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.
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.
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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

- HIV+: 9% (N=34)
- HIV-: 51% (N=43)

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)
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)  
  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

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Vaginal Gel</th>
<th>Oral Tablets</th>
<th>Dual</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=851‡%</td>
<td>N=285%</td>
<td>N=282%</td>
<td>N=284%</td>
<td></td>
</tr>
<tr>
<td>% daily doses taken (mean, SD)†</td>
<td>94.0 (10.8)</td>
<td>94.4 (12.2)</td>
<td>93.9 (10.1)</td>
<td>93.8 (10.2)</td>
</tr>
<tr>
<td>&gt;=90% doses taken</td>
<td>81%</td>
<td>85%</td>
<td>79%</td>
<td>79%</td>
</tr>
</tbody>
</table>

†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**

- Mean
- Lower 95% CI
- Upper 95% CI
- Lower 99% CI
- Upper 99% CI
- C_{24}
- Lower 99% CI
- Upper 99% CI
- Oral Pre-Dose
- Dual Pre-Dose

**Vaginal Dose Phase**

- Mean
- Lower 95% CI
- Upper 95% CI
- Lower 99% CI
- Upper 99% CI
- C_{24}
- Lower 99% CI
- Upper 99% CI
- Vaginal Pre-Dose

Reference Cohorts: JHU (ICTR, \(^{14}\text{C-TFV}\)), MTN-006, CONRAD Gel Study (Jill Schwartz)
How to measure how much drug a 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
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
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.
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?