Research needs and potential for EDCTP supported projects on PMTCT and paediatric HIV care

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EDCTP Stakeholders Meeting, 3-4 Sept 2013
What has been acquired from PMTCT research

• **Prevention of de perinatal HIV transmission:**
  ✓ Early initiation of prophylaxis during pregnancy;
  ✓ Combination ART are more effective than monoprophylactic regimens;
  ✓ Some drugs are more efficacious, some may be hazardous (Efavirenz and neurological defects)* ;
  ✓ The target of elimination (MTCT < 5%) seems achievable, if no breastfeeding.

• **Prevention of postnatal (breastfeeding) HIV transmission:**
  ✓ No prophylactic trial covering the whole duration of breastfeeding exposure (= 12 months);
  ✓ Important residual transmission (3,6% at 6 months in the Kesho Bora trial);
  ✓ Concerns about adherence ;
  ✓ The target of elimination seems out of reach.

* Sibiude et al, CROI 2013, Atlanta
Objectives of the UN Agencies for 2015

- Reduction of the MTCT rate < 5% (definition of « elimination »)
- 90% reduction of new paediatric infections (430,000 en 2009, 43,000 en 2015?)
- 50% reduction of HIV-related maternal mortality
Reduce the Number of New HIV Infections among children by 90% by 2015

Estimated new Paediatric Infections in Low and Middle Income Countries (LMICs)

- New Infections 2009: 430,000
- New Infections 2010: 390,000
- New Infections 2011: 330,000
- New Infections 2015 (Goal): 43,000

Country Contribution to 390,000 Paediatric HIV Infections in LMICs in 2010

- Nigeria: 29%
- DRC: 13%
- Uganda: 10%
- Malawi: 7%
- Kenya: 6%
- Mozambique: 6%
- India: 6%
- Tanzania: 6%
- Zimbabwe: 6%
- Ethiopia: 6%
- Other Priority Countries: 7%
- Other LMICs: 7%

Source: 1. UNAIDS, Together we will end AIDS, 2012
2. HIV/AIDS Response – Epidemic Update and Health Sector Progress Towards Universal Access 2011
Coverage of antiretroviral medicine for preventing mother-to-child transmission: most effective regimens, low- and middle-income countries, by region, 2011

Source: UNAIDS. Together we will end AIDS 2012
WHO guidelines for PMTCT and infant feeding (June 2013)

Maternal therapeutic ART (AZT/TDF + 3TC/FTC +NVP/EFV)

- Option A: AZT + 3d-NVP
- Option B: Maternal ART prophylaxis (AZT+3TC+LPV/r or EFV or ABC)
- Option B+: Maternal ART for life (TDF/3TC/EFV)

... but research on breastfeeding transmission should continue!
Option A, B or B+? A critical analysis

• Alarming inflation in the number of WHO-UNICEF PMTCT recommendations (’90s: n=1, 2000s: n=4, 2011-2013: n=2);

• Current WHO PMTCT recommendations are not evidence-based;

• Push for option B+ is based on mathematical models, best guess estimates on feasibility but NOT on measured efficacy or efficiency.

Van de Perre P; BMJ 2013
Option B ou B+ ?

- **Suboptimal efficacy on postnatal transmission** in the Kesho Bora trial: in mothers with > 350 CD4/µl, 6-month efficacy = 29% (NS)*;

- **Suboptimal adherence**: in a metanalysis of more than 20,000 pregnant women, adherence of 53% at 12 months post partum**;

- **Extremely high rate of resistance in infants who get HIV-infected despite maternal prophylaxis*****

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* Kesho Bora Study Group, Lancet Infect Dis, 2011
** Nachega et al, AIDS 2012
*** Zeh, PlosMed 2011; Fogel, Clin Infect Dis 2011; Lidström, CROI 2010
Option A?

- Until now, unknown efficacy if infant PreP is extended during the whole duration of exposure (12 months breastfeeding recommended by WHO);

- Adherence and tolerance uncompletely explored;

- Results of the ANRS 12274-PROMISE-PEP trial
PMTCT: Scientific/programatic questions?

• What is the community effect of rolling out option B/B+? Acceptability? Adherence? Protection of future pregnancies? Reduction of breastfeeding transmission events?
• How to operationalize the access to prevention and therapy within national programs (coverage, acceptability, adherence, retention, ...)?
• How to optimise recommended PMTCT regimens in order to cover breastfeeding? Combine B/B+ and A?
• Infant PreP: a place for extra-long acting ARV drugs (rilpivirine-LA, GSK 744, others)?
• What is the role of co-infections (herpesviruses, MTB, others...) in MTCT?
• How to take into account acute maternal infections (2+-fold risk of transmission) in PMTCT?
• Is there a place for alternative strategies in PMTCT? Passive immunoprophylaxis (NIH45-46G54W based cocktails)? Vaccine? Control of co-infections?
Paediatric HIV care
The Children with HIV Early Antiretroviral Therapy (CHER) trial: Children Initiating Treatment Immediately have better chance of survival

Most deaths occurred within first 6 months (i.e., before age 10 months)

**PATIENTS AT RISK**

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P=0.0002

76% REDUCTION IN THE RISK OF DEATH

Violari et al. NEJM 2008

Trends in pediatric age distribution at ART initiation (2005-2010)

Paediatric Antiretrovirals: simplified dosing formats and analysing their adverse events

CHAPAS-1 trial
PK sub-study 2007 → FDA licensing

CHAPAS-2
LPV/r liquid vs tablets vs sprinkles PK study

CHAPAS-3
Looking at specific toxicities in children

d4T vs AZT vs ABC

Source: Dr Gibb for the Chapas Trials
Increasing HIV Prevalence in Adolescents

South Africa: HIV Prevalence Among Adolescents and Young People

Mozambique: HIV Prevalence Among Adolescents and Young People

Paediatric HIV care: Scientific/programmatic questions?

- How to operationalize the access to prevention and therapy within national programs (coverage, acceptability, adherence, retention, ...)?
- How to expand early infant diagnosis? New diagnostic tools and procedures?
- How to simplify antiretroviral regimens? Extend the offer of paediatric drugs? Paediatric Single Tablet Regimens? Extra-long acting ARV drugs (rilpivirine-LA, GSK 744, others)?
- Second line paediatric ART. Which regimen? When to switch? How to ensure access?
- Adolescents with HIV: ensuring the continuum of care and prevention?
- What is the optimal point of entry for an integrated (familial?) HIV/TB/other co-infections care & prevention program?
- Exposed Non Infected: morbidity and outcomes?