HIV-1 Resistance Outcomes in Seroconverters from the MTN 003 (VOICE) Study

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Objective

- The emergence of drug resistance is a major concern when using antiretroviral agents for HIV prevention.
- We aimed to assess the frequency of HIV-1 drug resistance in women from MTN-003 (VOICE) who acquire HIV infection while using study product by standard genotype analysis

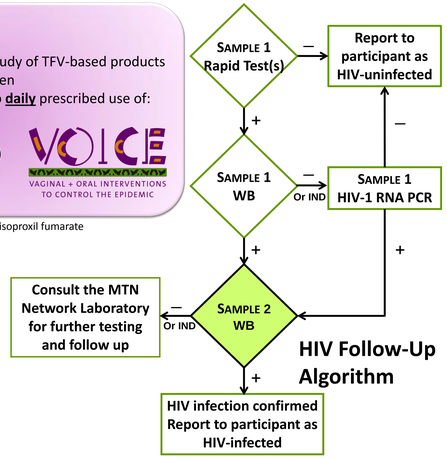
Study Design

MTN 003

- Safety and effectiveness study of TFV-based products for HIV prevention in women
- Participants randomized to **daily** prescribed use of:
  - TFV 1% gel (n=1007)
  - Oral TDF (n=1007)
  - Oral TDF-FTC (n=1003)
  - Oral placebo (n=1009)
  - Gel placebo (n=1003)

VOICE — VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

TFV = tenofovir; TDF = tenofovir disoproxil fumarate



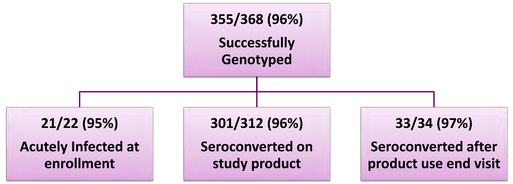
SAMPLE 2
Plasma collected a median of 13d (IQR 16d) after detection of seroconversion and cessation of study product

HIV-1 Genotyping

- Performed on SAMPLE 2 from all seroconverters with plasma HIV-1 RNA ≥ 200 copies/ml
- ViroSeq 2.0 Genotyping Method (Celera, Alameda, CA)
- Sequenced HIV-1 *pol* region (codons 1-99 of *pro* & codons 1-350 of *rt*)
- All sequences were manually edited and nucleotide positions with multiple peaks present at >20% above background were considered mixtures.
- Resistance mutations were identified using the Stanford Calibrated Population Resistance Tool (http://hivdb.stanford.edu/).

Objective

Genotyping Success



No result (n = 13) due to:
- No stored plasma (n = 1)
- Insufficient copies of HIV-1 RNA for extraction (n = 11)
- PCR amplification failure (n = 1)

NNRTI Resistance Unrelated to Product (Transmitted)

PID	Arm	Site	Major NNRTI Mutations
1	Gel Placebo	Chatsworth	V106M/V
2	Gel Placebo	Umkomaas	A98G, K101E, E138K, Y181C
3	Oral Placebo	Isipingo	K103K/N
4	Oral Placebo	Tongaat	K103N, V106I
5	Oral Placebo	Overport	K101E, E138K
6	TFV Gel	Overport	K103N
7	TFV Gel	eThekwini	K103N
8	TDF-FTC	Tongaat	K103K/N, V106M/V, Y181C/Y
9	TDF-FTC	Tongaat	K103N

34 (9.6%) participants had additional RT mutations from the 2009 World Health Organization transmitted drug resistance list, including A62V, D67N, T69N, K70R, V90I, A98G, K101E, V106I, E138A/K, V179 E/D/T, T215A and H221Y.

Selection of Resistance by Study Arm

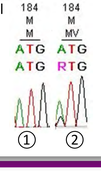
REVERSE TRANSCRIPTASE MUTATION CONFERRING RESISTANCE	TDF (n = 70)	TDF-FTC (n = 71)	Oral Placebo (n = 69)	TFV Gel (n = 71)	Gel Placebo (n = 74)
K65R	0	0	0	0	0
K70E	0	0	0	0	0
M184V – Overall	0	3/71 (4.2%)	0	0	0
Retrospectively found to be HIV-1 infected at enrollment	0	**2/9 (22%)**	0	0	0
Acquired HIV-1 after enrollment	0	**1/55 (1.8%)**	0	0	0
Acquired HIV-1 after product use end visit	0	0	0	0	0
M184I – Overall	0	1/71 (1.4%)	0	0	0
Retrospectively found to be HIV-1 infected at enrollment	0	**1/9 (11%)**	0	0	0
Acquired HIV-1 after enrollment	0	0	0	0	0
Acquired HIV-1 after product use end visit	0	0	0	0	0

3 CASES OF M184I/V (Lamivudine and Emtricitabine Resistance) Selected by TDF-FTC

CASE 1
INFECTED AT ENROLLMENT

① Enrollment visit – mid Sept
- HIV RNA 1,610,381 cp/ml
- Genotype: WT

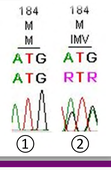
② Follow-up: mid-Nov
- 26d on oral TDF-FTC
- HIV RNA 48,200 cp/ml
- Genotype: M184M/V



CASE 2
INFECTED AT ENROLLMENT

① Enrollment visit – early Aug
- HIV RNA 49,818 cp/ml
- Genotype: Q58E

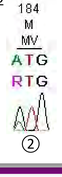
② Follow-up: mid-Sep
- 29d on oral TDF-FTC
- HIV RNA 68,400 cp/ml
- Genotype: M184M/I/V and Q58E



CASE 3
ACQUIRED HIV AFTER ENROLLMENT

① Enrollment visit – mid-July 2010
- Negative serology
- Undetectable HIV RNA

② Follow-up: Jun 2011
- 309d on oral TDF-FTC
- HIV RNA 33,170 cp/ml
- Genotype: M184M/V



Summary

Of 355 seroconverters genotyped in VOICE (212 on active product arms):
- No resistance to oral tenofovir or tenofovir gel
- 9 cases (2.5%) of transmitted resistance with major NNRTI mutations
- 3 cases (0.8%) of FTC resistance ; all from TDF-FTC arm (3/71; 4.2%)

Resistance in PrEP Trials

Study	Infected Post Enrollment		# Resistant to TDF or FTC	Acutely Infected at Enrollment		# Resistant to TDF or FTC
	PLB	Active		PLB	Active	
Bangkok TFV [1]	33	15	0	2	0	0
CAPRISA 004 [2]	0	35	0	0	0	-
Fem-PrEP [3]	35	33	1 PLB (M184V) 4 TDF-FTC (M184I/V)	4	1	0
iPrEX [4]	64	36	0	8	2	1 PLB (M184V) 2 FTC-TDF (M184I/V)
Partners PrEP [5]	51	27	0	6	8	1 TDF (K65R) 1 TDF-FTC (M184V)
TDF2 [6]	24	9	1 PLB (K65R <1%)	2	1	1 TDF-FTC (K65R/M184V)
VOICE	**128**	**173**	**1 TDF-FTC (M184V)**	**4**	**18**	**2 (M184I/V)**
TOTAL	**7/663 (1%)** **Active arms only: 5/328 (1.5%)**			**8/56 (14%)** **Active arms only: 7/30 (22%)**		

[1] Choopanya *et al.* 2013 *Lancet*; 381: 2083. [2] Abdool Karim *et al.* 2010 *Science*; 329:1168. [3] van Damme *et al.* 2012 *NEJM*; 367:411. [4] Grant *et al.* 2010 *NEJM*; 363:2587. [5] Baeten *et al.* 2012 *NEJM*; 367:399. [6] Thigpen *et al.* 2012 *NEJM*; 367:423.

Conclusions

- Acquired resistance to PrEP ARVs is rare
- Transmitted NNRTI resistance (2.5%) more likely than acquired resistance to product (3/212; 1.4%)
- Better point-of-care tests are needed to exclude acutely infected individuals from prevention trials
- Limitations
  - Low product use in VOICE may underestimate resistance selection
  - Evaluation of low frequency resistance (<20% of population) is needed

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