The journey towards making elimination of mother to child HIV transmission (eMTCT) a reality; contribution of clinical research

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Investigator
Introduction: Burden of Mother to Child HIV transmission (MTCT)

eMTCT-a snapshot of progress in high priority countries

The Journey to eMTCT-what has clinical research contributed?

Towards eMTCT: Landmark PMTCT clinical trials done at MUIHU Research collaboration, Kampala, Uganda

Making eMTCT a reality- addressing the gaps through research

Conclusions
90% of all HIV infections in children are through MTCT

Between 2009 and 2015, about 4.5 million women of childbearing age in 21 African countries were newly infected with HIV

2015 estimates of HIV burden in children < 15 years

Global burden
- 1.8m living with HIV
- 150,000 new infections
- 110,000 deaths

Burden in Africa Alone
- 1.5m living with HIV
- 124,000 new infections
- 91,100 deaths

Source: UNAIDS Global AIDS Update 2016
Journey to eMTCT

Early 1990’s

No ARV interventions

- MTCT Rates: 15-30% developed countries and Up to 45% in developing countries (Breastfeeding populations)
- Breastfeeding transmission: 5-20%

Mid 1990’s

ARV prophylaxis interventions

- Reduced MTCT rates: up to > 50% ↓ in developing countries
- MTCT rates as low as 2% in developed countries

2011 Global plan to eliminate new paediatric HIV infections

PMTCT scale up, More effective ART regimens

- eMTCT target: achieve <5% MTCT rates
Global Plan towards elimination of new HIV infections in children and keeping mothers alive (launched 2011)

Goals by end of 2015:
- >90% reduction in new infections in children (<5% MTCT in BF settings and <2% in non BF settings)
- >50% reduction in HIV-associated maternal deaths
- Focus on 22 high priority countries
eMTCT- a snap shot of progress thus far

eMTCT- status update 2015 (21 Global plan priority countries)

- 170,000: The number of new infections among children in 2014
- 48%: Decrease in the number of new HIV infections among children, 2009–2014
- 8 out of 10: Pregnant women living with HIV received antiretroviral medicines to prevent mother-to-child transmission of HIV
- 14%: Mother-to-child HIV transmission rate, including during breastfeeding

Source: UNAIDS 2015 Progress report on Global plan
**eMTCT: Component of Fast track global agenda**

**Fast-Track Targets**

- **by 2020**
  - **90-90-90**
    - HIV treatment
  - **500 000**
    - New HIV infections or fewer
  - **ZERO**
    - Discrimination

- **by 2030**
  - **95-95-95**
    - HIV treatment
  - **200 000**
    - New HIV infections or fewer
  - **ZERO**
    - Discrimination

- **Accelerating delivery of high impact HIV prevention and treatment services**

- **Focus on 30 countries with highest HIV burden**

- **UNAIDS: Fast-Track ending AIDS epidemic 2030**

**eMTCT fast track target:**

- New HIV infections among children eliminated and their mother’s health and well-being is sustained

**Result areas:**

- Immediate ART accessible to all pregnant women living with HIV (Option B+)

- Integration of HIV, sexual and reproductive health, including family planning, TB and MCH services

- HIV prevention services for male partners promoted, including testing and treatment
Number of new infections among children in 21 Global plan priority countries 2000-2015

Source: UNAIDS 2016 Progress report on Global plan
eMTCT- a snap shot on progress thus far

Percentage of HIV infected pregnant women who received ARV medicines for PMTCT by country in 2015

Source: UNAIDS 2016 estimates
eMTCT- a snap shot on progress thus far

Six week and final mother to child transmission rate by country 2015

Source: UNAIDS 2016 estimates
The Journey to eMTCT-what has clinical research contributed?

Clinical research

- Evidence on most effective and safe ARV regimens
- Evidence on best practices to promote service delivery
- Evidence on supporting adherence and retention

- Evolution of prevention strategies
- Informing best practices for safe infant feeding
- Service delivery models
- Advances in Diagnostic approaches
- Innovations on tracking systems
- Best practices for adherence support
- Promoting male partner involvement

INFORM PMTCT POLICIES.
Towards eMTCT- PMTCT clinical trials conducted
MUJHU Research collaboration CRS, Uganda
Landmark PMTCT studies done at MUJHU CRS, Uganda

Which ARV regimens are best?

HIVNET 012 (1997)
- Sd NVP to mother at onset of labour and to baby within 72 hours Vs AZT regimen through labour and to baby for 7 days
- 50% reduction in HIV transmission with sdNVP (breastfeeding setting)

Petra (1996-2000)
- RCT done in S. Africa, Uganda (MUJHU), and Tanzania. About 1800 participants enrolled
- Compared prepaturm+intrapartum+postpartum regimen vs intrapartum+ postpartum vs intrapartum regimen
- 6 week transmission rate was lowest with the prepaturm+intrapartum+postpartum regimen (5.7%)

Guay L et al. 1999; Brooks J et al 2003; Petra study Team 2002
Landmark PMTCT studies done at MUJHU CRS, Uganda

**HPTN 046: Extended Infant NVP prophylaxis, 2008-2010**

1527 infants enrolled and randomized

Extended NVP arm
N=762
NVP through 6 months of age

Placebo arm N=765
NVP for 6 weeks then placebo through 6 months

Study done in **Uganda (MUJHU CRS), Tanzania, South Africa, Zimbabwe**

*Kaplan-Meier analysis of cumulative rates of HIV-1 infection, by study group*

Hoosen M Coovadia et al 2012
Main Goals

- Maximize prevention of mother-to-child HIV transmission (PMTCT) and optimize maternal/child health and survival.

- Assess the relative safety and efficacy of triple ARVs compared to other proven regimens among healthy HIV women with higher CD4 counts.

Study Sites in:
- India (1)
- Malawi (2)
- South Africa (5)
- Tanzania (1)
- Uganda (MUJHU CRS)
- Zambia (1)
- Zimbabwe (3)

Sample size
3543 Mother-infant pairs
Recent PMTCT study: Which ARV regimens are best?

**PROMISE study Randomizations**

<table>
<thead>
<tr>
<th>Antepartum</th>
<th>Labor/ Delivery</th>
<th>Postpartum (for duration of BF)</th>
<th>Maternal Health (after BF cessation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(14 wks-term)</td>
<td></td>
<td>Maternal CD4 &gt;350</td>
<td>infant uninfected at birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZDV</td>
<td>Mother</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZDV + sdNVP+ TRV</td>
<td>Continue Triple ARV Regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triple ARV Prophylaxis</td>
<td>Stop All ARVs</td>
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<tr>
<td></td>
<td></td>
<td>Late Presenters</td>
<td></td>
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</tbody>
</table>

MG Fowler et al CROI 2015
Recent PMTCT study: Which ARV regimens are best?

**Antepartum** (14 wks-term)  
**Labor/ Delivery**  
**Postpartum** (for duration of BF)  
**Maternal Health** (after BF cessation)

- **Maternal CD4 >350**
  - **Randomize**
  - **Triple ARV Prophylaxis**
  - **Tripler ARV Prophylaxis**
  - **ZDV**
  - **ZDV + sdNVP+ TRV**

- **infant uninfected at birth**
  - **Randomize**
  - **Triple ARV Prophylaxis**
  - **Infant NVP Prophylaxis**
  - **Late Presenters**

- **Mother**
  - **Randomize**
  - **Continue Triple ARV Regimen**
  - **Stop All ARVs**

**ENROLLED 3,529 WOMEN**  
*MG Fowler et al CROI 2015*
Recent PMTCT study: Which ARV regimens are best.....?

PROMISE Antepartum component results: MTCT Through Age 14 days significantly lower in triple ARV Arms

- **ZDV (Arm A)**: 0.56% transmission through age 14 days
- **Triple ARV (Arms B+C)**: 1.8% transmission through age 14 days

**Difference in MTCT Risk (Repeated Confidence Interval):** -1.28% (95% CI -2.11%, -0.44%)

*MG Fowler et al CROI 2015*
Recent PMTCT study: Which ARV regimens are best....?

**PROMISE Study: Antepartum Component results: Adverse events**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Any Grade 2+ AE</th>
<th>Any Grade 2+ Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV (Arm A)</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td>3TC-ZDV+LPV-RTV (Arm B)</td>
<td>16%</td>
<td>1%</td>
</tr>
<tr>
<td>FTC-TDF+LPV-RTV (Arm C)</td>
<td>16%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- **Arm A vs. B** $P<0.008$
- **Arm A vs. C** $P=0.03$

MG Fowler et al CROI 2015
Recent PMTCT study: Which ARV regimens are best…?

A vs C
P=0.04

ZDV (Arm A)  3TC-ZDV+LPV-RTV (Arm B)  FTC-TDF+LPV-RTV (Arm C)

% with Event

A vs C
P=0.004

Birth weight  Gest. Age

B vs C
P=0.02

Any <2500g <37 wks Any <1500g <34 wks

B vs C
P=0.04

Birth weight  Gest. Age

Recent PMTCT study: Which ARV regimens are best…?

MG Fowler et alCROI 2015
**Research informing policy: Evolving WHO PMTCT guidelines**

**PMTCT**
- **2001**: 4 weeks AZT; AZT+ 3TC, or SD NVP
- **2004**: AZT from 28 wks + SD NVP
- **2006**: AZT from 28 wks + sdNVP +AZT/3TC 7days
- **2010**: Option A (mat AZT + infant NVP to end BF)  
  Option B (mat triple ARVs to end of BF)
- **2013**: Option B or B+ Moving to ART for all pregnant / BF women
- **2015**: TREAT All

**KEY STUDIES**
- **HIVNET 012 PETRA**
- **HIVNET 012 THAI STUDY**
- **DITRAME SWEN**
- **HPTN 046 BAN KESHO BORA**
- **SMART HPTN 052 PROMISE**
- **START TEMPRANO**

<table>
<thead>
<tr>
<th>ART</th>
<th>None</th>
<th>CD4 &lt;200</th>
<th>CD4 &lt;200</th>
<th>CD4 &lt;350</th>
<th>CD4 &lt;500</th>
<th>Test and Treat All</th>
</tr>
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</table>

Research has informed move to use of **more effective ARV drugs, extending coverage throughout MTCT risk period, and ART for the mother’s health as well as safe infant feeding options**
Making eMTCT a reality—what are the challenges?

Main challenges

- Unmet family planning needs
- Low PMTCT coverage
- Adherence challenges with life long ART (Option B+)
- Poor retention in care
- Stigma
- Male involvement and community support
- Intergration of Maternal and child health services

Retention of mothers in eMTCT—Uganda data 2015

Source: Uganda MOH eMTCT review report 2016
Making eMTCT a reality—addressing the gaps through research

Promoting Adherence and retention is critical to get to Zero new infections

- Evidence on long acting regimens
- Evidence on use of mhealth/ehealth
- Evidence on community based models of adherence support
- Evidence on best practices to promote male involvement

Getting to Zero new infections

- Evidence on Prep in pregnancy and B/F
- Exploring new approaches for HIV testing
- Community, self and home based testing

Promoting primary prevention

- Evidence on best practices for integration of services
- Evidence on community based ART provision
- Evidence on point of care test models

Addressing stigma is key
Making eMTCT a reality-addressing the gaps through research

- Evidence on long term safety of different ARV regimens
- Infant neurodevelopment and growth, maternal and infant organ toxicities
- Finding best prophylactic interventions to prevent vertical transmission
- Comparing efficacy of different ARV regimens including newer drugs
- Evidence on immune based interventions
- HIV antibody and vaccine immunization for prevention
## Making eMTCT a reality—addressing the gaps through research
(ongoing studies at MUJHU CRS, Uganda)

### Assessing strategies to support adherence and retention

<table>
<thead>
<tr>
<th>Friends for life circles for Option B+</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rural and Urban hospital setting in Uganda)</td>
<td>(N= 540)</td>
</tr>
<tr>
<td>Formative research</td>
<td></td>
</tr>
<tr>
<td>To assess attitudes, experiences and knowledge about Option B+</td>
<td>To compare a community based peer support system (with IGA component) to MOH standard adherence support</td>
</tr>
</tbody>
</table>

#### Study status

- **Formative phase:**
  - Conducted 7 Key Informant Interviews (health workers, community leaders, policy makers)
  - Conducted 6 Focus Group Discussions (women on PMTCT Option B+ and their partners)

- **RCT:** 25 women enrolled as of 01 Jul

- Formative data analysis—ongoing
Making eMTCT a reality - addressing the gaps through research (ongoing studies at MUJHU CRS, Uganda)

Assessing options for Early Infant Diagnosis (EID)

- Cross sectional performance evaluation of point of care test (Simple AMplification Based Assay) for EID in RLS
- Population: HIV exposed and HIV infected infants 1 year or younger

Study status
- Completed enrollment
- (200 HIV exposed uninfected babies and 75 HIV infected babies enrolled)
- Data analysis ongoing
Conclusion

- Scientific evidence is critical to inform policies and programmes to advance the agenda to eliminate new pediatric HIV infections by 2020.

- A lot has been achieved, but a lot still needs to be done.

- Together, we have the power to end the AIDS epidemic.
Acknowledgement

- Center For AIDS Research (CFAR)
- Site leadership - MUJHU Research Collaboration, Kampala, Uganda
- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network
- US National Institutes of Health (NIH)
Thank You