The Evolution of the BHIVA Guidelines 2001-2014

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Setting the scene

Attitudes to Pregnancy Pre HAART

- Reproductive possibilities were much restricted in the first years of the HIV pandemic
  - Centers for Disease Control and Prevention (CDC) discouraged pregnancy in HIV-infected persons due to the poor prognosis of the disease and the risk of transmission to the neonate
  - American College of Obstetrics and Gynaecology, which recommended HIV-infected women not to become pregnant
  - In 1994 the American Society for Reproductive Medicine suggested other alternative options such as donor insemination or child adoption
  - HIV-positive individuals continued to seek pregnancy, assuming the risk of sexual and/or vertical transmission of HIV

Attitudes to Pregnancy Post HAART

- In 2001 CDC revised their advice stating
  - “healthcare professionals should ‘provide information and give support to any reproductive option for HIV-positive patients’, particularly when HIV infection is under medical control”

- The growth in plans for pregnancy among HIV-infected individuals along the HAART era has been highlighted in many reports 1-5

- In the UK, dedicated guidelines for
  - HIV in Pregnancy, 2001 6
  - Sexual and reproductive health, 2008 6

HIV +ve: Reproductive options 2001

**HIV+ woman & HIV- man**
- Insemination of partner’s sperm at ovulation (whether or not on ARVs / detectable viral load)
- Assisted reproduction in case of fertility disorders
- Adoption

**HIV+ man & HIV- woman**
- IUI, IVF or ICSI following sperm washing (not available on NHS)
- Insemination of donor sperm at ovulation
- Adoption

**HIV+ man & HIV+ woman**
- Natural conception (if effective viral suppression) timed ovulatory intercourse only
- Insemination of sperm at ovulation
- Adoption

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**Treatment as Prevention**

- Swiss statement 2008
- HPTN 052
- Partners in Prevention
- Partner Study
HIV +ve: Reproductive options 2015

**HIV+ woman & HIV- man**
- Treatment of woman to VL<40c/ml then UPSI
- PrEP-C
- Insemination of partner’s sperm at ovulation (whether or not on ARVs / detectable viral load)
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  - Adoption

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Antiretroviral Therapy

Principles of Treatment

- 15 compounds available
- Only Zidovudine specifically licensed
- Treatment may be stopped for first trimester!
- Antiviral pregnancy register started Jan 1989
Principles of Treatment

2001
- 15 compounds available
- Only Zidovudine specifically licensed
- Treatment may be stopped for first trimester!
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2014
- 32 compounds in use
- Ongoing

Monotherapy
PI Monotherapy

- Ritonavir 300mg BD increased to 600md BD
- MTCT rate 9.5%
- 10/86 discontinued because of hepatotoxicity
HIVNET 012: HIV transmission
Intrapartum/postpartum nevirapine vs zidovudine

Stat dose NVP for mother and infant vs ZDV for mother in labour and neonate 1/52

Adapted from Guay et al. Lancet 1999;354:795–802
Dual Therapy

- AZT/3TC prospective non randomised study
  MTCT 2.6% but high rates resistance 15/132 (11%) if duration over 4 weeks
- Small studies showed higher resistance 80% when compared with ZDV mono
- Not recommended

Triple therapy/HAART/cART
### Triple Therapy - PI based

**2001**
- MTCT 1.1% vs 7.8%
- Preterm delivery noted
- US cohort meta analysis ACTG 1998-99 PTD rate 20% but not attributable to a single drug class
- European data countered this
- Better if stopping therapy post delivery

**2014**
- Preterm delivery an issue with PIs
- ATV/r less problematic than LPV/r
- More significant clinically in resource poor countries
**Triple Therapy NNRTI based - NVP**

**2001**
- NVP was added to mono, dual and triple therapy
- MTCT 1.5% vs predicted 5%
- But stopped study as could not discern what was best use of NVP
- Resistance 11% if VL >400c/ml at delivery

**2014**
- Still part of triple therapy
- Stepped down in BHIVA adult guidelines - no longer recommended or preferred

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**When to start therapy in pregnancy**

**2001**
- Avoid first trimester - consider stopping!
- Consider avoiding D4t/DDI
- Switch Efavirenz
- Advised for woman’s own health if CD4 200-350 cells/mm3
- Short Term Anti Retroviral Therapy
When to start therapy in pregnancy

2001
- Avoid first trimester - consider stopping!
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2014
- Avoid first trimester if possible but VL guided
- D4t/DDI contraindicated
- Continue Efavirenz
- START trial means earlier CD4 count at initiation now recommended
- DO NOT STOP

Results: 77.2% overall undetectable at delivery

Read et al. AIDS 2011.
Relative risk of birth defects on efavirenz vs non-efavirenz regimens following first trimester exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Reference</th>
<th>Relative risk (95% CI)</th>
<th>Events/ Treatment</th>
<th>Events/ Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral pregnancy register</td>
<td>2011</td>
<td>11</td>
<td>0.92 (0.58, 1.50)</td>
<td>17/623</td>
<td>147/4932</td>
</tr>
<tr>
<td>Bera et al.</td>
<td>2010</td>
<td>15</td>
<td>0.86 (0.68, 1.11)</td>
<td>5/194</td>
<td>5/133</td>
</tr>
<tr>
<td>Townsend et al.</td>
<td>2010</td>
<td>18</td>
<td>0.75 (0.32, 1.77)</td>
<td>5/204</td>
<td>48/1479</td>
</tr>
<tr>
<td>Machado et al.</td>
<td>2010</td>
<td>17</td>
<td>0.22 (0.04, 0.78)</td>
<td>1/178</td>
<td>5/1112</td>
</tr>
<tr>
<td>Gonzales-Tome et al.</td>
<td>2010</td>
<td>13</td>
<td>0.15 (0.03, 0.74)</td>
<td>7/131</td>
<td>95/286</td>
</tr>
<tr>
<td>Busseraud et al.</td>
<td>2010</td>
<td>19</td>
<td>0.19 (0.07, 0.51)</td>
<td>5/522</td>
<td>2/213</td>
</tr>
<tr>
<td>Floridia et al.</td>
<td>2010</td>
<td>20</td>
<td>1.22 (0.26, 6.03)</td>
<td>2/302</td>
<td>10/105</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>2010</td>
<td>22</td>
<td>1.33 (0.54, 3.31)</td>
<td>0/19</td>
<td>14/770</td>
</tr>
<tr>
<td>Elsworth et al.</td>
<td>2011</td>
<td>9</td>
<td>(Excluded)</td>
<td>0/15</td>
<td>0/502</td>
</tr>
<tr>
<td>Phongsak et al.</td>
<td>2011</td>
<td>4</td>
<td>(Excluded)</td>
<td>0/4</td>
<td>0/21</td>
</tr>
<tr>
<td>Crossley et al.</td>
<td>2011</td>
<td>5</td>
<td>(Excluded)</td>
<td>0/5</td>
<td>0/21</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.85 (0.61, 1.19)</td>
<td>38/1290</td>
<td>316/9122</td>
</tr>
</tbody>
</table>


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**START**

Strategic Timing of Antiretroviral Treatment

A Multicenter Study of the International Network for Strategic Initiatives in Global HIV Research (INSIGHT)
**START design**

HIV positive people, ART-naïve with CD4+ count > 500

**Early ART**

Initiate ART immediately following randomization (N=2,000)

**Deferred ART**

Defer ART until the CD4+ count declines to < 350 or AIDS (N=2,000)

Follow until 370 endpoints reached

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**Primary endpoints**

*Table 1b. Relative rates of primary endpoints in each arm (15 May 2015)*

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate per 100 PY</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early arm (A)</td>
<td>Late arm (B)</td>
</tr>
<tr>
<td>Category 1: AIDS, serious non-AIDS, or death (primary).</td>
<td>0.60</td>
<td>1.25</td>
</tr>
<tr>
<td>Category 2: AIDS or AIDS death.</td>
<td>0.20</td>
<td>0.66</td>
</tr>
<tr>
<td>Category 3: Serious non-AIDS or non-AIDS death.</td>
<td>0.41</td>
<td>0.59</td>
</tr>
</tbody>
</table>

* PY = patient years, ** NS = not statistically significant
# Toxicity

**2001**

- **D4t/DDI** - Lactic acidosis
- **NVP** - rash/hepatotoxicity
- **RTV** - hepatotoxicity
- **PI toxicity** - gestational DM
- **PTD**
  
  Septrin - 1\textsuperscript{st} trimester exposure causes NTD, cardiac and renal defects

**2014**

- **Contraindicated**
- **CD4 guidance on starting**
- **Used only as a booster**
- **Same**
- **PTD**
  
  Use increased dose folic acid to avoid toxicity
Mode of delivery

European mode of delivery study 1999

- n=370, 1993–1998
- Randomised to vaginal delivery (VD) or elective caesarean section (ECS) at 38 weeks
- 90% had CD4 >200
- 65% took AZT during pregnancy

HIV infected infants

<table>
<thead>
<tr>
<th>Mode of Delivery</th>
<th>Cases</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLCS</td>
<td>3/170</td>
<td>1.8%</td>
</tr>
<tr>
<td>VD</td>
<td>21/200</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

p<0.001

- 0.8% transmission rate in women on AZT who had an elective CS


Mother-to-child transmission (MTCT) rates

<table>
<thead>
<tr>
<th>MTCT rates (%)</th>
<th>n infected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAART</td>
<td>1.0</td>
<td>4120</td>
</tr>
<tr>
<td>HAART from conception</td>
<td>0.1</td>
<td>928</td>
</tr>
<tr>
<td>HAART + viral load &lt;50 c/mL</td>
<td>0.1 (0.0–0.4)</td>
<td>2117</td>
</tr>
</tbody>
</table>

- 2 of the 3 had evidence of in utero infection

NSHPC

For women with a plasma viral load of <50c/ml at 36 weeks, and in the absence of obstetric contraindications, a planned vaginal delivery is recommended

- Elite controllers on ART can aim for a NVD
- For women with a plasma viral load of 50-399 at 36 weeks, a pre-labour caesarean section (PLCS) should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman’s views
- PLCS advised at 38-39 weeks to maximise fetal maturation

Townsend et al. AIDS 2008;22:973–981
BHIVA HIV in Pregnancy Audit 2014 Obstetric procedures

Guidelines: No evidence for avoiding these, treat as if HIV negative

Avoid/do not offer

- Episiotomy*
- Amniotomy*
- FBS/scalp monitor*
- External cephalic version

*at VL <50 copies/ml.
Breastfeeding

- 1992: additional 14% risk
- 1999 data re: ‘exclusive’ breastfeeding
- 2001: formula feeding safe
- 2005: favoured bottle feeding
- Recent WHO revision following excess morbidity and mortality associated with early cessation of breastfeeding

Mma Bana: Primary MTCT Endpoint

<table>
<thead>
<tr>
<th>HIV Infections Among Live-Born Infants, n (%)</th>
<th>ZDV/3TC/ABC (n = 283)</th>
<th>ZDV/3TC + LPV/RTV (n = 270)</th>
<th>ZDV/3TC + NVP (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 mos</td>
<td>5 (1.8)*</td>
<td>1 (0.4)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

* P = .95 for difference in between randomized arms.

- 1% overall transmission through 6 mos
  - 95% CI for overall MTCT rate = 0.5% to 2.0%


BHIVA Guidelines
Amendment February 2010

- Exclusive formula feeding should still be recommended to all HIV-positive mothers in the UK
- Breastfeeding by women with detectable viraemia remains a safeguarding concern
- Women with fully suppressed HIV on ART, who choose to breastfeed should be supported to maximise adherence & encouraged to breast feed for the shortest time possible
- Monthly testing should be undertaken on mother (HIV RNA) and infant (HIV RNA or DNA) during breast feeding
Late presenting woman not on treatment 2001

- IV Zidovudine infusion
- Triple therapy for the infant

Late presenting woman not on treatment 2014

IT’S NEVER TOO LATE!
Late presenting woman not on treatment 2014

• A woman who presents after 28 weeks should commence HAART immediately based on the epidemiological incidence of resistance
• If her viral load is >100,000 c/ml or unknown, she should commence a 3 or 4 drug regimen to include Raltegravir
• A normal vaginal delivery is possible if a VL <50 copies/ml is achieved by 36 weeks

Late presenting woman not on treatment 2014

• An untreated woman presenting in labour at term should be given
  ◦ a stat dose of nevirapine 200mg
  ◦ commence fixed-dose zidovudine
  ◦ with lamivudine and raltegravir
  ◦ and have a continuous IV infusion of intravenous zidovudine for the duration of labour and delivery
World AIDS Day Number 1 2001 Blue
World AIDS Day Number 1 2014
Band Aid 30

Band AID 1984
Evidence available BHIVA 2001

- RCTs or large meta analyses only available for
  - Formula Feeding
  - Pre-Labour Caesarean Section
  - Zidovudine monotherapy

- Relied heavily on expert opinion
- 170 references
- Multidisciplinary authorship
BHIVA Guidelines 2014

- All evidence Graded
- 363 references
- Increased multidisciplinary authorship

Summary

- BHIVA HIV in Pregnancy guidelines have evolved using the increased evidence base on
  - ART efficacy in reducing MTCT
  - ART toxicity data
    - Studies
    - Antiviral pregnancy registry
  - Mode of delivery studies
  - Invasive Obstetric procedures
  - Breastfeeding studies
  - Late presenting woman
MTCT rates in diagnosed women, UK & Ireland 2000-2011

~12,500 singleton births; significant decline in MTCT over time (p<0.001)


Prevention of Infant HIV Infection: Aiming for zero transmission

A multidisciplinary conference for obstetricians, gynaecologists, HIV physicians and allied healthcare professionals

Friday 27 November 2015
ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS
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