviral therapy-naïve adults with CD4 counts < 750 cells/mm^3 were eligible for the trial with a planned follow-up time of 48 weeks; people with an HIV-1/HIV-2 dual infection were excluded from this trial. There were multiple prespecified endpoints: death *or* a new WHO stage 3/4 event *or* virological failure at 48 weeks. Eventually, a total of 30 PWH-2 were included, of which the majority was female (80%) with nearly 37% ($n = 11$) of the subjects having a CD4 + cell count < 350 cells/mm^3. At baseline, in half of the PWH-2 there was a quantifiable HIV-2 RNA detectable (median 41 copies/ml). After 48 weeks of treatment initiation, there were no deaths or WHO 3/4 clinical events; one participant was lost to follow-up. In the modified intent-to-threat analysis, 28 out of 30 (93.3%) achieved/maintained virological suppression with one participant with confirmed virological failure. This individual developed significant INSTI resistance after the selection of G140S + Q148R mutations. The median CD4 + cell increase in the cohort was 161 cells/mm^3 and there were no drug-related grade 3–4 adverse events. In their manuscript, the authors conclude that E/C/FTC/TDF is safe, effective, and well-tolerated as HIV-2 treatment option.

In France, Matheron et al. conducted a phase II clinical trial with 30 ART-naïve patients with symptomatic HIV-2 infection testing the efficacy of a RAL-containing regimen [45]. The study treatment consisted of TDF/FTC plus

RAL (400 mg bid). The primary endpoint was outcome 'therapeutic success', a composite criterion of the following: surviving at 48 weeks without any of the following events from treatment initiation: a CD4 + cell increase < 100 cells/mm^3 from baseline to 48 weeks, plasma viral load ≥ 40 copies/ml from 24 weeks confirmed within the next 4 weeks, RAL discontinuation, or new a Centers for Disease Control and Prevention group B or C-defining event. In the cohort, the majority of the participants (n = 20 (66.7%)) had a detectable HIV-2 VL—defined as ≥ 40 copies/ml; the median CD4 count at baseline was 436 (IQR 314–507). At week 48, failure—occurring in 60% of the population, was mainly due to not reaching the immunological criterion. Nevertheless, the RAL-containing regimen was very effective in reaching undetectable level of VL in almost all patients (96%) and it was well tolerated with only one patient developing gastrointestinal symptoms (grade 3) at day 1 of treatment initiation. In addition, median CD4 count increase at week 48 was 87 cells/mm^3. The single patient with virological failure developed drug resistance mutations in the integrase region (E92Q, T97A, and Y143C/G/H/R).

The most recent clinical trial on the effect of INSTI-based cART was published in 2023, in this Portuguese phase II study the safety and efficacy of triple therapy with two NRTIs plus DTG was evaluated [49]. The study included 30 PWH-2 who were treatment-naïve and who were started on once-daily DTG/ABC/3TC (600/300/50 mg) (n = 21 (70%)) or once-daily TDF/FTC plus DTG 50 mg (n = 9 (30%)). The primary endpoint was the proportion of patients with 'global success' at week 48; again this was a composite variable defined as a suppressed HIV-2 VL (< 40 copies/ml) *and* a change in CD4 cell count that was ≥ 100 cells/mm^3 if initial CD4 ≤ 500 cells/mm^3, or if initial value was ≥ 500 cells/mm^3 an increase of ≥ 50 cells/mm^3. The separate virological and immunological success were also reported in the results. At baseline, the median CD4 cell count was 438 cells/mm^3 and advanced immunodeficiency – defined as CD4 + cells < 200 cells/mm^3—was rare (n = 3 (10%)); the majority of the cohort (n = 17 (57%)) had a detectable HIV-2 VL (≥ 40 copies/ml) with a median of 190 copies/ml. Virological efficacy was excellent, with no virological failures occurring. In the intention-to-treat analysis, 27/30 participants (90%) had a plasma VL of < 40 copies/ml at week 48. In per-protocol analysis, all participants achieved an undetectable viral load. The mean increase in CD4 count was 95 cells/mm^3. This increase was more pronounced if baseline CD4 was < 500 cells/mm^3 (+ 145 cells/mm^3) compared to if baseline CD4 count was > 500 cells/mm^3. When assessing the efficacy using the 'global success' criterium, 55.6% of the participants achieved this goal. Again, this low percentage was mainly driven by insufficient immunological recovery. The most prevalent drug-associated AE were headache (20%) and nausea (13.3%). One subject discontinued the treatment due to drug-related insomnia, anxiety, and memory disturbance.

DISCUSSION

In this narrative review, we outlined all published clinical data on INSTI use in PWH-2 and show that the current available data support the use of RAL, DTG, BIC and EVG in treatment-naïve patients. The best available evidence consists of three single-arm clinical trials in treatment-naïve PWH-2 [44, 45, 49], showing an excellent virological response with 90% of the trial participants achieving or maintaining an undetectable VL after 48 weeks; the immunological response was moderate with a median increase of CD4 + cell count of 96 cells/mm^3. For the treatment-experienced population, the effectiveness is lower but the INSTIs proved to be a valuable therapeutic option in those who experienced virological failure on earlier treatment regimens, with a significant proportion of the PWH-2 achieving virological suppression.

The most notable from this narrative review is that, when it comes to the use of INSTI in the treatment of HIV-2, the current guidelines are based on very limited evidence, both in terms of quality and quantity. The majority of the literature consists of small case series/reports and only three small single-arm clinical trials accounting for 90 PWH-2: therefore, the

current recommendations are mainly based on in vitro data and the outcomes in less than 400 PWH-2, with a limited follow-up time. Next to the small numbers, the large heterogeneity in the primary endpoints between the prospective studies is remarkable. Some studies focus on virological outcomes, while others use a composite endpoints that includes both virological and immunological response. Moreover, the definition of immunological success differs between studies. Lastly, it should be noted that clinical outcomes are not regularly reported in the included studies. This lack of uniformity makes it difficult to compare outcomes and therefore, future studies should preferably include a longer follow-up time and an universally accepted definition of treatment success in HIV-2.

As mentioned earlier, the BHIVA guideline also includes dosing recommendations, advising the use of twice-daily DTG, considering the potential risk for resistance development and the limited treatment options in HIV-2 in general [13]. Although the INSTI dosage was reported only in a limited number of studies, we found no evidence to support the BHIVA recommendations, especially not in treatment-naïve PWH-2: In the study of Pacheco et al., once-daily dosing DTG was used and was associated with favorable outcomes [49] and also for the two other trials, no dosage adjustment of the INSTI-component was made [44, 45]. Next to these trials, we observed favorable outcomes in those receiving fixed-dose EVG/c containing cART [34, 46], and BIC/FTC/TAF [48], which are used in the same dosage as for HIV-1. So although the cautious approach in the guidelines is conceivable, we believe that for treatment-naïve PWH-2 there is currently no indication to adjust the dosing of the INSTI-component of cART. Furthermore, from the perspective of treatment compliance, the use of a once-daily regimen is preferable over more frequent dosing. Following through on this, the question that remains to be answered is whether the virological efficacy of once-daily RAL 1200 mg is as high as the twice-daily 400-mg dosing in the setting of HIV-2, as it is in HIV-1. With respect to treatment-experienced PWH-2, especially those with prior exposure to INSTIs, a more tailor-made dosing approach is recommended to optimize virological efficacy and to prevent the selection of resistance-associated mutations.

Although our review supports the use of INSTI in the treatment of HIV-2, the question remains how the outcomes of INSTI-based therapy compare to the alternative first-line option, namely PI-based cART. Until recently, there was a lack in studies that systematically evaluated outcomes in both PI- and INSTI-based cART. However, in October 2023, a non-peer-reviewed manuscript describing the outcomes of the FIT-2 trial was published on the website of the Social Science Research Network [50]. In this randomised, open-label, multicenter, phase II trial conducted between January 2016 and May 2019, the efficacy and safety of three treatment options for HIV-2 was evaluated. A total number of 210 treatment-naïve PWH-2 with a CD4 cell count ≥ 200 cells/mm^3 were randomized to a triple NRTI combination (TDF plus FTC or 3TC) plus AZT) (n = 71), a PI-based combination (TDF-FTC (3TC) plus LPV/r) (n = 69) and a INSTI-based regimen (TDF-FTC (3TC) plus RAL) (n = 70), with a follow-time of 96 weeks. In this trial, treatment success was defined as survival with a HIV-2 VL < 50 copies/ml, the non-occurrence of AIDS-defining events and non-AIDS severe morbidities, and a delta of CD4 depending on the initial CD4 count (an increase of 100 cells/mm^3 for initial CD4 counts between 201 and 500 or a stable CD4 cell count for individuals with a CD4 ≥ 500 cells/mm^3). At baseline, the median CD4 cell count in the three arms varied between 648 and 760 and HIV-2 RNA was < 50 copies/ml in 70–86% of the population. During follow-up, five participants died (two in the triple NRTI, two in the PI-based, and one in the INSTI-based cART arm) and 20 permanently discontinued ART (four in the triple NRTI, eight in the PI-based, and eight in the INSTI-based arm). After 2 years, the data safety monitoring board recommended premature termination of the triple NRTI arm for safety reasons, although this was not further defined in the manuscript. Eventually, treatment success was achieved in 57% of the PI-based arm and 59% in the INSTI-arm; in the intention-to-treat analysis the number of PWH-2 achieving or maintaining an undetectable VL at week 96 was comparable for LPV/r

(89.8%) and RAL (92.8%). A significant CD4 cell increase was reported in 57.9% in the LPV/r arm and 60.0% in the RAL-arm. Based on these data, the authors concluded that RAL-based and LPV/r-based cART are both efficient and safe and recommend a head-to-head comparison in future phase III trials. Although this manuscript has not yet been peer-reviewed and the combinations used might be somewhat outdated, this is the first study to evaluate multiple treatment regimens for HIV-2 in a standardized manner. The importance of such a study is underlined by the earlier findings by Ekouevi et al. [12] and our manuscript, and this will hopefully give rise to more future trials, evaluating novel modern antiretroviral treatment regimens in HIV-2.

In conclusion, in this narrative review we describe treatment outcomes of INSTI-containing cART regimens in PWH-2. Although the quality of evidence is improving with now three single-arm trials and one non-peer-reviewed RCT published in recent years, much work needs to be done. Future studies should compare modern cART combinations and report outcomes in an universally accepted manner.

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Declarations

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