BIOGRAPHIES:

Diane V. Havlir, MD

Dr. Havlir is Professor of Medicine at UCSF and Chief of the HIV/AIDS Division at San Francisco General Hospital. She was a physician in training at UCSF when the AIDS epidemic emerged in the 1980s and has cared for HIV-infected patients for over 25 years. She is an active researcher who pioneered some of the first studies of HIV antiretroviral therapy and drugs to prevent AIDS complications. Her recent efforts showed that prompt initiation of antiretroviral therapy in patient with HIV and tuberculosis can significantly reduce mortality and AIDS. She is principal investigator for the ACTG unit at UCSF and the PROMOTE program project which is studying HIV and malaria. She founded the SEARCH collaboration which is evaluating medical, economic and education outcomes of universal HIV therapy through a streamlined delivery approach in East Africa.

Dr. Havlir has played an active role on the global stage as an author of the first WHO Global HIV Treatment Guidelines. In concert, she helped establish a Global HIV Drug Resistance surveillance program. She is a member of the Board of the STOP TB partnership and chair of the HIV and TB working group. She served on the Governing Council for the International AIDS Society and is an advisor to the Infectious Disease Center for Global Health Policy. She has won numerous academic awards, and in 2012 she was featured as a “Pioneering Leader in the Fight Against AIDS“ in Vanity Fair. Dr. Havlir was, the United States Co-chair of the International AIDS Conference in Washington DC in July, 2012, the largest ever gathering of the AIDS community which marked the beginning of the end of the AIDS epidemic.

BIBLIOGRAPHY:


Oliver Bacon, MD

Oliver Bacon, MD, MPH is an Associate Professor of Clinical Medicine at UCSF in the HIV Division at San Francisco General Hospital, and the San Francisco Site Medical Director of the U.S PreP Demonstration Project, based at SF City Clinic. He received a BA in English and an MD at Yale, and completed residency training in internal medicine at Johns Hopkins. Since finishing Infectious Disease Fellowship training at UCSF in 2002, he has worked in the HIV clinics at UCSF and SFGH, and from 2008-2012 was co-director of the ASPIRE program, a PEPFAR-funded collaboration with the Elizabeth Glaser Pediatric AIDS Foundation to train and mentor healthcare workers in HIV care in Cote d’Ivoire, Kenya, South Africa, Tanzania, and Zambia. He has also participated in an evaluation study of task-shifting in the public HIV care system in Mozambique. His areas of interest include antiretroviral therapy, diagnosis and treatment of sexually transmitted infections, evaluating quality of HIV care, new HIV testing strategies, and biomedical prevention.

BIBLIOGRAPHY:

Peer-reviewed Publications


Non Peer-Reviewed Publications


Office of Clinical Public Health Programs for the Public Health Strategic Health Care Group, U.S. Dept. of Veterans Affairs. The Primary Care of Veterans with HIV: Hypertension; Depression; Renal Disease; Hypogonadism; and Cancer Screening. Washington, D.C. September 2009.
HIV Prevention and Global Health

- The Global HIV Epidemic
- Breakthroughs in HIV prevention
- Challenges
- Progress
- Innovative approaches

Snapshot of Global HIV Epidemic

- 2.5 million new infections
- 300,000 in children
- 1.7 million deaths
- 34 million living with HIV

UNAIDS Report, 2012

The number of new HIV infections has peaked

The number of people living with HIV is still increasing

In Millions


The impact of the HIV epidemic is not uniform around the world

People Living with HIV/AIDS: Top 15 Countries by Number and by Adult HIV/AIDS Prevalence, 2010

Countries most affected by the HIV epidemic

Women

HIV and Women

- HIV is the leading cause of death and disease among women of reproductive age (15-49 years) worldwide.
- Approximately half of adults with HIV/AIDS worldwide are women.
- Experiencing violence increases the risk of HIV infection by a factor of three; up to 70% of women experience violence in their lifetime.

Factors that shape the epidemic

- The majority of people with HIV do not know their status.
- People who do know their status are receiving treatment and living longer.
- Yet, millions of persons living with HIV are still in need of services.
- HIV/AIDS is multiple epidemics. Not all communities, regions and populations are affected in the same way.
  - Key populations at higher risk are men who have sex with men, sex workers and people who inject drugs.
  - Other vulnerable populations include women, young people and children.

Scientific Breakthroughs in Prevention

- Key scientific advances
  - Treatment as Prevention
  - Pre-Exposure Prophylaxis (PrEP)
  - Adult male circumcision

What do we mean by “treatment as prevention”?

- HIV treatment lowers levels of HIV in the blood and secretions.
- Lower levels of HIV confers lower HIV transmission.
- In other words, HIV treatment “interrupts transmission.”

Examples where Treatment as Prevention has been evaluated

- HIV serodiscordant couples
- Pregnant and nursing women

Treatment as Prevention in Serodiscordant populations

- No HIV treatment: HIV infected population
- HIV treatment: HIV infected, on treatment
- HIV susceptible population
How well does “treatment as prevention” work?

- One way to study this question is to provide treatment to HIV + adults in HIV serodiscordant relationships who do not yet meet current guidelines to start therapy because their CD4+ cells are too high.

But Wait…

- Does HIV treatment offer any benefit to HIV + persons at high CD4+ cell count?
- What are the ethics of offering treatment to HIV+ person purely for the sake of preventing HIV transmission?

Using HIV treatment to prevent mother to child transmission of HIV

1. Mother to child Transmission
2. MTCT prevention approaches
3. Consequences

HIV treatment as prevention…

- Is highly effective reducing forward transmission by 96%
- Confers benefit to those treated, even at high CD4 cell counts
- Keeps mothers healthy, permits breast feeding and reduces transmission to infants
Male Circumcision for HIV prevention works

- Proven efficacy: 53-60% protection against HIV infection for males from heterosexual transmission
- Durable protection
- Cost analysis: aver 1 HIV infection by 5-20 circumcisions for $150 -900 over a 10 year horizon

What if we apply the evidence?

<table>
<thead>
<tr>
<th>Basic Program Activities</th>
<th>Outcomes by 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMTCT</td>
<td>Infections averted 12.2 million</td>
</tr>
<tr>
<td>Condom</td>
<td>Life-years gained 29.4 million</td>
</tr>
<tr>
<td>Key populations</td>
<td>Deaths averted 7.4 million</td>
</tr>
<tr>
<td>HIV testing and ART</td>
<td></td>
</tr>
<tr>
<td>Male circumcision</td>
<td></td>
</tr>
<tr>
<td>Harm reduction</td>
<td></td>
</tr>
</tbody>
</table>

And what if we do not?

Challenges in the Real World

- Cascade of Care
- Affected populations
- Cost

Challenge: Treatment requires a functional “Cascade of Care”

From the CDC, IAC, 2012
**Gaps in knowledge of HIV prevalence among MSM globally**

*Image showing a world map highlighting gaps in knowledge of HIV prevalence among MSM globally.*


**MSM: Highly affected population globally**

*Bar chart showing prevalence of HIV in different regions globally.*

*Source: *Beyrer, Lancet, 2012

**Financing the Global Response**

*Graph showing HIV investment US$ (billions) vs. new HIV infections (millions) from 2011 to 2020.*

*Source: *Schwartländer et al., Lancet, 2011

**The vast majority of people living with HIV will be in middle-income countries**

*Bar chart showing the proportion of people living with HIV by country income category from 2000 to 2020.*

*Source: UNAIDS, IMF 2012

**Options for domestic financing of HIV**

*Bar chart listing options for domestic financing of HIV with contributions from various sources.*

Some evidence of progress

- 13 million persons were tested for HIV in South Africa in 2010
- Globally, 8 million people had access to ART, an increase in 20% from 2010
- There has been a 31-55% reduction in new HIV infections among children between 2009-2011 in 8 African countries
- With ART coverage >30%, risk for HIV acquisition 38% less in South Africa

Source, UNAIDS, Tanser, 2012

Fig. 3 Distributions of lengths of life are presented for 2003 (solid red line) and 2011 (broken blue line).

J. Bor et al. Science 2013;339:961-965
Published by AAAS

SEARCH – Sustainable East Africa Research for Community Health

- Evaluate health economic education outcomes of CD4 independent ART in rural East Africa
- Apply science, conduct “science of care delivery” and leverage HIV to address non-HIV diseases
- Inform policy makers on community level health interventions

The 2000 -2010 approach

J. Kim and P. Farmer, NEJM, 2006
CD4+ Counts and Opportunistic Infections

- CD4 > 500
- CD4 350-500
- CD4 200-350
- CD4 < 200

Opportunistic Infections
- Minimal symptoms
- Bacterial pneumonia
- Skin infections
- Elevated TB risk
- Cotrimoxazole

Multiple concomitant therapies

Early Mortality
- Antibiotics
- Anti-TB therapy

SEARCH: Cluster randomized trial of universal vs. standard ART

16 villages; n = 10,000 each

- Universal ART (all CD4 counts)
- Country-guided ART (CD4<350)

Community Health:
- HIV incidence
- HIV population viral load
- AIDS
- Maternal and child health
- TB incidence

Outcomes
- Community Productivity
- Workforce participation
- Child labor prevalence
- Agricultural output
- Household income
- Educational attainment
- Healthcare utilization

SEARCH Partners
- NIH
- WHO
- PEPFAR
- World Bank
- Uganda MOH
- Kenya MOH

UGANDA
KENYA
Mbarara
Tororo
Nyanza

Control Communities:
- Intervention Communities:
  - HIV Screening/Diagnosis
  - Malaria testing & care
  - HTN and Diabetes testing
  - Maternal/child health
  - Annual Community Health Campaigns

16 villages; n = 10,000 each

June 4, 2011

Local Council (LC) leaders from all villages designed and executed community mobilization during the month prior to campaign
- Church (Easter) & Mosque announcements
- Posters & pamphlets distributed widely
- Radio announcements

Community Mobilization

Campaign Field Laboratory

- 18 Lab technicians
- Rapid HIV Ab testing/confirmation
- Point-of-care CD4+ T cell count
- Finger-prick HIV viral load
- Blood glucose
- Blood pressure

Rural Uganda: Community Health Campaign- HIV + other diseases

Adults with HIV 8%
Hypertension 8%
Diabetes 12%

Reasons for ART Initiation in Rural Uganda

- 186/188 (99%) of patients with CD4>350 offered ART chose to initiate
- Reasons for consenting to ART (n=186):
  - 90% ARVs will keep me healthy
  - 52% ARVs will allow me to continue working
  - 52% ARVs will improve chances of living for family
  - 21% ARVs will improve chances of surviving to children
  - 15% Avoid transmitting to others
  - 12% ARVs will maintain health for my future
  - 5% My spouse/partner is on ARVs
  - 4% My sponsor/partner is on ARVs

Jain, CID, 2012

Decrease in Measured Population RNA

<table>
<thead>
<tr>
<th></th>
<th>2011 CHC-1 (165 HIV+ adults)</th>
<th>2012 CHC-2 (210 HIV+ adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable VL, n (%)</td>
<td>62 (37%)</td>
<td>115 (55%)</td>
</tr>
<tr>
<td>VL 486-10,000 copies/mL, n (%)</td>
<td>40 (24%)</td>
<td>48 (23%)</td>
</tr>
<tr>
<td>VL 10,000-100,000 copies/mL, n (%)</td>
<td>42 (25%)</td>
<td>40 (19%)</td>
</tr>
<tr>
<td>VL &gt;100,000 copies/mL, n (%)</td>
<td>21 (13%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Median VL, log (95% CI), copies/mL</td>
<td>2.165 (1.490—3.345)</td>
<td>2.288 (1.468—3.808)</td>
</tr>
<tr>
<td>Mean log(VL) (95% CI), copies/mL</td>
<td>3.62 log (4.46—3.78 log)</td>
<td>3.29 log (3.06—3.51 log)</td>
</tr>
</tbody>
</table>

Jain, IAC, 2012
Significantly higher employment at CD4≥500 among adults

- Compared to CD4<200, CD4≥500 associated with
  - 5.8 more days/month
  - 2.2 more hours/day (40% more than ref. mean of 5.5)

Those with CD4≥500 worked nearly 1 week/month more than those with CD4<200, and as much as HIV-uninfected adults

<table>
<thead>
<tr>
<th>Regression model coefficients</th>
<th>(1)</th>
<th>(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days worked in the past month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4&lt;200 Reference</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>CD4 200-499</td>
<td>4.6</td>
<td>5.1</td>
</tr>
<tr>
<td>CD4 ≥500</td>
<td>5.8*</td>
<td>2.2*</td>
</tr>
<tr>
<td>Observations</td>
<td>167</td>
<td>207</td>
</tr>
</tbody>
</table>

- Linear regression model with age, age-squared, and sex included as controls
- ** p<0.05, * p<0.10
- Reference group has CD4<200

Thurminathy, AIDS, 2012

AIDS – The Beginning

Friedman-Kien, Color Atlas of AIDS

The Beginning of …

June 4, 2011

The end of AIDS?
PrEPing for Success: An Update on Pre-Exposure Prophylaxis for HIV

March 2013
Oliver Bacon, MD, MPH
UCSF HIV Division at SFGH
San Francisco City Clinic

Objectives

• Why do we need more HIV prevention tools?
• What is PrEP, and what role might it play?
• What do clinical trials tell us?
  – MSM
  – Women
• Key Questions: Efficacy, Safety, Behavior, Resistance, Adherence
• Implementation Research and Dissemination:
  How will PrEP work outside a randomized trial?
• Future Directions

Why do we need more HIV prevention tools?

HIV Prevention: What we have

• Testing and Counseling
• Condoms
• Serosorting and Seropositioning
• ART as prevention
  – Test and Treat (HIV+s)
  – PEP
  – Microbicides?
  -PrEP?

Why PrEP?

• Despite effective testing, counseling, condoms, and ART, 40,000-50,000 new infections annually in the U.S.
• Incidence far higher in Global South

Acknowledgements

• SF PrEP Demo Team
  – Al Liu
  – Stephanie Cohen
  – Amy Hilley
  – Robert Blue
  – Nikole Trainor
  – Debbie Nguyen
  – Tony Sayegh
  – Tamara Ooms
  – Amanda Jernstrom
  – Aaron Hostetler

• Susan Buchbinder
• Robert Grant
• Annie Luetkemeyer
• Lynae Darbes
Estimated number of new HIV infections, 2006-2010, San Francisco

Percent of MSM reporting unprotected anal intercourse in the last six months, the STOP AIDS Project, 2006-2011

MSM and Black heterosexuals account for most new HIV infections

What is PrEP?

- Pre-Exposure Prophylaxis in 2013:
  - FTC/TDF (Truvada®), taken daily by HIV-uninfected persons during a period of time of increased risk for HIV infection
  - Regular monitoring for HIV infection
  - Regular monitoring for toxicity
Using Antiretroviral Medications for Bio-Behavioral HIV-1 Prevention

**PrEP**
- Time of transmission
- After infection

**PEP**

**ART**

Adverse Events
- Demonstrated efficacy
- Efficacy
- Adherence
- Safety
- Challenges
- Resistance
- Primary Side Effects
- Target

Advantages
- Shortened course than PEP
- Clinical benefits and reduced infectiousness

Challenges
- Toxicity/Side effects
- Compliance
- Resistance

**FTC/TDF**
- For both

**MTF**

**PrEP** for MSM and MTF: iPrEx

- 2499 HIV(-) adults enrolled in the Americas, Thailand, South Africa randomized to daily FTC/TDF vs Placebo
- All received monthly risk reduction counseling
- Risk: mean of 18 partners and 60% URAI in 12w, 80% UAI w HIV(+)/unk and 41% transactional sex and 2% known HIV+ partner in 24w
- HIV testing: rapid at screening, enrollment, and all monthly f/u visits; retrospective HIV RNA at seroconversion to detect earliest lab evidence of infection
- Outcomes: Safety and Efficacy

**PrEx: Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>FTC/TDF (n=1251)</th>
<th>Placebo (n=1248)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 event</td>
<td>12 (248)</td>
<td>13 (285)</td>
<td>0.51</td>
</tr>
<tr>
<td>Death</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>4</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>5 (76)</td>
<td>5 (87)</td>
<td>0.57</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>2 (28)</td>
<td>1 (15)</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine elevation confirmed on next visit</td>
<td>0.4</td>
<td>7.0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Why FTC/TDF for PrEP?**

- Effective prevention against SHIV in macaques
- Daily or 3d pre/2h post rectal virus application
- Licensed for ART and reassuring safety profile
- Long half-life
- Concentrated in rectum
- Few drug interactions

**Clinical Trial Data**

**iPrEx Outcomes:**
- Safety: no significant difference in creatinine elevation in FTC/TDF; increased nausea and wt loss in FTC/TDF (P=0.04 for both); small but sig. decrease in BMD
- Adherence: 89-95% (self-report and pill count); drugs detected in 8% of cases and 54% of controls "on treatment" by pill count or self report
- Adherence correlated with age>25, US site, recent URAI
- Efficacy: 10 infections at enrollment, 39% during f/u (36 in FTC/TDF, 64 in placebo, 42% risk reduction; 95% CI 15-63, P=0.005)
- In FTC/TDF group: 95% (70-99, P=0.001) risk reduction if detectable drug level (adjusted for URAI)


**Grant R, et al. CROI 2011. Abstract 82**
Grant R, et al. NEJM 2010

**iPrEx: Nausea on History**

---


**iPrEx: Numbers of Sexual Partners**

---


**iPrEx: Condom Use With High-Risk Sex**

---


**iPrEx: Breakthrough Infections and Resistance**

- **New HIV infections** (91 samples tested)[1]
  - No drug resistance in participants on FTC/TDF
  - 2 with minor variant drug resistance on placebo (1 to TDF, 1 to FTC)
- **HIV infections already present** at enrollment
  - 2 cases of FTC resistance in FTC/TDF arm[2]
  - Resistance dropped to undetectable levels within 6 mos after stopping PrEP[1]


**iPrEX take-home**

- Reasonably effective: 44% overall, higher if adherence high (higher adherence→higher protection)
- Safe and well-tolerated
- Resistance, Risk Compensation rare in RTC with monthly visits, testing, counseling
- Crucial to rule out acute infection before starting

**PrEP for heterosexual protection**

- Partners PrEP: serodiscordant couples
- TDF2: high-risk hetero men and women
- FEMPREP: high risk women
- VOICE: high risk women
- Bangkok Tenofovir Study (IDU)
Serodiscordant Heterosexuals: Partners PrEP

- 4758 serodiscordant couples in Kenya, Uganda randomized to daily FTC/TDF vs TDF vs Placebo
- HIV(+) partner NOT eligible for ART at time of enrollment by national guidelines but counseled to start when eligible
- At all HIV(-) monthly and HIV(+) quarterly visits: counseling, condoms, testing (HIV)
- Risk: median 7 yrs marriage and 4 sex acts in prior month; 28% unprotected sex in prior month; median VL 3.9log (HIV+)
- HIV testing: rapid at screening, enrollment, and all monthly f/u visits; retrospective HIV RNA at seroconversion to detect earliest lab evidence of infection
- Outcomes: Safety and Efficacy


Partners PrEP: efficacy

- Stopped early by DSMB: Efficacy vs. placebo 67% (44-81, P<0.001) for TDF and 75% (55-87, P<0.001) for FTC/TDF; no significant difference between treatment arms
- Equal protection: 63% (men) and 71% (women) for TDF; 84% (men) and 66% (women) for FTC/TDF; no significant interaction for sex
- Detectable drug: 86%(TDF)-90%(FTC/TDF) protection
- 21% of HIV+ partners started ART. No effect on efficacy when time on ART censored; No effect of VL>50K
- Adherence high by pill count, unannounced home visits; drug detected in 82% of nonseroconverters and 31% of seroconverters (randomly selected); detectable drug in 31% (infected) vs 82% (uninfected)


Partners PrEP: Safety

- No difference in deaths, SAEs, serum phosphorus or creatinine
- Neutropenia: 17% (FTC/TDF> 15%(TDF)> 12% (placebo)
- Mild increase in nausea, fatigue during 1st month of TDF, FTC/TDF therapy (startup syndrome)


Partners PrEP: Resistance

- 14/96 infections at enrollment (seroneg/RNA+)
  - 5 (TDF) 3(FTC/TDF) 6(placebo)
  - 1 K65R in TDF group; 1 M184V in FTC/TDF group developed during study
- No resistance in infections during follow-up


FEM-PrEP

- FEM-PrEP: Phase III study of oral TDF/FTC planned for 3000 high-risk women in Africa (1931 enrolled)
  - Announced April 18, 2011, that study was ended prematurely because of lack of efficacy
  - 56 new infections, evenly divided between arms
- Higher risk cohort of women than TDF2 or Partners PrEP
  - 1 or more vaginal sex acts in previous 2 weeks or more than 1 partner in previous month
  - Higher rates of exchange sex
  - Higher rates of STDs at baseline (GC, CT, syphilis)
- Safety
  - Increased rate of nausea, vomiting and ALT elevations
  - Increased pregnancy rate
- Poor adherence
  - 28% of seroconverters and 30% of nonseroconverters had drug detected at beginning of 6th month


FDA approval: 16 July 2012

- FTC/TDF approved for prevention for individuals at high risk of HIV infection and who may engage in sexual activity with HIV infected partners
  - MSM
  - Women in discordant relationships or otherwise at risk
- To be used daily in combination with comprehensive prevention strategy including safer sex practices, risk reduction counseling, and regular testing
- HIV testing at baseline and every 3 months
- REMS (Risk Evaluation and Mitigation Strategy) for providers, focused on efficacy and preventing resistance
- Gilead required to study viral isolates of seroconverters, outcomes in pregnant women, adherence
**CDC Guidance: Jan 2011 and Aug 2012**

- Document negative HIV Ab test and test for AHI if symptomatic
- Confirm pt is at “substantial, ongoing, high risk for acquiring HIV infection”
- Prescribe no more than 90 days at a time
- Link known HIV positive partners to care
- Caution during pregnancy; Don’t use while breastfeeding
- Monitoring
  - q2-3 mo. HIV testing, counseling and condoms
  - q6 mo STD screening
  - Creatinine at 3 months, than q6mo

**VOICE: efficacy, safety**

- VOICE: Phase III placebo-controlled trial of 5,029 women in South Africa, Uganda, and Zimbabwe, starting in 2009
- Mean age 25.3y; 79% single
  - Daily oral TDF vs TDF/FTC vs placebo (n=3,016) OR daily vaginal TDF 1% gel vs placebo (n=2,010)
  - All received risk reduction counseling, condoms, STI treatment
- TDF and gel arms halted 2011 by the DSMB for lack of efficacy
- TDF/FTC vs placebo arms (n=2,016) presented at CROI on 4 March 2013
  - HIV incidence: 61/994 (4.7%) in TDF/FTC vs. 60/1,008 (4.6%) in Placebo
  - 8.8% for unmarried women (<25y)
  - 0.8% for married women >25y
- No safety concerns identified

**VOICE: adherence**

- Self report and pill counts: 90% (all arms)
- Prevalence of detectable blood levels: 29% (FTC/TDF)
  - 21% if unmarried, <25y
  - 54% if married, >25y

**Drug exposure & adherence are critical**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Overall Efficacy (mITT)</th>
<th>Risk reduction with drug detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fem-PrEP</td>
<td>2120 high-risk women</td>
<td>Study stopped due to futility</td>
<td>&lt;26% women in FTC/TDF group had consistently detectable drug; “adherence too low to assess efficacy”</td>
</tr>
<tr>
<td>PrEp</td>
<td>2,499 MSM</td>
<td>42%</td>
<td>92% risk reduction with detectable drug</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>4758 heterosexual discordant couples</td>
<td>TDF: 67% FTC/TDF: 75%</td>
<td>90% risk reduction with detectable drug</td>
</tr>
<tr>
<td>TDF2</td>
<td>1200 heterosexual men and women</td>
<td>62%</td>
<td>78% risk reduction excluding participants with no refills for &gt;30 days</td>
</tr>
</tbody>
</table>

Grant IHS 2011; Baeten CROI 2012; Thigpen IHS 2011; van Doremare CROI 2012; MTN Press release

**Summary of the data**

- PrEP found to be moderately efficacious in at-risk MSM
  - May be highly efficacious in those who take it consistently
  - Pill use was a significant challenge (higher use in the US)
- Efficacy results in women mixed
  - Adherence is a major factor
  - Differential cervicovaginal vs rectal tissue penetration?
  - Other local tissue phenomena: STDs, trauma, tissue integrity…?
  - Stage of infection in source partner?
- No increase in risk behavior in context of blinded use
- Resistance: crucial to rule out acute HIV at initiation; not seen with high or low adherence. What about intermediate adherence? What about longer intervals between visits?
- FTC/TDF in HIV negatives appears safe and well-tolerated across a number of PrEP studies for women

Implementation Questions

• How will PrEP work outside of RCTs?
  – Acceptance?
  – Adherence?
  – Resistance?
  – Safety?
  – Diversion?
  – Effectiveness?
  – Sustainability?

PrEP Demonstration Projects in the US

<table>
<thead>
<tr>
<th>Study (sponsor)</th>
<th>Population (N)</th>
<th>Sites</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx OLE (Open Label Extension) [NIAID]</td>
<td>MSM previously enrolled in iPrEx RCT (N~300)</td>
<td>San Francisco Boston Chicago</td>
<td>Enrollment in US completed, Results 2014</td>
</tr>
<tr>
<td>California HIV Research Program (CHRP)</td>
<td>MSM and transgender women (N=700)</td>
<td>Los Angeles Long Beach San Diego Oakland</td>
<td>Enrollment 2013</td>
</tr>
<tr>
<td>Adolescents Trials Network (ATN)</td>
<td>Young MSM: 18-22 yr in ATN 110 (N=200) 15-17 yr in ATN 113 (N=100)</td>
<td>All 14 ATN sites</td>
<td>Enrollment to begin late summer 2012</td>
</tr>
<tr>
<td>NIH</td>
<td>MSM</td>
<td>NYC (Cullen Lorde)</td>
<td>Planning</td>
</tr>
<tr>
<td>NIH</td>
<td>Serodiscordant couples (N=250 dyads)</td>
<td>NYC: South Bronx, Harlem E. Brooklyn</td>
<td>Planning</td>
</tr>
</tbody>
</table>

The Demo Project

• NIAID-funded PrEP Demonstration Project
• NCT# 01632995
• Multi-site, prospective, open-label
• 500 at-risk HIV-negative MSM and transgender women
• Offered up to 48 weeks of PrEP (FTC/TDF)

Demonstration Project Timeline

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sites</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIAID</td>
<td>MSM</td>
<td>San Francisco Boston Chicago</td>
<td>Enrollment 2013</td>
</tr>
<tr>
<td>NIAID</td>
<td>MSM</td>
<td>Miami</td>
<td>Enrollment 2013</td>
</tr>
<tr>
<td>NIH</td>
<td>Serodiscordant couples (N=250 dyads)</td>
<td>NYC: South Bronx, Harlem E. Brooklyn</td>
<td>Planning</td>
</tr>
</tbody>
</table>

PrEP Research Agenda

• New agents
  – HPTN 069 (NEXT-PrEP)
    • Maraviroc + FTC
    • Maraviroc + TDF
    • Maraviroc alone
    • Truvada alone
• Alternate dosing
  – ADAPT
    • Daily dosing
    • Time-driven (twice weekly + dose post-exposure)
    • Event-driven (before and after exposure)
  – IPERGAY
    • Before and after sex
  – Other routes of exposure
    – Bangkok Tenofovir Study (IDU)
  – Other routes of delivery
    – Vaginal microbicides
    – Vaginal rings
    – Rectal microbicides
    – Long acting IM

Alternate Dosing - IPERGAY

- Daily dosing
- 2nd dose 1 tablet
- 3rd dose 2 tablets before and after sexual contact
- 1st dose 1 tablet
- 2nd dose 1 tablet
- 3rd dose 2 tablets before and after sexual contact
- 4th dose 1 tablet
Thank You For Your Time!!!!