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Acquisition of TDF-Susceptible HIV Despite High Level Adherence to Daily TDF/FTC PrEP as Measured by Dried Blood Spot (DBS) and Segmental Hair Analysis

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Background

- Pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir (TFV) disoproxil fumarate (FTC/TDF) is highly protective against HIV infection
- Five prior published case reports of HIV acquisition despite high level adherence to PrEP confirmed by drug level testing
- In four of these five prior published cases, the virus had an M184V mutation in reverse transcriptase, conferring resistance to FTC
- Three of these four viruses also had resistance mutations causing reduced susceptibility to TDF (K70R or K65R)

Case

- A 21 year-old Latino man who has sex with men, cis women and trans women partners, initiated oral daily PrEP at a municipal STD clinic. At PrEP enrollment, he had a negative rapid HIV Ab test and HIV RNA via a standard HIV pooling algorithm.
- Patient (pt) was prescribed 30 days of FTC/TDF with 2 refills; instructed to return every 3 months for follow-up. Pt HIV-negative (by both rapid Ab and pooled HIV RNA) at 3, 6 and 10 months after PrEP initiation. At month 12, he was diagnosed with and treated for urethral gonorrhea (GC); all other STD testing was negative.
- At his month 13 PrEP visit, pt reported recent methamphetamine use and condomless receptive anal sex with a male partner, both for 1st time in > 1 year. Reported excellent PrEP adherence. Rapid HIV Ab negative. PrEP prescription renewed. 5 days after this visit, HIV RNA returned at 559 copies/mL.
- Pt promptly notified of result, linked to care and immediately initiated on once daily antiretroviral treatment (ART)) with FTC/TAF, dolutegravir, darunavir and ritonavir. At that visit, HIV RNA 1544 copies/ml; HIV Ag/Ab and confirmatory HIV 1/2 differentiation antibody positive (Figure 1).
- Pt participated in partner services (PS); one of four of his named partners was known to be living with HIV and not in care (NIC)

Methods and Results

METHODS

- HIV genotyping/ phenotyping conducted by Monogram Biosciences® from plasma from day of first positive HIV RNA (Phenosense GT™) and ART initiation visit (GenoSure MG®)
- Hair (collected on day of ART initiation) and dried blood spots (DBS) (collected 2 days after) analyzed for PrEP or PrEP drug metabolite levels using liquid chromatography/tandem mass spectrometry (LC-MS/MS)
- Stored plasma from the 10-month visit tested for FTC/TFV levels via LC-MS/MS and for HIV RNA using a integrase single-copy assay (iSCA)
- Single-genome sequencing (SGS) was performed on proviral DNA obtained from PBMCs collected 7 days after ART initiation to look for minority resistance mutations and estimate duration of infection

RESULTS of DRUG LEVEL TESTING (Also see Figures 1 and 2)

Specimen	Collection date	Results (See Figures 1 and 2)	Interpretation
Plasma	12 weeks prior to HIV diagnosis	TFV = 188.2 ng/mL FTC = 870.5 ng/mL	Recent dosing preceding visit
Segments of cut hair	Day of ART initiation	TFV levels all > 0.038 ng/mg	Consistently high PrEP adherence over preceding 6 months
Dried Blood Spots	2 days after ART initiation	TFV-DP = 1012 fmol/punch FTC-TP = 0/266 fmol/punch	≥ 4 doses/wk on average over preceding 6 weeks

RESULTS of DRUG RESISTANCE TESTING

- GenoSure® MG: RT mutations L74V, L100I, **M184V,** and K103N
- Phenosense GT™: Susceptibility to TDF (IC_{50} 0.377; fold change 0.39) and resistance to FTC
- SGS: Consistent with GenoSure® MG with L74V, L100I, **M184V**, K103N; K65R and K70E not detected
- Genetic diversity of the proviral population (excluding APOBEC-3G induced G>A hypermutants) was 0.001, suggestive of acute infection & transmission within the previous few weeks

Figure 1. Timeline of events

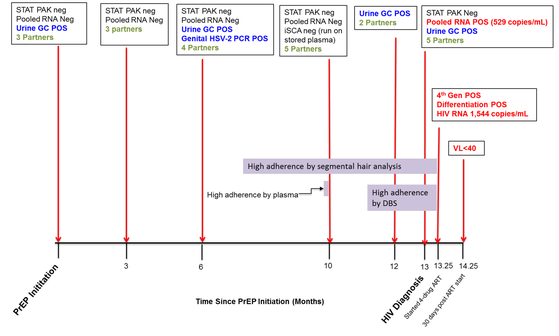
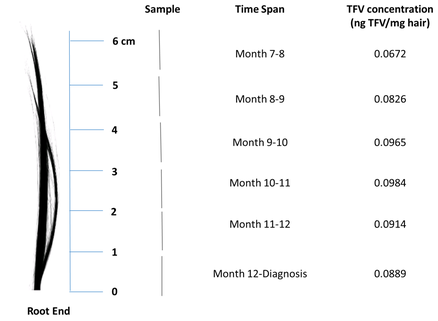


Figure 2. Segmental hair analysis



OUTCOMES of PARTNER SERVICES

- NIC named partner re-linked to care
- NIC partner's VL at re-linkage visit: 15,000 copies/ml
- Partner's HIV genotype (mandatorily reported to surveillance) had the same RT mutations as the case patient

Summary

- We report the 6th case of HIV seroconversion despite high adherence to daily FTC/TDF-based PrEP
- This is the 3rd case in which transmitted viral strain genotypically susceptible to TDF
- Thorough evaluation including: Drug level testing from DBS, hair and plasma; genotypic and phenotypic resistance and SGS; highly sensitive HIV testing at PrEP initiation and throughout PrEP use; identification of likely transmission partner during PS, confirming resistance was transmitted and not acquired on PrEP

Implications

- HIV acquisition can occur on FTC/TDF-based PrEP in the setting of FTC-resistance, even when adherence is high and the virus is susceptible to TDF
- Individuals taking PrEP and health care providers should be aware that PrEP failure is very rare, but not impossible, even with consistent adherence

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