Objective Measures of Adherence in VOICE

Jeanne Marrazzo MD MPH

MTN Annual Meeting 2011

Overview

- Definition of biomarkers
- Rationale for biomarkers in VOICE
  - iPrEx, CAPRISA 004, MTN 001
- Current status
- DISCUSSION

- A reminder: there will be a discussion on adherence and PrEP trials on Tuesday morning (Connie Celum, MD)

VOICE Adherence Objectives

- To evaluate adherence to daily regimens of vaginal gel (tenofovir and placebo) vs. oral tablets (TDF, FTC/TDF, and placebos) used to prevent HIV infection
- To evaluate whether sexual activity, condom use, and intravaginal practices change over time in women who use either daily vaginal gel or daily oral tablets

MTN
microbicide trials network

Biomarker

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 69 NUMBER 3 MARCH 2001

COMMENTARY

Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework

Biomarkers Definitions Working Group *Bethesda, Md*

MTN microbicide trials network

Biomarker

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 69 NUMBER 3 MARCH 2001

COMMENTARY

Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework

Biomarkers Definitions Working Group *Bethesda, Md*

MTN microbicide trials network

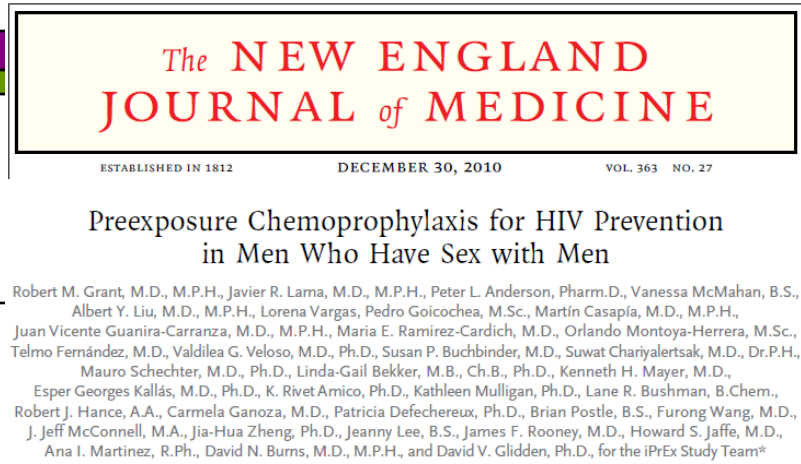
Biomarkers & Adherence: Why?

- In 2010, two PrEP studies demonstrated efficacy of vaginal tenofovir gel (CAPRISA 004) & oral TDF/FTC (iPrEx) in preventing HIV acquisition

However…

- Adherence data yielded some surprising findings in both studies, and emphasized that accurate measures of study product adherence are especially critical in prevention studies!

The iPrEx Study



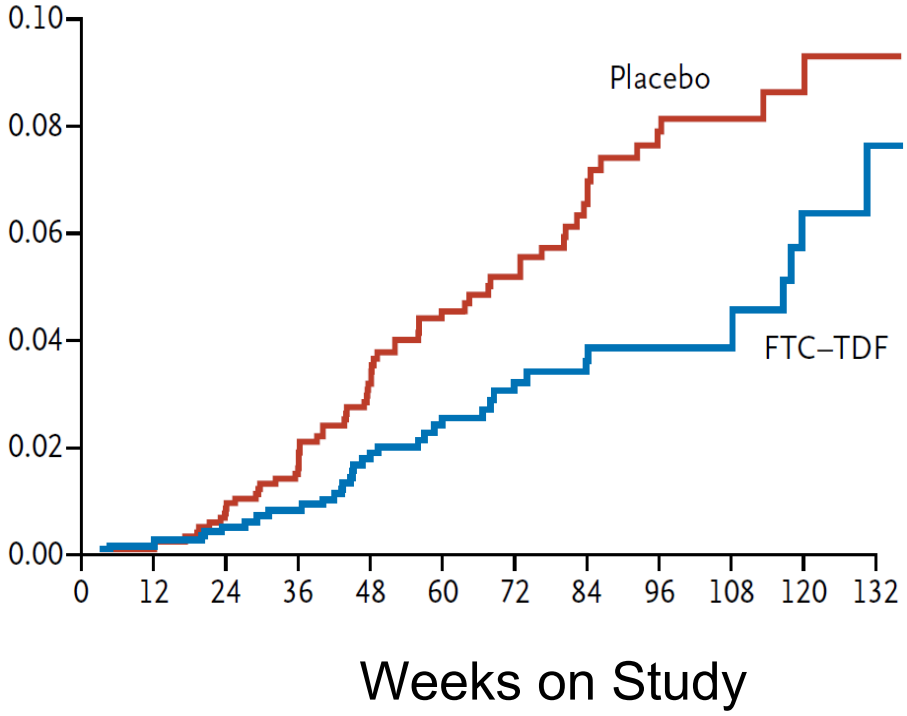
- 2499 young high-risk MSM
  - 50% <25 yrs
  - Median 18 partners in 12 wks prior to enrollment
  - 60% with unprotected receptive anal sex in prior 12 wks
- South Africa, North America, South America
- Randomized 1:1 daily oral PrEP
- FTC/TDF vs Placebo
- Followed on drug for:
  - HIV seroconversion
  - Adverse events (renal & liver)
  - Metabolic effects (bone, fat, lipids)
  - HBV flares among HBsAg+
  - Risk behavior & STIs
  - Adherence

iPrEX Efficacy

100 infections after randomization

36 on FTC/TDF

64 on placebo



Efficacy estimate (mITT):
44% reduction in HIV acquisition
(95% CI 15%-63%)

However…

- Based on self report, drug dispensation logs, monthly pill counts, & drug levels (N=79), adherence was not high
  - Limits interpretation of safety & resistance data
  - Emphasizes need for further study in other populations & need for strong adherence counseling with accurate measurement
- Substantial over-reporting of adherence
  - Self reported adherence increased while drug dispensation decreased from 99%→91% from enrollment to 12 mos
  - May support use of objective measures (MEMS caps or gel applicator bag)

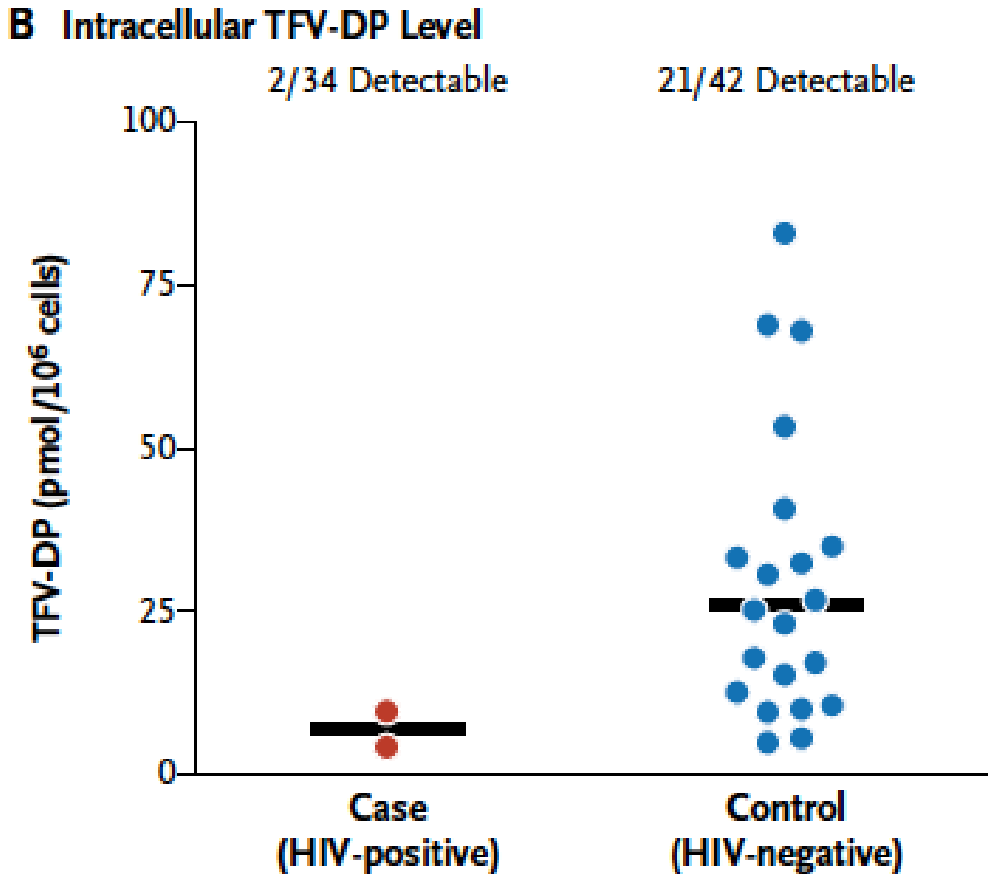
Did it matter? Yes!

- Greater adherence associated with more protection
  - According to self-reporting and pill/bottle counts, those who adhered to daily regimen more than 90% of the time had 73% reduction in HIV risk
- Detectable drug in blood strongly correlated with effect
  - 90% reduction in HIV among those with detectable levels of activated drug in blood

iPrEX: Adherence is Critical

By pill count/self-report:

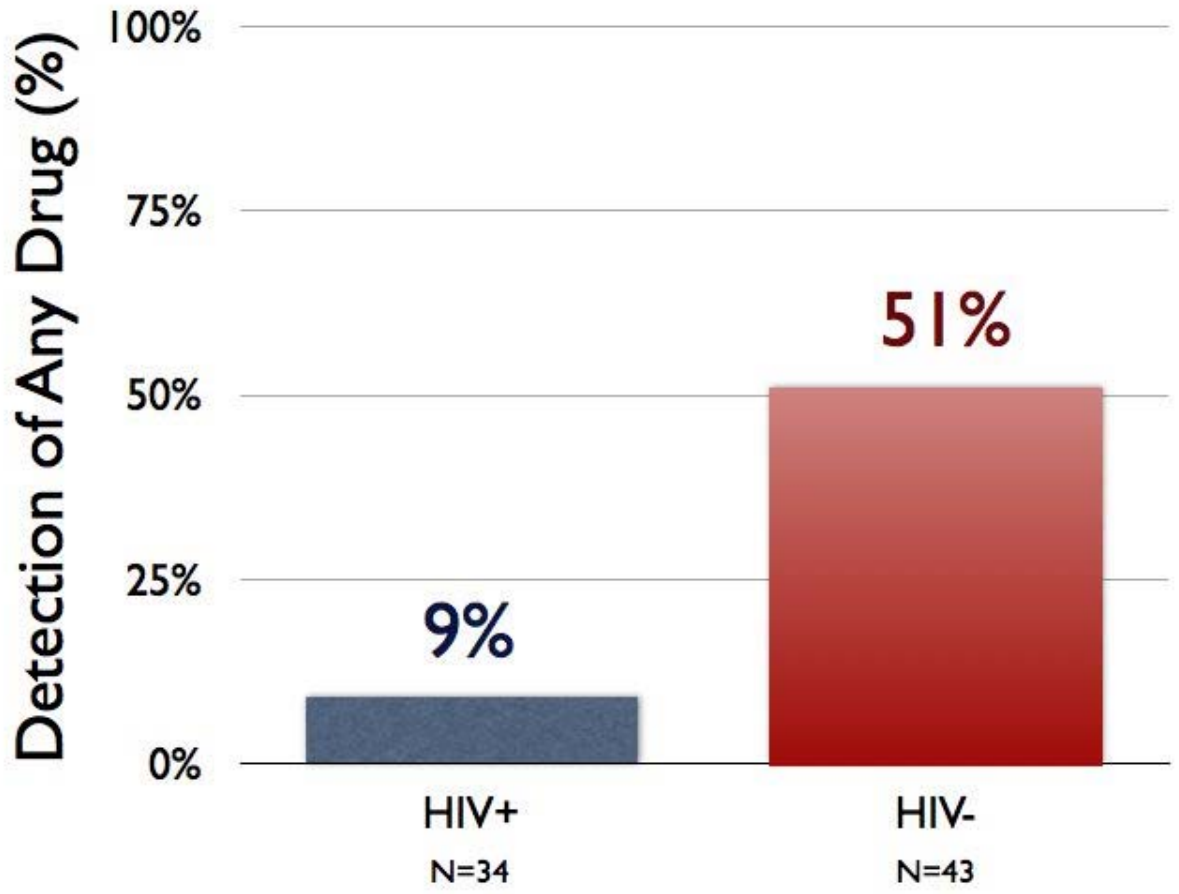
- High (>90%) adherence **73% effective**
- Intermediate (50-90%) adherence **50% effective**
- Low (<50%) adherence **32% effective**



Grant et al, NEJM 2010

- 92% estimated efficacy if drug present

Drug Detection by HIV Status in the FTC/TDF Group



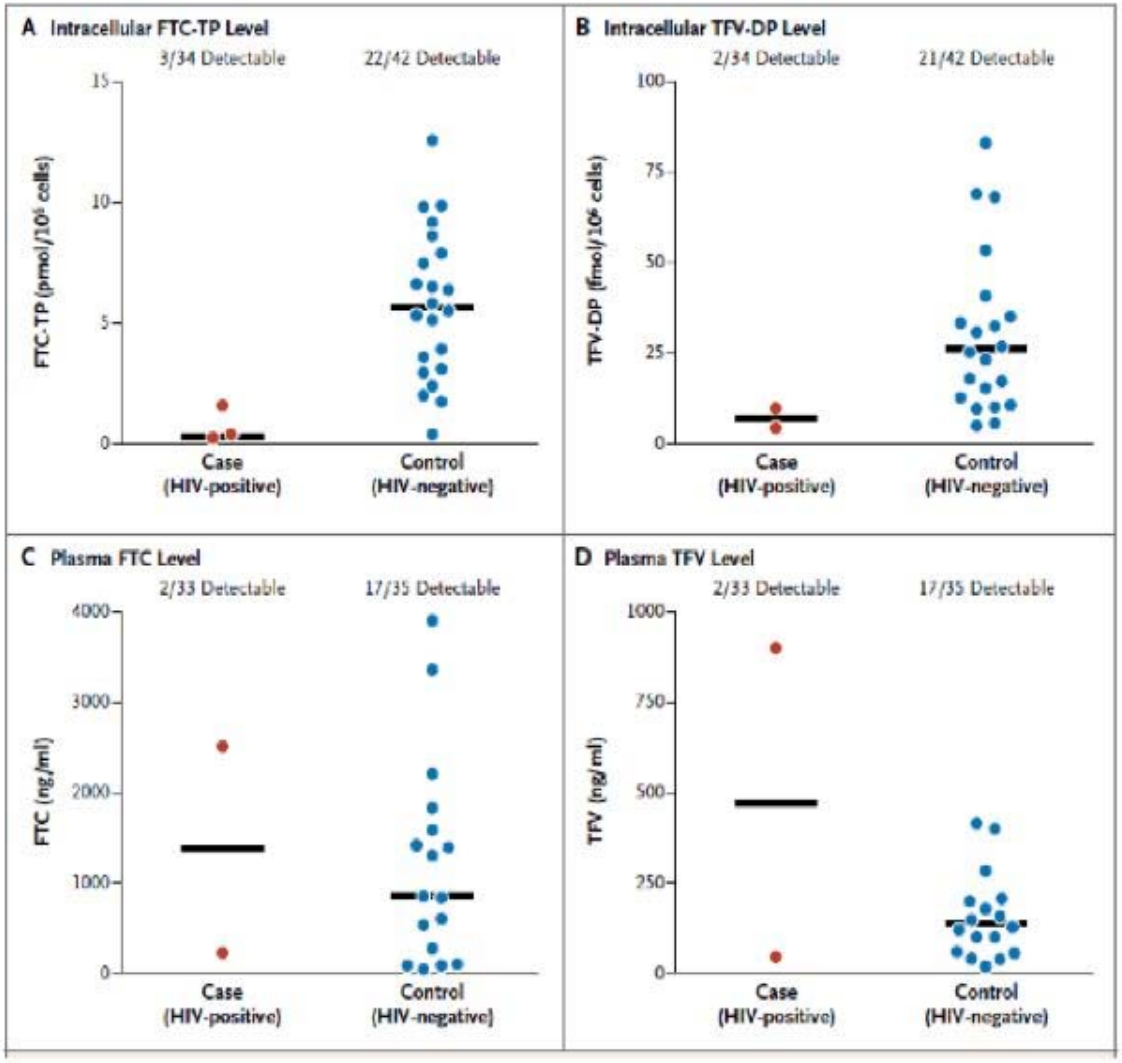
New England Journal of Medicine, online Nov 23, 2010

Wait…

- Aren't we getting tenofovir blood levels in VOICE?

- Yes, but….
  - These reach steady-state levels in blood in 1-2 days if taking standard doses of tenofovir
  - In contrast, PBMCs* reflect relatively long-term intake of drug (months)

Drug Levels



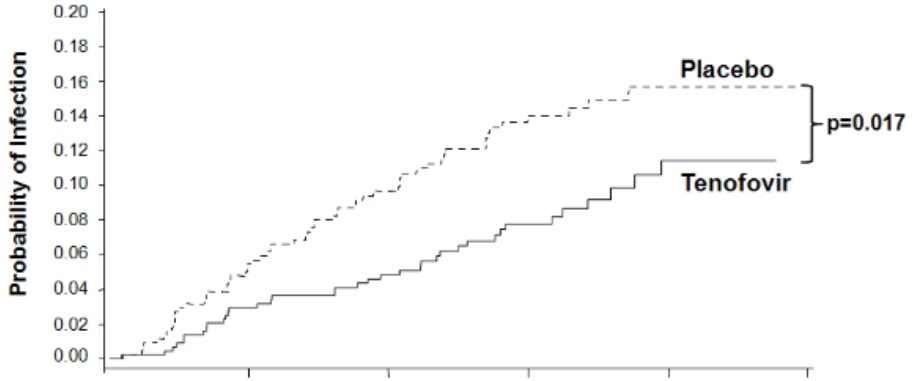
New England Journal of Medicine, online Nov 23, 2010

Implications for VOICE

- VOICE is studying
  - Different population: women
  - Different primary route of HIV transmission: vaginal intercourse
- Suboptimal adherence in iPrEx of notable concern
  - Will this differ in VOICE participants?
  - Will it differ by product administration route (oral / vaginal)?
- While safety data for iPrEx were encouraging, keep in mind that adherence was suboptimal

CAPRISA 004: 1% tenofovir gel

- ✓ **Phase 2B trial in 889 women**, ages ≥18 years in South Africa
- ✓ **Coitally dependent**: gel within 12 hours before & 12 hours after sex
- ✓ **Study population**: Young women (mean age 23), unmarried, from rural (69%) & urban (31%)
- ✓ **Good safety profile** (↑ diarrhea compared to placebo)



Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness (p-value)	**47% (0.064)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

Abdool Karim et al, Science July 2010

CAPRISA 004 Incidence by Adherence

- High (>80%) gel use, n=336:
  Tenofovir gel: 4.2%
  Placebo gel: 9.3 % P=0.025 **54% effective**
- Intermediate (50-80%), n=181
  Tenofovir gel: 6.3%
  Placebo gel: 10.0% P=.343 **38% effective**
- Low (<50%), n=367
  Tenofovir gel: 6.2%
  Placebo gel: 8.6 % P=.303 **28% effective**

Abdool Karim et al, Science July 20, 2010

MTN 001

- Participants reported very high adherence
- However, non-adherence estimates using blood tenofovir levels ranged from 35% to 65%!

Hendrix CROI 2011

Self-Reported Product Adherence

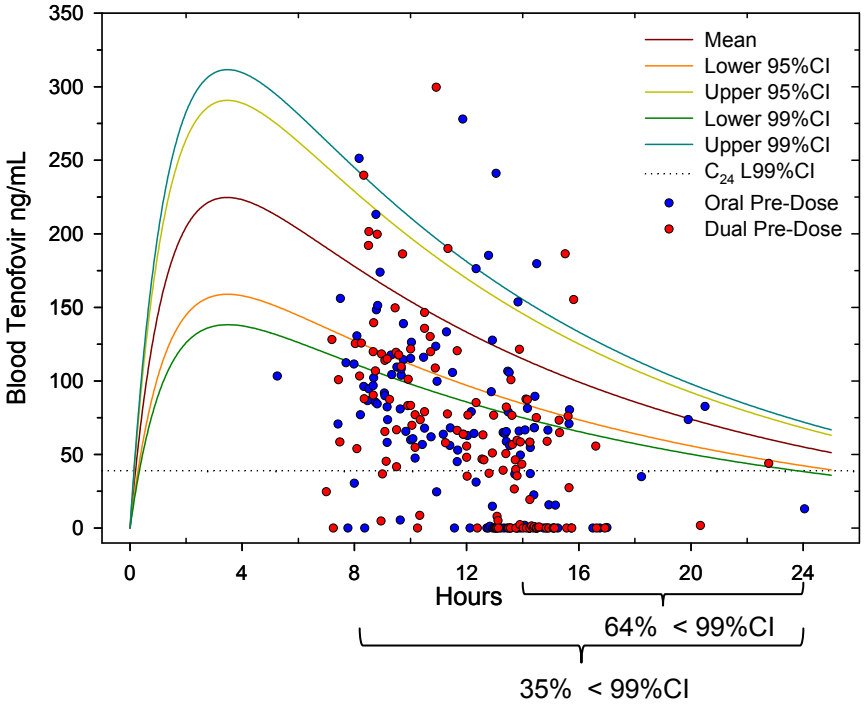
	Overall	Vaginal Gel	Oral Tablets	Dual
	N=851‡	N=285	N=282	N=284
	%	%	%	%
Adherence Measures				
% daily doses taken (mean, SD)†	94.0 (10.8)	94.4 (12.2)	93.9 (10.1)	93.8 (10.2)
>=90% doses taken	81	85	79	79

†p=0.8 (mixed effect model with Gaussian link and fixed effects for treatment, period, sequence; random effect of participant within sequence).
‡N=visits among 144 participants; maximum of 864 possible visits.

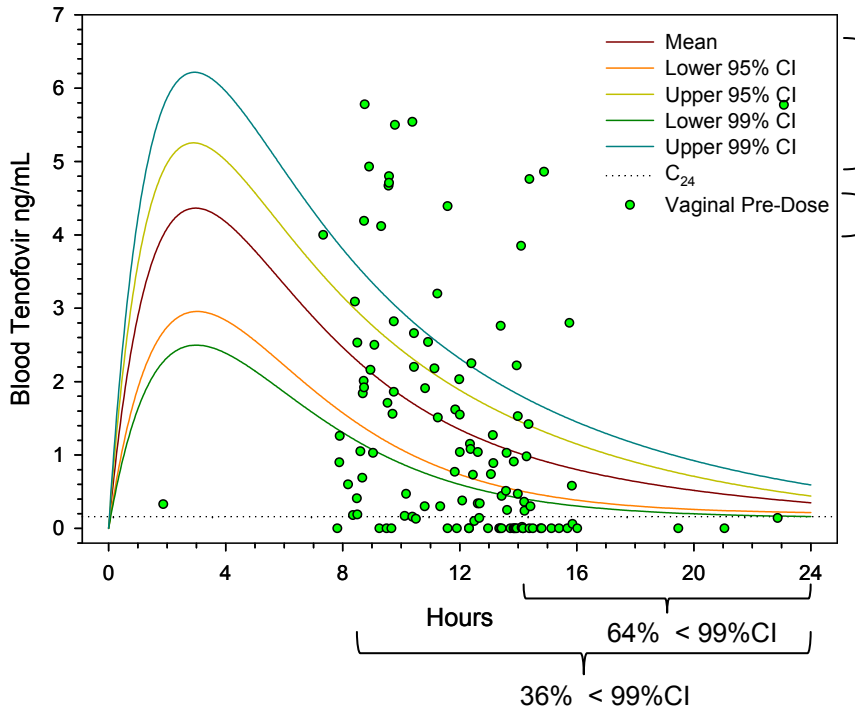
No differences in among regimens or across study sites.

PK as Adherence Measure

Oral/Dual Dose Phase



Vaginal Dose Phase

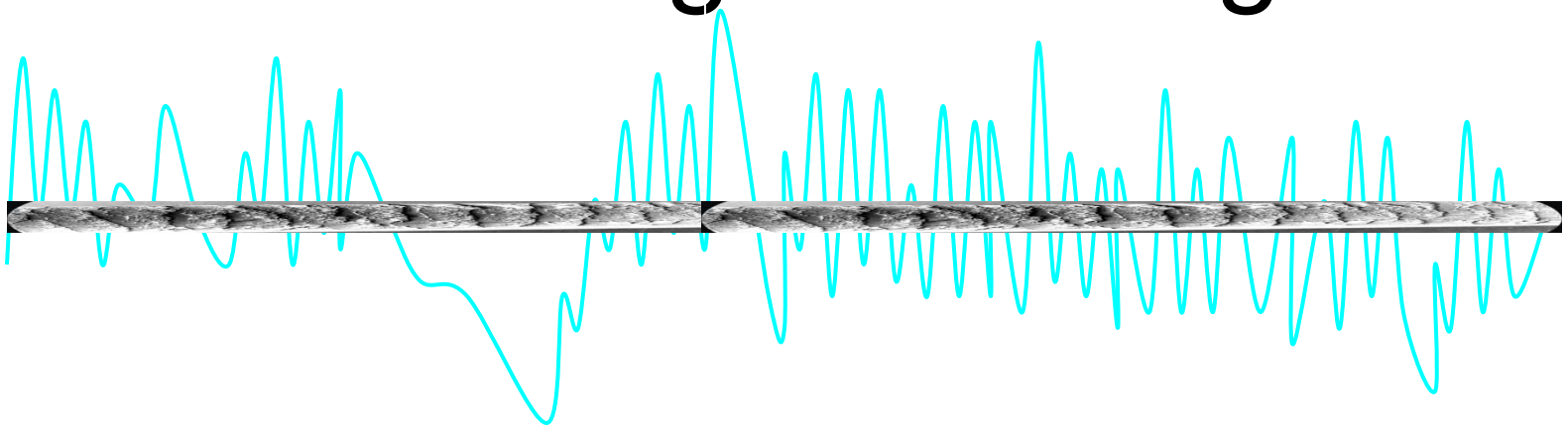


Expected (Witnessed Dose Cohort)

Actual (unobserved MTN-001)

Reference Cohorts: JHU (ICTR, ^{14}C-TFV), MTN-006, CONRAD Gel Study (Jill Schwartz)

How to measure how much drug person is taking on average?



PBMC*

- Add **PBMC** archive collection for consenting VOICE participants
  - Collect at the first quarterly visit following consent and again 6 months later, during scheduled study participation
  - Upon documentation of two positive rapid HIV tests during a follow-up visit, participants who have provided consent for PBMC collection will have blood drawn for this purpose (at sites with capacity).
  - Letter of Amendment in process
    - Includes new consent language

* Peripheral blood mononuclear cells

MTN microbicide trials network

Drug Levels & Hair

- Drug measured in a small sample of hair gives info on average exposure over about 1 month
- Humans lose about 100 hairs per day from their scalp
- Propose collecting 100 hair strands every 2-3 months in VOICE for drug assays
- Prior experience in Africa and elsewhere for this purpose with good results and acceptability

Poster #995

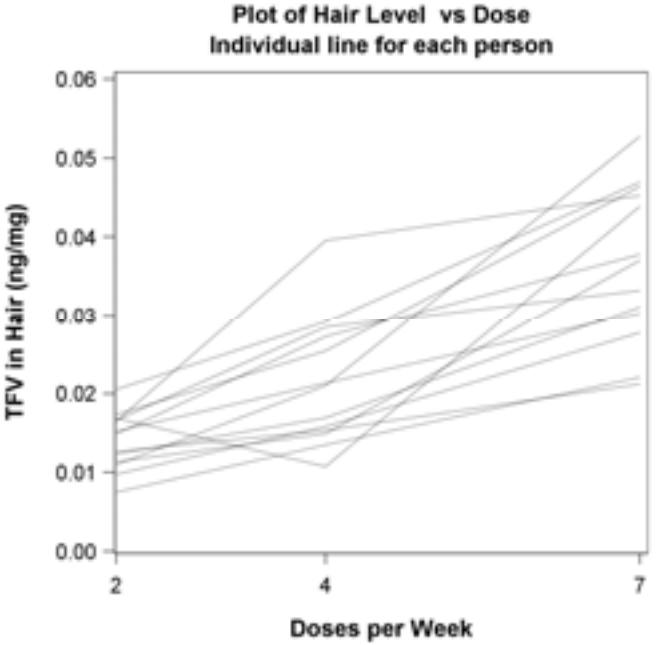
Validating Hair as a Biological Marker of Tenofovir Drug Exposure in HIV pre-exposure prophylaxis (PrEP)

A Liu[1,2], M Gandhi[2], P Bacchetti[2], Y Huang[2], P Anderson[3], K Goggin[4], S Buchbinder[1,2], R Grant[2,5], RM Greenblatt[2]

[1]San Francisco Department of Public Health, San Francisco, CA; [2]Univ of California San Francisco, San Francisco, CA; [3]Univ of Colorado, Denver, CO; [4]Univ of Missouri-Kansas City, Kansas City MO; [5]Gladstone Institutes, San Francisco, CA.

Revised Abstract

- 15 HIV-uninfected, dark-haired ppts at low-risk for HIV took directly observed tenofovir 300 mg in a cross-over study with 3 dosing periods: 2, 4, and 7 doses/week.
- Occipital scalp hair sampled after each 6-week dosing period; 24-hour intensive PK study performed at steady state (day 28) of the daily dosing period
- Log-linear relationship seen between doses per week and TFV hair level, with a 65% (95% CI 48-84%, p<0.0001) increase in hair level per 2-fold dose increase; minimal inter-individual variability in dose effect suggests similar effects across subjects



Poster #995

Validating Hair as a Biological Marker of Tenofovir Drug Exposure in HIV pre-exposure prophylaxis (PrEP)

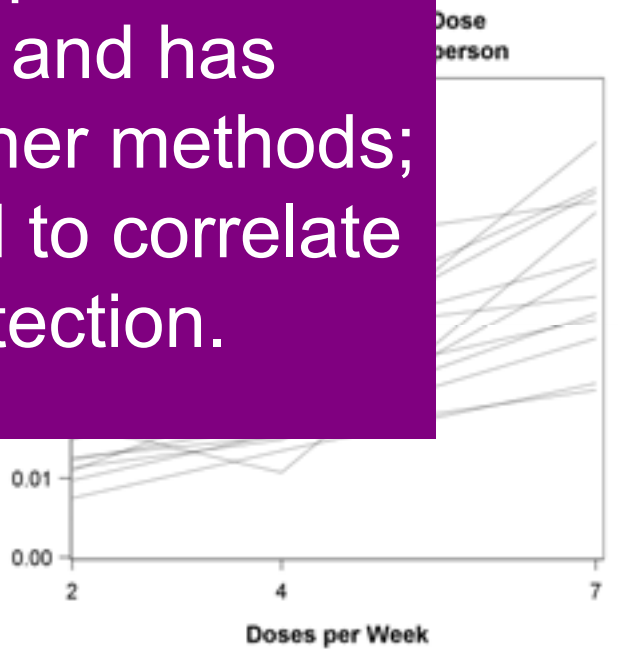
A Liu[1,2], M Gandhi[2], P Bacchetti[2], Y Huang[2], P Anderson[3], K Goggin[4], S Buchbinder[1,2], R Grant[2,5], RM Greenblatt[2]

[1]San Francisco Department of Public Health, San Francisco, CA; [2]Univ of California San Francisco, San Francisco, CA; [3]Univ of Colorado, Denver, CO; [4]Univ of Missouri-Kansas City, Kansas City MO; [5]Gladstone Institutes, San Francisco, CA.

Revised Abstract

- 15 HIV uninfected, dark haired ppts at low risk for HIV to
- O
- Lo
  be
  TF
  Cl
  ha
  increase; minimal inter-individual variability in dose effect suggests similar effects across subjects

Conclusions: TFV levels in scalp hair demonstrate a clear and consistent correlation with dose. Hair is a promising biomarker of TFV dosing/exposure for PrEP trials and programs and has feasibility advantages over other methods; additional studies are needed to correlate TFV hair levels with protection.



Easy process

- Takes about 2 minutes of time once staff gets a hang of it
- Tiny snip of hair cut from back of the head
- Since only small amount of hair needed, should not disrupt hairstyle
- Painless – no need for blood draw!
- Sample can be stored at room temperature and is not hazardous (hair doesn't transmit HIV)

Thanks!

- Questions?