HIV in the Next Generation: the Rocky Road to Elimination  
(*focus on Africa*)

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Outline

- Millennium Development Goals
- Prevention of Mother-To-Child Transmission (pMTCT)
  - Where have we come from?
- Strategies for pMTCT
  - From Option A to Option B plus
- Paediatric diagnosis & linkage to care
  - Where are all the children?
- Prevention of HIV in adolescents
Where are We in 2015?

Integration of MDGs*
Reduce HIV/AIDS
Increase Child Survival

Millennium Development Goals 4, 5 & 6

*Double Dividend:
An initiative between UNICEF, WHO and EIFPAF, launched 2013.
Sources: 1. UNAIDS. The gap report 2014

Where are We in 2015?

eMTCT
(Virtual) Elimination of Mother to Child Transmission

- MTCT <5% in breastfed infants
- <40,000 new infections/year (UNAIDS Global Plan 2011-2015)

Integration of MDGs*
Reduce HIV/AIDS
Increase Child Survival

Millennium Development Goals 4, 5 & 6

*Double Dividend:
An initiative between UNICEF, WHO and EIFPAF, launched 2013.
Sources: 1. UNAIDS. The gap report 2014
In 2013:
*240,000 children acquired HIV
 ~660 new infections/day
*3.2 million children <15 years living with HIV
91% in SubSaharan Africa
“Virtual elimination” of MTCT in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>MTCT</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>1.0%</td>
<td>2005-2009</td>
</tr>
<tr>
<td>Italy</td>
<td>1.0%</td>
<td>2005-2010</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.5%</td>
<td>2000-2008</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.6%</td>
<td>1999-2003</td>
</tr>
<tr>
<td>Spain</td>
<td>1.6%</td>
<td>2000-2007</td>
</tr>
<tr>
<td>Ukraine</td>
<td>4.1%</td>
<td>2008-2010</td>
</tr>
<tr>
<td>Russia</td>
<td>3-4%</td>
<td>2010</td>
</tr>
<tr>
<td>UK</td>
<td>0.57%</td>
<td>2007-2011</td>
</tr>
</tbody>
</table>


UK and Ireland

MTCT rates 2000-2011

- 33 infected infants among 5788 singleton live births

1987: HIV Treatment Era Begins

- AZT (ZDV) approved by FDA in March 1987 for treatment of adults

- Despite concerns about AZT toxicity, given high mortality of paediatric AIDS, paediatric and obstetric researchers proposed giving AZT to infected pregnant women to reduce MTCT.
“Treatment as Prevention”: PMTCT With AZT in 1991

- Giving a potentially toxic drug to pregnant women and exposing their fetuses was highly controversial.

- Before approving the 076 trial, the FDA held a special public meeting to discuss the ethics of giving AZT to pregnant women.

The AZT Regimen in PACTG 076 Was Designed to Target Multiple Potential Time Points of Transmission

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Labor/Delivery</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment CD4 &gt; 200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT 100 mg 5 times daily</td>
<td>AZT IV 2 mg/kg 1 mg/kg/hr</td>
<td>AZT 2 mg/kg q 6 hr x 6 weeks</td>
</tr>
<tr>
<td>In Utero (after 1st trimester)</td>
<td>Intrapartum</td>
<td>Postpartum</td>
</tr>
</tbody>
</table>

Pre-Exposure Prophylaxis (PrEP) | Post-Exposure Prophylaxis (PEP)
DSMB Stopped PACTG 076 Trial at First Interim Efficacy Analysis in February 1994

First demonstration of treatment as prevention!

076: Moving Rapidly from Evidence to Policy and Implementation in Less than One Year
Translation of Trial Results into Practice – US

Estimated Number of Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985-2004 – United States

Global HIV Epidemic in Children

- After 1994, pMTCT implemented in resource-rich countries & attention turned to the developing world, where most HIV-infected children live.
- By 1994, an estimated 1 million HIV-infected infants born.

- In 1999, an estimated 570,000 children aged 14 or younger became infected with HIV. Over 90% were babies born to HIV-positive women, who acquired the virus at birth or through their mother’s breastfeeding. Of these, almost nine-tenths were in sub-Saharan Africa.

No. children 0-14 years living with HIV globally
World Health Organization Response to PACTG 076 Results

- June 23-25 1994, WHO held a meeting of scientists & MOH to discuss implications of 076 trial for the developing world.

- Concluded that best approach was to do randomized, placebo-controlled trials of shorter and simpler regimens of AZT.

“ZDV regimen studied in ACTG 076 not applicable [high cost; operational requirements] in parts of the world where most MTCT of HIV occurs, placebo-controlled trials offer the best option for obtaining rapid and scientifically valid results…no other effective alternative .”

The Conduct of Placebo-Controlled Trials Raised New Controversies

- Despite controversy, several critical placebo-controlled trials of shorter AZT regimens developed for developing countries.

- Investigators collaborated and shared trial design, endpoints, and conducted meta-analyses.

- Trials built sequentially on each other to enable evolving and improving PMTCT standards for developing world.
Building the Evidence Road for PMTCT

1994 US: FACTG 076: AZT
1996: Bangladesh CDC: Short AZT
1996 Côte d'Ivoire: Wiktor CDC: Short AZT
1999 Thailand: HIVNET 012: Short AZT
2000 Thailand: PHPT: Short vs Long AZT
2004 Thailand: PHPT-II: Short AZT + SD NVP
2004 Botswana: MASHI: Infant
2008 Ethiopia, India, Uganda: Infant NVP 6 wk
2008 Malawi: PEPI-Malawi: Infant NVP or NVP/AZT 14 wk
2009 Tanzania: MITRA-plus: Maternal ARV
2009 Thailand: Short AZT
2009 HIVNET 012: SD NVP
2009 Gambia: SD NVP and AZT/3TC for 7 days
2010 Botswana: Mma Bana: Maternal ART
2010 Malawi: BAN: Infant NVP vs. Maternal ART
2010 Malawi: BAN: Infant NVP vs. Maternal ART
2011 Africa: Kesho Bora: Maternal ART 6 mo
2012 Tanzania: PEPI-Malawi: Infant NVP or NVP/AZT 14 wk
2013 Botswana: MITRA-plus: Maternal ART
2014 Africa: HPTN 046: Infant NVP 6 mo
2015 Africa: ANRS 12714: Infant 3TC or LPV/r 12 mos

Modified from James McIntyre MD

WHO Guidelines 2010: Option A or Option B

Pregnancy
Labor & Delivery
Breastfeeding
New Pregnancy

Maternal lifelong ART (CD4 <350, WHO 3,4)

- CD4 < 350
- CD4 > 350

Option A
AZT
SD NVP and AZT/3TC for 7 days
Daily Infant NVP

Option B
Maternal triple ART prophylaxis

CD4 test
WHO stage
CD4 result
Re-identify at ANC
CD4 test
WHO stage
Re-identify at ANC
Triple antiretroviral therapy is best for reducing MTCT  
(Fowler MG, Abstract 31LB, CROI 2015)

Transmission Risk by Study Arm

- Maternal ZDV etc & Infant NVP – Option A: 1.8%
- ZDV/3TC+LPV/RTV: 0.5%
- TDF/FTC + LPV/RTV: 0.6%

Difference (CI)
-1.28% (-2.11 to -0.44)

Evolution of WHO PMTCT Guidelines Over Time - As New Evidence Becomes Available

- 2001: No rec, ART if CD4 <200
- 2004: ART if CD4 <200
- 2006: ART if CD4 <350
- 2010: ART if CD4 <500

Breakthrough: prevention of breastfeeding MTCT
- Use of more effective drugs
- Extend coverage through BF
- ART for maternal health
- Program simplification
New guidelines recommend **universal ART** for pregnant and breastfeeding women

**IN 2015**: ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong

*Strong recommendation, moderate-quality evidence*

- In 2010 we had Option A and B
- In 2013 Option A no longer recommended; instead Option B and B+
- Now lifelong ART for ALL people diagnosed with HIV Therefore, the new guidelines do not speak of “options” but “universal ART”
- But the rationale behind this isn’t from PMTCT literature....

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The START trial enrolled over 4000 people with CD4>500 at 211 sites in 35 countries

- Europe 33%, S. America 25%, Africa 21%, N. America 11%, Asia 10%
- Median age 36 years; 25% women
- Med CD4: 651 (range 503 to 2296) and Med VL: 12,000
- Patients randomized to early start or waiting till CD4 fall <350
- Trial was closed early by the DSMB because of higher than expected benefit of ART
When looking at the primary outcome of death or severe disease, immediate ART was protective.

Overall there were 42 “events” in the immediate arm and 96 in the deferred arm, p = 0.001. No difference in drug toxicities between arms and no evidence of harm caused by ART even in clients with HIV CD4.

Strong recommendations for all BHIVA 2015

US 2015

WHO 2015

EACS 2015

New ART initiations among pregnant and breastfeeding women, percentage of all new ART initiations attributed to this population, Malawi 2008-2012 (CDC, MMWR 2013)

B Plus in Malawi - starting in 2011

2004-2008, only 9% of HIV+ pregnant women started on ART (Braun et al, JAIDS, 2010)

In 1st year of B+ implementation, the number of pregnant and breastfeeding women initiating ART increased 748% (CDC, MMWR 2013)
### Balance of Risks and Benefits for universal ART

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>HARMS</th>
</tr>
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<tbody>
<tr>
<td>Prevent transmission in future pregnancies</td>
<td>Additional risk of toxicity because of additional time on ART</td>
</tr>
<tr>
<td>Reduced transmission to uninfected partners</td>
<td>Programmes are seeing high rates of LTFU; may have implications for resistance</td>
</tr>
<tr>
<td>Avoid stopping and restarting ART for future pregnancies</td>
<td>Potential risk of loss in transition from MCH delivered ART services to routine ART services</td>
</tr>
<tr>
<td>No need to establish eligibility prior to initiating ART regimen</td>
<td>Increased net immediate cost (although maybe cost effective in the long term)</td>
</tr>
<tr>
<td>Improved maternal mortality &amp; slower disease progression with continuous vs. interrupted ART</td>
<td>Additional potential risk of resistance, especially if women stop ART or are poorly compliant</td>
</tr>
</tbody>
</table>

### No studies comparing Option B with B+

But.... there are data on stopping ART

- Postpartum women discontinuing ART experience CD4 decline; heterogeneity from studies:
  - **CD4 at BASELINE of <500**, resulted in 6-20% of women reaching treatment threshold within 6 months of stopping (vs only 1.5% if CD4 >500)
  - May present for next pregnancy with CD4 below threshold for ART initiation (also suggested from UK data)
For most countries, Universal ART for pregnant women (B+) is already national policy

Policies adopted in 144 LMIC
80% - Option B+

New Vision, Uganda, January 28, 2015

New HIV prevention strategy yields results

“…..reduction in the number of HIV-positive children born by HIV positive mothers from 6% to 2%, following the introduction of the option B+ treatment”
New Paediatric HIV infections among the 21 Global Plan countries dropped below 200,000 in 2014

ART access for pregnant women has increased with the adoption and implementation of B+.
BUT

Is the policy shift to Universal ART for Pregnant and Breastfeeding women the magic bullet to control MTCT?
HIV testing still low; in 2013 only 44% of pregnant women were HIV tested, 73% of HIV+ women received any ARV in 2014, and 50% infants received infant ARV prophylaxis.

But when you look at individual countries there is a lot of heterogeneity in terms of coverage.
**Zimbabwe MTCT Rates & eMTCT Coverage, 2002-2013/4**

**Goal:** Reducing new Pediatric infections by 90% & a MTCT of HIV < 5% end 2015

**PMTCT Coverage:**
- Significant reduction in MTCT rate from 30% in 2009 and 5.3% in 2014
- ARV prophylaxis for pregnant women has remained high at 84% in 2010 and 2014
- HIV exposed infants receiving ARV prophylaxis for PMTCT increased from 74% in 2010 to 88% in 2014
- Rapid expansion of Option B+ to 1,457 health facilities

**Main Challenges:**
- Late booking and home deliveries
- Loss to follow for HIV exposed infants

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**pMTCT Cascade (Continuum) with Option B+**

Malawi HIV Programme Report April-June 2014

- 97% women come to ANC but ~15% not tested
- ~23% new B+ women lost <6m
- ~30% new B+ women lost by 24m

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Source: Integrated HIV Program Report MOH, Malawi April-June 2014
Retention on ART in adults in rural Zimbabwe
ICASA conference, Harare 2015

<table>
<thead>
<tr>
<th>Retention on ART 12 months post initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Men &amp; non B+ women</td>
</tr>
<tr>
<td>B+ women</td>
</tr>
</tbody>
</table>

Safety of EFV and TDF in pregnancy

Efavirenz

Risk of birth defects with EFV not increased

Systematic review (11 studies; Antiretroviral Pregnancy Registry data):
• outcomes of 1,290 live births in women receiving EFV in 1st trimester;
  **no increase in overall birth defects**

Insufficient data to exclude >3 X risk in low-incidence birth defects – e.g. neural tube defects

Tenofovir

TDF in pregnancy are limited

Concerns include renal toxicity, adverse birth outcomes, effects on bone density

Systematic review of foetal exposure to TDF:
• In Antiretroviral Pregnancy Registry, prevalence of 2.4% with TDF 1st trimester exposure for all birth defects (same as background)
• No association with neuro-developmental outcomes in infants 9-15 month
• Lower 12 month growth with TDF exposure
• Promise trial had increased early deaths with LPV/r and TDF

Option B+ & eMTCT?

- Triple ART is best for reducing MTCT
- Coverage increasing but eliminating MTCT has a way to go
- B+ has benefits:
  - Reduce pMTCT in future pregnancies
  - simplicity; ↑rollout of ART for all alongside pMTCT
  - reducing partner transmission
  - improving maternal health
- The big risk is failure to retain in care and its consequences
  - Involvement of male partners is important

PMTCT Does Not End at Delivery: Infants Are Not Being Diagnosed

<table>
<thead>
<tr>
<th>Country</th>
<th>% with viral test by age 2 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swaziland</td>
<td>89</td>
</tr>
<tr>
<td>South Africa</td>
<td>78</td>
</tr>
<tr>
<td>Botswana</td>
<td>58</td>
</tr>
<tr>
<td>Namibia</td>
<td>56</td>
</tr>
<tr>
<td>Zambia</td>
<td>55</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>50</td>
</tr>
<tr>
<td>Kenya</td>
<td>42</td>
</tr>
<tr>
<td>Uganda</td>
<td>36</td>
</tr>
<tr>
<td>Lesotho</td>
<td>36</td>
</tr>
<tr>
<td>Mozambique</td>
<td>35</td>
</tr>
<tr>
<td>Ghana</td>
<td>30</td>
</tr>
<tr>
<td>Tanzania</td>
<td>26</td>
</tr>
<tr>
<td>Cameroon</td>
<td>21</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>21</td>
</tr>
<tr>
<td>Angola</td>
<td>17</td>
</tr>
<tr>
<td>Burundi</td>
<td>17</td>
</tr>
<tr>
<td>DRC</td>
<td>15</td>
</tr>
<tr>
<td>Nigeria</td>
<td>10</td>
</tr>
<tr>
<td>Chad</td>
<td>4</td>
</tr>
</tbody>
</table>

Source: Global Update on the Health Sector Response to HIV 2014

Only 44% of HIV-Exposed Infants Received Early Infant Diagnostic Testing

In 6 priority countries, less than 1 in 20 HIV-exposed children had early infant diagnostic services, and in 2, less than 1 in 10.
Early Infant Diagnosis Tests & Results by Entry point: Kenya 2014

Testing all Children admitted to Malnutrition and Acute Care Units must be **High priority**

Stunting  
Wasting
Engagement with Communities is Vital

- If parents (mother) dies, child often returns to the village
  - grandmother carers cannot easily travel
- Stigma and lack of male involvement
- In 30/1351 households in a survey in North Uganda, informants “worried a child in the household had HIV” but “did not know where to test”

What is Needed:

At Primary Health Facilities
- Knowledge of paediatric HIV
- On-site mentorship
- Health system strengthening
- Innovative ways to engage Men:
  - At ANC
  - Bring in the children
Deaths in Infants and 1-4-year-olds
At home and in health facilities
Africa Centre Demographic surveillance
Rural KZN
South Africa

~40% infant die at home
~60% 1-4 year-olds die at home

WHY and what of?
How much is undiagnosed HIV
Despite good pMTCT coverage?
Summary: Early Diagnosis and Treatment

- Without early HIV diagnosis and ART, 50% children die <2 yrs
- Very early diagnosis & treatment reduces viral reservoirs and has future potential **BUT >90% infected children are to be found outside pMTCT settings**
- **Provider initiated testing & linkage to care and ART** needs to be increased at multiple entry points
- ...and **near where children live** (strengthening capacity at lower level health centres (supply))
- **Community mobilisation** to understand HIV in children and bring for testing and treatment (demand)

Outline

- Milenium Development Goals
- Prevention of Mother-To-Child Transmission (pMTCT)
  - **Where** have we come from?
- Strategies for pMTCT
  - From Option A to Option B plus
- Paediatric diagnosis & linkage to care
  - **Where** are all the children?
- Management of HIV-infected adolescents and Prevention of HIV in adolescents
**Perinatal HIV in the US and UK**

10,798 persons with perinatal HIV living in the US in 2010

CDC HIV Surveillance Report 2011

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**Issues for HIV-infected Teenagers:**

- Disclosure and Stigma
- Chronic ill-health
- Poor growth and development
- Orphanhood and Poverty
- Adherence to medication and Side effects (efavirenz)
- Sexual Health & Teenage Pregnancy

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...and UK/Ireland

Age by year of follow-up, 1996-2013

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Introduction

- Often, adolescents fall through the cracks and prefer not to seek care
- There is no primary health care offered to adolescents in many African Health care institutions
Responding to the needs of Teenagers

- Simpler and more ‘forgiving’ ART regimens:
  - Once daily
  - Long-acting Injectables
  - ‘Weekend breaks’ (BREATHER Trial (PENTA 16))
- Non-judgemental information
- Peer support

**HIV Incidence Among Young Women**

*More Than 1/3 New HIV Infections Globally Occur Among Young Women in Africa*

Estimated number of new HIV infections per week among young women aged 15-24 years in East and Southern Africa, 2012

Source: PEPFAR and UNAIDS 2013
New Attention Being Paid to Global Adolescent HIV Infections


- Energize, mobilize, empower youth
- Better data collection to inform programs
- Innovation to adapt services to youth
- Adolescent HIV on political agenda

Elimination (virtual) of Paediatric HIV: not there yet!

In 2013:
*240,000 children acquired HIV
~660 new infections/day
*3.2 million children <15 years living with HIV
91% in Sub-Saharan Africa

Sources:
1. UNAIDS. 2013 HIV and AIDS estimates, 2014
Summary

- **PMTCT and eMTCT**
  - Increasing coverage is priority; some way to go to eMTCT
  - Reduce new HIV infections in women & unmet family planning needs

- **Infant/Child diagnosis is challenging**
  - Priority to increase testing and linkage to care outside pMTCT settings, near where children live and to involve communities

- **Adolescence through to adulthood**
  - There is an imperative to address wider needs of adolescents
    - Reducing pregnancies and preventing HIV
    - Long term follow up into adulthood is the responsibility of success

We have come a long way
BUT there is more work to be done!

Thanks to: Lynne Mofensen and Shaffiq Essajee (WHO)