Tenofovir based PrEP technologies in women: what do we currently know?

Linda-Gail Bekker
The Desmond Tutu HIV Centre
University of Cape Town.

Expanding HIV Prevention Options for Women.
The need for a female initiated, managed and controlled prevention methodology.
Highly active HIV prevention.

A term coined by Prof K Holmes, University of Washington School of Medicine, Seattle, WA, USA.

From Coates T et al 2008.
Targeted Prevention Packages

- CSW
- IDU
- MSM
- PMTCT

Young women
Antiretroviral therapy as Prevention?

**CAN A PILL A DAY PREVENT HIV?**

FOR INFORMATION ON THIS NEW AND EXCITING HIV PREVENTION STUDY

SMS "Info" at no cost to 30060 or e-mail MCMHP@hiv-research.org.za

All participants will be compensated for their time and transport.

[Image of a pill bottle]
HIV transmission involves a discordant relationship.....

ART reduces VL
Reduce infectiousness

PrEP
ART prophylaxis aborts potential infection

Positive
Negative
Topical or microbicides

CAN A PILL A DAY PREVENT HIV?

Systemic

PrEP

Participants will be compensated for their time and transport.

MOTHER CITY MEN'S HEALTH PROJECT

TRIANGLE PROJECT

DURBAN UNIVERSITY OF TECHNOLOGY

SOUTH AFRICA

TRIANGLE PROJECT
Why Tenofovir in prophylaxis?

- Protective in Animals
- Licensed for Treatment
- Excellent Safety Record PO
- Long Half Life (>48 hours)
- Enriched in Genital Fluids
- No interactions with tuberculosis treatment or hormonal contraception
- Relatively high barrier to resistance mutations
So what's the evidence for systemic PrEP in women?
Evidence : Systemic PrEP

• 4 positive RPCTs involving >10 000 HIV negative individuals

• 4 different populations
  – MSM, hetero (M + F), discordant couples (M`+ F), IDU (M + F)

• Both hetero/homo sexual and IDU risk

• Truvada (TDF/FTC), Tenofovir

• PE : 44-75%
Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H.,
Peter L. Anderson, Pharm.D., Vanessa McNamah, B.S., Albert Y. Liu, M.D., M.P.H.,
Lorena Vargas, Pedro Goicochea, M.Sc., Martin Casapia, M.D., M.P.H.,
Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D.,
Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D.,
Valdilea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D.,
Suwat Charayalertsak, M.D., Dr.P.H., Mauro Schecter, M.D., Ph.D.,
Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D.,
Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D.,
Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D.,
Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D.,
J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S.,
James F. Rooney, M.D., Howard S. Jaffe, M.D., Ana I. Martinez, R.Ph.,
David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

Published online on November 23, 2010
Article and supplement available online

Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

J.M. Baeten, D. Donnell, P. Ndase, N.R. Mugoo, J.D. Campbell, J. Wangisi, J.W. Tappee, E.A. Bukusi, C.R. Cohen,
A. Mucunguzi, E. Nakku-Joloba, R. Twesigye, K. Ngure, C. Apaka, H. Tamboh, F. Gabona, A. Mujugira,
D. Panteleeff, K.K. Thomas, L. Kigoduchi, M. Krows, J. Revall, S. Morrison, H. Haugen, M. Emmanuel-Ogier,
L. Ondrejcek, R.W. Coombs, L. Frenkel, C. Hendrix, N.N. Bumpus, D. Bangsberg, J.E. Haberer, W.S. Stevens,
J.R. Lingappa, and C. Celum, for the Partners PrEP Study Team*

Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana

Michael C. Thigpen, M.D., Poloko M. Kebaabetswe, Ph.D., M.P.H.,
M.D., M.P.H., Dawn K. Smith, M.D., M.P.H.,
H. Fatma A. Soud, Ph.D., Kata L. Chilag, Ph.D.,
B., Ch.B., Lovemore Ian Chirwa, M.B., Ch.B., M.Phil.,
J.B., Daniel Abebe, M.B., Evans Buliva, M.B., Ch.B.,
M.S.P.H., Sandra Johnson, M.A., Thom Sukalac,
R., Clyde Hart, Ph.D., Jeffrey A. Johnson, Ph.D.,
Craig W. Hendrix, M.D., and John T. Brooks, M.D.,
for the TDF2 Study Group*
### Number of women in these trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>0 (few TGF)</td>
<td>2499</td>
<td>2499</td>
</tr>
<tr>
<td>TDF2</td>
<td>548</td>
<td>671</td>
<td>1219</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>2283</td>
<td>2475</td>
<td>4758</td>
</tr>
<tr>
<td>BK IDU</td>
<td>499</td>
<td>1924</td>
<td>2413</td>
</tr>
</tbody>
</table>

Total Women: 3330  Total Men: 7566  Total: 10896
## Partners PrEP: 4758 couples

<table>
<thead>
<tr>
<th>Group</th>
<th>TDF (1579)</th>
<th>TDF/FTC (1584)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>62 % (34-78)</td>
<td>73 % (49-84)</td>
</tr>
<tr>
<td>Women</td>
<td>68 % (29-85)</td>
<td>62 % (19-82)</td>
</tr>
<tr>
<td>Men</td>
<td>55 % (4-79)</td>
<td>83 % (49-94)</td>
</tr>
</tbody>
</table>
Discordant couples: “outside partners”

<table>
<thead>
<tr>
<th>Study</th>
<th>Total N</th>
<th>Linked</th>
<th>Indeterm</th>
<th>Unlinked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners in Prevention</td>
<td>108</td>
<td>72%</td>
<td>2%</td>
<td>26%</td>
</tr>
<tr>
<td>HPTN 052</td>
<td>38</td>
<td>76%</td>
<td>5%</td>
<td>18%</td>
</tr>
<tr>
<td>Zambia cohort</td>
<td>149</td>
<td>87%</td>
<td>--</td>
<td>13%</td>
</tr>
<tr>
<td>Rakai cohort</td>
<td>57</td>
<td>50%</td>
<td>36%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Even among stable serodiscodant couples, substantial % from outside partners
What’s the evidence for Topical PrEP
Evidence : Topical PrEP

- Single trial
- RPCT
- One country – 2 sites
- 889 Heterosexual, high incidence HIV neg women
- 1% Tenofovir gel
- PE: 39%
- Led to second confirmatory study :
  - FACTS 001
  - RPCT
  - 1 country, numerous sites
Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim,1,2,*† Salim S. Abdool Karim,1,2,3* Janet A. Frohlich,1 Anneke C. Grobler,1 Cheryl Baxter,1 Leila E. Mansoor,1 Ayesha B.M. Kharsany,1 Sengeziwe Sibeko,1 Koleka P. Mlisana,1 Zaheen Omar,1 Tanuja N Gengiah,1 Silvia Maarschalk,1 Natasha Arulappan,1 Mukelisiwe Mlotshwa,1 Lynn Morris,4 Douglas Taylor,5 on behalf of the CAPRISA 004 Trial Group‡

1Centre for the AIDS Program of Research in South Africa (CAPRISA), Durban, South Africa. 2Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA. 3University of KwaZulu-Natal, Durban, South Africa. 4National Institute for Communicable Diseases, Johannesburg, South Africa. 5FHI, North Carolina, USA.

*These authors contributed equally to this work.

†To whom correspondence should be addressed. E-mail: caprisa@ukzn.ac.za

‡The members of the CAPRISA 004 Trial Group appear at the end of this paper.

The CAPRISA 004 trial assessed effectiveness and safety of a 1% vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase inhibitor, for the prevention of HIV acquisition in women. A double-blind, randomized region which accounts for 70% of global burden of Human Immunodeficiency Virus (HIV) infection (1). Current HIV prevention behavioral messages on abstinence, faithfulness and condom promotion have had limited impact on HIV

Available for download from: http://www.sciencemag.org/scienceexpress/recent.dtl
Where were we then: PrEP efficacy trial results, March 2012

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>Women</td>
<td>889</td>
<td>39% efficacy vaginal TFV gel</td>
</tr>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>2499</td>
<td>44% efficacy FTC/TDF</td>
</tr>
<tr>
<td>TDF2 Study</td>
<td>Young men and women</td>
<td>1200</td>
<td>62% efficacy FTC/TDF</td>
</tr>
<tr>
<td>Partners PrEP Study</td>
<td>Heterosexual couples</td>
<td>4758</td>
<td>67% efficacy TDF 75% efficacy FTC/TDF</td>
</tr>
<tr>
<td>BK IDU</td>
<td>IDU Men and Women</td>
<td>2413</td>
<td>49% efficacy FTC/TDF</td>
</tr>
</tbody>
</table>

However.....
There are some trials with contrary results....
### Tenofovir-based prevention results, as of June 2013

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>Women</td>
<td>889</td>
<td>39% [CI = 6-60] efficacy coitally-dependent vaginal TFV gel</td>
</tr>
<tr>
<td>iPrEx</td>
<td>Gay men, other MSM, transgender women</td>
<td>2499</td>
<td>42% [CI = 18-60] efficacy daily oral FTC/TDF</td>
</tr>
<tr>
<td>TDF2 Study</td>
<td>Men and women</td>
<td>1200</td>
<td>62% [CI = 22-83] efficacy daily oral FTC/TDF</td>
</tr>
<tr>
<td>Partners PrEP Study</td>
<td>Serodiscordant couples</td>
<td>4758</td>
<td>67% [CI = 44-81] efficacy daily oral TDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75% [CI = 55-87] efficacy daily oral FTC/TDF</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Women</td>
<td>1950</td>
<td>Futility of daily oral FTC/TDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6% [CI = -52-41]</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>5029</td>
<td>Futility of daily vaginal TFV gel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14.7% [CI = -21-40]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Futility of daily oral TDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-48.8% [CI = -129-3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Futility of daily oral FTC/TDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-4.2% [CI = -49-27]</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>IDUs</td>
<td>2400</td>
<td>49% [CI = 10-72] efficacy daily oral TDF</td>
</tr>
<tr>
<td>FACTS 001</td>
<td>Women</td>
<td>2900</td>
<td>Coitally-dependent vaginal TFV gel enrolling Results expected in 2015</td>
</tr>
</tbody>
</table>
Post-VOICE

• In a case-cohort subset, TFV was detected on average in **28%** of available quarterly plasma samples among participants randomized to TDF, **29%** to TDF/FTC, and **22%** to TFV gel.

• Predictors of plasma TFV detection in the case cohort group were being **married**, **age >25 years**, and reporting a primary male partner >28 years. No safety concerns were identified.
# Tenofovir-based prevention results, as of June 2013

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Age</th>
<th>Married/Stable partner</th>
<th>Product tested*</th>
<th>Efficacy</th>
<th>Adherence (as per drug levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP 004</td>
<td>24</td>
<td>88%</td>
<td>TFV gel <em>(BAT 24)</em></td>
<td>39% [CI = 6-60%]</td>
<td>50.5%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>27</td>
<td></td>
<td>Oral TDF/FTC</td>
<td>42% [CI = 18-60%]</td>
<td>51%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>36</td>
<td>98%</td>
<td>Oral TDF</td>
<td>67% [CI = 44-81%]</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral TFD/FTC</td>
<td>75% [CI = 55-87%]</td>
<td>81%</td>
</tr>
<tr>
<td>TDF-2</td>
<td>25</td>
<td>6%</td>
<td>Oral TDF/FTC</td>
<td>62% [CI = 22-83%]</td>
<td>80.5%</td>
</tr>
<tr>
<td>CDC/BTS</td>
<td>31</td>
<td>NA</td>
<td>Oral TDF</td>
<td>49% [CI = 10-72%]</td>
<td>83.8%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>24</td>
<td>31%</td>
<td>Oral TDF/FTC</td>
<td>No protection</td>
<td>24%</td>
</tr>
<tr>
<td>VOICE</td>
<td>25</td>
<td>21%</td>
<td>TFV gel <em>(BAT 24)</em></td>
<td>No protection</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral TDF</td>
<td>No protection</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral TDF/FTC</td>
<td>No protection</td>
<td>29%</td>
</tr>
<tr>
<td>FACTS</td>
<td>To come in 2015</td>
<td></td>
<td>TFV gel <em>(BAT 24)</em></td>
<td>To come in 2015</td>
<td></td>
</tr>
</tbody>
</table>

*All products tested for daily use, except as noted.
Dose-response curve...

No drug, no efficacy.
### Tenofovir levels and HIV-1 protection

- Objective adherence measures from trials show:

<table>
<thead>
<tr>
<th></th>
<th>Seroconverters</th>
<th>Non-seroconverters</th>
<th>Protection</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>9%</td>
<td>51%</td>
<td>92%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>25%</td>
<td>81%</td>
<td>90%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Donnell et al CROI 2012 Abstract 30
Grant et al N Engl J Med 2010
Tenofovir levels and HIV-1 protection

- Objective adherence measures from trials show:
  1) PrEP use was modest in iPrEx and high in Partners PrEP, consistent with overall efficacy

<table>
<thead>
<tr>
<th></th>
<th>% with tenofovir detected</th>
<th>HIV-1 protection: detection versus no detection of tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seroconverters</td>
<td>Non-seroconverters</td>
</tr>
<tr>
<td>iPrEx</td>
<td>9%</td>
<td>51%</td>
</tr>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>25%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Donnell et al CROI 2012 Abstract 30
Grant et al N Engl J Med 2010
**Tenofovir levels and HIV-1 protection**

- Objective adherence measures from trials show:
  1) PrEP use was modest in iPrEx and high in Partners PrEP, consistent with overall efficacy
  2) When PrEP was taken, protection appeared to be very high

<table>
<thead>
<tr>
<th></th>
<th>% with tenofovir detected</th>
<th>HIV-1 protection: detection versus no detection of tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seroconverters</td>
<td>Non-seroconverters</td>
</tr>
<tr>
<td>iPrEx</td>
<td>9%</td>
<td>51%</td>
</tr>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>25%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Donnell et al CROI 2012 Abstract 30
Grant et al N Engl J Med 2010
PrEP taken consistently or not at all
Partners PrEP Study

<table>
<thead>
<tr>
<th>Serum tenofovir levels</th>
<th>Infected cases</th>
<th>Uninfected cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable</td>
<td>20</td>
<td>164</td>
</tr>
<tr>
<td>0.3 - 10 ng/mL</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>≤10 – 40 ng/mL</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>≥ 40 ng/mL</td>
<td>7</td>
<td>640</td>
</tr>
</tbody>
</table>

Donnell, Abstract #30, CROI 2012
IDU PrEP study
BK IDU study

• In this study, efficacy increased from 46% to 56% in the per-protocol analysis based on observed adherence and to 74% when limited to participants with detectable tenofovir concentrations.

• Although the trial was not powered to assess efficacy in subgroups, we saw higher efficacy in women (79%) and in participants aged 40 years or older (89%)—two subgroups with high levels of adherence.
ADHERENCE

Partners PrEP

EFFICACY

BK IDU
TDF2
iPrEx
CAPRISA 004
FEMPREP
VOICE
# Tenofovir-based prevention results, as of June 2013

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Age</th>
<th>Married/Stable partner</th>
<th>Product tested*</th>
<th>Efficacy</th>
<th>Adherence (as per drug levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP 004</td>
<td>24</td>
<td>88%</td>
<td>TFV gel (BAT 24)</td>
<td>39% [CI = 6-60%]</td>
<td>50.5%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>27</td>
<td></td>
<td>Oral TDF/FTC</td>
<td>42% [CI = 18-60%]</td>
<td>51%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>36</td>
<td>98%</td>
<td>Oral TDF Oral TFD/FTC</td>
<td>67% [CI = 44-81%] 75% [CI = 55-87%]</td>
<td>83% 81%</td>
</tr>
<tr>
<td>TDF-2</td>
<td>25</td>
<td>6%</td>
<td>Oral TDF/FTC</td>
<td>62% [CI = 22-83%]</td>
<td>80.5%</td>
</tr>
<tr>
<td>CDC/BTS</td>
<td>31</td>
<td>NA</td>
<td>Oral TDF</td>
<td>49% [CI = 10-72%]</td>
<td>83.8%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>24</td>
<td>31%</td>
<td>Oral TDF/FTC</td>
<td>No protection</td>
<td>24%</td>
</tr>
<tr>
<td>VOICE</td>
<td>25</td>
<td>21%</td>
<td>TFV gel Oral TDF Oral TDF/FTC</td>
<td>No protection No protection No protection</td>
<td>23% 28% 29%</td>
</tr>
<tr>
<td>FACTS</td>
<td>To come in 2015</td>
<td></td>
<td>TFV gel (BAT 24)</td>
<td>To come in 2015</td>
<td></td>
</tr>
</tbody>
</table>

*All products tested for daily use, except as noted.*
### Tenofovir-based prevention results, as of June 2013

<table>
<thead>
<tr>
<th>Trial</th>
<th>Product tested*</th>
<th>Efficacy</th>
<th>Adherence (as per drug levels)</th>
<th>Adherence-adjusted efficacy (as per drug levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP 004</td>
<td>TFV gel (BAT 24)</td>
<td>39% [CI = 6-60%]</td>
<td>50.5%</td>
<td>54% [CI=4-80%]</td>
</tr>
<tr>
<td>iPrEx</td>
<td>Oral TDF/FTC</td>
<td>42% [CI = 18-60%]</td>
<td>51%</td>
<td>92% [40-99%]</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Oral TDF</td>
<td>67% [CI = 44-81%]</td>
<td>83%</td>
<td>86% [CI=67-94%]</td>
</tr>
<tr>
<td></td>
<td>Oral TDF/FTC</td>
<td>75% [CI = 55-87%]</td>
<td>81%</td>
<td>90% [CI=58-98%]</td>
</tr>
<tr>
<td>TDF-2</td>
<td>Oral TDF/FTC</td>
<td>62% [CI = 22-83%]</td>
<td>80.5%</td>
<td>84% [NS]</td>
</tr>
<tr>
<td>CDC/BTS</td>
<td>Oral TDF</td>
<td>49% [CI = 10-72%]</td>
<td>83.8%</td>
<td>70% [CI=2-91%]</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Oral TDF/FTC</td>
<td>No protection</td>
<td>24%</td>
<td>NA</td>
</tr>
<tr>
<td>VOICE</td>
<td>TFV gel</td>
<td>No protection</td>
<td>23%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Oral TDF</td>
<td>No protection</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Oral TDF/FTC</td>
<td>No protection</td>
<td>29%</td>
<td>NA</td>
</tr>
<tr>
<td>FACTS</td>
<td>TFV gel (BAT 24)</td>
<td></td>
<td>To come in 2015</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NS = not statistically significant; NA = data not available.
*All products tested for daily use, except as noted.
## Tenofovir-based prevention results, as of June 2013

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age</th>
<th>Married/Stable partner</th>
<th>Efficacy</th>
<th>Adherence (as per drug levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP 004</td>
<td>24</td>
<td>88%</td>
<td>TFV gel: 39% [CI = 6-60%]</td>
<td>50.5%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>27</td>
<td></td>
<td>TDF/FTC: 42% [CI = 18-60%]</td>
<td>51%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>36</td>
<td>98%</td>
<td>Oral TDF: 67% [CI = 44-81%] Oral TDF/FTC: 75% [CI = 55-87%]</td>
<td>83% 81%</td>
</tr>
<tr>
<td>TDF-2</td>
<td>25</td>
<td>6%</td>
<td>Oral TDF/FTC: 62% [CI = 22-83%]</td>
<td>80.5%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>24</td>
<td>31%</td>
<td>Oral TDF/FTC: 6% [CI = -52-41%]</td>
<td>24%</td>
</tr>
<tr>
<td>VOICE</td>
<td>25</td>
<td>21%</td>
<td>TFV gel: 14.7% [CI = -21-40%] Oral TDF: -48.8% [CI = -129-3%] Oral TDF/FTC: -4.2% [CI = -49-27%]</td>
<td>23% 28% 29%</td>
</tr>
<tr>
<td>VOICE-SA</td>
<td>25</td>
<td>8%</td>
<td></td>
<td>To come</td>
</tr>
<tr>
<td>VOICE-Ug</td>
<td>28</td>
<td>50%</td>
<td></td>
<td>To come</td>
</tr>
<tr>
<td>VOICE-Zim</td>
<td>28</td>
<td>94%</td>
<td></td>
<td>To come</td>
</tr>
<tr>
<td>CDC/BTS</td>
<td>31</td>
<td>NA</td>
<td>Oral TDF: 49% [CI = 10-72%]</td>
<td>83.8%</td>
</tr>
<tr>
<td>FACTS</td>
<td></td>
<td></td>
<td></td>
<td>2015</td>
</tr>
</tbody>
</table>
## Daily oral ARV for PrEP Efficacy Trial Results

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Participants</th>
<th>Product</th>
<th>mITT efficacy</th>
<th>Adherence-adjusted efficacy based on TDF detection in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (95%CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>Injecting drug users</td>
<td>TDF</td>
<td>49 (10-72)</td>
<td>70 (2-91)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>HIV discordant couples</td>
<td>TDF</td>
<td>67 (44-81)</td>
<td>86 (67-94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>75 (55-87)</td>
<td>90 (58-98)</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexually active men and women</td>
<td>TDF/FTC</td>
<td>62 (22-83)</td>
<td>84 NS</td>
</tr>
<tr>
<td>iPrEX</td>
<td>MSM</td>
<td>TDF/FTC</td>
<td>42 (18-60)</td>
<td>92 (40-99)</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>Heterosexually active women</td>
<td>TDF/FTC</td>
<td>NS --</td>
<td>NA --</td>
</tr>
<tr>
<td>VOICE</td>
<td>Heterosexually active women</td>
<td>TDF</td>
<td>NS --</td>
<td>NA --</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>NS --</td>
<td>NA --</td>
</tr>
</tbody>
</table>

Abbreviations: mITT = modified intent to treat analysis, excluding persons determined to have had HIV infection at enrollment; NS = not statistically significant; NA = data not available.

Is Tenofovir based PrEP safe in healthy women??
Trials have shown:

TDF/FTC well tolerated, with the rate of both serious and mild adverse events generally balanced between those receiving PrEP and those receiving placebo.

The most prominent side effects were gastrointestinal (eg, nausea), and these symptoms were present only in a minority of subjects (10% or less), were mild in severity, and were generally limited to the first month after initiation of the medication.
# Safety:

## Renal monitoring of PrEP users

<table>
<thead>
<tr>
<th>Study/sub-category</th>
<th>Total</th>
<th>MD [95% CI], ml/min</th>
<th>Mean Difference [95% CI], mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART experienced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BICOMBO 2009</td>
<td>333</td>
<td>-0.70 [-2.73, 1.33]</td>
<td></td>
</tr>
<tr>
<td>De Jesus 2009</td>
<td>300</td>
<td>-0.60 [-1.71, 0.51]</td>
<td></td>
</tr>
<tr>
<td>ART naive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEAT 2009</td>
<td>672</td>
<td>-3.00 [-9.06, 3.06]</td>
<td></td>
</tr>
<tr>
<td>Arribas 2008</td>
<td>458</td>
<td>-3.00 [-6.77, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Gallant 2004</td>
<td>600</td>
<td>-5.00 [-8.80, -1.20]</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>-1.50 [-2.96, -0.005]</td>
<td></td>
</tr>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART experienced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinai 2009</td>
<td>63</td>
<td>-17.00 [-31.35, -2.65]</td>
<td></td>
</tr>
<tr>
<td>Goicoechea 2008 NNRTI</td>
<td>62</td>
<td>-0.22 [-11.18, 10.74]</td>
<td></td>
</tr>
<tr>
<td>Goicoechea 2008 RPI</td>
<td>84</td>
<td>-7.88 [-18.66, 2.90]</td>
<td></td>
</tr>
<tr>
<td>HOPS 2007</td>
<td>736</td>
<td>-4.40 [-6.97, -1.83]</td>
<td></td>
</tr>
<tr>
<td>Winston 2006</td>
<td>948</td>
<td>-6.33 [-14.85, 2.19]</td>
<td></td>
</tr>
<tr>
<td>ART naive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fux 2007</td>
<td>284</td>
<td>-4.90 [-8.58, -1.22]</td>
<td></td>
</tr>
<tr>
<td>Fux 2007 N</td>
<td>569</td>
<td>-8.20 [-13.13, -3.27]</td>
<td></td>
</tr>
<tr>
<td>Gallant 2005</td>
<td>658</td>
<td>-5.80 [-8.70, -2.90]</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>-5.45 [-7.02, -3.89]</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>-3.90 [-5.66, -2.14]</td>
<td></td>
</tr>
</tbody>
</table>

Cooper, CID 2010
Renal fxn in PrEP studies

• Of 1251 pts receiving FTC-TDF in iPrEx,
  – 5 pts had elevated creatinine ≥ 2 sequential visits
  – All resolved when drug stopped
  – 4 re-challenged without problem

• Partners PrEP, TDF-2, Fem-PrEP
  – No significant difference between active, placebo arms

• Although nephrotoxicity not seen in this HIV negative population:
  – Excluded pts with baseline renal disease
  – Relatively small numbers, short follow-up
Bone

• 1% reduction in BMD
• No associated increase in fractures.
Resistance -
Good news:

• In 4 published RCTs of PrEP:
  – Partners, iPrEx, TDF2, CAPRISA 004

• No infection on PrEP: No RESISTANCE

• No exposure to PrEP: resistance rare, but INFECTION
**HIV-1 Drug Resistance from PrEP**

- **Infrequent** cases of drug resistance among PrEP study participants who seroconverted while receiving active drug

<table>
<thead>
<tr>
<th>Study</th>
<th>Infections on Study</th>
<th># infected</th>
<th># resistant to FTC or TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td></td>
<td>131</td>
<td>None</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td></td>
<td>82</td>
<td>None</td>
</tr>
<tr>
<td>TDF2</td>
<td></td>
<td>33</td>
<td>1 placebo (K65R &lt;1%)*</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td></td>
<td>68</td>
<td>1 placebo (M184V)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 FTC/TDF (M184V/I)**</td>
</tr>
</tbody>
</table>

* Transmitted (primary) resistance can occur independent of PrEP, which likely explains resistance in the placebo arm

** 1 probable and 2 possible transmitted resistance; 1 uncertain timing of infection (HIV RNA detectable at first follow-up visit)
Theoretical Infection-Exposure-Resistance Relationships

- No Drug
- No Resistance
- Infection

Zone of Resistance Risk

- No Infection
- No Resistance

Fraction infected or resistant

Drug Exposure

Low

High
Good news:

- Resistance NOT seen in topical PrEP
- CAPRISA 004 (Tenofovir gel)
- No minor or major resistance
Bad news:

- Resistance risk increased if PrEP started during unrecognised acute HIV infection.

### Resistance More Likely if PrEP is Given During Unrecognized Acute Infection*

<table>
<thead>
<tr>
<th>Study</th>
<th># Infected</th>
<th># Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>10</td>
<td>2/2 active (M184V/I)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>14</td>
<td>2/8 active (1 K65R, 1 M184V)</td>
</tr>
<tr>
<td>TDF2</td>
<td>3</td>
<td>1/1 active (K65R, M184V, A62V)</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>2</td>
<td>0/1 active</td>
</tr>
</tbody>
</table>

*Infection + incomplete suppression of replication selects resistance

Transmitted (primary) resistance can occur, independent of PrEP, which likely explains resistance in the placebo arm.
What about women and PrEP adherence???
Adherence Factors....

- **External support.**

In qualitative work, support from the HIV-infected member of a serodiscordant couple seems to be related to better PrEP pill taking in the Partners PrEP Study, and participants in iPrEx noted the importance of support from research staff, family, and friends.
Factors....

• **low perception of HIV risk**

FEM-PREP: 70% of women reported they felt themselves at little risk for acquiring HIV, despite a nearly 5% annualized HIV incidence in that trial.

In iPrEx, PrEP efficacy was higher in men reporting (versus not reporting) unprotected receptive anal sex at baseline.
Factors...

• **Additional factors**
  in Partners PrEP: younger age, male gender, higher socioeconomic status, and heavy alcohol use;
  in iPrEx, younger age and region (non-US sites compared with US sites) were also associated with lower adherence.
  In VOICE, adherence was lower in younger unmarried women, who also had the highest HIV incidence in this trial.
Adherence in IDUs

• Adherence was better in participants aged 40 years and older than it was in younger participants
• Controlling for age, better in women than men.
• Participants were on DOT an average of 86.9% of the time; median adherence on DOT was 94.8% and on non-DOT was 100%.
So what has gone wrong?

Is it simply choice?
Will it work?
Will it work?
Will women take/use it??
Is it dosing??
Sexual frequency in women in CAPRISA 004
Incidence in placebo arm: 9.1/100wy

Abdool Karim, Science 2010
A Lexicon of Intermittent PrEP
J. McConnell/AVAC

1. Fixed or time-based dosing

2. Event-based dosing

3. Time-based plus event-based dosing

4. Periodic dosing
Acceptability of oral intermittent pre-exposure prophylaxis as a biomedical HIV prevention strategy: Results from the South African ADAPT (HPTN 067) Preparatory Study

Daniella Mark¹, Rivet Amico², Melissa Wallace¹, Surita Roux¹, Robert Grant³,⁴ and Linda-Gail Bekker¹,⁵

¹Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town; ²Center for Health Intervention and Prevention, University of Connecticut; ³Gladstone Institute of Virology and Immunology; ⁴University of California; ⁵Department of Medicine, University of Cape Town

Oral Abstract TUPDC0303
XIX International AIDS Conference
Washington, DC, USA
July 24, 2012
Background/ Methods

• Intermittent PrEP dosing or iPrEP (time- or event-driven) is being explored for the sake of convenience, cost-effectiveness and reduction in side effects
• Acceptability data in at-risk communities is needed to evaluate likely uptake and potential impact

✓ 8 focus groups in Cape Town, South Africa - 6 with adults, 2 with counselors working in high-incidence populations (n-52)
✓ Semi-structured guide and sexual exposure/ forecasting survey
✓ Framework analysis for qualitative data
**Results**

**ACCEPTABILITY**
- PreP acceptability due to potential for non-consensual use
- Barriers: aversion to novelty, PrEP seen as treatment, fear of stigma, risk compensation
- iPrEP favoured for lower time burden and side effects
- Concerns around iPrEP complexity

**SEXUAL EXPOSURE**
- Median of 2 sex days in previous week
- 0% reported daily sex as average
- Highest sex activity over weekends

**SEXUAL FORECASTING**
- 51% forecasted last sex act (men 75% vs. women 32%)
- 77% forecasted some, and 51% all sex events in previous week
- 88 sex days reported in previous week, of which 67% were forecasted.
Dosing

• The level of adherence needed to achieve HIV protection is not clear; however, PrEP use may potentially permit behavioral imperfection.

• In the iPrEx study, statistical modeling combining pharmacokinetics and drug data estimated that 2 PrEP doses per week might achieve a 76% reduction in HIV, rising to >95% for >4 doses per week.

• Potentially related to the intensity and route of viral exposure (eg, penile, vaginal, parenteral, rectal) and the drug (TDF, FTC/TDF, or other agents).

• There are currently no data to guide less-than-daily dosing of oral FTC/TDF as PrEP.
TDF-DP Levels in PBMC with 2-7 days DOT
Understanding iPrEx results

**Diagram:**
- **STRAND**
- Dosing regimens: 2/wk, 4/wk, 7/wk
- Sample sizes: n = 21, 21, 22
- TFV-DP (fmol/10^6 cells)
- % detected: 100% 100% 100%
- Median: 11, 32, 42

- "Consistent" dosing: 16 fmol/10^6 cells
- "Inconsistent" dosing
PBMC levels of TFV-DP (95% CI)
May need several (3-4) doses to get to protective level

Level for 90% efficacy (modeled)

Anderson, Poster 587, CROI 2012
HPTN 067 : ADAPT

A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)

- Alternative
- Dosing
- to Augment PrEP
- Pill
- Taking

= ADAPT
Primary Objective:

- To test the hypothesis that recommending intermittent (non-daily) usage of oral FTC/TDF chemoprophylaxis, compared with recommending daily usage, will be associated with:
  - Equivalent coverage of sex events with pre- and post-exposure dosing
  - Lower number of pills needed for coverage and fewer pills used
  - Decreased self-reported symptoms/side effects (both severity and frequency) during 24 weeks of self-administered use
Randomization Scheme

300mg TDF/200mg FTC Tablets (Truvada®)

Week 6 Randomization

Arm 1 Daily
- 180 MSM
- 60 WSM

Arm 2 Time-driven
- 180 MSM
- 60 WSM

Arm 3 Event-driven
- 180 MSM
- 60 WSM
Study Design: 3 arms

• **Daily:**
  - One tablet of FTC/TDF once a day regardless of sexual activity

• **Time Driven:**
  - One tablet of FTC/TDF 2 days/week and a post-exposure booster dose within 2 hours after sexual intercourse

• **Event Driven:**
  - One tablet of FTC/TDF prior to sexual intercourse & a post-exposure booster dose within 2 hours of sexual intercourse
Secondary Objectives:

- Develop objective measures of drug exposure among PrEP users by **obtaining steady state PK** during a 6 week directly-observed therapy (DOT) phase

- To **describe safety outcomes** among PrEP users and resistance among any seroconverters

- Assess **differences between arms in the acceptability** of different PrEP regimens and in perceptions of advantages and disadvantages of different regimens
Secondary Objectives (cont):

- Assess differences by arm in adherence
- Evaluate the potential influence of PrEP usage on
  - changes in sexual behavior,
  - planning for sex,
  - prediction of risky situations, and
  - recognition of possible HIV exposure from baseline to final on-drug assessment in relation to PrEP optimism
Study Sites:

• Cape Town (WSM) – F/up almost complete

• Bangkok (MSM) - enrolling

• Harlem (MSM) - enrolling
292 screened, 191 enrolled, 179 randomised
Median age: 26 yrs
80% unmarried.
Women tend not to carry pills with them. Given unpredictable nature of sex, makes remembering even more difficult:

“Another thing that made it difficult was that maybe on a Saturday – okay, let’s say you took your pills at seven in the evening. Now you get ready and leave the house before seven. When you have already arrived at your destination, you then recall that you haven’t taken your pills along. And then you tell yourself that you’re going to make up for it tomorrow. And then I would take two the next day.” (Daily arm participant)
Fear of association with chronic illness and/or HIV

Some people might be embarrassed about taking the pills, you know… Like, it’s something that I first experienced. I thought: “I have to keep so many pills on me as if I am a sickly person.” (Event arm participant)

I don’t think it will be acceptable because some people are scared of the fact that this pill is being taken by positive people – they are looking for people who are negative. They are scared and say: ‘I would never take it!’ (Daily arm participant)
Study participation has health promoting effects

Well, I didn’t even think about testing. I just told myself I would deal with it when I get it [HIV]. So coming here and being tested, I started thinking ‘let me start protecting myself’, maybe there will be a difference…Yes, that was encouraging because I told myself that from today I will never make that mistake again (Time arm participant)
Future access to PrEP might include information or counseling groups.

*They should be given knowledge about these pills...In the way that it happens here at the clinic. Like at the clinic, you’re not just given the pills. You are first told what the pills are for and then you take them. If maybe someone just goes to the chemist and buys them there, perhaps they won’t tell them what these pills will do to them.* (Time arm participant)

*There should be groups like these being held where they are, so that they can be told about these pills...In the area where they stay...*(Event arm participant)
Is it trial design?

Placebo is off-putting and confusing-
iPrEx Open Label Extension (OLE)

• All participants previously enrolled in iPrEx were eligible to enroll in the iPrEx OLE.
  – Visits in the blinded randomized phase of the main iPrEx study occurred through November 2010, except substudy visits not considered here.
  – iPrEx OLE started as soon as all applicable authorities approved the modified protocol (enrollment from June 2011 to June 2012).

• 1529 (65%) iPrEx participants enrolled in OLE
• In Cape Town : 88 MSM enrolled in iPrEx (85%)
• 55 enrolled in OLE (98%)
Cape Town OLE

- Declined OLE Enrollment: 15
- Relocation: 5
- Life-Style Change: 9
- Availability: 1

- OLE Enrollment: 55
- Initiated Drug: 40
- SC (Pre-OLE): 8
- Declined Drug: 7

- Declined Drug: 7
- Life-Style Change: 6
- Side Effects: 1

- Discontinued drug: 9
- SC: 4 (<25YRS)
- Side effects: 2
- Lifestyle change: 2
- Personal Choice: 1

Adherence on drug levels >70%
Lesson?

- When told something works-
- People who have had a chance to experience a product-
- Can make healthy decisions about whether to use it or not-
- Suggesting they CAN and WILL align their risk and need for protection.....
Tenofovir as a first-generation PrEP agent

Is it simply choice and preference?........
The Microbicide Pipeline?
Possible Dosage Forms

Vaginal Rings:
- Silicone
- Matrix
- EVA
- Reservoir
- PU
- Insert

Single Use:
- Gels
- Creams
- Films
- Tablets
- SGC

Other Devices:
- Diaphragm
- Duet
- Non-woven
- Female Condom
The Microbicide Pipeline?
Partial Listing of API

**RT Inhibitors:**
- Tenofovir
- Dapivirine
- MIV-150
- UC781
- IQP-0528
- DABO

**Protease Inhibitors:**
- Darunavir
- Lopinavir
- Ritonavir
- Sequinivir

**Lectins:**
- Cyanovirin N
- Griffithsin
- BanLec
- Actinohivin

**Entry Inhibitors:**
- Maraviroc
- Dendrimers (Vivagel)
- Defensins (RC101)
- DS003 (BMS793)
- PSC Rantes
- β cyclodextrin
- IQP-0831 (Isis 5320)
- SAMMA
- mABs
- HNG-156
- T1249
- C52L
- L’167
- L’872
- L’882
- L’644

**Nucleic Acids:**
- Aptamers
- siRNA

**Food Products:**
- Praneen
- Green Tea Extracts
- Pomergranate Juice

**Other:**
- GML
- Lactobacillus
- Top. Estrogen
- Zinc
- Thiolesters
## The Microbicide Pipeline?
### Combinations and MPT

<table>
<thead>
<tr>
<th>Combination HIV Prevention Products</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapivirine-Maraviroc Vaginal Ring</td>
<td>IPM</td>
</tr>
<tr>
<td>Dapivirine-Maraviroc Gel</td>
<td>IPM</td>
</tr>
<tr>
<td>Maraviroc-Tenofovir Film</td>
<td>IPM</td>
</tr>
<tr>
<td>Dapivirine-Tenofovir Vaginal Ring</td>
<td>IPM</td>
</tr>
<tr>
<td>MIV-150-Zn Acetate-Carageenan Gel</td>
<td>Pop Council</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multi-Purpose Prevention Technologies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir Gel</td>
<td>Gilead</td>
</tr>
<tr>
<td>Tenfovir-Levonorgestrel Vaginal Ring</td>
<td>CONRAD</td>
</tr>
<tr>
<td>ARV-Hormone Vaginal Ring</td>
<td>IPM/Pop Council</td>
</tr>
<tr>
<td>Tenofovir-Acyclovir Vaginal Ring</td>
<td>CONRAD</td>
</tr>
<tr>
<td>CV-N Expressing Lacto/Mucocept</td>
<td>Osel</td>
</tr>
<tr>
<td>Barrier Devices + ARV</td>
<td>Various</td>
</tr>
</tbody>
</table>
Can it be?

• Peoples’ needs vary
• Peoples’ needs vary over time
• People have preferences
• Perhaps HIV protection should be tailored to need and preference....??
What is the approach?

- Prep
- Pills
- Prep LA
- MMC
- Vaccine
- Microbicide gel
- Microbicide ring
- Treat partner
- LIFESTYLE
- CLIENT CENTRED PROTECTION
- RISK
- CHOICE
- PREFERENCE
<table>
<thead>
<tr>
<th>Product (Study, Results published)</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate ART for HIV+ partner (HPTN 052, 2011)</td>
<td>96% (82, 99)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (Partners PrEP, 2011)</td>
<td>75% (55, 87)</td>
</tr>
<tr>
<td>TDF oral PrEP (Partners PrEP, 2011)</td>
<td>67% (44, 81)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (TDF2, CDC, 2011)</td>
<td>62% (22, 83)</td>
</tr>
<tr>
<td>TDF oral PrEP (Bangkok Tenofovir Study, CDC, 2013)</td>
<td>49% (10, 72)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (iPrEx, 2010)</td>
<td>44% (15, 63)</td>
</tr>
<tr>
<td>1% tenofovir gel (CAPRISA 004, 2010)</td>
<td>39% (6, 60)</td>
</tr>
<tr>
<td>1% tenofovir gel (MTN003/VOICE, 2011)</td>
<td>15% (-21, 40)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (FEM-PrEP, 2011)</td>
<td>6% (-52, 41)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (MTN003/VOICE, 2011)</td>
<td>-4% (-49, 27)</td>
</tr>
<tr>
<td>TDF oral PrEP (MTN003/VOICE, 2011)</td>
<td>-49% (-129, 3)</td>
</tr>
</tbody>
</table>
HIV Prevention Options Timeline

2004
- RV 144

2005
- Bangkok Tenofovir Study/CDC 4370

2007
- TDF2/CDC 4940
- iPrEx
- CAPRISA 004

2008
- Partners PrEP
- VOICE/MTN 003

2009
- FEM-PrEP
- VOICE/MTN 003

2010
- TDF2 Open-Label Extension
- iPrEx Open-Label Extension (OLE)
- FACTS 001

2011
- FACTS 002 and other adolescent studies
- MTN 017
- The Ring Study/IPM 027
- ASPIRE/MTN 020

2012
- Various Phases of Long-Acting Injectables (SSAT 040 & MWRI-01)

2013
- Various Phase I/II preliminary and bridging studies

TIMELINE LEGEND
- Positive efficacy result
- No effect
- Regulatory submission/filing
- Planned
- Final results pending
- Earliest regulatory submission
- Earliest regulatory submission
- US FDA approval

TIMELINE LEGEND
- Oral TDF
- Oral TDF/FTC
- TFV gel
- Rectal TFV gel
- DPV ring
- TMC278 LA Injectable
- DNA/Ad5
- Pox-Protein


** Not all trials included are effectiveness trials. Trials included on this list are mainly phase IIb, IIIb and IV trials.

* Trial end-dates are estimates; due to the nature of clinical trials the actual dates may change. For full trial details, see www.avac.org/pxrd.
So, what next??
Support for ongoing research

• Ongoing Phase 3 studies
  – IPERGAY study

• Phase 3 study extensions and rollovers
  – Partners PrEP
  – iPrEx OLE
  – TDF2

• Demonstration projects
  – CDC demonstration project in US
  – San Francisco/Miami/Washington DC demonstration project
  – PROUD study in London
Support for ongoing research

• Phase 1 and 2 studies of alternative dosing strategies and regimens and populations
  – Intermittent dosing
    • HPTN 066, 067 (ADAPT)
  – Alternative regimens
    • HPTN 069 (miravirroc+/- TDF or FTC)
  – Alternative populations
    • Adolescent studies in young MSM ages 15-22 (ATN)

• Support for microbicide gel research; vaginal, rectal, new formulations and patient populations, safety and efficacy trials

• New drugs; new prodrug of tenofovir GS 7340; new prevention specific ARVs?
# Phase 3/4 Research and Demonstration Projects in Heterosexual Women and Men

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing Phase 3 Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners PrEP (discordant couples)</td>
<td>4758 couples</td>
<td>12 month extension</td>
<td>Kenya, Uganda</td>
</tr>
<tr>
<td>CDC Bangkok TDF (IVDU)</td>
<td>2413</td>
<td>Endpoint driven</td>
<td>Thailand</td>
</tr>
</tbody>
</table>

| **Demonstration Projects and Open-Label Extensions (planned and ongoing)** |
|---------------------------|-------|---------------------|------------------------------|
| CDC PrEP Demo* (men and women) | 600 | 12 months | U.S. |
| HPTN 069** | 200 | 48 weeks | U.S. |
| HPTN 067** | ~180 | 34 weeks | U.S., Thailand, S. Africa |
| TDF2 Open-Label Extension (men and women) | 900 (all rollover) | 12 months | Botswana |
| CHAMPS (men and women) | 150 | 12 months | South Africa |

| UW Partners PrEP Demo (discordant couples) | 1000 | 24 months | Kenya, Uganda |

**TOTAL: 8**

*CDC PrEP Demo includes both MSM and heterosexual men and women (1200 participants total)

**Includes both MSM and heterosexual women (estimated 50% MSM, 50% heterosexual women)

*Excluding rollover participants
# Phase 3/4 Research and Demonstration Projects in MSM

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing Phase 3 Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPERGAY</td>
<td>1900</td>
<td>24 months</td>
<td>France, Canada</td>
</tr>
<tr>
<td><strong>Demonstration Projects and Open-Label Extensions (planned and ongoing)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPrEx OLE</td>
<td>1770</td>
<td>72 weeks</td>
<td>Americas, Thailand, S. Africa</td>
</tr>
<tr>
<td>DAIDS PrEP MSM Demo</td>
<td>500</td>
<td>12 months</td>
<td>U.S.</td>
</tr>
<tr>
<td>CDC PrEP Demo*</td>
<td>600</td>
<td>12 months</td>
<td>U.S.</td>
</tr>
<tr>
<td>PROUD</td>
<td>5000</td>
<td>12 months on tx, 12 month follow-up</td>
<td>U.K.</td>
</tr>
<tr>
<td>(500 as pilot)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Project PrEPare 110</td>
<td>200</td>
<td>48 weeks</td>
<td>U.S.</td>
</tr>
<tr>
<td>SFDPH EPIC PrEP</td>
<td>300</td>
<td>12 months</td>
<td>U.S.</td>
</tr>
<tr>
<td>ALERT</td>
<td>400</td>
<td>12 months+</td>
<td>U.S.</td>
</tr>
<tr>
<td>Los Angeles PATH</td>
<td>300</td>
<td>48 weeks</td>
<td>U.S.</td>
</tr>
<tr>
<td>Seattle PrEP</td>
<td>300</td>
<td>48 weeks</td>
<td>U.S.</td>
</tr>
<tr>
<td>NYC PrEP</td>
<td>200</td>
<td>12 months</td>
<td>U.S.</td>
</tr>
<tr>
<td>Brazilian PrEP</td>
<td>400</td>
<td>12 months</td>
<td>Brazil</td>
</tr>
<tr>
<td>Rio PrEP</td>
<td>65</td>
<td>12 months</td>
<td>Brazil</td>
</tr>
<tr>
<td>HPTN 073</td>
<td>225</td>
<td>12 months</td>
<td>U.S.</td>
</tr>
<tr>
<td>HPTN 069**</td>
<td>400</td>
<td>48 weeks</td>
<td>U.S.</td>
</tr>
<tr>
<td>HPTN 067**</td>
<td>540</td>
<td>34 weeks</td>
<td>U.S., Thailand, S. Africa</td>
</tr>
<tr>
<td>HVTN 505</td>
<td>1000</td>
<td>5 years</td>
<td>U.S.</td>
</tr>
<tr>
<td><strong>TOTAL: 17</strong></td>
<td><strong>14,100</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CDC PrEP Demo includes both MSM and heterosexual men and women (1200 participants total)
** Includes both MSM and heterosexual women (estimated 50% MSM, 50% heterosexual women)
Ongoing and Planned Phase 3/4 Research, Including Demonstration Projects

- Phase 3 studies are continuing to evaluate PrEP in various demographic groups
- Gilead is committed to post-marketing demonstration studies in the U.S. and globally
- Collaborators: ANRS, CDC, FHI, MRC, NIAID (DAIDS), NICHD (ATN), SFDPH, U. Washington, and Gilead Sciences

<table>
<thead>
<tr>
<th>Population</th>
<th>Studies</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>17</td>
<td>14,100</td>
</tr>
<tr>
<td>Heterosexual Men &amp; Women Serodiscordant Couples</td>
<td>8</td>
<td>10,201</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>24,301</strong></td>
</tr>
</tbody>
</table>

ANRS = French National Agency for AIDS Research; CDC = Centers for Disease Control and Prevention; FHI = Family Health International; MRC = Medical Research Council (UK); NIAID = National Institute of Allergy and Infectious Diseases; DAIDS = Division of AIDS; NICHD = National Institute of Child Health and Human Development; SFDPH = San Francisco Department of Public Health
Youth and HIV prevention??
MP3(2): CHAMPS-SA

Pilot 1. Circumcision
- MMC vs TMC

Pilot 2. PrEP
Truvada
- Adherence
- Monitoring
- Risk

Pilot 3. Routes
- Injectable
- Oral
- Ring

Pilot 4. Choices
A Phase II Randomised Controlled Trial to Assess the Safety and Acceptability of the Vaginal Microbicide 1% Tenofovir Gel in Healthy, HIV-Uninfected, Sexually-Active Women 16 and 17 Years of Age
Adolescent Trials Network

- ATN 110 : PrEP 18-24 yo MSM (USA)
- ATN 113 : PrEP 15-17 yo MSM (USA)
MEN & WOMEN DEMAND RECTAL MICROBICIDES
RECTAL MICROBICIDES

Most anal intercourse around the world is unprotected.
Prevention package?

Will it include oral and topical PrEP?
Thanks

• Prevention divisions at DTHF
• John Mellors
• Mitchell Warren
• Jared Baeten
• Connie Cellum
• Susan Buchbinder
• Bob Grant
• Jim Rooney
• Slim and Quarraisha Kariem
• Judy Auerbach
• AVAC, HVTN, MTN, HPTN, FACTS, iPrEx (OLE).