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

P035

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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 issues[3]
- 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

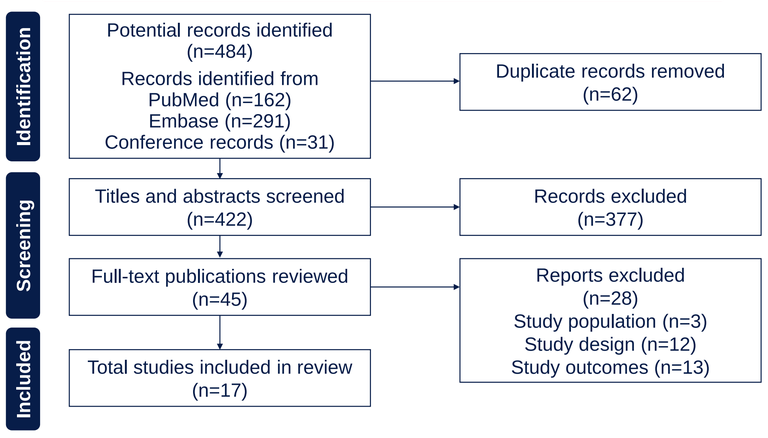
- Eligible studies included
  - Reports on people with HIV aged <18 years who were taking an INSTI-based oral ARV regimen (RAL, EVG, DTG, or BIC) and had
    - Virologic failure outcomes reported
    - HIV-1 genotypic drug resistance sequencing performed for some or all individuals after a virologic 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-naive 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

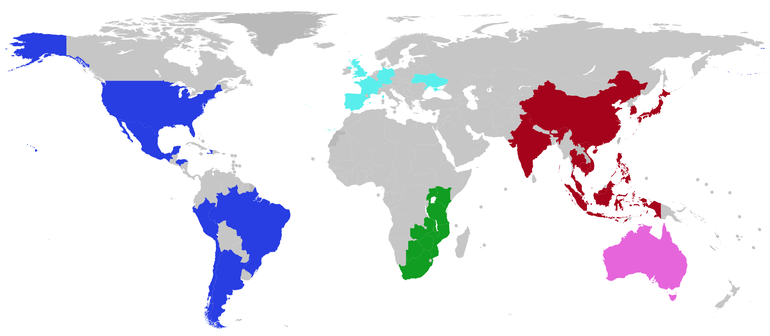
- A total of 422 unique articles and conference abstracts were identified, with 377 excluded during abstract and title screening, and 28 excluded during full-text review (Figure 1)
  - During full-text screening, the most common reason for exclusion was resistance testing only in non-INSTI ART classes (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 (Steegen 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-naive	12-18	EVG	50	3	6 (1, 17)	0	0 (0, 7)
4	GS-US-236-0112	Global	ART-naive	12-17	EVG	21	1	5 (0, 24)	0	0 (0, 16)
5	IMPAACT P1093	Global	ART-naive/ART-experienced	4 wk-17 y	DTG	142	36	25 (18, 33)	8	6 (2, 11)
6	ODYSSEY	Global	ART-naive (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	78	72*	51 (43, 60)	0	0 (0, 5)
					RAL	11			1	9 (0, 41)
					EVG	52			1	2 (0, 10)
2	Abo 2019	UK	ART-naive/ART-experienced	0-17	DTG	29	8†	14 (6, 26)	1†	2 (0, 10)
					RAL	21				
					EVG	6				
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-naive/ART-experienced	0-17	RAL	110	19	17 (11, 26)	5	5 (1, 10)
					EVG	73	3	4 (0, 12)	2	3 (0, 10)
					DTG	134	5	4 (1, 8)	0	0 (0, 3)
					BIC	1	0	0 (0, 98)	0	0 (0, 98)
5	Briand 2017	France	ART-naive/ART-experienced	12-17	DTG	50	17	34 (21, 49)	0	0 (0, 7)
6	Frange 2019	France	ART-naive/ART-experienced	5-25	DTG	109	22	20 (13, 29)	0	0 (0, 3)
7	Frange 2021	France	ART-naive/ART-experienced	6-18	DTG	134	43	32 (24, 41)	1	1 (0, 4)
8	Steegen 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 DRMs[4] 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

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