HPTN 071 (PopART)
Treatment for prevention: a new paradigm for HIV control

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WASHINGTON DC
ACKNOWLEDGEMENTS

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  – NIAID, the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA)
Overview of presentation

• Background and rationale
• Objectives and design of HPTN 071/ PopART trial
ART for prevention: background

• HIV incidence continues to be unacceptably high in many countries in Africa
• Lack of proven effective HIV prevention strategies
• Unless incidence can be reduced dramatically it will become increasingly difficult over time to sustain effective ART services
Figure 2.8

HIV trends in sub-Saharan Africa

Number of people living with HIV

Number of people newly infected with HIV

Number of children living with HIV

Adult and child deaths due to AIDS

Dotted lines represent ranges, solid lines represent the best estimate.

Source: UNAIDS.
ART for prevention: background

- HIV incidence continues to be unacceptably high in many countries in Africa
- Lack of proven effective HIV prevention strategies
- Unless incidence can be reduced dramatically it will become increasingly difficult over time to sustain effective ART services
- Risk of HIV transmission closely correlated with HIV viral load and ART can be used to reduce HIV viral load and hence infectivity
Rakai Study of viral load and HIV transmission
Evidence from HPTN 052

1763 sero-discordant couples: HIV +ve partners

Early
Immediate ART
CD4 350-550
1 transmission

Randomization

Late
Delayed ART
CD4 <250
28 transmissions

Primary Transmission Endpoint
Virally linked transmission events

96% reduction

Hazard ratio = 0.04 95% CI: 0.01-0.27
ART for prevention: background

• HIV incidence continues to be unacceptably high in many countries in Africa
• Lack of proven effective HIV prevention strategies
• Unless incidence can be reduced dramatically it will become increasingly difficult over time to sustain effective ART services
• Risk of HIV transmission closely correlated with HIV viral load and ART can be used to reduce HIV viral load and hence infectivity
• Current guidelines limit ART to those with late-stage HIV infection (CD4<350) but most transmission occurs before that
Universal test and treat intervention

- Promote universal HIV voluntary counselling and testing at regular intervals
- All those diagnosed HIV positive are started on ART immediately
- Mathematical models show immediate increase in numbers needing treatment but in medium-term, HIV incidence and prevalence are reduced dramatically
- In long-term, numbers needing ART are reduced.
Additional benefits of intervention

• Reduction of morbidity and mortality in those receiving ART through earlier onset of treatment
• Simplification of ART delivery and monitoring
• Reduction of adverse effects of treatment
• Reduction of clinic burden of TB and other illnesses
• (Potential) elimination of mother to child HIV transmission
• (Eventual) cost savings
• Normalisation of HIV and reduction in HIV-related stigma
• Reduces need for specially targeted interventions
Why is a trial needed?

- Not known whether a UTT intervention can be delivered with high uptake and acceptability
- Many uncertainties in model parameters
- Population-level impact of (feasible) intervention package is not known
- Many potential adverse effects, such as toxicity, drug resistance, sexual risk disinhibition, HIV-related stigma, overload of health services
- A rigorously designed trial can measure the costs and benefits of this strategy and provide reliable evidence on cost-effectiveness for health policy makers
HPTN 071
The PopART Study
PopART: Population effect of universal testing and immediate ART therapy to Reduce HIV Transmission
HPTN 071/PopART Team

Imperial College
London

Zambart Project

National Institute of Allergy and Infectious Diseases

NIMH
National Institute of Mental Health

NIDA
NATIONAL INSTITUTE ON DRUG ABUSE

Bill & Melinda Gates Foundation

PEPFAR
Universal voluntary HIV testing with appropriate combination prevention offered to all those testing HIV negative - in addition to immediate ART for all those testing HIV positive - will have a substantial impact on HIV incidence at population level.
Universal voluntary HIV testing delivered annually through door-to-door, home-based testing

Active linkage to care, referral and support for retention/adherence by CHiPs for the following:

- Voluntary medical male circumcision for HIV-ve men
- PMTCT for HIV+ve pregnant women
- HIV treatment and care for all HIV+ve individuals
- Promotion of sexual health and TB services
- Condom provision

Immediate ART offered at health center for all testing HIV+ve

CHiPs = Community HIV-care Providers
Trial Design: three-arm, two-country, cluster-randomized trial

- 21 clusters (communities): 12 in Zambia, 9 in South Africa
- Average of ~50,000 in each cluster (~50% adults)
- Incidence measured in Population Cohort: 2,500 adults in each cluster, followed up after 1, 2 and 3 years

<table>
<thead>
<tr>
<th>Arm A (7 sites)</th>
<th>Arm B (7 sites)</th>
<th>Arm C (7 sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full PopART</td>
<td>PopART <em>but</em> CD4&lt;350</td>
<td>Standard of Care</td>
</tr>
</tbody>
</table>

*PopART*
- Clusters matched into triplets by HIV prevalence: 4 triplets in Zambia, 3 in S Africa
- Clusters randomly allocated to 3 study arms within each matched triplet
- Restricted randomisation used to ensure balance on ART uptake, population size and HIV prevalence
Study Locations:

- 12 communities in Zambia
- 9 communities in the Western Cape of South Africa
Primary Objective
- To measure the impact of the PopART intervention in reducing HIV incidence
- Measured in a cohort of 52,500 adults over 3 years
Objectives

• Secondary Objectives
  – Uptake of intervention components
  – Retention in HIV care
  – Sexual risk behaviour
  – HIV-related stigma
  – HIV disease progression and death
  – TB case notification rate
  – HSV-2 incidence
  – ART Toxicity
  – ART adherence and viral suppression *
  – Community viral load*
  – ART drug resistance*

See Table 10 of Protocol for further details

* if further funding obtained
Qualitative and case-control studies

- Rapid participatory research during Y1 to support development of intervention
- Acceptability of intervention and barriers to access
- Functioning of CHiPs
- Effects on social networks, stigma, sexual behaviour, gender-based violence etc.
- Nested case-control studies to explore factors related to:
  - Uptake of testing during first round of home-based testing
  - Uptake of immediate treatment
  - Uptake of testing during second round of home-based testing
Mathematical modelling

Individual-level stochastic model will be fitted and used to:

- Interpret results of trial (impact on HIV incidence)
- Project long-term outcome
- Explore contribution of individual intervention components
- Project impact of alternative intervention packages
- Explore likely impact in different geographical settings
- Estimate contribution of new (acute) infections occurring between annual testing rounds to HIV transmission
- Estimate effects of contamination (partners from outside study population)
- In combination with health economics data to estimate cost-effectiveness over different time horizons
Parameter values assumed for the model of the impact of the intervention for central and optimistic target scenarios, and projected impact on HIV incidence in Arms A and B compared with Arm C, assuming intervention roll-out over a 6-month time period.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Central Target</th>
<th>Optimistic Target</th>
</tr>
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<tbody>
<tr>
<td>Annual coverage of test and treat campaign</td>
<td>70%</td>
<td>75%</td>
</tr>
<tr>
<td>Treatment failure &amp; drop-out rate, per year</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Effectiveness of ART in blocking transmission</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>Take up of male circumcision when offered</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Impact on cumulative incidence (3 years) Zambia</td>
<td>58%</td>
<td>25%</td>
</tr>
<tr>
<td>Impact on cumulative incidence (2 first years) Zambia</td>
<td>54%</td>
<td>23%</td>
</tr>
<tr>
<td>Impact on HIV incidence during Year 1 Zambia</td>
<td>45%</td>
<td>19%</td>
</tr>
<tr>
<td>Impact on HIV incidence during Year 2 Zambia</td>
<td>63%</td>
<td>28%</td>
</tr>
<tr>
<td>Impact on HIV incidence during Year 3 Zambia</td>
<td>68%</td>
<td>31%</td>
</tr>
<tr>
<td>Impact on cumulative incidence (3 years) South Africa</td>
<td>57%</td>
<td>23%</td>
</tr>
<tr>
<td>Impact on cumulative incidence (2 first years) South Africa</td>
<td>52%</td>
<td>21%</td>
</tr>
<tr>
<td>Impact on HIV incidence during Year 1 South Africa</td>
<td>44%</td>
<td>18%</td>
</tr>
<tr>
<td>Impact on HIV incidence during Year 2 South Africa</td>
<td>62%</td>
<td>26%</td>
</tr>
<tr>
<td>Impact on HIV incidence during Year 3 South Africa</td>
<td>66%</td>
<td>29%</td>
</tr>
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Arm A | Arm B | Arm A | Arm B

Zambia

South Africa
### Sample size for Arm A or B vs C

<table>
<thead>
<tr>
<th>HIV incidence</th>
<th>Coeff of variation k</th>
<th>Effectiveness %</th>
<th>Power %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.15</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td>1.0</td>
<td>0.15</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>1.0</td>
<td>0.15</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>1.0</td>
<td>0.15</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>1.5</td>
<td>0.15</td>
<td>30</td>
<td>81</td>
</tr>
<tr>
<td>1.5</td>
<td>0.15</td>
<td>40</td>
<td>98</td>
</tr>
<tr>
<td>1.5</td>
<td>0.15</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>1.5</td>
<td>0.15</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
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Progress with trial implementation

- October 2012: Approval of Version 1.0 of protocol
- December 2012: Conditional approval of life-of-project budget
- November 2012 - January 2013: Ethical approval by LSHTM, CDC, University of Stellenbosch (awaited from University of Zambia)
- December 2012: Start of formative research
- February 2013: Public randomisation ceremony in Lusaka and Cape Town
- April 2013: First meeting of DSMB
- June 2013: Start of intervention and population cohort enrolment in Zambia and S Africa
Thanks to

- Sarah Fidler
- Helen Ayles
- Nulda Beyers

And all members of the HPTN 071 Study Team!