New biomedical technologies.
Pre-exposure prophylaxis:
Systemic and topical.

Linda-Gail Bekker
The Desmond Tutu HIV Centre
UCT
SA HIV Clinicians Society Conference 2012
And the last parachute goes to.....
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
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
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.

Antiretroviral therapy as Prevention?
Prevention of MTCT

ART reduces VL
Reduce infectiousness

ART prophylaxis aborts potential infection
HIV transmission involves a discordant relationship..

- ART reduces VL
  - Reduce infectiousness

- ART prophylaxis aborts potential infection
Topical or microbicides

PrEP

Systemic
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COMING 01-07-08

MCMHP@hiv-research.org.za
And the last parachute goes to.....
Evidence : Systemic PrEP

• 3 RPCTS involving 8457 HIV negative individuals
• 3 different populations
  – MSM, hetero (M + F), discordant couples (M`+ F)
• Both hetero and homo sexual risk
• Truvada (TDF/FTC), Tenofovir
• PE : 44-75%
FDA approves TRUVADA as PrEP in July 2012
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>
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<tbody>
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<td>Women</td>
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</tr>
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<td>TDF2 Study</td>
<td>Young men and women</td>
<td>1200</td>
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</tr>
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<td>Partners PrEP Study</td>
<td>Heterosexual couples</td>
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Where are we now:
PrEP efficacy trial results, March 2012

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</tr>
<tr>
<td>FEM-PrEP</td>
<td>High risk women</td>
<td>1950</td>
<td>FTC/TDF = futility</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>5029</td>
<td>TDF = futility Vaginal TFV gel = futility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FTC/TDF ongoing</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>IDUs</td>
<td>2400</td>
<td>TDF ongoing</td>
</tr>
<tr>
<td>FACTS001</td>
<td>Women</td>
<td>2200</td>
<td>TFV gel enrolling</td>
</tr>
</tbody>
</table>
MMC already left with the second last parachute
Point efficacy...

• TasP

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

• 1763 discordant couples - hetero
• Treated immediately/deferred
• 39 infections: 27 vs 1 in linked transmissions
• 96% reduction in HIV transmission
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 serodiscordant couples, substantial % from outside partners
MMC already left with the second last parachute
First Signal of Efficacy in an HIV Vaccine Clinical Trial

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S Rerks-Ngarm, JH Kim et al. for the MOPH–TAVEG Investigators
RV144 ALVAC Prime, AIDSvax B/E Trial
31.2% Estimated Vaccine Efficacy

Adherence....
HPTN 052: Consistent Use of ART

Proportion of participants with VL<400 at each visit

Immediate Arm
Delayed Arm (not on ART)
Delayed Arm (on ART)
Tenofovir levels and HIV-1 protection

- Objective adherence measures from trials show:

<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>
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<td>Partners PrEP</td>
<td>25%</td>
<td>81%</td>
</tr>
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</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

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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>Seroconverters</th>
<th>Non-seroconverters</th>
<th>HIV-1 protection: detection versus no detection of tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>9%</td>
<td>51%</td>
<td>Protection = 92%</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>25%</td>
<td>81%</td>
<td>Protection = 90%</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.002</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
And the last parachute goes to.....
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
Why intermittent PrEP?

**PRO**
- Periods without risk
- Cost
- Toxicity
- Adherence
- Tolerability

**CON**
- Failure to recognize risk
- Resistance
- Adherence
- Tolerability
TDF-DP Levels in PBMC with 2-7 days DOT
Understanding iPrEx results

STRAND

2/wk 4/wk 7/wk
n: 21 21 22

% detected: 100% 100% 100%
median: 11 32 42
IQR: 6-13 25-39 31-47

"Consistent" dosing
16 fmol/10^6 cells

"Inconsistent" dosing
Planning for the pre-event dose
US online survey, 1013 MSM

Last anal sex planned?

How far ahead planned?

<table>
<thead>
<tr>
<th>Time</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutes</td>
<td>17</td>
</tr>
<tr>
<td>Hours</td>
<td>45</td>
</tr>
<tr>
<td>1-3 days</td>
<td>22</td>
</tr>
<tr>
<td>&gt; 3 days</td>
<td>17</td>
</tr>
</tbody>
</table>
Sexual frequency in women in CAPRISA 004
Incidence in placebo arm: 9.1/100wy

Proportion acts with condoms

Mean # sex acts/month

Abdool Karim, Science 2010
PBMC levels of TFV-DP (95% CI)
May need several (3-4) doses to get to protective level

Anderson, Poster 587, CROI 2012
Lessons from NHP studies

- PrEP can protect against repeated low-dose rectal challenge
- Systemic
  - Daily dosing protects at high levels
  - Event-based dosing protects with possible trend toward best if:
    - Pre-exposure dose 1-7 days pre-challenge
    - Post-challenge dose provided
  - Event-based dosing can protects against M184V strain
- Topical
  - Pre-exposure dose needed
- Great headway with closer replication to human challenge but need human data to validate these models
And the last parachute goes to.....
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><strong>Subtotal</strong></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>Kinal 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>
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<tr>
<td>HOPS 2007</td>
<td>736</td>
<td>-4.40 [-6.97, -1.83]</td>
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<tr>
<td>Winston 2006</td>
<td>948</td>
<td>-6.33 [-14.85, 2.19]</td>
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<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><strong>Subtotal</strong></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>
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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
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

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

- HIV infection
- Resistant infection

- No Drug
- No Resistance
- Infection

Fraction infected or resistant

Drug Exposure

Low → High
Theoretical Infection-Exposure-Resistance Relationships

- HIV infection
- Resistant infection

Zone of Resistance Risk
- No Drug
- No Resistance
- Infection

Fraction infected or resistant

Drug Exposure

Low → High
Theoretical Infection-Exposure-Resistance Relationships

- Low Drug Exposure:
  - No Drug
  - No Resistance
  - Infection

- Zone of Resistance Risk:
  - HIV infection

- High Drug Exposure:
  - No infection
  - No 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**

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<th># resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>10</td>
<td>2/2 active (M184V/I) 1/8 placebo (M184V)</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.*
Good news:

• Resistance NOT seen in topical PrEP
• CAPRISA 004 (Tenofovir gel)
• No minor or major resistance
Resistance from ART is common

- 15-20% of first-line therapy
- Evidence of spread: prevalence pretherapy has increased in some countries from <5% to >12%
- Uganda, Cameroon

Hamers et al., Lancet Infectious Dis 2011
And the last parachute goes to.....
Tenofovir as a first-generation PrEP agent

Pill

Gel

Vaginal film

Vaginal ring

Injectable

Great things in the pipeline........
The Microbicide Pipeline?
Partial Listing of API

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

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

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

**Nucleic Acids:**
- Aptamers
- siRNA

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

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

**Other:**
- GML
- Lactobacillus
- Top. Estrogen
- Zinc
- Thiolestes
The Microbicide Pipeline?
Possible Dosage Forms

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

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

Other Devices:
- Diaphragm
- Duet
- Non-woven
- Female Condom
# 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>Varios</td>
</tr>
</tbody>
</table>
Highly active HIV prevention.

A term coined by Prof K Holmes, University of Washington School of Medicine, Seattle, WA, USA.5

From Coates T et al 2008.
## New biomedical intervention strategies

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime-boost HIV Vaccine (Thai RV144)</td>
<td>31% (1, 51)</td>
</tr>
<tr>
<td>1% tenofovir gel (Caprisa 004, Karim et al.)</td>
<td>39% (6, 60)</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in MSM (iPrEx, Grant et al. 2010)</td>
<td>44% (15, 63)</td>
</tr>
<tr>
<td>Medical male circumcision (MMC) (Orange Farm, Rakai, Kisumu)</td>
<td>57% (42, 68)</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in heterosexuals (TDF2, CDC)</td>
<td>63% (22, 83)*</td>
</tr>
<tr>
<td>TDF oral-PrEP in serodiscordant Partner (Partners PrEP)</td>
<td>62% (34, 78)*</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in serodiscordant Partner (Partners PrEP)</td>
<td>73% (49, 85)*</td>
</tr>
<tr>
<td>Immediate ART for positive Partners (HPTN052)</td>
<td>96% (82, 99)*</td>
</tr>
</tbody>
</table>

*Provisional
Prevention plane is on track to land safely

Not going to need parachutes at all......
Thanks

- Prevention divisions at DTHF
- John Mellors
- Jared Baeten
- Connie Cellum
- Susan Buchbinder
- Bob Grant
- Slim and Quarraisha Kariem
- HVTN, MTN, HPTN, FACTS, iPrEx (OLE).