**Introduction**

- INSTIs are globally preferred first-line antiretroviral agents for treatment in infants, children, and adolescents with HIV.
- First-generation INSTIs, raltegravir (RAL) and elvitegravir (EVR), 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 regarding 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.
- This systematic review summarizes the frequency of documented treatment-emergent 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 CROI-VRH

**Results**

**Included Studies**

- A total of 432 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 (nonsusceptible reverse transcriptase inhibitors, nornucleoside reverse transcriptase inhibitors, and protease inhibitors) before widespread availability of 4-class resistance testing.

**Outcomes**

- Results were reported for 352 RAL-based regimens (122 from 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), 1) Failure events were most common on RAL-based regimens (105/313; 33.5%), with 28 (8.9%) experiencing INSTI failures; 2) Virologic failures occurred in 16.1% of DTG-based exposures, with 3.3% of DTG exposures developing incident DRMs; 3) There were relatively few RAL- and EVG-based exposures, but there were 4.1% with documented DRM failure and 1.1% with new INSTI DRMs among EVG regimens, and 2% with documented failure and 0% with emergent DRMs among BIC regimens; 4) There were 2 non-interventional studies (Levy 2020, Abc 2019) evaluated outcomes for all INSTI regimens together; 1 non-interventional study (Steegen 2019) used a denominator of individuals with virologic failure only and reported on INSTI regimens.

**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.
- This systematic review, including ATRI, particularly second-generation INSTIs, were associated with low rates of documented emergent drug resistance after virologic failure.