Pre-Exposure Topical Microbicides and Oral Prophylaxis Trials:

Rationale, Designs & Issues

Connie Celum, MD, MPH

Patrick Ndase, MBChB, MPH

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Importance of HIV prevention

- Antiretroviral treatment alone will not be able to stem this epidemic
- No intervention is likely to be fully protective
  - Need multiple approaches to HIV prevention (eg., male circumcision, HSV-2 suppression, PrEP)
  - Need short-term interventions while working towards effective HIV vaccines and microbicides
- Need interventions that target reduced HIV infectiousness & decreasing HIV susceptibility

Interventions unlinked from timing of risk behavior

HSV-2 suppression

Pre-exposure Prophylaxis (PrEP)

HAART to Treat HIV in Infected Persons

Topical microbicides

HIV vaccines

Rationale for Oral Chemoprophylaxis for HIV Prevention

- Vaccines & microbicides in early testing
- Continuous oral prophylaxis works against malaria and HIV PMTCT
- Efficacy demonstrated in animal models
- Can be combined with other prevention strategies
- Could be used by both genders
- Potentially could be effective against vaginal, anal, & parenteral transmission

Why test TDF and Truvada?

- Single daily dosing
- Potent NRTIs
- Safe profile (in HIV+)
- Limited resistance generated (in HIV+)
- Generic production underway
- Macaque data are encouraging re efficacy, low resistance

Macaque PrEP studies

- Tenofovir delayed time to infection
- Truvada (tenofovir/FTC) may have greater efficacy (in small animal studies)
- Studies underway in macaques:
  - PrEP with frequent, low dose challenges
  - Effect of PrEP on resistance in breakthrough infections
  - Compare viral set-point in those monkeys which received TDV vs TDV/FTC and among those, with and without resistant mutations

Design of PrEP Trials in Humans

- Placebo controlled, double-blind, randomized
- Primary endpoint is efficacy
  - In context of condoms, counseling & STI treatment
- Safety endpoints
  - Phosphorus (bone mineralization) & fractures
  - Kidney (renal insufficiency, Fanconi syndrome)
  - Hepatitis flares in persons with chronic Hepatitis B
- Adherence
- Risk behavior by arm and over time
- In seroconverters
  - Resistance to TDF or FTC/TDF
  - Effect on disease progression

Existing Trials: Number of HIV Events

Study Location (Sponsor)	PrEP Strategy	Risk Group	N	Power	Effect size	Number of Events
Completed Trial						
West Africa (FHI/Gates)	Tenofivir	Women	1,200 (936)	90%	70%	30 events (2 TDF and 6 Placebo)
Ongoing Trials						
Thailand (CDC)	Tenofivir	IDUs 78% M 22% F	2,000	87%	67%	~ 50 events
Botswana (CDC)	Truvada	Heterosexual 50% M 50% F	1,200	80%	65%	~ 45 events
Planned Trials						
Peru/Ecuador (NIH)	Truvada	MSM	A: 1,400	A: 87% (rule out 0%)	A: 70%	~ 52 events
			B: 3,200	B: 90% (rule out 30%)	B: 60%	~ 85 events
Aborted Trial						
Malawi (FHI/UNC/Gates)	Tenofivir	Heterosexual Men/Women	700 M 400 W	80%	80%	13 events
				80%	57%	45 events
Cambodia (NIH/Gates)	Tenofivir	Women	960	87%	67%	31 events

Statistical Center for HIV/AIDS Research & Prevention
SCHARP

MTN

Summary of PrEP trials

Location	Sponsor	Pop'n	PrEP drug	Status	Approach to preg	Approach to BF
Phase II						
Ghana	FHI/USAID & Gates	936 high risk women	TDF	Completed	- no req't for contraception	- BF excluded
US	CDC	400 MSM	TDF	Enr ends fall 2007	N/A	N/A
Phase III						
Thailand	CDC	2000 IDUs	TDF	Enrollment finished 2007	Non-barrier cont req'd	- BF excluded
Botswana	CDC	1200 young heterosex	Truvada	Enrollment resumed Mar 07	Non-barrier cont req'd	- BF excluded
Andes	NIAID	1400 MSM	Truvada	Enrollment May 2007	N/A	N/A
Africa	BMGF (pending)	3900 HIV discordant couples	TDF & Truvada	If funded, start fall 2007	Contraception offered (not req'd)	BF allowed
Africa	USAID/ BMGF	4000 high-risk women	Truvada	Start late 2007	Non-barrier cont req'd	- BF excluded?

Andean MSM PrEP Trial (IPrEX)

- 1400 MSM (likely to be increased to 2300) randomized to Truvada or placebo
- Will have 85 endpoints
- Efficacy of PrEP estimated to be 60%, sufficient statistical power to rule out low efficacy (<30%)
- Will do bone scans on subset
- Will evaluate cellular immune responses against HIV
- Will evaluate effect of Truvada discontinuation on hepatitis B flares

HIV discordant couples: Significance, Challenges, & Prevention Needs

- Majority of HIV transmissions in Africa occur in HIV discordant couples
- Identification of these couples is challenging
- Partners Study required large community outreach activities
  - ~48,000 couples tested for HIV (e.g., at VCTs); ~15% HIV discordant
  - 6,126 HIV discordant couples pre-screened for study eligibility
  - 3,148 couples enrolled (HIV+ partner HSV-2+ with CD4>250)
- HIV-negative women in discordant couples seek prevention strategies that allow them to safely become pregnant

Partners PrEP Scientific Objectives:
Proof-of-Concept in HIV discordant couples

- Primary Objectives:
  - Efficacy of PrEP: Power to assess predicted 60% efficacy
    - 90% power for pooled PrEP arms vs placebo
    - 82% power for each active arm vs placebo
    - Power to ‘rule out’ < 30% efficacy
  - Safety (overall and specific rates of SAEs)

- Secondary Objectives:
  - Rates of resistance in breakthrough infections (& their partners)
  - PrEP efficacy by gender
  - Impact of source partner HIV viral load on PrEP efficacy
  - Study drug adherence
  - Risk compensation

Proposed PrEP trial among HIV-negative partners in HIV discordant couples

3900 HIV- discordant couples with HIV+ partner >250

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Randomize HIV- partners with normal liver, renal, hematologic function

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Truvada once daily | Tenofovir once daily | Placebo once daily

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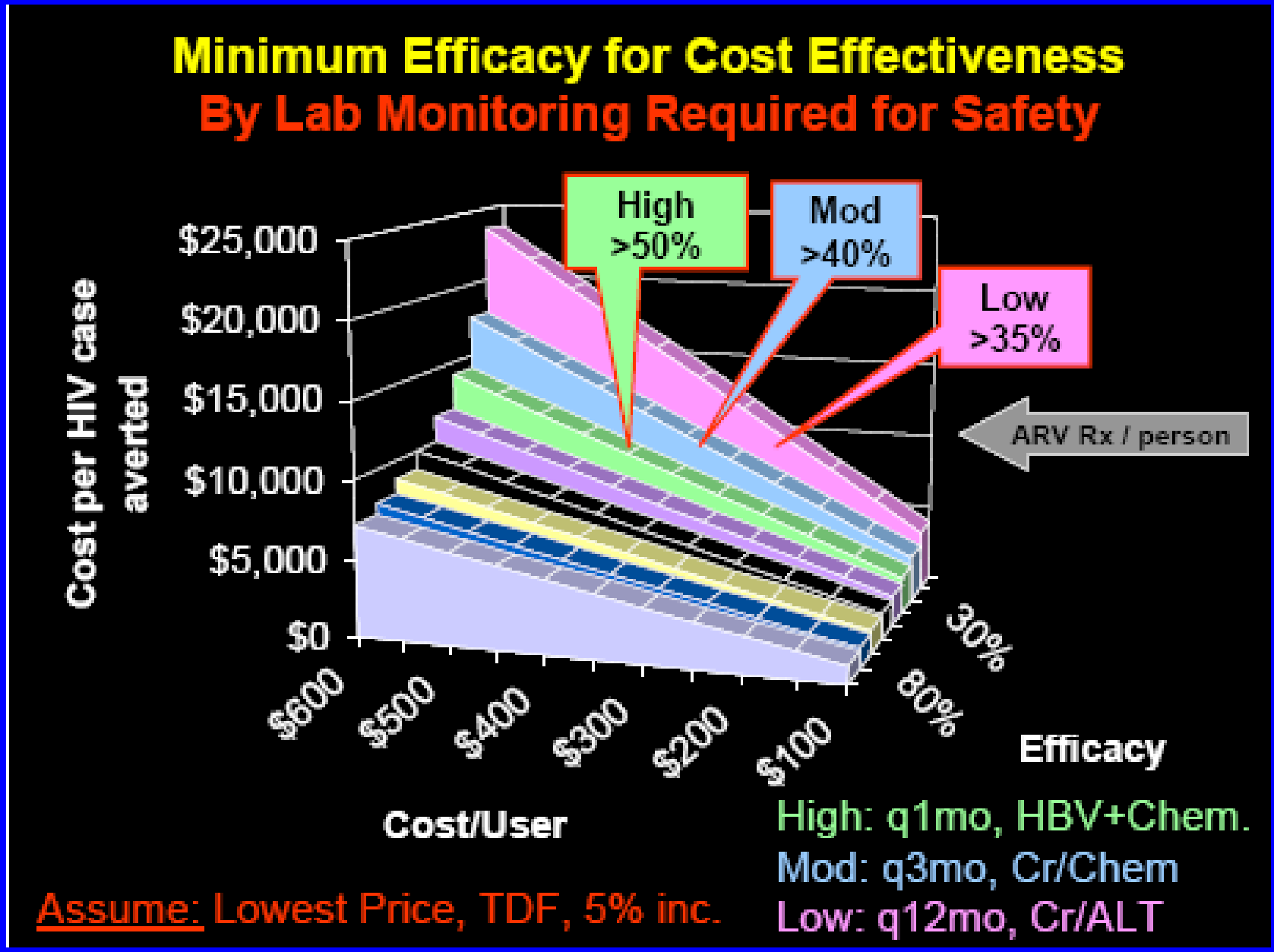
Follow couples for up to 2 years

1° endpoint: HIV infection in HIV-negative partner

(estimated 3% in placebo arm)



Courtesy of Bob Grant

A few of the challenges ahead, if PrEP trial is funded

- More intensive protocol with additional lab testing & adverse event evaluation than for acyclovir suppression and microbicides trials
- Need well-trained, prepared sites to be able to recruit & retain couples, monitor safety, manage side effects, be able to refer ineligible couples for care
- Requires extremely vigiliant site coordination, many logistics, and highly motivated, cohesive site team
- Need extensive community preparation & understanding of concept

Once you get the funding, you think it's going to be like this….

Western Utah Range Country

But then it ends up being like this…

The Trollstigen (Troll's Path), Isterdalen, Norway

Community challenges with ART based oral & topical microbicides Trials

Patrick Ndase MBChB, MPH

MTN Regional Physician

Community challenges with ART based oral & topical microbicides

- Context: Not clear what results will be for current products under trial (two failed products)
- More transparency about the why and the how of moving into ART based microbicide research
  - Inevitably need to engage community in regard to previous failures & successes
  - May require a more proactive approach with both community & media
- Extensive community consultation (Cabs, IRB, gov't' treatment activists etc) to develop appropriate central & site specific communication education plans
- Partnerships and planning to rapidly integrate results (involvement of potential implementers)

Ctn: Community Issues

- Understanding HIV prevention trials
  - Particularly concept of using ARVs to prevent rather than treat HIV (prevention paradox)
- Drug sharing
  - Bigger issue in Household with HIV + members
- Resistance in breakthrough infections
  - Lots of discussion, limited data
  - Valuable lessons to be learnt from CDC Truvada trial in Botswana
- Follow-up and treatment of seroconverters
  - Standard in HIV microbicide trials (MTN 015 – sero-converter protocol)

Access & Programmatic Issues for PrEP

- Access of ARVs for HIV+
  - Controversy assoc with PrEP when ARV supply isn't sufficient to treat HIV+ cases
- Cost of scale up, if topical or oral ART works
  - Will be expensive relative to other potential strategies (acyclovir suppression, diaphragm, male circumcision)
- Need for pharmaco-vigilance surveillance
  - Unprescribed ARV use & resistance at population level
- Ways to monitor impact on risk behavior and HIV incidence (? Assumption that change in behavior could offset as much as 50% effectiveness in PrEP)