U.S. HIV Drug Resistance: Implications for Current and Future PrEP Regimens

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Background

- HIV pre-exposure prophylaxis (PrEP) is a critical HIV prevention tool, but its effectiveness might be diminished by drug resistant virus; M184V and K65R mutations have been associated with PrEP failure.
- Analysis of drug resistance mutations (DRMs) among persons with diagnosed HIV (PWH) with no evidence of viral suppression provides insight into resistance relevant to current and investigational PrEP drugs.
- HIV sequence data from routine drug resistance tests generated by conventional bulk sequencing methods are reported to the U.S. National HIV Surveillance System (NHSS) by state and local health departments.
- We used NHSS data to describe the prevalence of drug resistance mutations (DRMs) to approved (TDF/TAF + FTC) and investigational (cabotegravir, CAB) PrEP drugs.

Methods

- We analyzed reverse transcriptase (RT) and integrase (IN) sequences reported to NHSS by June 2019 for all persons with HIV-1 diagnosed by December 2018 who had an unsuppressed viral load (<200 copies/mL) or no viral load reported in 2018.
- DRMs were detected via the SIERRA web service[1] and defined by the CDC HIV-1 surveillance mutation list[2].
- For persons with multiple sequences reported, we combined DRMs from all sequences and reported DRM prevalence using total HIV cases (not total sequences) as the denominator.
- We reported DRM prevalence for nRTI and INSTI drug classes overall, and reported DRM prevalence for TDF/TAF+FTC and CAB using the following mutations:

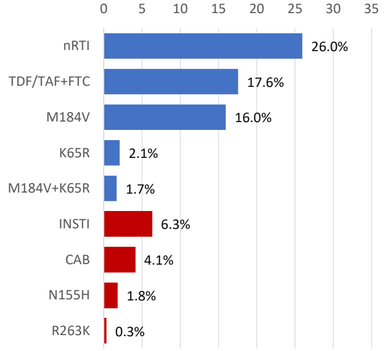
TDF/TAF + FTC	K65R, T69i, K70E, Q151M, M184V
CAB	T66K, G118R, E138A/K/T, G140A/C/S, Q148H/K/R, N155H, R263K

- We estimated the contribution of transmitted DRMs by analyzing the subset of sequences generated ≤3 months after HIV diagnosis from persons with newly diagnosed HIV and no evidence of prior ART use.

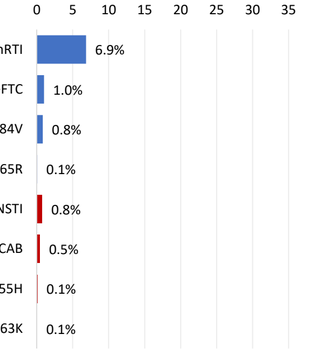
Results

Drug resistance mutations to current and investigational PrEP regimens were common among persons with diagnosed HIV with no evidence of viral suppression.

DRM prevalence among PWH with ≥1 RT (N=232,429) or IN (N=80,669) sequence without evidence of viral suppression in 2018



Transmitted DRM prevalence among PWH with an eligible RT (N=70,374) and/or IN (N=9,532) sequence and without evidence of viral suppression in 2018



DRM prevalence among PWH without evidence of viral suppression in 2018, by select characteristics (Total PWH with ≥1 RT=232,429; ≥1 IN=80,669)

	Total PWH		TDF/TAF + FTC			M184V			K65R			CAB		
Characteristics	**≥1 RT**	**≥1 IN**	**N**	**(%)**	**PR (95% CI)**	**N**	**(%)**	**PR(95% CI)**	**N**	**(%)**	**PR(95% CI)**	**N**	**(%)**	**PR(95% CI)**
Total	**232,429**	**80,669**	**40,809**	**(17.6)**	**—**	**37,074**	**(16.0)**	**—**	**4,838**	**(2.1)**	**—**	**3,308**	**(4.1)**	**—**
Sex at birth														
Male	178,382	63,084	30,106	(16.9)	Referent	27,251	(15.3)	Referent	3,597	(2.0)	Referent	2,435	(3.9)	Referent
Female	54,047	17,585	10,703	(19.8)	1.17 (1.15,1.20)	9,823	(18.2)	1.19 (1.17,1.21)	1,241	(2.3)	1.14 (1.07,1.21)	873	(5.0)	1.29 (1.19,1.39)
Race/ethnicity														
Black/African American	100,264	34,709	18,415	(18.4)	1.18 (1.15, 1.21)	16,682	(16.6)	1.18 (1.15,1.20)	2,233	(2.2)	1.24 (1.15,1.34)	1,547	(4.5)	1.30 (1.19,1.42)
Hispanic/Latino	61,482	20,078	10,777	(17.5)	1.12 (1.09, 1.15)	9,874	(16.1)	1.13 (1.10,1.17)	1,242	(2.0)	1.13 (1.04,1.23)	826	(4.1)	1.20 (1.08,1.32)
White	52,684	19,756	8,219	(15.6)	Referent	7,460	(14.2)	Referent	944	(1.8)	Referent	678	(3.4)	Referent
Other	17,999	6,126	3,398	(18.9)	1.21 (1.17,1.25)	3,058	(17.0)	1.20 (1.15,1.25)	419	(2.3)	1.30 (1.16,1.46)	257	(4.2)	1.22 (1.06,1.41)
Transmission category														
MSM	131,352	47,886	19,732	(15.0)	Referent	17,669	(13.5)	Referent	2,449	(1.9)	Referent	1,674	(3.5)	Referent
IDU	24,551	7,687	5,684	(23.2)	1.54 (1.50,1.58)	5,306	(21.6)	1.61 (1.56,1.65)	616	(2.5)	1.35 (1.23,1.47)	404	(5.3)	1.50 (1.35,1.67)
MSM and IDU	14,531	5,148	2,954	(20.3)	1.35 (1.31,1.40)	2,714	(18.7)	1.39 (1.34,1.44)	325	(2.2)	1.20 (1.07,1.36)	216	(4.2)	1.20 (1.04,1.38)
Heterosexual contact	57,570	18,481	10,722	(18.6)	1.24 (1.21,1.27)	9,774	(17.0)	1.26 (1.23,1.29)	1,366	(2.4)	1.27 (1.19,1.36)	903	(4.9)	1.40 (1.29,1.51)
Other	4,426	1,468	1,717	(38.8)	2.58 (2.48,2.69)	1,611	(36.4)	2.71 (2.60,2.82)	83	(1.9)	1.00 (0.81,1.25)	110	(7.5)	2.14 (1.78,2.58)

Abbreviations: ART=antiretroviral therapy; FTC=emtricitabine; IDU=injection drug use; INSTI=integrase strand transfer inhibitor; MSM=male-to-male sexual contact; nRTI=nucleoside reverse transcriptase inhibitor; PR=prevalence ratio; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

Discussion

- DRM prevalence among PWH without evidence of recent viral suppression represents potential risk for people on PrEP who are exposed to HIV.
- We document an established reservoir of M184V and low prevalence of K65R.
  - M184V reduces susceptibility to FTC, but its impact on PrEP efficacy is not clear; it also reduces transmission fitness and increases susceptibility to tenofovir.
- Prevalence of DRMs predicted to affect CAB (>4%) reflects cross-resistance with other current INSTIs.
- Transmitted DRM prevalence is much lower than overall DRM prevalence for mutations affecting TDF/TAF+FTC and CAB.
  - This likely reflects the impact of these DRMs on viral fitness, which can limit their transmission and detection.
  - This suggests acquired drug resistance is a larger contributor to overall DRM prevalence and a key source of exposure to drug-resistant viruses for persons on PrEP.
- DRM prevalence varies significantly by sex at birth, race/ethnicity, and transmission category, and is notably higher among persons with a transmission category of IDU or "other".
- Population monitoring is essential for identifying threats to PrEP effectiveness in an era of expanding use.

Limitations

- NHSS includes limited information about ART use or the reason for ordering a drug resistance test which limits insight into the clinical course of individual patients.
- HIV sequence results from conventional bulk sequencing underestimate DRM prevalence.

References

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2. Wheeler WH, Ziebell RA, Zabina, H, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.–2006. AIDS 2010, 24:1203–1212.

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