

Treatment-Emergent Integrase Inhibitor Resistance Among Pediatric and Adolescent Populations With HIV-1: A Systematic Review

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Key Takeaways

- This systematic literature review sought to summarize the frequency of treatment-emergent INSTI DRMs in pediatric and adolescent CLWHIV
- Dolutegravir (DTG)-based INSTI regimens were the most commonly described ART in non-interventional settings, reflecting wider real-world use relative to other INSTIs
- INSTI-based regimens, particularly second-generation INSTIs, were associated with low rates of treatment-emergent drug resistance after virologic failure

Introduction

- INSTIs are globally preferred first-line antiretroviral agents for treatment in infants, children, and adolescents with HIV^{1,2}
- First-generation INSTIs, raltegravir (RAL) and elvitegravir (EVG), and second-generation INSTIs, dolutegravir (DTG) and bictegravir (BIC), are approved for use in children and adolescents (<18 years) meeting indication criteria. RAL and DTG are also available in pediatric formulations
- There are clear advantages with the INSTI class with regards to effectiveness and high barrier to resistance; however, second-generation INSTIs have a higher barrier to resistance as compared to first-generation INSTIs. Overall, the INSTI class is an important treatment option for children and adolescents, who are often heavily treatment-experienced and have limited treatment options due to transmitted resistance as well as adherence and tolerability issues³
- This systematic review summarizes the frequency of documented treatment-emergent INSTI drug resistance mutations (DRMs) in pediatric and adolescent populations with HIV-1

Methods

Data Sources and Search Strategy

- A systematic literature review of English language articles published since January 2010 was conducted in June 2021 and updated in August 2022 using PubMed and Embase
- Conference abstracts from HIV- or infectious disease-focused conferences presented between 2013 and 2021 were also searched

Eligibility Criteria and Study Selection

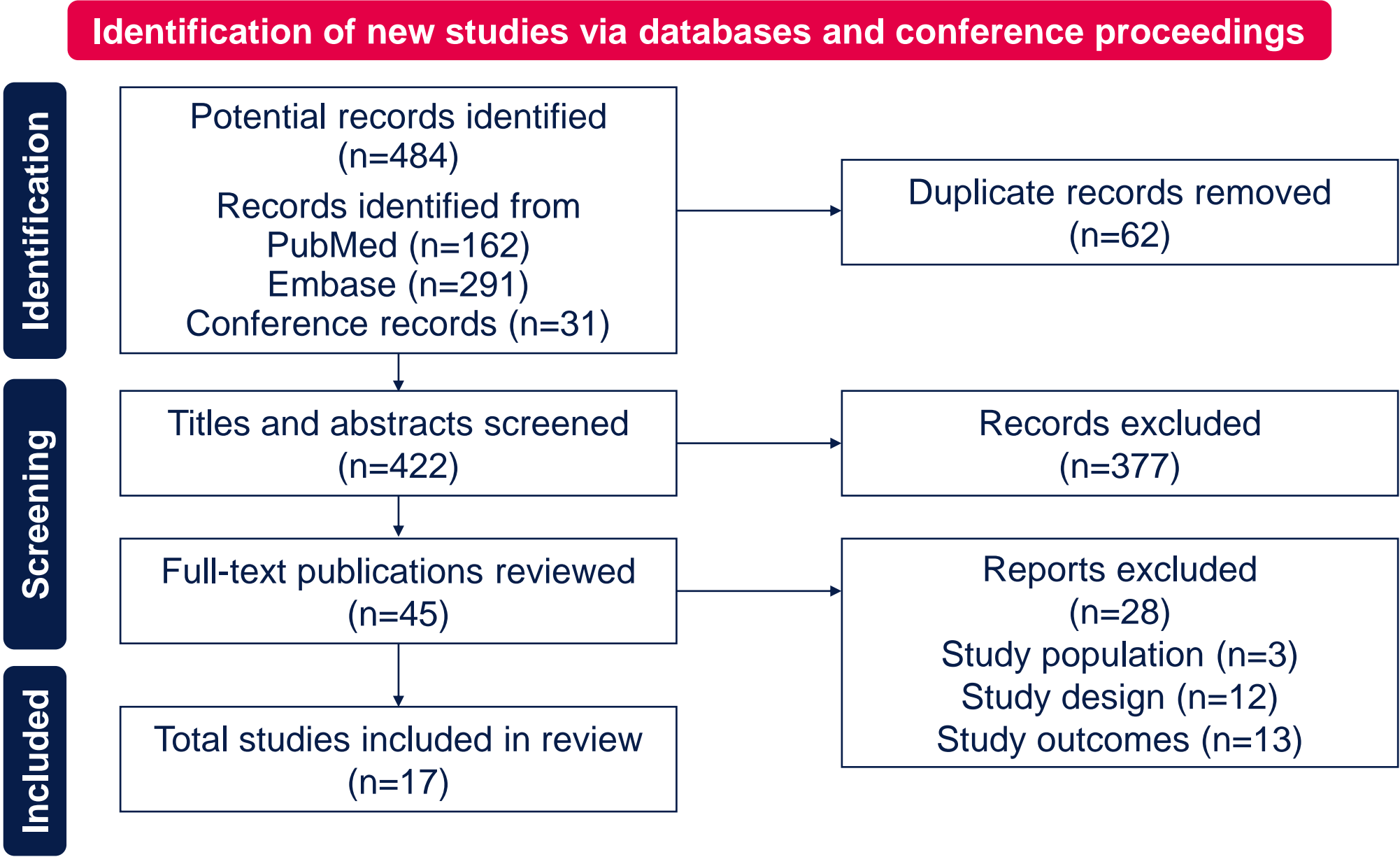
- Eligible studies included
 - Reports on people with HIV aged <18 years who were taking an INSTI-based oral ARV regimen (RAL, EVG, DTG, or BIC) and had
 - Virologic failure outcomes reported
 - HIV-1 genotypic drug resistance sequencing performed for some or all individuals after a virologic failure event
 - Outcomes across studies were reported as proportions with 95% confidence intervals
 - Both clinical trials and non-interventional studies were eligible for inclusion, with results reported separately by study design
 - Studies from any geographic region were considered
 - Studies were not excluded based on the ART history of the population (ART-naïve and ART-experienced included)
 - Studies including young adults (18-25 years) were not excluded if individuals aged <18 years were also included in the study population
 - Where available, specific emergent DRM frequencies were identified and reported by INSTI regimen (RAL, EVG, DTG, or BIC) in CLWHIV

Results

Included Studies

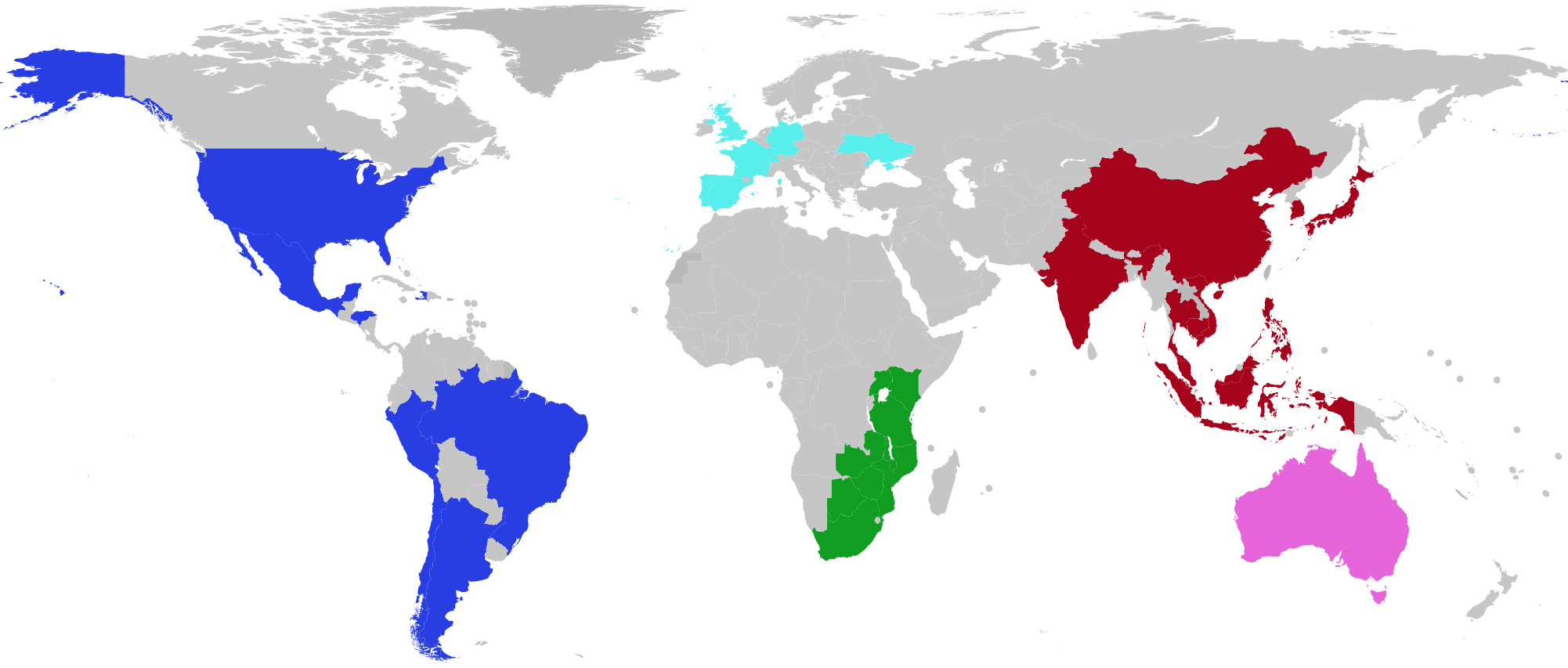
- A total of 422 unique articles and conference abstracts were identified, with 377 excluded during abstract and title screening, and 28 excluded during full-text review (Figure 1)
- During full-text screening, the most common reason for exclusion was resistance testing only in non-INSTI ART classes (non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, and protease inhibitors) before widespread availability of 4-class resistance testing

Figure 1. PRISMA Flowchart Detailing Selection of Publications for Review



- In total, 17 articles met inclusion criteria
- 8 clinical trials and 9 non-interventional studies
- Study participants were included from 40 countries, primarily through multinational trials (n=8) and cohorts (n=1). The most represented countries were South Africa (n=9 studies), Thailand (n=8), Uganda (n=7), and the United States (n=7; Figure 2)

Figure 2. Countries Contributing Data From Selected Studies (N=17)



Outcomes

- Results were reported for 352 RAL-based regimens (122 from 1 clinical trial and 230 from non-interventional studies), 225 EVG-based regimens (94 from 3 clinical trials and 131 from 3 non-interventional studies), 1184 DTG-based regimens (650 from 3 clinical trials and 534 from 6 non-interventional studies), and 101 BIC-based regimens (100 from 1 clinical trial and 1 from a single non-interventional study)
- In studies reporting virologic failure stratified by INSTI regimen (Tables 1 and 2)
 - Failure events were most common on RAL-based regimens (105/313; 33.5%), with 28 (8.9%) experiencing incident INSTI DRMs
 - Virologic failures occurred in 16.1% of DTG-based exposures, with 1.3% of total DTG exposures developing incident DRMs
 - There were relatively few EVG and BIC exposures, but there were 4.1% with documented virologic failure and 1.1% with new INSTI DRMs among EVG regimens, and 2% with documented failure and 0% with emergent DRMs among BIC regimens
- 2 non-interventional studies (Levy 2020, Abo 2019) evaluated outcomes for all INSTI regimens together; 1 non-interventional study (Steegeen 2019) used a denominator of individuals with virologic failure and only reported on incident DRMs

Table 1. INSTI Resistance Reported After Failure on an INSTI-Based Regimen in Clinical Trials (n=8)

	Study	Region/ Country	Population	Age range (y)	INSTI used	Total on INSTI	Treatment failure on INSTI		New INSTI DRMs after failure	
							n	% of total on INSTI (95% CI)	n	% of total on INSTI (95% CI)
1	IMPAACT P1066	Global	ART-experienced, viremic	4 wk-18 y	RAL	122	60	49 (40, 58)	19	16 (10, 23)
2	GS-US-292-0106	Global	ART-experienced, suppressed	6-11	EVG	23	0	0 (0, 15)	0	0 (0, 15)
3	GS-US-292-0106	Global	ART-naïve	12-18	EVG	50	3	6 (1, 17)	0	0 (0, 7)
4	GS-US-236-0112	Global	ART-naïve	12-17	EVG	21	1	5 (0, 24)	0	0 (0, 16)
5	IMPAACT P1093	Global	ART-naïve/ART-experienced	4 wk-17 y	DTG	142	36	25 (18, 33)	8	6 (2, 11)
6	ODYSSEY	Global	ART-naïve (Cohort A)/ART-experienced, viremic (Cohort B)	4 wk-17 y	DTG	350	47	13 (10, 17)	4	1 (0, 3)
7	SMILE PENTA-17	Global	ART-experienced, suppressed	6-18	DTG + DRV/r*	158*	8*	5 (2, 10)	0*	0 (0, 2)
8	GS-US-380-1474	Global	ART-experienced, suppressed	6-17	BIC	100	2	2 (0, 7)	0	0 (0, 4)

*153 took DTG + DRV/r; 5 took EVG + DRV/r; outcomes were not reported separately for DTG- and EVG-based regimens.

Table 2. INSTI Resistance Reported After Failure on an INSTI-Based Regimen in Non-interventional Studies (n=9)

	Study	Region/ Country	Population	Age range (y)	INSTI used	Total on INSTI	Treatment failure on INSTI		New INSTI DRMs after failure	
							n	% of total on INSTI (95% CI)	n	% of total on INSTI (95% CI)
1	Levy 2020	US	ART-experienced	0-24	DTG RAL EVG	78 11 52	72*	51 (43, 60)	0 1 1	0 (0, 5) 9 (0, 41) 2 (0, 10)
2	Abo 2019	UK	ART-naïve/ART-experienced	0-17	DTG RAL EVG	29 21 6	8†	14 (6, 26)	1†	2 (0, 10)
3	Briz 2012	Spain	ART-experienced, viremic	6-18	RAL	19	2‡	11 (1, 33)	0	0 (0, 18)
4	Torres-Fernandez 2022	Spain	ART-naïve/ART-experienced	0-17	RAL EVG DTG BIC	110 73 134 1	19 3 5 0	17 (11, 26) 4 (0, 12) 4 (1, 8) 0 (0, 98)	5 2 0 0	5 (1, 10) 3 (0, 10) 0 (0, 3) 0 (0, 98)
5	Briand 2017	France	ART-naïve/ART-experienced	12-17	DTG	50	17	34 (21, 49)	0	0 (0, 7)
6	Frange 2019	France	ART-naïve/ART-experienced	5-25	DTG	109	22	20 (13, 29)	0	0 (0, 3)
7	Frange 2021	France	ART-naïve/ART-experienced	6-18	DTG	134	43	32 (24, 41)	1	1 (0, 4)
8	Steegeen 2019	South Africa	ART-experienced (third-line)	0-17	RAL	7§	7	100 (59, 100)	2	29 (4, 71)
9	Patten 2020	Global	ART-experienced, viremic	0-17	RAL	62	24¶	39 (27, 52)	4¶	6 (2, 16)

*Aggregated results for all INSTI-based regimens reported for virologic outcomes; 55/70 individuals not suppressed at baseline never achieved suppression or had viral rebound after suppression; 17/35 suppressed at baseline did not maintain suppression through follow-up. †Aggregated results for all INSTI-based regimens reported. ‡2/19 never achieved viral load <400 copies/mL during follow-up (non-responders). §Study looked at samples from individuals currently failing INSTI-based regimens; there were 7 samples from individuals aged <18 years. ¶16/62 never achieved viral load <400 copies/mL during follow-up and 8/62 experienced virologic rebound ≥1000 copies/mL after achieving suppression. ¶4 discontinuations were attributed to virologic failure, immunologic failure, or resistance, with no additional details given.

Table 3. Major INSTI DRMs⁴ Reported After Virologic Failure on an INSTI-Based Regimen

Study	INSTI regimen	Number of failure events with post-failure sequencing	Number of failures with major INSTI DRMs	Major INSTI DRMs reported (n)*
IMPAACT P1066	RAL	50	19	N155H (14), Q148H/K/R (10), G140S/A/C (9)
IMPAACT P1093	DTG	36	8	G118R (5), R263K (1), E92Q (1), T66I (1)
ODYSSEY (Cohort B: ART-experienced)	DTG	22	4	Q148R/K (2), G118R/S (2), R263K (1)
Torres-Fernandez 2022	RAL	15	5	E138A (1), E138K (1), Y140S (1), Y143R (1), S147G (1), Q148H (1), Q148R (2), N155H (1)
	EVG		2	N155H (1)
Frange 2021	DTG	43	1	G118R (1)

*Emergent accessory resistance mutations not included in table.

Conclusions

- Despite growing recommendations for and use of INSTIs among children and adolescents living with HIV, there were relatively few (n=17) published studies looking at treatment-emergent INSTI DRMs
- In this review, regimens containing INSTIs, particularly second-generation INSTIs, were associated with low rates of documented emergent drug resistance after virologic failure
- DTG-based INSTI regimens were the most commonly described ARV in non-interventional settings, reflecting wider real-world use relative to other INSTIs. This is due, in part, to its broader indication for use across HIV treatment groups and multiple dose and formulation options for children
- For the first-generation INSTI, RAL, virologic failure events and resulting documented emergent INSTI DRMs were higher as compared to the second-generation INSTI DTG. While fewer exposures to EVG and BIC were available in this review, similar trends were seen with the first-generation EVG having higher failure events and emergent INSTI DRMs as compared to the second-generation INSTI BIC

Acknowledgments: This study was funded by ViiV Healthcare. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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