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2015 - Aiming for Zero Transmission
HIV Exposed Uninfected Infants - HEUs are there any problems?

Hermione Lyall
Imperial Healthcare
NHS Trust
27.11.15

Acknowledgements:
Chrissie Jones, Andrew Prendergast, Pat Tookey, Claire Townsend, Claire Thorne, Graham Taylor, Gareth Tudor-Williams Marc Lallement, Catherine Peckham
The “foetal-infant” environment & HIV

**Resource Rich**

**Resource Poor**

### Foetal environment
- Genetics
- Nutrition
- Immune function
- Immune activation
- HIV Viral Load
- ART drugs
- Other drugs
- Other infections
- Prematurity
- Smoking
- etc

### Post natal environment
- Genetics
- Environment
- Nutrition
- Breast / formula
- Immune function
- Immune activation
- Maternal microbiome
- Maternal well being
- Poverty / Orphanhood
- etc

<table>
<thead>
<tr>
<th>HIV un-exposed un-infected</th>
<th>HUU</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV exposed un-infected</td>
<td>HEU</td>
</tr>
<tr>
<td>HIV exposed infected</td>
<td>HEI</td>
</tr>
</tbody>
</table>

Effects of HIV / Drug exposure?

**Resource Rich**

**Resource Poor**

**Mortality / Survival**
- Brain
- Skin
- Gut
- Growth
- Bones
- Endocrine
- Haematology
- Cardiovascular
- Infections
- Immunology
- Immunology
- Carcinogenesis
- Mitochondria
- OTHERS??
Mortality among HEU African infants

- Malnutrition
- Gastroenteritis
- Maternal CD4 <200
- Malaria

Mortality up to 3 years, but not at 5-8 years

Infectious morbidity in HEU infants – in Africa

- Low birth weight & low birth Neutrophils \(\rightarrow\) ↑ morbidity & mortality
- Hospitalisation for infection ↑↑ 20% in HEUs
- ↑↑ severe infections, more complications
- ↑↑ LRTI (> in mothers with advanced HIV)
- ↑↑ Pneumococcal infections
- ↑↑ oral thrush
- ↑↑ TB (inc congenital TB)
- OIs – PJP, CMV

- ↑↑ Post-operative infections & mortality (SA)
- ↑↑ diarrhoea, is probably related more to mode of feeding than HIV exposure.

Cotrimoxazole \(\rightarrow\) ↓ morbidity & mortality in HEU infants

USA - HEU - morbidity & mortality
during the first 2 yrs of life
Women & Infants Transmission Study (WITS).

1990-2001 evaluation at birth, 1, 2, 4, 6, 9, 12, 18, 24 months
Growth, hospitalization, clinical disease (HEU 955, HEI 163)

Over 11 yrs - morbidity & mortality during the first 24 months of life decreased substantially for HEU infants.

HEU: ↑ short stature, poor weight gain & wasting compared to the general population.
Two or more changes in caretaker → growth deficiency
Fetal exposure to tobacco → height abnormalities.
Anemia common → associated with ZDV prophylaxis.

Paul et al, Pediatr Infect Dis J. 2005

Infectious morbidity in HEU infants – Europe

French Perinatal Cohort – n = 7638, 2002-10 (only HEU)
↑↑ hospitalisation for infection in first year of life (9.3%)
699 serious infections, 159 bacterial
Bacterial infection - ↑ with ↓ maternal CD4 (esp encapsulated)
Viral infection – no effect of maternal CD4

Risk factors for severe infection in this cohort:

- Prematurity
- ↑↑ 21x neonatal period
- ↑↑ 3x post-neonatal
- Born in post ARV era
- ↑↑ with /without ART

Infectious morbidity in HEU infants – Belgium

Belgian single centre cohort, n=537
Severe infections in 1st year of life – 16.8/100 HUE years
Compared to general population: Strep pneumo ↑↑ 4x, Group B Strep ↑↑ 13x

Group B Strep infection ↑↑ in HEU

**Africa – South Africa**
- antibodies to GBS:
  - ↓ in pregnant women with HIV
  - ↓ in new-born HEU infants (trans-placental)
  - ↓ in HEU infants at 16 weeks of age
- *Increased risk of EOS and LOS disease*

**Europe – Belgium**

<table>
<thead>
<tr>
<th></th>
<th>HEU</th>
<th>HUU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>1.55%</td>
<td>0.08%</td>
</tr>
<tr>
<td>6/322</td>
<td>16/20158</td>
<td></td>
</tr>
</tbody>
</table>

Late onset infection

- 5/6
- 2/16

HEU had more severe disease.
most were leukopaenic at presentation.


Le Doare K, *Vaccine*, 2015

Increased risk of mortality from invasive pneumococcal disease in HEU infants aged <1 year in South Africa, 2009-2013.

Invasive pneumococcal disease, n = 2099 cases, 2009 / 2013
92% known HIV exposure status, 86% known outcomes

<table>
<thead>
<tr>
<th>Exposure</th>
<th>IPD rate / 100,000</th>
<th>Case Fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2009</td>
<td>2013</td>
</tr>
<tr>
<td>HEI</td>
<td>654</td>
<td>272</td>
</tr>
<tr>
<td>HEU</td>
<td>88</td>
<td>33</td>
</tr>
<tr>
<td>HUU</td>
<td>28</td>
<td>18</td>
</tr>
</tbody>
</table>

*rel risk 1.76x

Need to prioritise HEU for pneumococcal immunisation

von Mollendorf, Clin Infect Dis. 2015

Congenital CMV and HEU infants

Canadian study n = 1255 – 2.2% cCMV
↑↑ in mothers with ↓↓ CD4 counts, born earlier, lower birth weight
Gantt S, J Med Virol. 2015

South African study n = 748 – 2.9% cCMV (96% of women on ART)
↑↑ 2.9x in mothers ↓↓ CD4 <200
No significant effect of: maternal age, type of ART, length of ART, gest age / birth weight.

French Perinatal Cohort n = 4797 – overall 2.3% cCMV
HEU 10.3% HEU 2.2%
HEU 1997- 1998 3.5% 2003 - 2004 1.2%
Logistical regression analysis – significant factors:
Delivery period, maternal age, maternal CD4 < 200, time of starting ART.

Postnatal CMV infection in HEU ↑ if mother not on ART, or CD4<200
Immune abnormalities in HIV-exposed, uninfected infants

- CD4 ↓ CD8 ↑
- Cytokines ↓↑
- Immune activation ↑
- Naïve T cell ↓ Memory T cell ↑

Reviewed in Afran 2013, Clin Exp Imm

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### Immune abnormalities in HIV-exposed, uninfected infants

<table>
<thead>
<tr>
<th>Feature</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced transfer of maternal antibody including IgG</td>
<td>de Moraes-Pinto et al. [40]; Fanjul et al. [46]; Cumberland et al. [42];</td>
</tr>
<tr>
<td></td>
<td>Scott et al. [45]; Bunders et al. [44]; Jones et al. [93]</td>
</tr>
<tr>
<td>Altered CD4+ and CD8+ T cell counts</td>
<td>Clerici et al. [33]; Miles et al. [98]; Baggs et al. [11]</td>
</tr>
<tr>
<td></td>
<td>Borges-Almeida et al. [126]</td>
</tr>
<tr>
<td>Increased proinflammatory responses in cord blood to polyclonal stimulation</td>
<td>Figdor et al. [47]; Horing et al. [48]</td>
</tr>
<tr>
<td>Increased T cell immune activation</td>
<td>Rich et al. [36]; Clerici et al. [33]; Romano et al. [99]; Vigano et al. [54]</td>
</tr>
<tr>
<td>Skewed T cell memory and differentiation subset distributions</td>
<td>Rich et al. [36]; Clerici et al. [33]; Nicolson et al. [120]; Vigano et al. [54]</td>
</tr>
<tr>
<td>Increased susceptibility to T cell apoptosis</td>
<td>Miles et al. [98]</td>
</tr>
<tr>
<td>Increased plasma IL-7 levels</td>
<td>Economides et al. [49]</td>
</tr>
<tr>
<td>Altered DC phenotype and in-vitro IL-12 production</td>
<td>Chougnet et al. [51]; Vettila et al. [53]</td>
</tr>
<tr>
<td>Reduced thymic size</td>
<td>Kuhl et al. [56]</td>
</tr>
<tr>
<td>Reduced TRIC levels in periphery</td>
<td>Nicolson et al. [128]</td>
</tr>
<tr>
<td>Skewed maturation of B cell subsets and susceptibility to apoptosis</td>
<td>Bunders et al. [44]; Miyamoto et al. [129]; Borges-Almeida et al. [126]</td>
</tr>
</tbody>
</table>

IgG = immunoglobulin; IL = interleukin; TRIC = T cell receptor excision circles.

**Clinical & Experimental Immunology** Afran 2013
Immunology in HEU

European Collaborative Study  n= 1663 HEU, followed from birth – for at least 8 yrs
Standard protocol to measure TLC, CD4 & CD8 cell counts.

Ethnicity
black children - ↓TLC, CD4, CD8 cell counts than white
black children - ↑ TLC, CD4 & CD8 lymphopaenic counts

ART exposure
ART - ↓ TLC & CD4 cell counts in 1st year of life
ART - ↓ CD8 cell counts until at least 8 years of age
ART duration & intensity - associated with TLC levels

Bunders et al, AIDS, 2005

Placental transfer of maternal antibody – reduced in HEU

HEU infants are more vulnerable to infections
➢ Timely infant vaccination
➢ Consider immunisation in pregnancy to protect in early life

Table 2. Influence of Maternal HIV Infection on Placental Antibody Transfer

<table>
<thead>
<tr>
<th>Specific Antibody</th>
<th>HIV-Infected Mother-Exposed</th>
<th>HIV-Uninfected Mother-Unexposed</th>
<th>Reduction, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae type b</td>
<td>0.87 (0.45-0.79)</td>
<td>0.74 (0.61-1.06)</td>
<td>23</td>
<td>.002</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>0.91 (0.61-1.31)</td>
<td>1.51 (1.19-2.06)</td>
<td>40</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>0.62 (0.41-0.77)</td>
<td>0.73 (0.53-0.94)</td>
<td>15</td>
<td>.06</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>0.95 (0.80-1.12)</td>
<td>1.30 (1.09-1.48)</td>
<td>27</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Jones, 2011,
Le Doare, Vaccine, 2014
De Moraes-Pinto, 1996 & 1998
Cumberland, 2007
Scott, 2007
# Responses to Vaccination in HEU and HUU

<table>
<thead>
<tr>
<th></th>
<th>HEU</th>
<th>HUU</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diphtheria</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Simani, AIDS, 2014</td>
</tr>
<tr>
<td><strong>Tetanus</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Jones, JAMA, 2011</td>
</tr>
<tr>
<td></td>
<td>Similar</td>
<td>Similar</td>
<td>Reikie, CVI, 2013</td>
</tr>
<tr>
<td><strong>Pertussis (PT &amp; FHA)</strong></td>
<td>Higher</td>
<td>Lower</td>
<td>Jones, JAMA, 2011</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>Lower</td>
<td>Reikie, CVI, 2013</td>
</tr>
<tr>
<td><strong>PT</strong></td>
<td>Higher</td>
<td>lower</td>
<td>Simani, AIDS, 2014</td>
</tr>
<tr>
<td><strong>FHA</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Simani, AIDS, 2014</td>
</tr>
<tr>
<td><strong>Hib (PRP)</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Jones, JAMA, 2011</td>
</tr>
<tr>
<td></td>
<td>Similar</td>
<td>Similar</td>
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<tr>
<td></td>
<td>Similar</td>
<td>Similar</td>
<td>Simani, AIDS, 2014</td>
</tr>
<tr>
<td><strong>PRP SBA</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Simani, AIDS, 2014</td>
</tr>
</tbody>
</table>

- Higher in exposed
- Similar in exposed & unexposed
- Lower in exposed

### HBsAg
- Higher proportion of non-responders and good responders
- Lower proportion of non-responders or good responders

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<tr>
<td><strong>Pneumococcus</strong></td>
<td>Higher</td>
<td>Lower</td>
<td>Jones, JAMA, 2011</td>
</tr>
<tr>
<td><strong>Serotype-specific</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Madhi, JID, 2010</td>
</tr>
<tr>
<td><strong>OPA</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Madhi, JID, 2010</td>
</tr>
<tr>
<td><strong>Measles 1st dose</strong></td>
<td>Higher</td>
<td>Lower</td>
<td>Simani, AIDS, 2013</td>
</tr>
<tr>
<td></td>
<td>Similar</td>
<td>Similar</td>
<td>Reikie, CVI, 2013</td>
</tr>
<tr>
<td><strong>Measles 2nd dose</strong></td>
<td>Lower</td>
<td>Higher</td>
<td>Simani, AIDS, 2013</td>
</tr>
</tbody>
</table>

- Higher in exposed
- Similar in exposed & unexposed
- Lower in exposed
Responses to Vaccination in HEU and HUU

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<tr>
<th></th>
<th>HEU</th>
<th>HUU</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td>BCG at birth</td>
<td>Altered</td>
<td></td>
<td>Van Rie, 2008, CVI</td>
</tr>
<tr>
<td></td>
<td>patterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG at 6 weeks</td>
<td>Similar</td>
<td>Similar</td>
<td>Jones, AIDS, 2014</td>
</tr>
<tr>
<td>BCG at birth</td>
<td>Similar</td>
<td>Similar</td>
<td>Mansoor, JID, 2009</td>
</tr>
<tr>
<td>BCG at birth</td>
<td>Similar</td>
<td>Similar</td>
<td>Elliott, 2010, Vaccine</td>
</tr>
<tr>
<td>BCG</td>
<td>Similar @ 6/52</td>
<td>Similar @ 6/52</td>
<td>Kidzeru, 2014, AIDS</td>
</tr>
<tr>
<td>BCG</td>
<td>Higher @ 14/52</td>
<td>Lower @ 14/52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower polyfunc</td>
<td>Higher polyfunc</td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>Higher CD4</td>
<td>Lower CD4</td>
<td>Mazzola, 2011, AIDS</td>
</tr>
<tr>
<td></td>
<td>Lower GD</td>
<td>Higher GD</td>
<td></td>
</tr>
</tbody>
</table>

In general, HEU infants mount a robust antibody responses to vaccines and are likely to be equally protected as HUU.

Intra-uterine Growth in European HUE

European Collaborative Study - weight, height, & OFC, n=1912

**Birth weight / OFC**
Born at term or before 34 weeks no difference if exposed to mono/ no ART or cART
Born at 34 -36 weeks, increased weight if on cART

Gestational age and maternal illicit drug use were strongly associated with growth, effect of cART was marginal.

USA similar growth & body composition - HEU & HUU.

HEU weigh less at birth → slightly ↑ growth in the first 2 years of life. HEU had less subcutaneous fat and decreasing mid-upper arm circumference over time when compared with US standards.

Growth & Development in Zambian HEU / HUU

111 HEU, 279 HUU, aged 6-12 years, assessed →

Anthropometry

Health questionnaire & clinical exam
BP, Hb, HbA1c, glucose, cholest, CRP
Most recent school report

• HEU smaller and less fat than HUU
  → difference became non-significant when adjusted for socio-demographic variables
• HEU ↑ minor illness and ↑ meds prescribed
• No difference between HEU and HUU in biochemical markers
• HEU lower maths grades
  → difference maintained when adjusted for socio-demographic variables

Growth, Bones & Tenofovir

Infant growth outcomes after maternal tenofovir use during pregnancy.
IMPAACT P1025 (infants born 2002-2011)
n=2025 at birth (31% TDF exposed); n=1496 at 6 mths (31% TDF exposed)
By most measures, in utero exposure to tenofovir did not significantly predict infant birth weight or growth through 6 months of age.
Ransom et al, J Acquir Immune Defic Syndr, 2013

New born meconium TDF concentrations
↑ meconium TFV concentrations → greater gestational ages (p = 0.29, P = 0.03) and lower maternal HIV RNA before delivery (p = -0.29, P = 0.04).
Meconium TFV concentrations were not associated with infant weight, length (n = 58) or bone mineral content (n = 49).
Pediatric HIV/AIDS Cohort Study (PHACS), PIDJ 2015

Haematology - Neutrophils

ECS - Levels and patterns of neutrophil counts for first 8 years of life. HEI n=156 HEU n=1533

HIV-infection: after 4 months of age,
neutrophil counts were consistently and substantially lower.
Advanced HIV disease & ARV ↓ ↓ neutrophil count.

Ethnicity: black children ↓ lower counts than white across the age range

HEU: male gender, & ARV exposure were associated with reduced neutrophil count until at least 8 years of age.

clinical relevance of reduced levels of neutrophils?

European Collaborative Study AIDS, 2004
USA Women & Infants Transmission Study (WITS)

HEU n=1820 ARV-exposed
HEU n= 351 ARV-unexposed
0 – 24 months of age

0-2 mths ART-exposed:
↓ Hb, Neut, TLC, CD4+

6-24 mths ART-exposed:
↓ platelet, TLC, CD4+
↓ CD8+

cART compared to mono-ART:
↓ Neut, TLC, CD8+ at 0-2 mths
↓ CD8+ at 6-24 mths

Small differences – is there a clinical significance?

HEU Mitochondrial Morbidity & Exposure to Nucleoside Analogues?

The French Perinatal Cohort Stephane Blanche et al 2002

* Crude rate in French cohort 3 / 1000
Observed back ground rate 1 / 10 000

ART exposed Un-exposed
French Cohort 2644 1748

MITOCHONDROPATHY
Significant evidence for: 28 1
“Possible” 14 0
“Established”* 7 0

USA retrospective review of perinatal exposure to ART in PACTS Study.
No NRTI exposed HEU died of mitochondrial disorders (n=118 deaths < 5 years)
No living HUEs had symptoms of mitochondrial dysfunction (n=1951).


“MITOC” study commissioned by EMA → results still awaited……
Transient lactic acidemia in HEU infants exposed to perinatal ART

Plasma lactate > normal, at least once in 35 / 38 (92%) infants
Reached levels > 5 mmol/l in 10 (26%) infants
78 /117 (68%) lactates were elevated (11 > 5 mmol/l)
No infants received ART beyond 6 weeks
Elevated lactates persisted up to age 6 months
2 infants had symptoms consistent with lactic academia
No association between the infant peak lactate and the type or duration of ART during pregnancy

Alimenti et al, Pediatr Infect Dis J, 2003

In utero NRTI exposure & possible mitochondrial dysfunction in HEU.

PACTG 219/219C n=1037 HEU born 1991-2002
Possible cases with signs of MD according to “Enquête Périnatale Française” criteria were identified retrospectively
Cases (n = 20) significantly more likely to be male and born in earlier years than non-cases (n = 1017)

Overall no association between in NRTI exposure & MD

When adjusted for year of birth the odds of first exposure in the third trimester to 3TC (OR, 10.57; 95% CI, 1.93-75.61) and ZDV/3TC (OR, 9.84; 95% CI, 1.77-71.68) higher among cases than non-cases.
Unable to control for confounding by maternal viral load or psychoactive drug use.

Some evidence of small changes in mDNA in cases.

Brogly et al, AIDS Res Hum Retroviruses, 2011
Antiretroviral exposure and lymphocyte mtDNA content among HEU

mtDNA - stored PBMCs (Primagen Retina Mitox assay)
411 HUU and 213 HEU (+/- in-utero and neonatal ARV)
mtDNA ↓ in HEU compared to HUU
mtDNA ↑ in HEU+ART compared to HEU-ART
By 5 years of age:
mtDNA ↑ to normal levels in HEU+ART, but remain lower in HEU-ART

Is it HIV or ART?

Cardiac effects of in-utero exposure to antiretroviral therapy in HEU children.

Pediatric HIV/AIDS Cohort Study’s Surveillance Monitoring for ART Toxicities study.

*No significant differences in echocardiographic Z-scores between 417 HEU and 98 HUU, aged 2-7 years.*

Subclinical differences in left ventricular structure and function with 1st trimester exposure to cART.

- lower stress-velocity Z-scores
- lower LV dimension Z-scores
- higher mean LV posterior wall thickness
- lower mean LV wall stress Z-scores

Lipshultz et al, *AIDS*, 2015
**Brain - cognitive & academic outcomes**

<table>
<thead>
<tr>
<th>Test</th>
<th>number</th>
<th>% ART exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPPSI-III</td>
<td>350</td>
<td>84%</td>
</tr>
<tr>
<td>WASI</td>
<td>337</td>
<td>64%</td>
</tr>
<tr>
<td>WIAT-II-A</td>
<td>415</td>
<td>67%</td>
</tr>
</tbody>
</table>

Cognitive Performance: No association with ART regime or class

Same factors as associated with lower performance in general pop applied in this cohort: prematurity, SGA, maternal alcohol, lower maternal IQ etc.


**USA PACT 219/219C**  
$n = 1840$, born 1993-2006, 92% ART exposed

Bayley Scales of Infant Development (BSID) at 2yrs of age

No effect of ART exposure on BSID scores

LBW infants had higher scores if ART exposed

17% of mothers used illicit drugs, no effect on BSID scores


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**Cognitive & Academic outcomes in HEU compared to HUU**

**Zambia** – B+ era, ART exposure (inutero & BF)

Capute Full-Scale Develop quotient  
HEU $n=97$  HUU $n=103$

*No significant difference in performance*  
Ngoma et al, *AIDS*, 2014

**Thailand & Cambodia** – HEU $n = 160$, HUU $n = 167$

Beery Visual Motor Integration (VMI) test, Color Trails, Perdue Pegboard, and Child Behavior Checklist (CBCL), Thai children ($n = 202$) also completed the Wechsler Intelligence Scale (IQ) and Stanford-Binet II memory tests.

Adjusted for caregiver education, parent as caregiver, income, age, ethnicity.

*Slightly lower scores* on verbal IQ, full-scale IQ, & Binet Bead Memory in HEU, uncertain significance.

*No differences* in performance IQ, other Binet memory domains, Color Trail, Perdue Pegboard, Beery VMI, or CBCL test scores.

Kerr et al, *AIDS Care*, 2014
ART & Language Outcomes in HEU Infants.

Risk for late language emergence after in utero ART exposure in HEU infants.
1129 language assessments were conducted among 792 1- and 2-year-old children. In utero cARV exposure showed little association with LLE, except for higher risk of language delay observed in 1-year-old infants with atazanavir exposure.

Pediatric HIVAIDS Cohort Study (PHACS), Pediatr Infect Dis J. 2013

Meconium ART concentrations
↑ meconium atazanavir concentrations were protective against developmental language delays at 1 year, suggesting the importance of fetal ATV detoxification into meconium. This supports ATV exposure safety for infant language development.

Pediatric HIVAIDS Cohort Study (PHACS), Pediatr Infect Dis J. 2015

Malignancy? – no data yet
NSHPC Data linkage - flagging

- Office for National Statistics
- Births, deaths, cancer registration, emigration
- Flagging studies provide event notification
- UK born infants born to infected women being flagged (no names – complex procedure)

- Numbers for babies
- Other data linkage possibilities
- Ethics and consent issues – public health considerations
Specific drug effects - Kaletra newborn toxicity

Kaletra liquid - 42% ethanol, & 15% propylene glycol
Neonatal ↓ liver metabolism – CP3A / alcohol dehydrogenase

FDA adverse events reporting system (AERS) <2yrs
10 cases of severe toxicity, 8 prems (28-35 wks)
7 Cardiac toxicity (cardiac failure, AV block, bradycardia)
5 acute renal failure (↑K common); 3 CNS effects
1 death (assoc with an over dose), rest improved on d/c Kal
Rx started on day 1 of life in 7/10
NB – no denominator data;

*FDA safety alert 8.3.11 – avoid Kaletra in <14 day old infants unless no alternatives – monitor organ function closely*

Association of prenatal & postnatal exposure to lopinavir-ritonavir & adrenal dysfunction among uninfected infants of HIV-infected mothers

**JAMA. 2011 Jul 6;306(1):70-8. ANRS French Perinatal Cohort Study Group**

French cohort
All term newborns on lopinavir-ritonavir were asymptomatic

3 premature infants life-threatening symptoms compatible →
adrenal in-sufficiency (hyponatremia, hyperkalemia with, in 1 case, cardiogenic shock)

All symptoms resolved off lopinavir-ritonavir treatment

- Kaletra 7 / 50 ↑17OHP levels – 14%
- Controls (ZDV) 0 / 108 ↑17OHP levels
- French Guthrie Card National rate ↑17OHP levels – 0.03%
Lopinavir - Ritonavir
- cytochrome inhibition
- $\downarrow$ cytochrome /enzyme CYP21
- $\uparrow$ 17- OHP $\uparrow$ DNEA
- adrenal insufficiency

Is this only due to Kaletra or is it a PI class effect?

PROMISE MTCT Through Age 14 Days
Significantly Lower in Triple ARV Arms

<table>
<thead>
<tr>
<th>% Transmission Through Age 14 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV (Arm A)</td>
</tr>
<tr>
<td>Triple ARV (Arms B+C)</td>
</tr>
</tbody>
</table>

1.8%

ZDV + sdNVP + FTC-TDF tail

0.6%

Triple ARV (Arms B & C Combined)

Difference in MTCT Risk (Repeated Confidence Interval):
-1.28% (95% CI -2.11%, -0.44%)

- 25 infections/1,326
- 9 infections/1,710
PROMISE summary of 1077BF/FF Antepartum Component Infant Safety Results

- There were no significant differences in infant signs/symptoms and lab AEs by study arm.
- There were 60 early infant deaths by 14 days; including 28 deaths in version 3.0.
- In V 3.0, there was a significantly lower risk of infant death for **ZDV/3TC vs TDF/FTC**:
  \[
  - 0.6\%(2/346) \text{ vs. } 4.4\% (15/341), \ p=0.001
  \]
  *The difference was primarily seen in deaths among infants less than <34 weeks gestation – why?*

Effects of HIV / ART exposure?

**Resource Rich**  
**Resource Poor**

**Mortality / Survival**

With maternal ART
- **↓** Infant HIV Tx
- **↓** HEU infections
- **↑** Prematurity
- **↑** Drug toxicities

Without maternal ART
- **↑** Infant HIV Tx
- **↑** Immune dysfunction
- **↑** HEU infections
- **↑** Orphans / poverty

*Well designed – large long term follow up studies in resource poor settings are essential to assess these effects*
Children enrolled in CHART


No health or developmental problem 107 (35%)
At least one “usual” problem 179 (58%)
e.g. childhood infections, asthma, gastroenteritis
Specific health / developmental problem 21 (7%)

<table>
<thead>
<tr>
<th>Congenital abnormalities (7)</th>
<th>Others (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior urethral valves</td>
<td>Febrile seizure (5)</td>
</tr>
<tr>
<td>Cleft lip &amp; palate</td>
<td>Sickle cell disease (4)</td>
</tr>
<tr>
<td>Hydrocephalus (aqueduct stenosis)</td>
<td>Cerebral palsy 2° to prematurity</td>
</tr>
<tr>
<td>Spina bifida &amp; hydrocephalus</td>
<td>Intraventricular haemorrhage (prem)</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>Head injury &amp; 2° developmental delay</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>Atopy with seizure</td>
</tr>
<tr>
<td>Talipes</td>
<td>Autism</td>
</tr>
</tbody>
</table>

Follow up of uninfected children exposed to ART:
UK CHART study 2002-05

Investigated logistics of long-term follow up of uninfected HIV-exposed children
Explored whether serious adverse outcomes associated with exposure to ART in fetal/early life were apparent in early childhood
Incorporated NSHPC data on ART exposure, delivery etc.
CHART data on health/development in early childhood
Prevalence of abnormal outcomes within UK norms, but numbers small and duration of follow up limited

Comprehensive long-term clinic-based follow up not feasible in UK
alternative approaches required, e.g. secure data linkage protocols

Hankin CD et al. AIDS Care 2009, 19(1):482-486
Elimination of infant HIV →

A dream in 1994 → Reality in 2015

access to HIV tests & effective ART

There are consequences for HIV & ART exposed uninfected infants – it's our job to minimise these effects and optimise outcomes –

How to do long term surveillance?

90% reduction in new HIV infections
90% reduction in stigma and discrimination
90% reduction in AIDS-related deaths

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