Pregnancy and HIV

Dr Annemiek de Ruiter

September 2009
Obstetric and paediatric HIV surveillance data from the UK and Ireland

National Study of HIV in Pregnancy and Childhood

Further information nshpc@ich.ucl.ac.uk  Principal Investigator Pat Tookey

The NSHPC is a collaboration between the Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health, the Health Protection Agency Centre for Infections, and Health Protection Scotland
Pregnancies in diagnosed women in the UK and Ireland 1994-2007*

Routine antenatal HIV screening
Timing of maternal HIV diagnosis
UK/Ireland pregnancies (all outcomes), reported to NSHPC by Sept 2008

Number

Before this pregnancy
During this pregnancy

Year of EDD

HIV prevalence\(^1,2\) among pregnant women by area of residence, England and Scotland

1 Unlinked anonymous seroprevalence of newborn infant dried blood spots
2 Includes previously diagnosed, those diagnosed through antenatal screening and those remaining undiagnosed

Unlinked anonymous prevalence monitoring
Geographical distribution of RCOG reports over time

Tookey P. National Study of HIV in Pregnancy and Childhood. 2005
Maternal country of birth by year of delivery

~7000 pregnancies in HIV infected women reported to the National Study of HIV in Pregnancy & Childhood by March 2007

* NSHPC unpublished data
Timing of transmission

- In utero
- At delivery
- Postnatal
Interventions

- Avoidance of breastfeeding
- Antiretroviral therapy
- Elective caesarean Section
## Mother to Child Transmission of HIV

### Vertical Transmission Rate

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Transmission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention</td>
<td>28%</td>
</tr>
<tr>
<td>Avoidance of breastfeeding</td>
<td>14%</td>
</tr>
<tr>
<td>Administration of Zidovudine, CS and avoiding breastfeeding</td>
<td>&lt;3%</td>
</tr>
</tbody>
</table>

*Duong et al BMJ 1999; 319:1227-9*

Unlinked Anonymous HIV Prevalence Monitoring Programme with ICH (London)
BHIVA Guidelines

CD4 < 250–300 cells/mm³
Commence HAART after first trimester
AZT + 3TC with a boosted PI/nevirapine

CD4 > 250–300 cells/mm³
NVD desired +/- VL > 10,000
HAART with boosted PI
Include AZT if possible
By 28 weeks (advised earlier at 24 weeks)
If VL > 100,000
start at 20-24 weeks

VL < 10,000
AZT + PLCS

BHIVA Guidelines 2008
Trends in uptake of ART and mother-to-child transmission (MTCT) rates, UK and Ireland

HAART = highly active antiretroviral therapy; PI = protease inhibitor; MTCT = mother-to-child transmission
Mode of delivery by year

~5900 deliveries in HIV infected women reported to the National Study of HIV in Pregnancy & Childhood by March 2007 *

* NSHPC unpublished data
Case 1

- 26 years old from Zimbabwe
- Diagnosed via ANC in this pregnancy
- G2 P1 EmCS 2 years earlier
- CD4 540
- VL 4673c/ml
- Keen on SVD
Case 1

- What should we treat her with?
- Is it OK to have an SVD?
- Would it be OK to use zidovudine monotherapy with PLCS?
- When should we start her ART?
- What should we counsel her about?
Very low risk of mother-to-child transmission of HIV in women on HAART achieving viral suppression in the UK and Ireland

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¹ UCL Institute of Child Health
² Imperial College Healthcare NHS Trust
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NSHPC
National Study of HIV in Pregnancy and Childhood
Background

British HIV Association (BHIVA) guidelines

- HAART and undetectable viral load (<50 copies/ml)
  - Elective caesarean section or planned vaginal delivery

- Zidovudine (ZDV) monotherapy if HAART not required for woman’s own health, and viral load <10,000 copies/ml
  - Elective caesarean section delivery
Results

• 5930 singleton births (2000-2006) to diagnosed HIV-infected women
  – Reported by June 2007

• Infection status available for 87% (5151/5930)
  – 91% of those born 2000-2005
Mother-to-child transmission (MTCT) rates

<table>
<thead>
<tr>
<th></th>
<th>MTCT rate (%)</th>
<th>95% CI</th>
<th>n</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.2</td>
<td>(0.9 - 1.5)</td>
<td>61</td>
<td>5151</td>
</tr>
<tr>
<td>2000 - 2002</td>
<td>1.6</td>
<td>(1.0 - 2.4)</td>
<td>23</td>
<td>1456</td>
</tr>
<tr>
<td>2003 - 2006</td>
<td>1.0</td>
<td>(0.7 - 1.4)</td>
<td>38</td>
<td>3695</td>
</tr>
<tr>
<td>At least 14 days of ART</td>
<td>0.8</td>
<td>(0.6 - 1.1)</td>
<td>40</td>
<td>4864</td>
</tr>
</tbody>
</table>

## Mother-to-child transmission (MTCT) rates

<table>
<thead>
<tr>
<th>MTCT</th>
<th>Rate (%)</th>
<th>95% CI</th>
<th>n infected</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAART + elective caesarean section</td>
<td>0.7</td>
<td>(0.4 - 1.2)</td>
<td>17</td>
<td>2337</td>
</tr>
<tr>
<td>HAART + planned vaginal delivery</td>
<td>0.7</td>
<td>(0.2 - 1.8)</td>
<td>4</td>
<td>565</td>
</tr>
<tr>
<td>HAART + emergency CS</td>
<td>1.7</td>
<td>(1.0 - 2.8)</td>
<td>15</td>
<td>877</td>
</tr>
<tr>
<td>ZDV mono + elective CS</td>
<td>0.0</td>
<td>(0.0 - 0.8)</td>
<td>0</td>
<td>467</td>
</tr>
</tbody>
</table>

Townsend et al, AIDS in press

### Mother-to-child transmission (MTCT) rates

<table>
<thead>
<tr>
<th></th>
<th>MTCT rate (%)</th>
<th>95% CI</th>
<th>n infected</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAART</td>
<td>1.0</td>
<td>(0.7 - 1.3)</td>
<td>40</td>
<td>4120</td>
</tr>
<tr>
<td>HAART from conception</td>
<td>0.1</td>
<td>(0.0 - 0.6)</td>
<td>1</td>
<td>928</td>
</tr>
<tr>
<td>HAART + viral load &lt;50 copies/ml</td>
<td>0.1</td>
<td>(0.0 - 0.4)</td>
<td>3</td>
<td>2117</td>
</tr>
</tbody>
</table>

2 of the 3 had evidence of in utero infection

- 2 PLCS
- 1 SVD

Townsend et al. AIDS in press
ZDV monotherapy + elective caesarean section

- There were no transmissions among 467 women who received ZDV monotherapy and had elective caesarean section deliveries
  
  MTCT rate = 0.0%  
  95% CI = 0.0-0.8%

- Median viral load near delivery was 400 copies/ml (interquartile range: 61-1992)

- Resistance to ZDV monoRx rare if prescribed according to BHIVA guidelines
  - Larbalestier et al, AIDS 2003 Dec 5;17(18):2665-7
  - Read et al, HIV Medicine 2008,9,448-451
• Longer duration of HAART was associated with reduced MTCT
• Transmitters started at median gestation of 30.1 wks (IQR 27.4–32.7)
• Non-transmitters started at median gestation of 25.9 wks (IQR 22.4–28.7) \( p<0.001 \)
• Each additional week of Rx resulted in a 10% reduction in risk of MTCT when adjusting for viral load, mode of delivery and sex

Townsend et al. AIDS 2008;22:973–981
Conclusions

- There was no difference in MTCT rates according to the management strategies outlined in the BHIVA guidelines:
  - HAART with elective caesarean section (0.7%)
  - HAART with planned vaginal delivery (0.7%)
  - ZDV monotherapy with elective caesarean section (0%)

- There were only three transmissions (0.1%) from women with viral load <50 copies/ml; two probably occurred *in utero*.

- The risk of MTCT in appropriately managed pregnancies in the UK and Ireland is very low.
Avoid HIV infection

Avoid maternal toxicity

SMART issues?

Avoid toxicity for baby

Premature delivery

Avoid compromising future maternal options
### Antiretroviral Pregnancy Registry

**Data to 31/1/09**

#### 2nd & 3rd trimester exposure – birth defects

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count/Total</th>
<th>Birth Defects Rate</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>162/6336</td>
<td>2.6%</td>
<td>(2.2-3.0)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>122/4846</td>
<td>2.5%</td>
<td>(2.1-3.0)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>61/2188</td>
<td>2.2%</td>
<td>(1.4-3.3)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>33/1373</td>
<td>2.4%</td>
<td>(1.7-3.4)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>27/1157</td>
<td>2.3%</td>
<td>(1.5-3.4)</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>25/1126</td>
<td>2.2%</td>
<td>(1.4-3.3)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>25/882</td>
<td>2.8%</td>
<td>(1.8-4.2)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>6/385</td>
<td>1.6%</td>
<td>(0.6-3.4)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>5/257</td>
<td>1.9%</td>
<td>(0.6-4.5)</td>
</tr>
</tbody>
</table>
Different toxicity focus for different drugs

- Zidovudine: Mitochondrial
- Tenofovir: Bone and renal
- Atazanavir: Neonatal hyperbilirubinaemia
- Efavirenz: Teratogenicity
- Nevirapine: Maternal toxicity
- d4T & ddI: Maternal toxicity
- Protease inhibitors: ?preterm delivery & ?gestational diabetes
What to treat with?

• HAART to continue?
  – NNRTI (nevirapine based HAART is an option)

• Temporary HAART?
  – Use protease inhibitor based HAART

• If good CD4 and low VL, zidovudine monotherapy and PLCS may be a reasonable option
Stopping drugs with different half lives

Drug concentration

Time (hours)

Last Dose

Zone of potential replication

Day 1

Day 2

MONOTHERAPY

IC$_{90}$

IC$_{50}$

S. Taylor et al. 11th CROI Abs 131
Case 1

- What should we treat her with?
- Is it OK to have an SVD?
- When should we start her ART?
- What should we counsel her about?
HAART and Premature delivery
Prematurity and antiretroviral therapy: population-based HIV surveillance in the UK and Ireland, 1990-2005

Figure 1: Percentage of deliveries at <37 weeks by type of ART and maternal characteristics, with 95% confidence intervals

Data from the National Study of HIV in Pregnancy and Childhood (NSHPC)
ART and premature delivery, diagnosed HIV infected women in UK and Ireland, 1990-2005

- Premature delivery rate (<37wks) **1.5 times higher** in women on HAART vs. mono/dual therapy
- Stronger effect at earlier gestational ages
  - <37 wks AOR=1.5 (1.2-1.9, p=0.001)
  - <35 wks AOR=2.3 (1.6-3.4, p<0.001)
  - <32 wks AOR=2.7 (1.5-4.9, p=0.001)

- AOR=odds ratio adjusted for HIV symptoms / AIDS, injecting drug use, ethnic origin & maternal age

  Townsend at al. AIDS 2007; 21:1019-26

- See also poster on prematurity and ART available on NSHPC website: [http://www.nshpc.ucl.ac.uk/slides/NSHPC_poster_AIDS_2006.pdf](http://www.nshpc.ucl.ac.uk/slides/NSHPC_poster_AIDS_2006.pdf)
Case 1

- Start on combivir & kaletra
- Returns 1 week later
- Some nausea and abdominal discomfort
Case 1

- Day7 ALT 61
- Day8 68
- Day9 77
- Day10 140
- Day13 443
Alanine Trans Level

Alanine Trans Level (IU/L)

MATENGE, LYDIA

Jun 09

Jul

Aug
Alanine Trans Level

Alanine Trans Level (IU/L)
Antenatal HIV Team

- Multidisciplinary team
- HIV physician
- HIV specialist midwife
- Obstetrician
- Paediatrician
- HIV Paediatric specialist nurse
- Pharmacist
- Virologist
Antenatal HIV Clinic

- History and examination
- Obstetric history
- Routine tests including CD4, Viral load, genotype, Hepatitis serology, Syphilis
- STI screening
Antenatal HIV clinic

- Testing children
- Disclosure
- Significance of her own HIV infection
- Prognosis
- Wishes regarding mode of delivery
- Breastfeeding
- Teenagers
- Traumatic past
Case 2

- Presents in labour untested
- Has point of care HIV test – positive
- What do you do?
Case 2

- Intravenous zidovudine
- Stat dose of nevirapine
- Combivir and kaletra
- Liaise re: optimal mode of delivery
- Neonate receives triple therapy
Case 3

- 23 years old
- On Atripla for 1 year
- 9 weeks pregnant
- What do you do?
Antiretroviral pregnancy registry  
Data to 31/1/09

- Birth defects following 1st trimester exposure

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Cases</th>
<th>Percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>93</td>
<td>3226</td>
<td>2.9% (2.4-3.5)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>95</td>
<td>3108</td>
<td>3.1% (2.5-3.7)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>37</td>
<td>1074</td>
<td>3.4% (2.4-4.7)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>20</td>
<td>883</td>
<td>2.3% (1.4-3.5)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>18</td>
<td>817</td>
<td>2.2% (1.3-3.5)</td>
</tr>
<tr>
<td>Stavudine</td>
<td>19</td>
<td>754</td>
<td>2.5% (1.5-3.9)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>16</td>
<td>678</td>
<td>2.4% (1.4-3.8)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>18</td>
<td>608</td>
<td>3.0% (1.8-4.6)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>14</td>
<td>477</td>
<td>2.9% (1.6-4.9)</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>8</td>
<td>470</td>
<td>1.7% (0.7-3.3)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>16</td>
<td>365</td>
<td>4.4% (2.5-7.0)</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>9</td>
<td>313</td>
<td>2.9% (1.3-5.4)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>7</td>
<td>292</td>
<td>2.4% (1.0-4.9)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>6</td>
<td>276</td>
<td>2.2% (0.8-4.7)</td>
</tr>
</tbody>
</table>
Case 4

- 33 year old
- Conceives on Truvada/NVP
- VL<40c/ml
- Very keen to breastfeed.
Will HIV+ve women be able to breastfeed in the future?
### Baseline Characteristics at Enrollment

<table>
<thead>
<tr>
<th>Baseline Characteristics at Enrollment</th>
<th>Arm A (TZV) N=285</th>
<th>Arm B (KAL/CBV) N=275</th>
<th>Obs Arm (NVP/CBV) N=170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median gestational age (weeks) (10th, 90th percentile)</td>
<td>27 (26, 33)</td>
<td>27 (26, 33)</td>
<td>26 (19, 31)</td>
</tr>
<tr>
<td>Median baseline CD4+ count (cells/mm³)</td>
<td>398</td>
<td>403</td>
<td>147</td>
</tr>
<tr>
<td>Median baseline HIV-1RNA (copies/mL) &gt;100,000 copies/mL (%)</td>
<td>13,300 15%</td>
<td>9,100 13%</td>
<td>51,700 37%</td>
</tr>
<tr>
<td>HLA-B*5701 (N=377 tested)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median duration of AP HAART</td>
<td>11 wks</td>
<td>11 wks</td>
<td>13 wks</td>
</tr>
</tbody>
</table>

**Mma Bana Study: Maternal Characteristics**
- 97% of women initiated breastfeeding (all on HAART)
  93% exclusively breastfed through weaning
- 71% breastfed for ≥ 5 months
- <1% breastfed beyond the 6 month visit

- only 6% reported missing 3 or more days of HAART
Viral Suppression to <400 copies/mL in Randomized Arms (Women with CD4 ≥200)
Shapiro R et al. IAS, Capetown, South Africa, July 2009, Abs. WeLBB101

% HIV RNA <400 c/mL

<table>
<thead>
<tr>
<th></th>
<th>Delivery</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT/3TC/ABC</td>
<td>96%</td>
<td>92%</td>
</tr>
<tr>
<td>AZT/3TC/LPV-r</td>
<td>93%</td>
<td>93%</td>
</tr>
</tbody>
</table>
Mma Bana: Primary MTCT Endpoint
Shapiro R et al. IAS, Capetown, South Africa, July 2009, Abs. WeLBB101

<table>
<thead>
<tr>
<th>Infections among live-born infants, by maternal arm</th>
<th>Arm A (TZV) N=283</th>
<th>Arm B (KAL/CBV) N=270</th>
<th>Obs Arm (NVP/CBV) N=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero</td>
<td>3 (1.1%)*</td>
<td>1 (0.4%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>2 (0.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total at 6 months</td>
<td>5 (1.8%)*</td>
<td>1 (0.4%)</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

Overall Transmission 1% (95% CI, 0.5-2.0%) Through Age 6 Months

P=0.53
Drug levels in pregnancy

Most of physiological changes in pregnancy would lead to lower total levels

BUT

Protein binding may decrease

&

Sex hormones compete with drug for binding
Median LPV levels in T3 (N=17) and post-partum (N=12)

[Graph showing median LPV levels over time with error bars for T3 and post-partum groups.]
Where and why do things go wrong?

- PROM
- Late presentation
- Seroconversion in pregnancy
- Immigration/access issues
- Social/mental health issues
- Stigma/denial