HIV and pregnancy

Michelle Giles
Viruses in May 2013
10th Anniversary Meeting
Overview

- Epidemiology
- Conception
- Pregnancy
  - Antiretrovirals
  - Mode of delivery
  - Breastfeeding
  - Follow up of neonate
Epidemiology of HIV in women

- HIV is now the leading cause of death and disability among women of reproductive age (15-44)
- Young women 15-24 are now the single most vulnerable demographic worldwide for new HIV cases
- What is placing women at risk for HIV?
- And then if infected what gender specific issues do they bring to our clinics?
Why are women more vulnerable?

**Physical Vulnerability**
- Biological
- Violence

**Emotional Vulnerability**
- Low power
- Low self esteem
- Dependency on men

**Environmental Vulnerability**
- Poverty/dependence on men financially
- Sex as a commodity (transactional)
- Low health literacy
- Access to healthcare
Snapshot in Australia

- By 31 December 2011
  - 31,645 diagnoses of HIV
  - 24,731 people living with HIV
- New diagnoses in 2011
  - 1137
  - Number gradually increased per year since 1999 n=719
- Attributable exposure heterosexual contact
  - 2002-2006 20%
  - 2007-2011 25%
- Between 2007-2011 1327 cases newly diagnosed HIV attributed to HS contact
  - 60% from HPC or partner from HPC
  - 70% SSA, 21% Sth East Asia

HIV, viral hepatitis and sexually transmissible infections in Australia Annual surveillance report 2011
Snapshot in Australia

• 2001-2010
  – Number women newly diagnosed risen
  – 44% increase 2001-2005 c.f. 2006-2010
  – Absolute numbers 481 c.f. 692
  – Majority through sexual contact
  – Women younger at diagnosis median age 29-31 c.f. 35-38
  – More likely to be tested because partner tests positive (17%) than part of “routine health check” c.f. MSM
  – More likely than homosexual men to be diagnosed late with a CD4 count <200
Conception
Options for conception

• 2003
  – Unprotected sexual intercourse
  – Self insemination

• 2013
  – Unprotected sexual intercourse
  – Self insemination
  – Unprotected sexual intercourse with PrEP
  – Assisted reproduction
Option: UPSI

- **UPSI**
  - Think “harm minimisation”
    - Treat STIs
    - Suppressive treatment for HSV
    - Fertility assessment (tubal patency/semen analysis)
    - Minimise exposure (ovulation)
    - Antiretrovirals (cART +/- PrEP/PEP)
Outcomes from the first assisted reproduction program for HIV-serodiscordant couples in Australia

| Table 2: Clients and outcomes of assisted reproduction program, 2003 – June 2010 |
|-------------------------------------------------|-----------------|-----------------|
| HIV-positive man with HIV-negative female partner | HIV-positive woman with HIV-negative male partner |
| Number of patients*                              | 27              | 8               |
| Completed cycles                                 | 136             | 26              |
| Pregnancies with an outcome                      | 22              | 4               |
| Miscarriages                                     | 7               | 0               |
| Babies born                                      | 15              | 4               |
| Ongoing pregnancies                              | 2               | 1               |
| Clinical pregnancy\(^\d\) rate per cycle        | 16.2%           | 15.4%           |
| Clinical pregnancy\(^\d\) rate per number of patients | 81.5%           | 50%             |

* Those with complete data who proceeded with treatment. † Fetal heartbeat at 6 weeks after embryo transfer or intrauterine insemination.
HIV infected women

• If discordant and no fertility issues
  • Monitor cycle
  • Fresh or stored sperm
  • IUI

• If fertility issues may go straight to IVF/ICSI

• Pre-treatment management plan including antiretrovirals, mode of delivery and breastfeeding
Pregnancy
Antenatal screening

• 2003
  – “risk factor based approach”
  – Universal screening only introduced in 2006 National policy
  – RANZCOG recommended all women be offered an HIV test 2005

• 2013
  – All women recommended to have an HIV test at the first antenatal visit
Victoria has the highest absolute number of deliveries per year.

### Table 1.4.1
Number and population rate\(^1\) of perinatal exposure to HIV among children born in Australia, 2002 – 2011, by State/Territory and year of birth

<table>
<thead>
<tr>
<th></th>
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<tbody>
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<td></td>
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<td>Rate</td>
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<td>0</td>
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<td>8.3</td>
<td>13</td>
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<td>5.7</td>
<td>1</td>
<td>2.9</td>
<td>4</td>
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<tr>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>VIC</td>
<td>4</td>
<td>3.3</td>
<td>7</td>
<td>5.6</td>
<td>17</td>
</tr>
<tr>
<td>WA</td>
<td>12</td>
<td>25.1</td>
<td>3</td>
<td>5.8</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>45</strong></td>
<td><strong>9.0</strong></td>
<td><strong>50</strong></td>
<td><strong>9.7</strong></td>
<td><strong>57</strong></td>
</tr>
</tbody>
</table>

\(^1\) Average annual rate of perinatal HIV exposure per 100,000 livebirths. Number of livebirths by State/Territory and year from Births, Australia (Australian Bureau of Statistics).

Source: Australian Paediatric Surveillance Unit; State/Territory health authorities.
Antiretroviral therapy
Antiretroviral recommendations in resource rich countries

• Aim *undetectable viral load*
• Drugs which are *safe* in pregnancy
• Well tolerated
• Minimise chance of drug resistance
  – adherence,
  – PK especially 3TM (lopinavir, atazanavir)
• Caution with nevirapine if CD4 >250
• The earlier the better (if VL >10,000 start by 20 weeks)
Efavirenz

- Anencephaly, anophthalmia, cleft palate observed in 3/20 (15%) monkeys given EFV 1TM similar to human doses
- 6 retrospective/2 prospective case report NTD 1TM exposure; 1 prospective case report anophthalmia with facial clefts, 1 of myelomeningocele
- “Use after 1TM can be considered”
Antiretroviral Pregnancy Registry (APR)

- APR
  - Sponsored by manufacturers of all ARVs
  - prospective cases 1989-ongoing
  - Aim- provide early warning signs of major teratogenicity
  - Reports from 54 countries (88% US, 0.3% Aus)
- CDC population birth defect 2.72% (live births)
- APR birth defect 3.0% 1TM, 2.7% 2/3 TM
- 80% power to detect 2X increase

### APR (1TM exposure)

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Defects/Live births</th>
<th>Prevalence % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>118/3620</td>
<td>3.3 (2.7, 3.9)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>118/3864</td>
<td>3.1 (2.5, 3.7)</td>
</tr>
<tr>
<td>Nevirapine*</td>
<td>25/987</td>
<td>2.5 (1.4, 3.7)</td>
</tr>
<tr>
<td>Stavudine*</td>
<td>19/797</td>
<td>2.4 (1.4, 3.7)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>33/1401</td>
<td>2.4 (1.6, 3.3)</td>
</tr>
<tr>
<td>Abacavir*</td>
<td>22/744</td>
<td>3.0 (1.9, 4.5)</td>
</tr>
<tr>
<td>Tenofovir*</td>
<td>26/1092</td>
<td>2.4 (1.6, 3.5)</td>
</tr>
<tr>
<td>Didanosine*</td>
<td>Of 17 birth defects</td>
<td>1x myelomeningocele; 1x anophthalmia</td>
</tr>
<tr>
<td>Didanosine*</td>
<td>17/623</td>
<td>2.7 (1.3, 5.0)</td>
</tr>
<tr>
<td>Atazanavir*</td>
<td>12/502</td>
<td>2.4 (1.2, 4.1)</td>
</tr>
<tr>
<td>Emtricitabine*</td>
<td>17/641</td>
<td>2.7 (1.5, 4.2)</td>
</tr>
<tr>
<td>Lopinavir*</td>
<td>16/738</td>
<td>2.2 (1.2, 3.5)</td>
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ADVISORY COMMITTEE CONSENSUS

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population based comparator, the MACDP. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Health care providers are encouraged to report eligible patients to the Registry at www.APRegistry.com.
Birth Defects and ART in the French Perinatal Cohort, a Prospective Exhaustive Study among 13,124 Live Births from 1994 to 2010

Jeanne Sibiude*1, L Mandelbrot1,2,3, S Blanche4, J Le Chenadec1,5, N Boullag-Bonnet1, A Faye2,6, C Dollfus7, R Tubiana8, J Warszawski1,9,10, and ANRS CO1/CO10/CO11

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Background: The use of ARV regimens during pregnancy has led to a spectacular decrease in MTCT, now on the order of 1% in industrialized countries. Potential adverse effects including teratogenic risk have to be evaluated. We aimed to estimate the prevalence of birth defects in children born to HIV+ women receiving ARV during pregnancy, and to assess the association with each in utero ARV drug.

Methods: Since 1986, the French Perinatal Cohort (EPF) prospectively enrolls pregnant HIV+ women delivering in 90 centers throughout France. Children are followed by pediatricians until 2 years of age. All live births between 1994 and 2010 were included. We excluded patients not treated during pregnancy. Birth defects were studied using both the EUROCAT and the MACDP classifications, and associations with ARV were evaluated using univariate and multivariate logistic regressions.

Results: We included 13,124 livebirths. The prevalence of birth defects was 4.4% (95% confidence interval [CI] 4.0-4.7; n = 575), according to EUROCAT and 7.0% (6.5-7.4; n = 914), according to the MACDP classification, which included minor defects when 2 were present in the same child. A significant association was found between exposure to efavirenz in the first trimester and neurological defects (adjusted odds ratio [aOR] = 3.15 [1.09-9.09]). Zidovudine in the first trimester was associated with congenital heart defects (aOR = 2.34 [1.39-3.94]), and didanosine with head and neck birth defects (aOR = 2.89 [1.03-8.11]). Lamivudine and indinavir in the first trimester were also associated with birth defects, but the association with lamivudine concerned mostly minor musculo-skeletal and head and neck defects, while indinavir was not associated with any specific defects in the multivariate analysis adjusting for potential confounding variables and concomitant medications.

Conclusions: This study, which is the largest prospective study of birth defects in ARV-exposed infants, shows a specific association between in utero exposure to efavirenz and neurological defects. As in other cohort studies, the rate of birth defects may be underestimated by including only live births. Recently, WHO and US Department of Health and Human Services guidelines have been changed to authorize the use of efavirenz even in the first trimester in women already treated with this drug. The association we observed between efavirenz and neurological defects has been previously described and calls for caution and continued follow-up.
Antiretroviral therapy

• 2003
  – HAART
  – Zidovudine backbone
  – Nevirapine/PI-nelfinavir
  – Intrapartum ZDV

• 2013
  – HAART
  – Backbone TDF/FTC or ABC/3TC
  – NNRTI or PI-lopinavir or atazanavir
  – Intrapartum ZDV depending on viral load
Mode of delivery
Mode of delivery

• 2003
  – Elective cesarean section
  – Avoid external cephalic version
  – Avoid VBAC
  – IV ZDV intrapartum irrespective of maternal viral load

• 2013
  – Vaginal birth if viral load
    • <50 copies
    • <1000 copies
  – External cephalic version
  – VBAC supported
  – IV ZDV intrapartum if maternal viral load >400 copies/mL
Breastfeeding
Breastfeeding

• 2003
  – All mothers advised to formula feed
  – Women who choose to breastfeed face referral to child protection services

• 2013
  – All mothers advised to formula feed
  – ?referral to child protection

8.4.2 In the very rare instances where a mother who is on effective HAART with a repeatedly undetectable viral load chooses to breastfeed, this should not constitute grounds for automatic referral to child protection teams. Maternal HAART should be carefully monitored and continued until 1 week after all breastfeeding has ceased. Breastfeeding, except during the weaning period, should be exclusive and all breastfeeding, including the weaning period, should have been completed by the end of 6 months. Grading: 1B

8.4.4 Intensive support and monitoring of the mother and infant are recommended during any breastfeeding period, including monthly measurement of maternal HIV plasma viral load, and monthly testing of the infant for HIV by PCR for HIV DNA or RNA (viral load). Grading: 1D
Follow up of the neonate
Follow up of neonate

- **2003**
  - 6 weeks zidovudine
  - 6 hourly
  - Bactrim prophylaxis from 6 weeks until 3 months

- **2013**
  - 4 weeks zidovudine
  - 12 hourly
  - No bactrim prophylaxis unless “high risk”
Summary

• The number of women diagnosed with HIV in Australia is increasing
• Reproduction is an important issue
• Conception counselling needs to cover
  • Options
  • Safety
  • Accessibility/cost
• Pregnancy
  • <1/1000 risk of MTCT
  • ARVs and avoidance of BF most important interventions
Thank you

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