Recent advances in HIV/AIDS

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MRC/UVRI Uganda Research Unit on AIDS
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Acknowledgements

• IPM (Zeda Rosenberg, Annalene Nel)
• DART trial team (Di Gibbs, Paula Munderi)
• IAVI (Pat Fast, Frances Priddy)
• Pontiano Kaleebu (UVRI)
• Shabbar Jaffar (LSHTM)
Who has contributed to these advances?
Overview

• HIV Prevention research

• Treatment and care research

• HIV vaccine research
A global view of HIV infection 2007
HIV Prevention Research
Male circumcision to reduce HIV infection

- HIV protection only in the HIV-uninfected and no evidence of benefit in circumcising HIV-infected men

- While efficacy has been established, how to scale-up the intervention in real-life is unclear and needs further research
WHO/UNAIDS recommendations on MC

- Compelling evidence that circumcision reduces risk of HIV infection in men (partial protection)

- Circumcision is an additional prevention strategy and should be used as part of comprehensive package

- Need to ensure procedure is conducted safely, with appropriate counselling and after-care
Rakai District, Uganda
Microbicide Research
Evidence that microbicides safe and acceptable?


• A randomized controlled safety and acceptability trial of DS gel in sexually active women in Uganda: AIDS. 2005;19 (18): 2149-56 Bakobaki J M et al
HPTN 035 trial: “Ray of Hope”

- Phase II/IIB “proof-of-concept”
- 3,099 participants, Africa and U.S. sites
- PRO 2000 (0.5%) safe for use as tested
- 30% effective in preventing HIV infections, not statistically significant
- Not effective in preventing other STIs
- Additional evidence needed to prove efficacy
<table>
<thead>
<tr>
<th>Product / Study</th>
<th>Phase</th>
<th>MoA</th>
<th>Sponsors</th>
<th>Countries</th>
<th>Status / Results</th>
</tr>
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<tbody>
<tr>
<td>PRO 2000 Gel (0.5%)</td>
<td>III</td>
<td>Entry Inhibitor</td>
<td>UK MRC, DFID</td>
<td>South Africa, Tanzania, Uganda, Zambia</td>
<td>Data Analysis Results Q4-09</td>
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<tr>
<td>MDP 301</td>
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<td>Tenofovir Gel</td>
<td>IIB</td>
<td>NRTI</td>
<td>SA govt, USAID, CONRAD</td>
<td>South Africa</td>
<td>Ongoing Results 2010</td>
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<td>CAPRISA 004</td>
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<tr>
<td>Tenofovir Gel</td>
<td>IIB</td>
<td>NRTI</td>
<td>NIH</td>
<td>South Africa, Uganda, Zambia, Zimbabwe, Malawi</td>
<td>Ongoing Results 2012</td>
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<td>MTN 003 (VOICE)</td>
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<tr>
<td>Tenofovir Gel</td>
<td>III</td>
<td>NRTI</td>
<td>UK MRC, UVRI, CONRAD</td>
<td>Mozambique, South Africa, Tanzania, Kenya, Uganda, Zambia</td>
<td>Planned 2010</td>
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<td>MDP 302</td>
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<tr>
<td>Dapivirine Gel, Dapivirine Ring</td>
<td>III</td>
<td>NNRTI</td>
<td>IPM</td>
<td>Africa</td>
<td>Planned 2011</td>
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<td>IPM 009</td>
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MDP 301 trial
MDP 301 Phase III trial:

- PRO 2000 0.5% gel study
- Started October 2005 (N= 9404), follow up has ended
- Initially 3-arm study (2%, 0.5% and placebo)
- February 2008, 2% arm dropped for futility
- Data base lock and analysis will shortly begin this month and results late 2009
# ARV-Based Microbicides in Development

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Developer</th>
<th>Development Stage</th>
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<tbody>
<tr>
<td>NNRTI</td>
<td>Dapivirine</td>
<td>IPM</td>
<td>Phase I/II</td>
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<td></td>
<td>UC-781</td>
<td>CONRAD</td>
<td>Phase I</td>
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<td></td>
<td>PC-815</td>
<td>Population Council</td>
<td>Phase I Preclinical</td>
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<tr>
<td></td>
<td>Pyrimidinediones</td>
<td>ImQuest</td>
<td>Preclinical</td>
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<td></td>
<td>S-DABO</td>
<td>Idenix</td>
<td>Preclinical</td>
</tr>
<tr>
<td>NRTI</td>
<td>Tenofovir*</td>
<td>IPM / CONRAD</td>
<td>Phase IIB/III</td>
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<tr>
<td>CCR5 blocker</td>
<td>Maraviroc*</td>
<td>IPM</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>Merck L-167</td>
<td>IPM</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>Merck L-872</td>
<td>IPM</td>
<td>Preclinical</td>
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<td></td>
<td>Merck L-882</td>
<td>IPM</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>RANTES analogs</td>
<td>Mintaka Foundation</td>
<td>Preclinical</td>
</tr>
<tr>
<td>gp41 binder</td>
<td>Merck L-644</td>
<td>IPM</td>
<td>Preclinical</td>
</tr>
<tr>
<td>gp120 binder</td>
<td>BMS-793</td>
<td>IPM</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Cyanovirin-N</td>
<td>Osel</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Zinc finger inhibitor</td>
<td>NCp7’s</td>
<td>ImQuest</td>
<td>Preclinical</td>
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</table>
Combination Microbicides

- IPM evaluating the first combination microbicide (maraviroc+dapivirine), currently in the preclinical and formulation stage

- The first Phase I of maraviroc-dapivirine gel and ring due to start early 2010; film will start in 2011
Delivery methods

Gel applicator

Ring

Tablet, capsule, film
## Rectal Microbicide Studies

<table>
<thead>
<tr>
<th>Product/Study</th>
<th>Phase</th>
<th>Sponsor/Developer</th>
<th>Countries</th>
<th>Results/Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC-781</td>
<td>I</td>
<td>NIH, CONRAD, UCLA</td>
<td>USA</td>
<td>COMPLETED Q1 2009</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- HIV- men and women</td>
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<td></td>
<td></td>
<td></td>
<td>- Follow-up ended Q1 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Results: Good safety profile, well tolerated, good adherence, showed good PD</td>
</tr>
<tr>
<td>TDF (MTN 006)</td>
<td>I</td>
<td>NIAID, DAIDS, MTN, CONRAD, Gilead</td>
<td>USA</td>
<td>PLANNED 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Oral and rectal tenofovir, HIV- men and women</td>
</tr>
<tr>
<td>TDF (MTN 007)</td>
<td>I</td>
<td>NIAID, DAIDS, MTN</td>
<td>USA</td>
<td>PLANNED 2009</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Short-term exposure of tenofovir gel on rectal mucosa</td>
</tr>
<tr>
<td>PRO 2000</td>
<td>I</td>
<td>UK MRC, MDP</td>
<td>TBC</td>
<td>PLANNED</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- HIV-, then HIV+ men</td>
</tr>
<tr>
<td>VivaGel</td>
<td>I</td>
<td>NIH, DMID, Starpharma, UCLA, Univ of Pittsburgh</td>
<td>USA</td>
<td>PLANNED</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Abstinent HIV- men and women</td>
</tr>
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PrEP Research
Why PrEP in HIV Prevention?

• Use one or more ARVs to protect HIV-ve at-risk of getting HIV infection

• builds on the concept
  • Malaria prophylaxis
  • PCP and TB prophylaxis
  • Endocarditis prophylaxis
  • PMTCT
Why PrEP now?

• Favourable safety profiles, good drug levels in genital tract and long intracellular half-lives (NRTIs: TDF & FTC)

• Modelling work:
  – Lives saved
    • Estimate that over 10 years 2.7 to 3.2 million infections could be prevented in southern Africa (Abbas et al. CROI 2007)
<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Sponsors</th>
<th>Countries</th>
<th>Population</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC 4370</td>
<td>II/III</td>
<td>CDC, Thailand MPH</td>
<td>Thailand</td>
<td>2400 male &amp; female IDUs</td>
<td>ONGOING since 2005</td>
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<td>• Results 2010</td>
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<td></td>
<td></td>
<td></td>
<td>• Oral tenofovir</td>
</tr>
<tr>
<td>iPrEx</td>
<td>III</td>
<td>NIH, BMGF</td>
<td>Peru, Ecuador, Brazil, South Africa, USA, Thailand</td>
<td>3000 high-risk MSM</td>
<td>ONGOING since 2007</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>• Results 2010</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>• Oral Truvada</td>
</tr>
<tr>
<td>CDC 4940 / BOTUSA MB06</td>
<td>III</td>
<td>CDC, Botswana MOH</td>
<td>Botswana</td>
<td>1800-2000 heterosexual young adults</td>
<td>ONGOING since 2007</td>
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<td></td>
<td>• Results 2011</td>
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<td></td>
<td>• Oral Truvada</td>
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<tr>
<td>Partners-PrEP</td>
<td>III</td>
<td>BMGF, Univ of Washington</td>
<td>Kenya, Uganda</td>
<td>3900 serodiscordant heterosexual couples</td>
<td>ONGOING since 2008</td>
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<td>• Results 2012</td>
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<td>• Oral tenofovir, oral Truvada</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>III</td>
<td>FHI, USAID, BMGF</td>
<td>Kenya, Malawi, South Africa, Tanzania, Zambia</td>
<td>3900 high-risk women</td>
<td>ONGOING since 2009</td>
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<td>• Results 2012</td>
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<td>• Oral Truvada</td>
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<tr>
<td>MTN 003 (VOICE)</td>
<td>IIB</td>
<td>NIH, MTN</td>
<td>Uganda, South Africa, Zambia, Zimbabwe, Malawi</td>
<td>~ 5000 women</td>
<td>ONGOING since 2009</td>
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<tr>
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<td></td>
<td>• Oral Truvada, oral tenofovir, tenofovir gel</td>
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Is daily therapy feasible, any role for intermittent PrEP?

- Daily therapy may not be feasible for many at-risk populations due to cost, drug accessibility and lifestyle or privacy issues.

- Availability of ARVs with long intracellular half-lives (TDF >60 hours; FTC ~39 hours) may make daily dosing unnecessary.

- Evidence that intermittent PrEP is effective in animal models (Garcia-Lerma CROI 2009).
IAVI Pilot studies (E001 and E002)

- to evaluate safety, acceptability, and adherence in at-risk populations of Pre-Exposure Prophylaxis (PrEP) in Kenya and Uganda
Immune Responses

Immunology relevant to vaccine development

- Animal studies suggest PrEP or PEP may allow effective immune responses to develop
- Does PrEP allow functional HIV-specific immune responses to develop in the setting of highly limited viral replication?
- Could these immune responses protect from future exposures off PrEP?
- Could PrEP and vaccine act in synergy?
Protocols E001 and E002: Objectives

**Primary**

- To evaluate the **safety** of daily and intermittent dosing of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF)
- To compare the **acceptability** of and **adherence** to daily and intermittent regimens
- To evaluate mean intracellular drug levels in the daily and intermittent regimens
- To evaluate the relationship between adherence and intracellular drug levels
- To evaluate changes in HIV associated risk behaviour
HIV Treatment Research
The Development of AntiRetroviral Therapy in Africa (DART) trial

Comparison of routine vs clinically driven laboratory monitoring in HIV-infected African adults over 5 years on ART
Main objective of DART

• To evaluate the need for routine laboratory monitoring of ART
  - in African adults who fulfilled clinical and CD4 criteria for ART initiation
  - in terms of clinical effectiveness, safety and costs

• Primary endpoints
  - **Efficacy:** new WHO stage 4 HIV event (AIDS) or death
  - **Safety:** any Serious Adverse Event which is not only HIV-related
3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease, CD4<200 cells/mm³ initiating triple drug ART

**Laboratory and Clinical Monitoring (LCM)**
- 12 weekly biochemistry, FBC & CD4
- Other investigations & concomitant medications if clinically indicated
- Switch to second-line for
  - new/recurrent WHO 4 (or multiple WHO 3)
  - CD4<100 cells/mm³

**Clinically Driven Monitoring (CDM)**
- 12 weekly biochemistry, FBC & CD4;
  - FBC & biochemistry only returned if clinically indicated; CD4 never returned
- Other investigations & concomitant medications if clinically indicated
- Switch to second-line for
  - new/recurrent WHO 4 (or multiple WHO 3)

As per WHO guidelines, switching before 48 weeks discouraged in both arms
Adverse events

Proportion event-free

Years from randomisation (ART initiation)

- SAE $p=0.20$
- ART-modifying AE $p=0.85$
- Grade 4 AE $p=0.18$
- Grade 3/4 AE $p=0.52$

LCM

CDM
Survival

Proportion alive

Years from enrolment

Entebbe Cohort (Uganda): pre-ART 1996-2000, median CD4 75 at enrolment: 57.7/100 PY

LCM: 2.2/100 PY
CDM: 2.9/100 PY

164 events
218 events
Progression to new WHO 4 event or death (primary endpoint)

HR(CDM:LCM) = 1.31 (95% CI 1.14-1.51) p=0.0001

Proportion alive without a new WHO 4 event

Years from randomisation (ART initiation)

LCM: n= 1656 1438 1364 1306 1255 682
CDM: n= 1660 1443 1354 1262 1184 613

356 events
LCM: 5.2/100 PY
CDM: 6.9/100 PY
459 events
Main Findings

• There is a small but statistically significant difference in mortality and disease progression between the two arms only from the third year on ART

• What causes this?

• Slightly later switching to second-line therapy in CDM leading to a few more patients in CDM living with lower CD4 counts on first-line and at increased risk of clinical events
Main Findings

• Under good clinical care, 5-year survival was 87% with **CM** and improving to 90% with the addition of CD4 monitoring

• 12-weekly CD4 monitoring had no impact on disease progression during the first 2 years on ART
  - there may be a role for targeted, as opposed to routine, CD4 monitoring from the second year on ART

• CEA: for ART management without routine toxicity monitoring but with 12-weekly CD4 monitoring after the first year to be cost-effective
  - CD4 tests would have to cost <$3.78
Gaps in HIV treatment

• when-to-start ART studies? – some work underway but still big research gap
• studies on when to switch and what to switch to? – EDCTP call
• how best to deliver HIV treatment and sustain care?
  – challenge both for the health service and the patient
The impact of home-based care compared with facility-based HIV-care on virologic failure and mortality: a cluster randomised trial
# Rates (95% CI) per 100-person-years

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<thead>
<tr>
<th></th>
<th>Home-based</th>
<th>Facility-based</th>
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<tr>
<td>Virologic failure</td>
<td>8.2</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>(6.8, 9.8)</td>
<td>(7.0, 10.8)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5.4</td>
<td>5.5</td>
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<tr>
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<td>(4.5, 6.5)</td>
<td>(4.4, 6.9)</td>
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RNA virological suppression

![Graph showing probability of viral suppression over time with data points for different arms.]
All-cause mortality

Number at risk
arm = facility 592 529 491 465 455 359 174 107
arm = home 857 765 730 710 682 525 276 168

Time in months
0 6 12 18 24 30 36 42

survival probability
0.00 0.20 0.40 0.60 0.80 1.00

dashed line arm = facility
solid line arm = home
Main findings

• Home-based model was equivalent to the facility-based model in terms of virological response, mortality, CD4 count, adherence.

• Costs of service provision were similar for both models.

• Cost of accessing care was considerably cheaper for patients in the home-based model.
HIV Vaccine Research
Long term goals for an AIDS vaccine

**Primary**
- Prevent the establishment of persistent HIV infection

**Secondary**
- Control HIV infection/progression to AIDS

**Tertiary**
- Reduce HIV transmission (public health vaccine)
AIDS vaccine development: Scientific Challenges

HIV integrates into the host cell genome, short window of opportunity before integration

HIV infects, suppresses, and destroys key cells of the immune system

HIV isolates worldwide are hypervariable

Natural immune responses do not eradicate HIV; Limitations in the animal models for HIV/AIDS; correlates of protective immunity remain undefined

HIV antigens required for protection remain undefined

AIDS vaccine efficacy trials long and complex
The Neutralizing Antibody Challenge

- Most licensed vaccines elicit neutralizing antibodies
- Neutralizing antibodies protect against SIV/HIV challenge in animal models
- Broadly neutralizing antibodies in humans against HIV exist
- However, no candidate vaccine elicits broadly neutralizing antibodies against HIV
The Neutralizing Antibody Challenge

Typically, HIV infection does not give good neutralizing antibody responses of the type required in a vaccine i.e. broadly neutralizing antibody responses.

However, a number of broadly neutralizing monoclonal antibodies (bnmAbs) have been isolated from infected individuals.

→ bnmAbs are key tools for a rational approach to vaccine design.
Status of HIV vaccine efficacy trials

Efficacy Trials Completed

- Antibody-based: VaxGen gp120 – No efficacy
- Cellular-based: Merck Ad5 gag-pol-nef – No efficacy
  - Apparent transient increased risk in subset
- Sanofi+VaxGen ALVAC+gp120
  - Thailand, general population, n=16,000
  - Data announced Sept 09

Efficacy Trials Ongoing

- HVTN 505: DNA-env,gag,pol,nef; Adeno5-env,gag,pol
  - Americas, Australia – initiated 2009, n~1350
  - MSM, circumcised, Ad5-antibody negative
Thai trial (RV 144)

- A Phase III clinical trial, 16,000 adults
- Prime boost combination of ALVACR HIV and AIDSVAXR
- Safe and modestly effective in preventing HIV infection
  - 74 HIV incident cases in placebo; 51 in the vaccine arm
  - Significantly lowered the rate of HIV infection by 31.2% compared with placebo (95% CI 1.1-52.1), p=0.039
  - No effect on the mean plasma VL load (vaccine 4.3 log$_{10}$; placebo 4.2 log$_{10}$)
HIV Treatment as Prevention: Can extended Voluntary Counselling and Testing and Universal ART Reduce HIV Transmission?
Rationale

• Correlation of viral load and risk of HIV transmission (Quinn et al NEJM 2000)

• effectiveness of ART in PMTCT

• only universal testing and immediate treatment would reduce the size of the epidemic
What would such trial involve and what would the costs be?
What would such trial involve?
Future?

• Look forward to the MDP 301 results and those of the PrEP trials

• Research will be needed to determine how to scale-up once proof of concept is demonstrated

• Important that funding agencies put high on agenda research on delivery models
Acknowledgements

• IPM (Zeda Rosenberg, Annalene Nel
• DART trial team (Di Gibbs, Paula Munderi)
  – CD on DART trial available
• IAVI (Pat Fast, Frances Priddy)
• Pontiano Kaleebu (UVRI)
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