

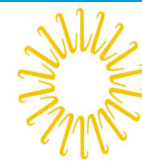
Preparing for PrEP and other Antiretroviral-Based Prevention



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AVAC Teleconference



WEB fenwayhealth.org



The Miriam Hospital
A Lifespan Partner

HIV Prevention: 2010

DECREASE SOURCE OF INFECTION

- Barrier protection
- Blood screening
- IDU harm reduction
- STI Treatment?
- Antiretroviral Therapy
 - PMTCT
 - Rx infected partners

DECREASE HOST SUSCEPTIBILITY

- Barrier protection
- Infection Control
- Circumcision
- Vaccines?
- STI Treatment?
- PEP
- Oral PREP
- Topical microbicides

ALTER BEHAVIOR

- Condom and HIV testing promotion
- Individual interventions
- Couples interventions
- Community-based interventions
- Structural interventions (e.g., economic)

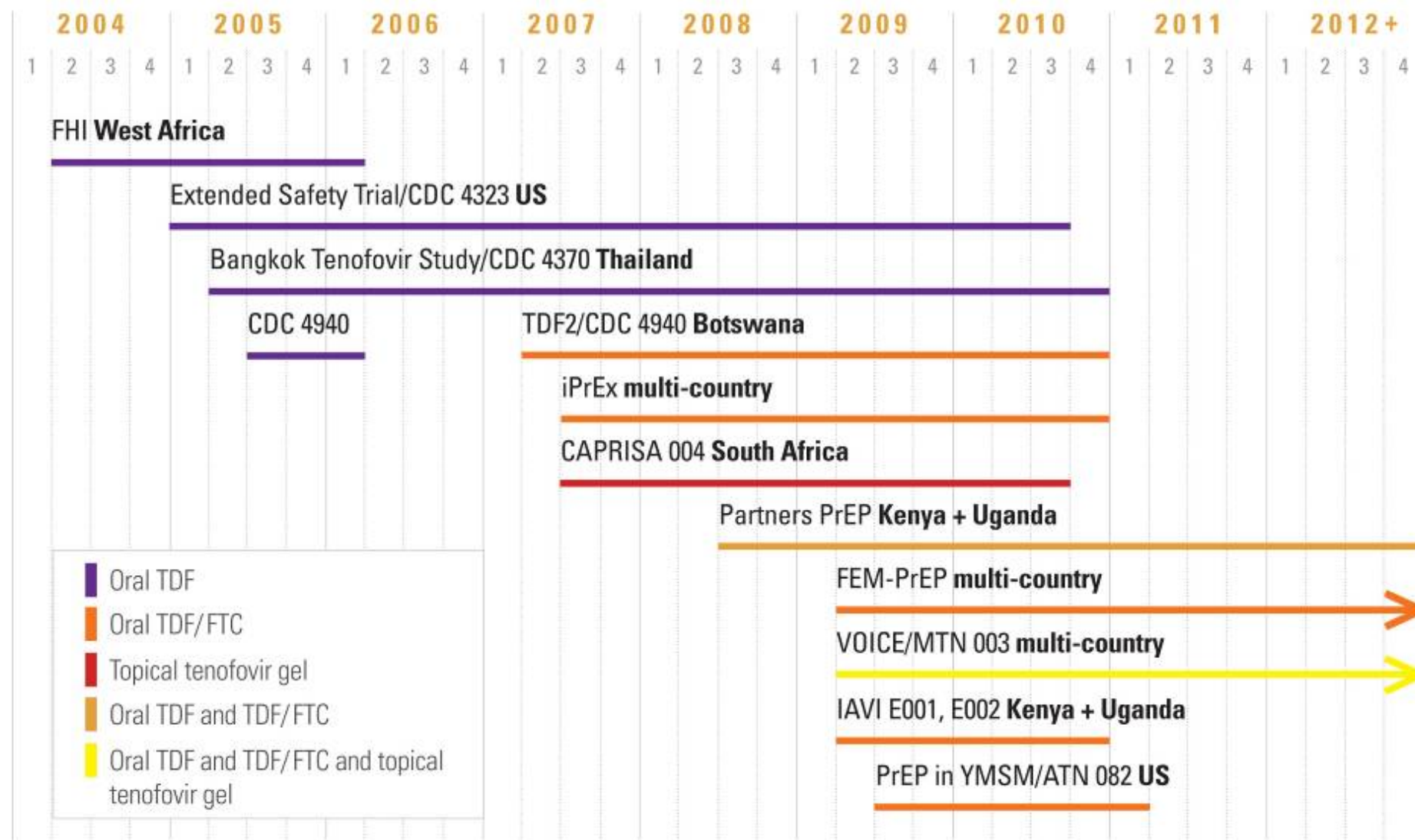
Why antiretrovirals for prevention?

- Animal data
- Increased tolerability of newer meds
- Challenges for other approaches, e.g. vaccines
- Human data with PEP
- Costs going down globally with generic meds

Non-occupational post exposure prophylaxis (NPEP)

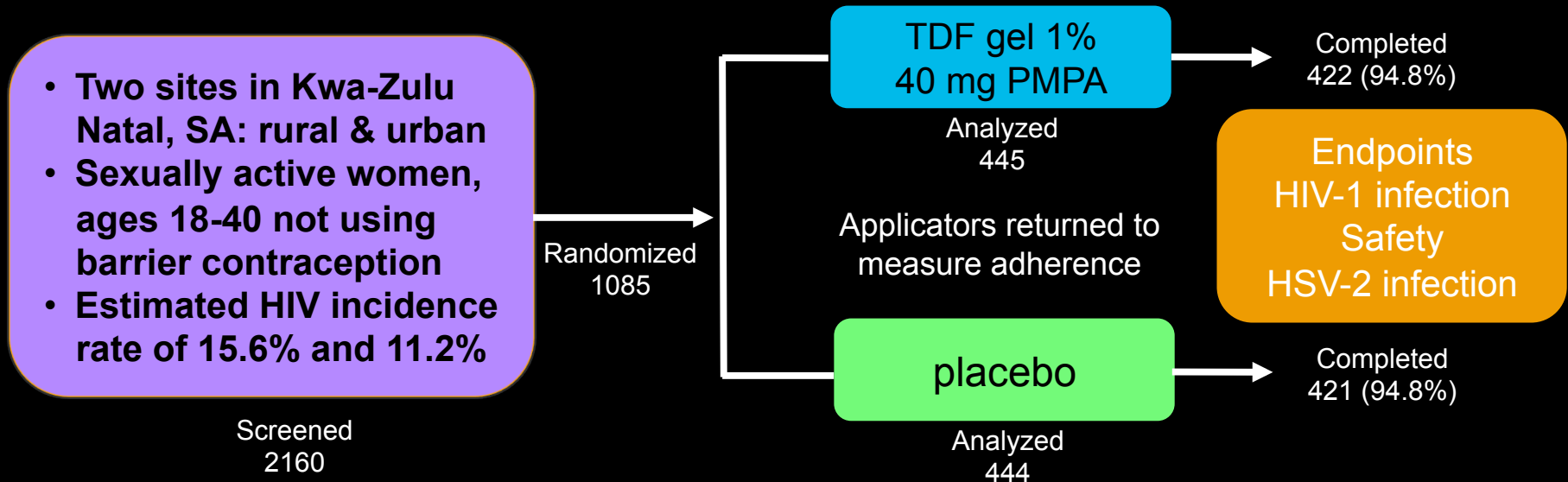
- § RCTs are not available; extrapolate from HCW
- § Variable effects on transmission (Kahn et al, 2001; Schechter et al, 2004; Poynten et al, 2009)
- § Animal data suggest timing is crucial (Garcia-Lerma et al, 2010)
- § Men fail to timely recognize high risk exposure, even in the presence of direct access to ARVs (Schechter et al, 2004)
- § Public health impact of NPEP is considered limited and only cost-effective in very specific situations (MMWR, 2005; Poynten et al, 2007)
- § TDF-based regimens have higher completion rates than historical controls (Mayer et al, 2008)

Timeline for Ongoing PrEP Trials (March 2010)



* The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor trial progress and will update the timeline accordingly. To view or download an updated timeline visit www.prepwatch.org.

CAPRISA 004: Study Design



Administration of TDF gel:

- Insert 1 dose within 12 hours Before sex
- Insert 1 dose ASAP, within 12 hours After sex
- No more than 2 doses within 24 hours

Impact of adherence on effectiveness of tenofovir gel

| | # HIV | N | HIV incidence | | Effect |
|--|-------|-----|---------------|---------|------------|
| | | | TFV | Placebo | |
| High adherers (>80% gel adherence) | 36 | 336 | 4.2 | 9.3 | 54% |
| Intermediate adherers (50-80% adherence) | 20 | 181 | 6.3 | 10.0 | 38% |
| Low adherers (<50% gel adherence) | 41 | 367 | 6.2 | 8.6 | 28% |

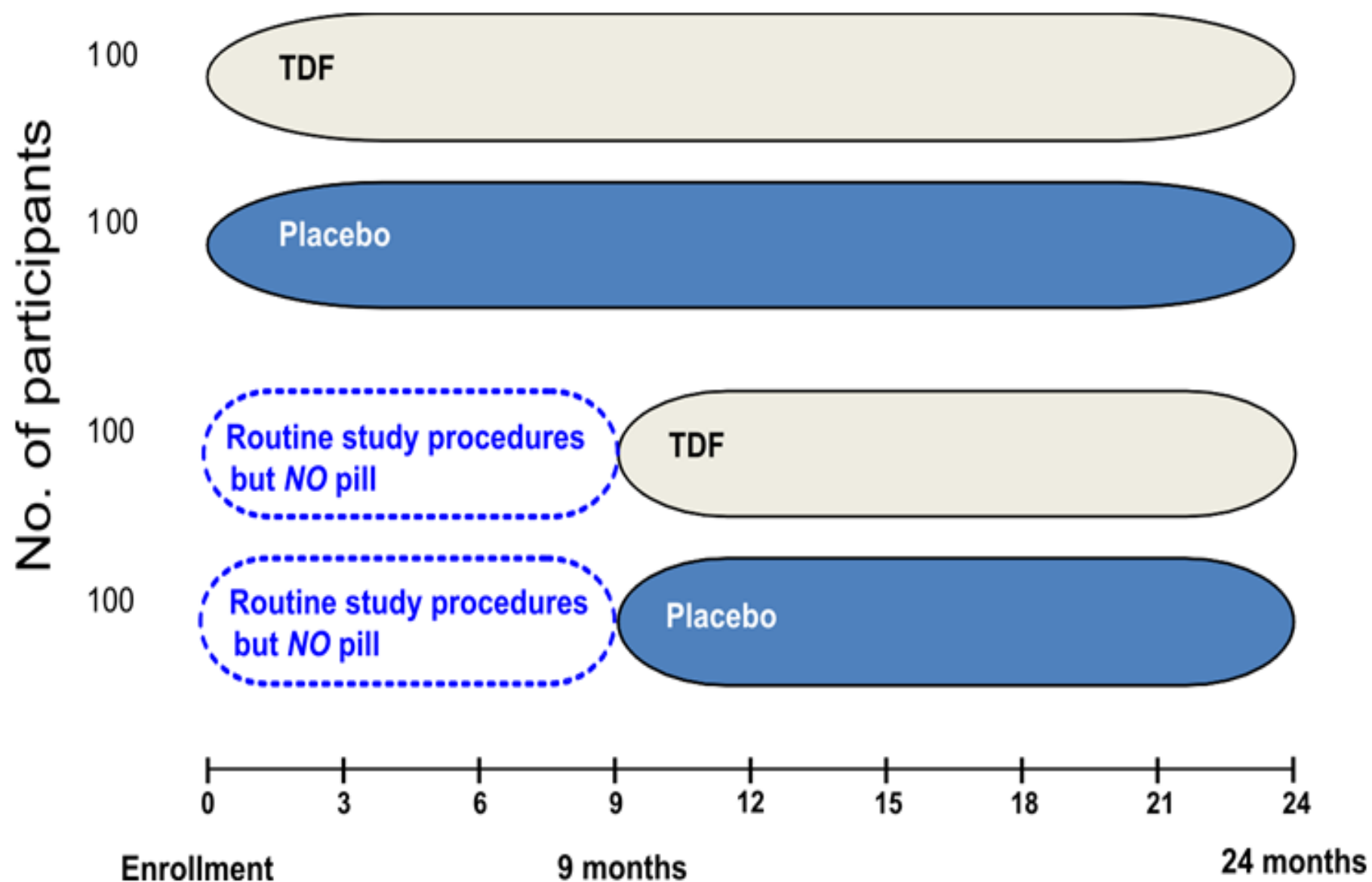
What about rectal gel?

- Tenofovir protects monkeys after rectal challenge
- Vaginal tenofovir gel used rectally was not optimal in LA/Pittsburgh study
- New formulation will be studied in MTN 007: Pittsburgh, Boston, Birmingham
- New formulation will also be studied in younger MSM: Pittsburgh, Boston, San Juan

CDC PrEP Study Study Design

- q RCT, placebo-controlled safety trial
 - § AIDS Research Consortium of Atlanta (ARCA)
 - § San Francisco Department of Public Health (SF)
 - § Fenway Health, Boston (FH)
- q 400 HIV-uninfected MSM randomized to receive TDF, 300mg/day or placebo
- q Visits every 3 months
 - § HIV testing, Risk reduction counseling
 - § Adverse events and laboratory safety parameters
 - § Adherence
- q Bone mineral density studies (DEXA)—SF

Study Design



CDC PrEP Study Conclusions

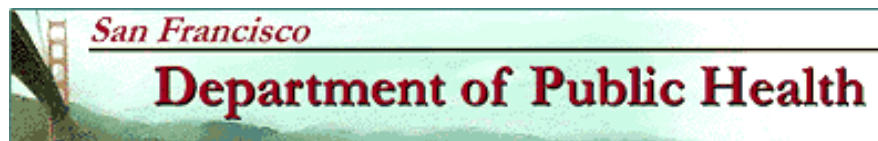
- q Daily oral TDF, 300 mg/day, was generally well-tolerated among this cohort of MSM
- q Kidney function abnormalities relatively uncommon, and did not occur more frequently on TDF than placebo
- q No evidence of behavioral disinhibition
- q 7 HIV infections, none in the men who took tenofovir



iPrEx: Safety, Efficacy, and Behavior



**Gladstone Institute
of Virology and
Immunology**



PrEP Initiative (iPrEx)



Men who have sex with men

Randomized 1:1 FTC/TDF vs Placebo

Daily oral

Followed for:

- HIV seroconversion
- Adverse Effects
- Metabolic Effects
- HBV exacerbations
- Risk behavior and STIs (including HSV)
- Adherence
- If infected
 - § Drug resistance
 - § Viral load
 - § Immunological responses and CD4 counts

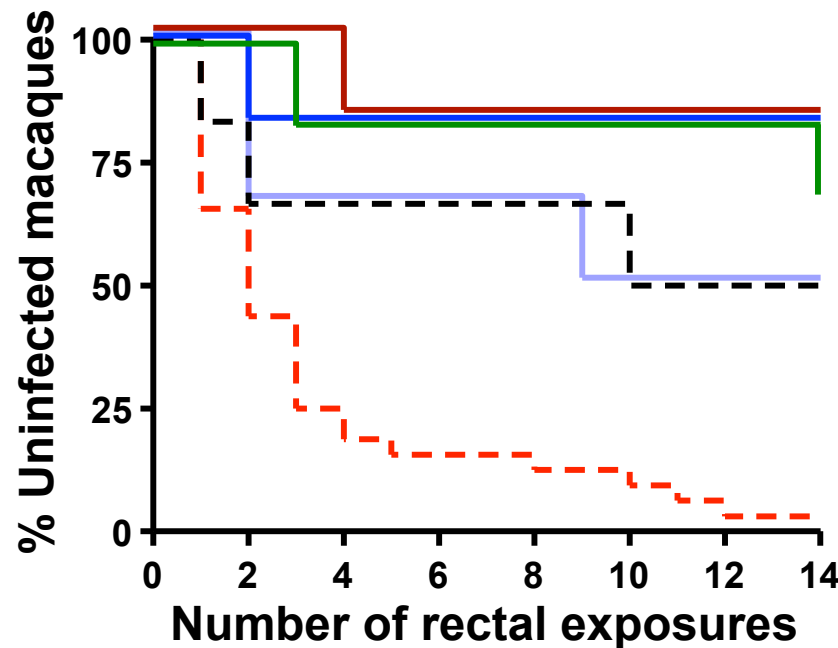
What if PrEP “Works”?

- **Block other steps in HIV life cycle:** e.g. binding and integration? Save some ART drugs for prevention?
e.g. Dapivirine, Maraviroc, Integrase Inhibitors
- **Topical vs. Oral:** gel/lube or pill?
- **What is the optimal drug delivery system:** gel, ring, suppository, diaphragm, injection, or pill?
- **How to best dose:** Fixed intervals vs. pre/post coital?
- **PrEP and the immune system:** adjuvant for vaccines?
- **Access for disenfranchised persons**
New Co-formulations and generics=cheaper PrEP?

Intermittent PrEP (iPrep)

- § May be more in line with sexual life style of most people, who are not risky all the time
- § Reduce pill burden
- § Reduce drug burden
- § Reduce side-effects
- § Decrease costs
- § May increase adherence and coverage
- § May increase safer sex behavior
- § Supported by animal models

Risk reduction by iPrEP with oral Truvada



-22h/+2h HR = 16.7, $p = 0.006$
-3 days/+2h HR = 15.4, $p = 0.008$
-7 days/+2h HR = 9.3, $p = 0.003$

+2h/+26h (PEP) HR = 4, $p = 0.03$
-2h/+22h HR = 4.1, $p = 0.02$

Untreated controls (n=32)
(9 real time and 23 historical)



Intermittent PrEP (iPrep)

- § Post IPREX generation of studies will be comparing continuous versus intermittent PrEP
 - Non-inferiority or equivalency studies (costly, large N)
 - Daily vs pre-post exposure
 - Daily vs standing doses plus post exposure dose
 - Daily vs standing doses

- § HPTN 067: the “ADAPT Study”
 - “Alternative Dosing to Augment Pill Taking Study”
 - Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Truvada
 - 3-armed study: daily, vs pre-post, vs bi-weekly standing plus post exposure dose
 - N=360, MSM n=180 Bangkok; HW n=180, Capetown
 - Adherence, coverage, PK and risk behavior
 - Start January 2011

Safety and adherence to intermittent Emtricitabine/Tenofovir for HIV pre-exposure prophylaxis (PrEP) in Kenya and Uganda

| | | Kenya (MSM/FSW) | Uganda (DC) |
|---|---|--------------------|----------------|
| DAILY ADHERENCE RATE Median [IQR] | Overall unadjusted | 83% [63-92] | 96% [93-100] |
| | Adjusted – Upper | 92% [79-99] | 97% [93-100] |
| | Adjusted – Lower | 82% [63-92] | 96% [93-100] |
| INTERMITTENT ADHERENCE RATE Median [IQR] | Overall unadjusted | 68% [63-78] | 80% [71-86] |
| | Fixed doses | 55% [28-88] | 91% [77-98] |
| | Post-coital doses | 26% [14-50] | 45% [20-63] |
| | Post-coital doses within 2hrs (self report and sexual events per SMS) | 105% [57-175] | 103% [62-133] |

Table 3. Adherence rates for daily and intermittent groups. Adjusted upper accounts for extra openings and extra tablets taken out. Adjusted lower excludes curiosity openings.

Non-Injection Drugs and HIV Spread

(Project Explore Seroconverters, N=4295)

| Drug | N at baseline | No. of infections | Hazard ratio* (95% CI) |
|--------------------------|---------------|-------------------|------------------------|
| Heavy alcohol** | 419 | 41 | 1.9 (1.2, 2.8) |
| Amphetamines | 527 | 67 | 1.9 (1.4, 2.6) |
| Alcohol/drugs before sex | 2952 | 205 | 1.6 (1.1, 2.3) |

*REF = no/light/moderate use of alcohol; no speed use; no use before sex

** 4+ drinks every day or 6+ drinks on a typical day

Clearview Complete HIV 1/2



Menu-based approach



- Can mix and match, based on “eligibility” (efficacy, CE), individual needs and acceptability
- More closely replicates how “prescribing” is done

In conclusion

- § PEP, and testing and linking infected people into care and prevention, should be scaled up
- § Daily oral PrEP results expected soon; if efficacious, studies will try to identify alternative regimens
- § Vaginal and Rectal PrEP: promising, but still long way to go
- § ART for prevention, seems reasonable, ecological evidence available, but implementation is challenging