HIV Drug Resistance in Women Randomized to DTG vs EFV or TDF vs TAF in Pregnancy

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BACKGROUND

Virologic failure and HIV drug resistance (**HIVDR**) in pregnant and postpartum women with dolutegravir (**DTG**)-containing antiretroviral treatment (**ART**) are not well described.

We compared virologic failure and HIVDR by study arm in IMPAACT 2010, a randomized trial of three ART regimens started in pregnancy.

METHODS

Study Participants & Design

- Enrolled 643 ART-naïve women living with HIV
  - Prior PMTCT, PrEP, or ART for ≤14 days during pregnancy (before screening) were permitted
- Enrolled between 14-28 weeks gestation
- Followed through 50 weeks postpartum
- Clinical sites in 9 countries (88% African)
- Participants randomized to:
  - DTG+emtricitabine (**FTC**)/tenofovir alafenamide (**TAF**)
  - DTG+FTC/tenofovir disoproxil fumarate (**TDF**)
  - Efavirenz (**EFV**)/FTC/TDF
- HIV RNA load at week 0, every 4 weeks antepartum, delivery & 14, 28, 36, and 50 weeks postpartum
- Virologic failure defined as HIV RNA ≥200 copies/mL for 2 consecutive tests at or after 24 study weeks

Laboratory Methods

- Sanger sequencing of specimen from confirmed virologic failure visit (and paired study entry specimen) to look for HIVDR
  - HIV *pol* encoding protease, reverse transcriptase, and integrase
  - Interpreted using Stanford HIV Database

Statistical & Descriptive Analyses

- Performed pairwise comparisons of rates of virologic failure and HIVDR at failure between treatment arms using the Wald test with 95% confidence intervals
- Described HIVDR mutations at study entry/baseline & additional mutations at virologic failure

- ➢ Women initiating ART during pregnancy who subsequently had virologic failure were found to have a high rate (15/35; 45%) of pre-ART HIV drug resistance – these mutations may have contributed to treatment failure.
- ➢ Women in the EFV arm compared to the DTG arms had both more frequent virologic failure and selection of new drug resistance mutations at failure.

RESULTS

- Women in both DTG arms had significantly lower rates of virologic failure and of HIVDR at failure compared to the EFV arm (**Table 1**)
- Sanger sequencing was successful on 35/42 (83%) specimens from women with virologic failure
  - HIVDR in 19/35 (54%) at virologic failure (**Table 2**)
  - Pre-ART HIVDR in 15/19 (79%) women with resistance at virologic failure
    - 10/13 randomized to EFV
    - 5/6 randomized to DTG -- 1 in TAF & 4 in TDF arms
- New HIVDR mutations detected in 9/19 (47%) women
  - EFV arm: 7/13 (54%) new EFV-associated mutations (K103N, V106M, or P225H)
    - 2/7 also had additional NRTI-associated mutations (K65R, Y115F, &/or M184V)
  - DTG arms: 2/6 (33%) women
    - 1st (in TDF arm) had N155H major & L74I, S147G, & S230R accessory integrase mutations
    - 2nd (in TAF arm) had K103N, a NNRTI major mutation

TABLE 1. Comparison of Virologic Failure and HIVDR Rates at Failure Between Treatment Arms

	DTG+FTC/TAF n/N (%)	DTG+FTC/TDF n/N (%)	EFV/FTC/TDF n/N (%)	Comparison	Difference in Proportions (95% CI)	P-Value
Proportion of Women with Virologic Failure	9/217 (4.1%)	11/215 (5.1%)		DTG+FTC/TAF vs DTG+FTC/TDF	-1.0% (-4.9%, 3.0%)	0.63
		11/215 (5.1%)	22/211 (10.4%)	DTG+FTC/TDF vs EFV/FTC/TDF	-5.3% (-10.4%, -0.2%)	0.040
	9/217 (4.1%)		22/211 (10.4%)	DTG+FTC/TAF vs EFV/FTC/TDF	-6.3% (-11.2%, -1.4%)	0.012
Proportion of Women with HIV Drug Resistance at Virologic Failure	2/217 (0.9%)	4/215 (1.9%)		DTG+FTC/TAF vs DTG+FTC/TDF	-0.9% (-3.1%, 1.3%)	0.40
		4/215 (1.9%)	13/211 (6.2%)	DTG+FTC/TDF vs EFV/FTC/TDF	-4.3% (-8.0%, -0.6%)	0.023
	2/218 (0.9%)		13/211 (6.2%)	DTG+FTC/TAF vs EFV/FTC/TDF	-5.2% (-8.7%, -1.8%)	0.0032

TABLE 2. HIVDR Mutations at Virologic Failure

Treatment Arm	Participant Count	HIVDR Mutation(s) at Virologic Failure
DTG + FTC/TAF	1	**K103N**
	2	V106VM
DTG + FTC/TDF	1	M184V, T215Y, **L74I, S147GS, N155HN, S230RS,** K103KN, Y181C
	2	A98G
	3	M41L, K103N, V106M
	4	M46ML
EFV/ FTC/TDF	1	**K103N**
	2	**K65KR, M184V, Y115YF, K103N, V108I, N348I**
	3	**K103N**
	4	A98G, K101KE, Y181YC, G190GA
	5	K103N
	6	**M184MV,** K103N, **P225PH**
	7	K103N
	8	**K103N,** P225H
	9	**V106M, N348NI,** E138EA
	10	E138G
	11	Q58E
	12	A98G, **K103N**
	13	A98G

Unbolded mutations were detected at study entry & virologic failure
Bolded mutations are "NEW" at virologic failure (i.e., selected mutations)

CONCLUSIONS

- Women randomized to EFV arm compared to DTG arms were more likely to experience virologic failure (10.4% vs. 4.6% failure rate)
- Women who experienced virologic failure had a high prevalence of pre-ART HIVDR detected, which may have contributed to virologic failure
- Women in the EFV arm had more frequent selection of new drug resistance mutations at failure compared to the DTG arms
- Notably, new DTG mutations were detected in 1 of 20 women with failure despite short treatment period

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