Emerging integrase resistance in the Perinatal Virtual Clinic: the need for protease inhibitors

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BACKGROUND

The perinatal virtual clinic (PVC): a monthly multidisciplinary forum which reviews complex management decisions for children and adolescents living with HIV (CALWHIV) referred from high (HIC) and low/middle income countries (L/MIC). The PVC supports decision making, maintenance of expertise and professional education.

We investigated the prevalence of emergent integrase drug resistance mutations (INSTI-DRMs) necessitating protease inhibitor (PI) based regimens.

METHODS

- Review of PVC referrals between October 2018-September 2023
- Demographic data included age, sex, country of residence
- Clinical data included: comorbidities, antiretroviral therapy (ART) history, HIV viral load (VL) and CD4 count
- Resistance mutations were interpreted using the Stanford HIV Drug Resistance database HIV Drug Resistance Database (stanford.edu) and CALWHIV with emergent INSTI-DRMs are described

PARTICIPANTS

- 341 CALWHIV discussed; 51 (15%) from L/MIC
- 106/341 (31%) referred for virological failure
- 96/106 (91%) resistance sequences available
- 54/96 (56%) prior INSTI based ART
- **17/96 (18%) INSTI-DRMs, 17/54 (31%) if prior INSTI-ART**
- 11/17 (65%) from L/MIC. By region; Africa (8), Americas (2), Europe (5) and Western Pacific (2)
- 6/17 had current AIDS diagnoses
- 4/17 receiving antimycobacterial therapy
- 12/17 (74%) were referred during 2022/23

341 CALWHIV → 106 (31%) VF → 96 (91%) Sequenced → 17 (18%) INSTI DRMs

ADDITIONAL INFORMATION

- **Author contact Information**: caroline.foster5@nhs.net
- **Acknowledgements**: We would like to acknowledge and thank all our colleagues who kindly submitted cases to the PVC and joined the monthly meeting to offer their advice and expertise.

The clinical cases of 96 children & adolescents with perinatal HIV with virological failure & resistance sequences available were reviewed. 18% had integrase drug resistance mutations; median age 11, weight 24kg, 65% L/MIC.

Global access to child-friendly formulations of boosted DRV, TXF and novel agents is essential.

RESULTS

- Of 17 CALWHIV with INSTI-DRMs: median (IQR) age 11 (6-14) years, weight 24 (17-49) kg, CD4 count 430 (77-805) cells/ul, and VL 35,000 (2380-132000) c/ml.
- 2/17 failed first line therapy with dolutegravir (case 1 and 2)
- 15/17 were on second/subsequent ART (median 2 [IQR 2-3] prior regimens) comprising nucleoside reverse transcriptase inhibitors (NRTI) with:
  - dolutegravir (DTG) (7)
  - raltegravir (4)
  - dolutegravir and darunavir/ritonavir (DRV/r) (4)
- Cumulative resistance by number of ART classes was 1 (1), 2 (5), 3 (7), 4 (4) with DRMs described in Table 1

PVC recommendations included:
- tenofovir (TXF) + lamivudine (3TC)/emtricitabine (FTC) (split adult tablets in 5)
- DRV/r (17): twice daily (BD) (6), the latter with BD DTG, novel agents sought (2).

Table 1 Cumulative DRMS by class, by number per patient and by frequency

DRM by class (n/17)	INSTI[1] (17)		NRTI (15)		NNRTI[2] (12)		PI (6)[3]	
DRMs per patient: 1/2/3/4+	10/3/1/3		4/0/3/8		3/1/5/3		0/1/3/2	
Frequency of common major DRMs (n/17)	E138K	5	M184VI	15	K103N	5	M46I	5
	G140SA	5	M184VI only	4	V106MI	4	**I47V**	1
	Y143CR	5	M184VI + TAMs	9	E138KQ	2	**I50V**L	2
	Q148HR	5	M184VI + other	2	Y181C	3	**I54LM**V	3
	N155H	6			G190A	4	**L76V**	1
	R263K	4			M230L	2	**I84V**	1

[1]Interpretation: high-level DTG-R (5), intermediate (5), low/other INSTI-DRM (7).
[2]non-nucleoside reverse transcriptase inhibitor; NNRTI. [3]DRV-associated DRMs in **bold**, all 6 having ≥ 1 major DRV-DRM.

Case 1

13 year old girl with first line DTG, 3TC, ABC failure after 5 years with poor adherence and prior low level viraemia.

INSTI Major Mutations:	E138K · S147G · Q148R · N155H
INSTI Accessory Mutations:	None
IN Other Mutations:	None

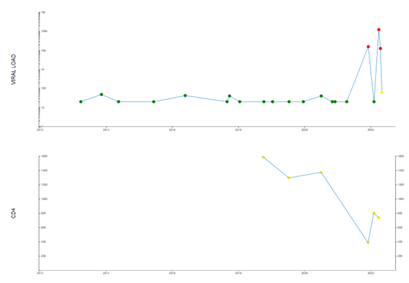
Integrase Strand Transfer Inhibitors

bictegravir (BIC)	High-Level Resistance
cabotegravir (CAB)	High-Level Resistance
dolutegravir (DTG)	High-Level Resistance
elvitegravir (EVG)	High-Level Resistance
raltegravir (RAL)	High-Level Resistance

NRTI Mutations:	M184V
NNRTI Mutations:	V106I · E138K
RT Other Mutations:	None

Case 2

15 year old girl suppressed on nevirapine, ABC, 3TC for 11 years simplified to a single tablet regime of DTG/ABC/3TC. 4 years later she experienced virological failure with an R263RK following poor adherence.



Drug resistance interpretation: IN

INSTI Major Mutations:	R263RK
INSTI Accessory Mutations:	None
IN Other Mutations:	None

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Intermediate Resistance
cabotegravir (CAB)	Intermediate Resistance
dolutegravir (DTG)	Intermediate Resistance
elvitegravir (EVG)	Intermediate Resistance
raltegravir (RAL)	Low-Level Resistance

CONCLUSIONS

- INSTI resistance is emerging in CALWHIV, most commonly in highly treatment experienced children from L/MIC.
- There continues to be a global need for access to paediatric DRV/r, TXF and novel classes, including formulations for children <35kg.

PVC referrals: anonymised cases can be submitted by completing the referral slide decks Chiva | Perinatal Virtual Clinic and emailing caroline.foster5@nhs.net

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