Prevention of mother-to-child transmission of HIV

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HIV

- HIV identified in 1983

- AIDS syndrome described in 1981
  - Kaposi’s sarcoma, Pneumocystis jiroveci pneumumonia and wasting often combined

- Retrospectively, cases of HIV seen in Central Africa already around 1930

- Around 33 million cases globally (2009)
Transmission modes

- Sexual intercourse
  - Vaginal and anal

- Contaminated needles
  - Intravenous drug users
  - Needle stick injuries
  - Injections

- Organ/ tissue donation
  - Blood
  - Semen
  - Kidneys
  - Skin, bone marrow, corneas, heart valves, tendons etc

- Vertical transmission (mother-to-child)
  - Pregnancy, delivery and breastfeeding

FIGURE 1
CHILDREN (15 YEARS) ESTIMATED TO BE LIVING WITH HIV, 2007

North America
11000
[4500 - 20000]

Western & Central Europe
3000
[2400 - 12000]

Eastern Europe & Central Asia
9500
[6600 - 15000]

Caribbean
11000
[9400 - 12400]

Middle East & North Africa
26000
[19000 - 34000]

East Asia
7900
[5400 - 11000]

Latin America
44000
[36800 - 58400]

Sub-Saharan Africa
1.8 million
[1.7 - 2.1 million]

South & South East Asia
14000
[9900 - 20000]

Oceania
1100
[<2000]

Total: 2.1 (1.9 - 2.4) million

Source: WHO-UNAIDS, 2007
Case: Peter

- Norwegian mother pregnant in week 28. Tested HIV-positive 7 weeks ago during antenatal visit.
  - CD4 650
  - HIV viral load 900/ml
  - Not started treatment yet

- What about treatment/prophylaxis?
  - When? With what?
  - To mother?
  - To child?

- What about delivery?
- What about breastfeeding?
- What will you say?
Case: Rachel

- Mother from Mali testing HIV-positive for HIV just before delivery. No clinical symptoms of HIV

- What about antiretroviral medicines or other treatment?
  - To mother?
  - To child?

- What about breastfeeding?
Transmission modes in children

- Mother-to-child
  - During pregnancy (In utero)
  - During delivery (intrapartum)
  - After birth through breastfeeding (postpartum)

- Some very few acquire it through needle stick injuries etc
Risk of HIV Passing From HIV-Positive Mothers to Their Babies During Pregnancy, Birth, and Breastfeeding

Number of babies infected with HIV through pregnancy and birth  Number of babies infected with HIV through breastfeeding  Number of babies not infected with HIV
Transmission risk of HIV related to maternal HIV stage

<table>
<thead>
<tr>
<th>Primary HIV</th>
<th>Asymptomatic HIV</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 months</td>
<td>5-10 years</td>
<td></td>
</tr>
<tr>
<td>Highly infective</td>
<td>Less infective</td>
<td>Highly infective</td>
</tr>
</tbody>
</table>

Viral load

CD4 count

0 3 months 5-10 years
Importance of interventions: HIV transmission to children

- 10-20% during delivery
- 5% through BF
- 60-80% not HIV-infected
- Nevirapine + zidovudine before delivery and nevirapine to infant post-partum
- ARV treatment during pregnancy
- PEP
- EBF
- RF

If optimal management

HIV-positive

60-80% not HIV-infected
HIV infections from mother-to-child

• Between 2000 and 2006, the transmission rate was 1.2% in the UK
  – due to high coverage of interventions

• Difference between about 1% and 30% transmission risk illustrates the importance of diagnosis and good management

HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics* 2008

HIV testing

• Direct demonstration of virus
  – PCR
  – Viral culture

• Indirect tests (antibody tests)
  – All rapid tests
  – ELISA tests
  – Confirmatory Western Blot
Rapid tests
Testing for HIV

• Rapid testing (for adults)
  – sensitivity ~100%, specificity 99.8%
  – Positive HIV antibody screening test results should be confirmed
    • PCR/Western blot

• Routine testing/ opt-out vs. VCT
  – Many countries now moving towards opt-out
Hepatitis B and C

• Screening for HBV recommended
  – If mother positive to HBsAg and HBeAg
    • Give HBV vaccination and HBV immunoglobulin to infant
  – When HIV and HBV co-infection
    • Include antiretroviral drugs with action also against HBV (such as lamivudine, emtricitabine or tenofovir)

• HIV and HCV co-infection
  – Increased transmission risk of HIV
  – Potent treatment/ prophylaxis is essential
Information to HIV-positive

- Importance of treatment/prophylaxis
- Transmission risks and preventive strategies
- Disease during treatment era
- Available psychosocial support (peer support groups, psychologists etc)
- Promote HIV-status disclosure (particularly between couples and to health workers)
Prophylaxis during pregnancy and delivery

- antiretroviral prophylaxis to the mother and newborn (if not already on treatment)
- Prophylaxis to mother usually from 2. trimester (between week 14 and 28)
- Prophylaxis regimen to mothers are usually similar to treatment regimen
  - usually 3 ARV drugs, e.g. 2 NRTI + NNRTI/PI
- If possible, avoid co-trimoxazole (folate antagonist) as prophylaxis/treatment for co-infection as it is a risk factor for neural tube defects

HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics* 2008

Prophylaxis during pregnancy and delivery

- **Aim**
  - undetectable viral load
- Recommended to avoid some drugs such as stavudine and didanosine (efivarenz is probably not particularly harmful)
- Assess viral load regularly to ensure good therapy/prophylaxis response
  - e.g. every 3 months, at delivery and 2 weeks after change in therapy
- Recommended to assess antiretroviral drug resistance after prophylactic regimen (particularly when using single or dual drug regimen)
  - Single dose nevirapine: 40% develops resistance
Different prophylactic regimen

• Zidovudine monotherapy during last trimester and delivery
  – 1-8% transmission risk (when not breastfeeding)

• Zidovudine + lamivudine more effective
  – ~2.3% transmission risk

• Nevirapine monotherapy
  – High risk of resistance
  – Long half-life: Important to have additional drugs in this period

• Triple therapy: ~1% transmission risk
Delivery

- Cesarean section reduce vertical HIV-transmission by ~50% if no antiretroviral therapy/prophylaxis
  - Uncertain whether beneficial if low viral load
    - Recommended if > 1000 HIV copies/ml (US)
    - Recommended if > 50 HIV copies/ml (UK)
  - before rupture of membranes in week 38
  - Antibiotic prophylaxis

- Vaginal delivery
  - Recommended when low viral load
  - Avoid artificial rupture of membranes
  - Importance of treating potential sexually transmitted infections (Chl.trachomatis, HSV, syphilis, N. gonorrhoea, etc)


Prophylaxis to child

• After delivery
  – nevirapine single dose and 4- 6 weeks of zidovudine (twice daily)
    • well documented
    • other regimen have been used, but most other regimen to non-breastfeeding children are less well studied

• If high viremia, combination therapy recommended

• If breastfeeding, prophylaxis during complete duration of breastfeeding

• Drug toxicity/ side effects of many of the antiretroviral drugs in children and especially drug combinations are largely unknown

• Normal vaccination program, but delay BCG vaccination to confirmed HIV negative
Main side effect mechanisms

- Most are quite well tolerated

- NRTI (nucleoside reverse transcriptase inhibitors, including lamivudine, zidovudine, emtricitabine, abacavir)
  - Some reduced mitochondrial function
    - Particularly stavudine, didanoside
    - Measure lactate

- NNRTI (non-NRTI, including nevirapine, efavirenz etc)
  - Hepatic impairment
    - Measure ALAT

- Protein inhibitors (including lopinavir-ritonavir, atazanavir etc)
  - Some reduced glucose tolerance

- Other drugs acting on e.g. integrase inhibitors (raltegravir), nucleotide analog RTI (tenofovir), fusion inhibitors such as CCR5 receptor antagonists (maraviroc) etc
  - Side effects on infants are less known
Infant feeding

• Breastfeeding 5-20% risk of HIV transmission (when no preventive actions are taken)
  – In high income countries with low morbidity burdens
    • Mother counseled not to breastfeed
    • Assistance with immediate initiation of hand and pump expression if confirmatory test result not available
    • Dopamin receptor antagonist (Cabergoline oral 1 mg) after delivery can be used to suppress breast milk production


World Health Organization (WHO), UNICEF, UNFPA, UNAIDS: Guidelines on HIV and Infant Feeding 2010
Is it better to avoid breastfeeding for all?
Breastfeeding has benefits related to

Morbidity

- Less infections (diarrhoea, pneumonia, otitis media etc)
- Less allergies and auto-immune diseases
- Better growth

Health aspects in adult life

Probably slightly better cognitive outcomes

Reduced risk of child deaths
Respiratory tract infections


Breastfeeding and child growth

Long duration of breastfeeding is beneficial and improves child growth (particularly in low-resource settings)


Slower decline in weight for age (0.3 Z-scores at 9 and 12 months among early weaned)


Longer duration of breastfeeding associated compared to shorter duration of breastfeeding

3.4 cm better length growth, 370 g higher weight

Regarding vulnerable children

Reduced risk of necrotising enterocolitis with breast milk feeding

3% absolute difference. Risk ratio of 0.4 (95%CI 0.2–1.0)


Breastfeeding during early months also protects against the risks associated with famines


(the Dutch Famine Birth Cohort Study, Hungerwinter Study)
How many child deaths can we prevent this year?


<table>
<thead>
<tr>
<th>Preventive Interventions</th>
<th>Estimated under-5 deaths prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of deaths ($\times 10^7$)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>1301</td>
</tr>
<tr>
<td>Insecticide treated materials</td>
<td>601</td>
</tr>
<tr>
<td>Complementary feeding</td>
<td>587</td>
</tr>
<tr>
<td>Zinc</td>
<td>459 (351)*</td>
</tr>
<tr>
<td>Clean delivery</td>
<td>411</td>
</tr>
<tr>
<td>Hib vaccine</td>
<td>403</td>
</tr>
<tr>
<td>Water, sanitation, hygiene</td>
<td>326</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>264</td>
</tr>
<tr>
<td>Newborn temperature management</td>
<td>227 (0)*</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>225 (176)*</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>161</td>
</tr>
<tr>
<td>Nevirapine and replacement feeding</td>
<td>150</td>
</tr>
<tr>
<td>Antibiotics for premature rupture of membranes</td>
<td>133 (0)*</td>
</tr>
<tr>
<td>Measles vaccine</td>
<td>103</td>
</tr>
<tr>
<td>Intermittent preventive treatment in pregnancy</td>
<td>22</td>
</tr>
</tbody>
</table>

| Treatment interventions                   |                                      |                                    |
| Oral rehydration therapy                  | 1477                                | 15%                                |
| Antibiotics for sepsis                    | 583                                 | 6%                                 |
| Antibiotics for pneumonia                 | 577                                 | 6%                                 |
| Antimalarials                             | 467                                 | 5%                                 |
| Zinc                                      | 394                                 | 4%                                 |
| Newborn resuscitation                     | 359 (0)*                            | 4% (0%)*                           |
| Antibiotics for dysentery                 | 310                                 | 3%                                 |
| Vitamin A                                  | 8                                   | <1%                                |

*Numbers represent effect if both levels 1 (sufficient) and 2 (limited) evidence are included; value number in brackets shows effect if only level-1 evidence is accepted. Interventions for which only one value is cited are all classified as level 1.

Table 2: Under-5 deaths that could be prevented in the 42 countries with 90% of worldwide child deaths in 2000 through achievement of universal coverage with individual interventions.
HIV and infant feeding studies - transmission

- Breast milk while giving other feeds (mixed feeding, MF) increased MTCT rates
  - First report from South Africa 1999
  - Re-analysis 2001:

Infant feeding patterns

• **Exclusive breastfeeding and predominant breastfeeding**
  • Relatively low risk of HIV-transmission
  • Positive effect on respiratory infections and risk of several diseases
  • Not beneficial after around 6 months of age

• **Complementary feeding/ partial breast-feeding/ mixed feeding**
  • Necessary to give more than breast milk after 6 months of age
  • Relatively high risk of HIV-transmission

• **Replacement feeding**
  • Low risk of HIV transmission (theoretically nearly zero)
  • Higher risk of other diseases as diarrhoea, pneumonia etc
Factors related with mother-to-child transmission of HIV

MATERNAL FACTORS-MILK
• Viral load (cell-free and cell-associated)
• Viral strain (HIV-1 more than HIV-2, some types of HIV-1 seems to transmit more often such as subtype C)

• Protective factors:
  – Lipids, lactoferrin, lysozymes, HIV antibodies, cytotoxic cells

MATERNAL HEALTH:
• Maternal immunosuppression
  – Low CD4
• Vitamin deficiencies

• Breast problems increasing white blood cells and number of virus particles in the milk:
  – Cracked or bleeding nipples
  – Mastitis (clinical/ sub-clinical)
  – Breast abscesses
  – Trush

Infectivity of milk

INFANT FACTORS

- Oral/ gastrointestinal (integrity of mucous membranes)
  - Stomatitis, oral thrush
  - Ulcerations
  - Pharyngitis, oesophagitis
  - Gastroenteritis

- Receiving solid or semi-solid food in addition to breast milk during the first months (mixed feeding)
- Low-birth weight
- Poor nutritional status

- Protective factors
  - Antiretroviral prophylaxis
  - Protective antibodies or cytotoxic CD8 cells

The Dilemma

BALANCE:

Risk of HIV-1 transmission through breast milk
&
Risk of child death through non-breastfeeding
Infant feeding

- Low income countries with high morbidity burdens
  - Exclusive breastfeeding recommended for 6 months with peri-exposure prophylaxis with antiretroviral prophylaxis
  - Complementary feeding up to the age when appropriate replacement feeding is feasible

- MTCT of HIV with breastfeeding and optimal prophylaxis is <1% in several studies
  - Several regimens have been studied
    - Lamivudine + zidovudine
    - Nevirapine
    - Lopinavir & ritonavir

HIV infected children

• Must be confirmed with PCR
  – (not rapid tests if younger than 16-18 months)
  – Testing when off-treatment/prophylaxis

• Breastfeeding is beneficial

• Early initiation of antiretroviral treatment

• Trimethoprim-sulfamethoxazole recommended as prophylaxis for co-infections
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• What about breastfeeding?
Summary

• 2.1 million children are living with HIV
  – Mainly infected during pregnancy, delivery or breastfeeding

• PMTCT aims to reduce or eliminate HIV transmission from mothers to children
  – Mother to children transmission of HIV can be reduced from around 35% to less than 1%

• Prophylaxis during pregnancy and delivery, and infant feeding strategy are important factors
Questions and comments