Outcomes of Uninfected, HIV-Exposed Infants

Stéphane Blanche

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE

2011-2015

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Outcomes of Uninfected, HIV-Exposed Infants

• Generally reassuring data, but not documented on the long term

• Alerts documented to varying degrees

• And millions of women to be treated!
A triple potential influence

Mother’s disease

Environnement

Antiviral drugs

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Increased infectious morbidity in HIV exposed - uninfected infants

Mother’s disease

Environnement

Antiviral drugs

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Invasive streptococcal infections in HIV-exposed uninfected infants

Epalza et al. Pediatrics 2010

<table>
<thead>
<tr>
<th></th>
<th>HIV exposed uninfected</th>
<th>Born to HIV neg mothers</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.55%</td>
<td>0.08%</td>
<td>19.6</td>
</tr>
<tr>
<td>Early-onset</td>
<td>0.31%</td>
<td>0.07%</td>
<td>4.5</td>
</tr>
<tr>
<td>Late-onset</td>
<td>1.24%</td>
<td>0.01%</td>
<td>125.2</td>
</tr>
</tbody>
</table>

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Increased infectious morbidity in HIV exposed - uninfected infants
HIV Disease in Mothers and Mortality among Uninfected Infants

Kuhn CID 2005
Maternal HIV infection and antibody responses against vaccine in uninfected infants.

Jones  JAMA 2011

Mother’s disease

Ab titers at birth
Is there a real, intrinsic immunodeficiency induced by the mother’s disease?

Exemple: Enhanced Th17 Phenotype in Uninfected Neonates Born from Viremic HIV-1-Infected Pregnant Women


Presented at the 3rd HIV Pediatrics Workshop, 15–16 July 2011, Rome, Italy
Increased infectious morbidity in HIV exposed -uninfected infants

Drug induced

Neutropenia
Lymphopenia

Le Chenadec AIDS 2003
ECS AIDS 2004; AIDS 2005
Pacheco J Infect Dis 2006
In utero exposure
drug related morbidity

- Prematurity
- Malformations

- Reversible, transient effect
- Long acting effect
In utero exposure drug related morbidity

- Prematurity
- Malformations
- Reversible, transient effect
- Long acting effect?
Is there an AZT-induced long acting effect?
AZT remains the reference molecule
AZT based combinations as *first-line* treatment in France

Source ANRS EPF and FHDH CO1, CO4, CO11

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
AZT is a nucleoside analogue

3’-azido-3’deoxy-thymidine

mt DNA
n DNA
1964 : AZT is first synthesized as a potential anti-cancer agent.

HORWITZ et al J Org Chem 1964; 29, 2076

The Journal of Organic Chemistry
Bacterial gene mutation -
Mamalian gene mutation +
L5178 YTK +/- assay +
Clastogenicity assay +
Micronucleus assay +
SCE assay +
Cell transformation +
Carcinogenicity +
AZT integration in DNA

Duration of AZT therapy in pregnancy

Olivero et al

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Does AZT durably impair fetal DNA?
Persistant mitochondrial dysfunction in AZT exposed infants

4392 children
2644 ARV exposed

21 children:
– severe neurological symptoms
– OXPHOS deficiency
– abnormal mt morphology
Neurodevelopment and In Utero ARV in HIV Uninfected Infants. PACTG 219C

Williams, Pediatrics 2010

ART exposed: 1694
ART unexposed: 146
Possible mitochondrial dysfunction in HIV-uninfected children. PACTG 219C

Brogly et al. AIDS 2007

1037 infants

20 cases of possible mt dysfunction

Significant association with first exposure during 3rd trimester to 3TC or ZDV/3TC

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Transplacental Nucleoside Analogue Exposure and Mitochondrial Parameters

Previously identified 20 children with signs of possible mt dysfunction in PACTG 219:

mtDNA levels were higher, OXPHOS protein levels and enzyme activities lower in cases than controls.
Neurological symptoms and in utero exposure to AZT

Provisional conclusions

• Rare, severe, unexplained neurological symptoms
• In some cases associated with proven persistent mitochondrial dysfunction
• Incidence and long-term evolution? Associated risk factors? Individual susceptibility?
Progressive mitochondrial compromise of primates exposed *in utero* to AZT

**IN BRAINS**

**AT 1 YEAR OF AGE:**

- Mitochondria contained significant morphological damage
- mtDNA levels were lower

References:

Divi R. *Toxicol. Sci.* 2010
Progressive mitochondrial compromise of primates exposed in utero to AZT

Divi Cardiovasc Toxicology 2005

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Cardiac Effects of ARV in Uninfected Infants Born to HIV+Mothers

• reduced LV mass, LV dimension, and septal wall thickness z-scores
• increased LV fractional shortening and contractility up to age 2 years.

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Tired of hearing about mitochondria?

Mild and transient anemia

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Hematopoïèsis
and in utero AZT exposure
Lechenadec AIDS 2003

• French perinatal cohort 1986-2002
• 4249 HIV-1 uninfected children
• AZT exposed or unexposed children

> 21 000 blood counts
Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy

Long lasting impairment on 3 lineages

Le Chenadec AIDS 2003

Neutrophils

Lymphocytes

Platelets

AZT -

AZT +
Neutrophils count in perinatally AZT exposed children until 8 years

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy

ECS AIDS 2005;19:1071
Hematopoietic stem cell CD34+ alteration?
Perinatal exposure to AZT induces biological effects that persist over the long term, even in a cell system with high turnover.
Impact on nuclear DNA ?
Genotoxicity after \textit{in utero} AZT exposure

- **Newborn mice**
  - AZT-DNA in many organs at birth
  - Mutations at 15 days
  - Shortened telomeres
  - Tumors in young adulthood

- **Fetal monkeys**
  - Drug-DNA incorporation at birth
  - Shortened telomeres
  - Micronucleus
  - Supernumerary centrosomes
Genotoxicity after *in utero* AZT exposure

- **Newborn mice**
  - AZT-DNA in many organs at birth
  - Mutations at 15 days
  - Shortened telomeres
  - Tumors in young adulthood

- **Fetal monkeys**
  - Drug-DNA incorporation at birth
  - Shortened telomeres
  - Micronucleus
  - Supernumerary centrosomes

- **Newborn infants**
  - AZT-DNA incorporation
  - *HPRT* and *GPA* mutagenesis
  - Micronucleus
  - Heterochromatin dispersion
Altered chromatin organisation after perinatal exposure to AZT

Figure 2. Box plots of the percentage of nuclei with at least one dispersed 1q12 spot in the three groups of children
AZT in utero exposure and risk of cancer

Benhammou AIDS 2008

To date, no increased risk

• 9127 AZT exposed children
• Median age: 5.4 y
• >53,000 patient-year
• 10 cases observed vs 9.6 expected

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Antiretroviral Drugs for Preventing Mother-to-Child Transmission of HIV: A Review of Potential Effects on HIV-Exposed but Uninfected Children

Shirin Heidari, PhD,† Lynne Mofenson, MD, † Mark F. Cotton, MMed, PhD, ‡ Richard Martin, MD, § Pedro Calaf, MD, PhD, ¶ and Elly Katahira MD

Abstract: The provision of antiretroviral drugs for the prevention of mother-to-child HIV transmission has been rising sharply in low- and middle-income countries. Changes to the World Health Organization guidelines support further extension of these programs. The results will be a greatly expanded population of HIV-exposed but uninfected children with substantial exposure to antiretroviral drugs, both in utero and while breastfeeding. There are limited data on possible toxicities in this growing population, and the long-term impact on the children remains uncertain.

Key Words: antiretroviral, PMTCT, HIV-exposed uninfected infants, childhood growth and development, drug complications

INTRODUCTION

The provision of antiretroviral drugs for the prevention of mother-to-child HIV transmission has been rising sharply worldwide in the last few years. Changes to the World Health Organization guidelines support further extension of antiretroviral pre-exposure prophylaxis. However, with the availability of antiretroviral drugs increasing globally, WHO’s expanded recommendations will lead to a rapidly growing number of antiretroviral-exposed, HIV-uninfected children. The total exposure of these uninfected infants to antiretroviral drugs will start in utero and continue until the end of breastfeeding. The exposure period to these drugs could be up to 2 years, yet there are limited data on safety. There is now an urgent need to better understand the consequences of extended exposure to HIV and antiretroviral drugs on HIV-uninfected children to contribute to improved monitoring and management of potential adverse effects. In this report, we review available literature describing the risks that HIV and antiretroviral drug exposure, in utero and postpartum, may pose for uninfected children.

The drug impact later in life is an open question. Larger and longer cohort studies are necessary to properly balance the risks and benefits of large-scale infant exposure to antiretroviral agents.
• Long-term follow-up of children who are not ill is quite impossible

• The cohort is not representative of the general population

• Under or over declaration bias

• *In utero* exposure not allways declared by the family
The Long-Term Effects of In Utero Exposures
The DES Story

15 to 20 million women received DES during pregnancy

risk of cervicovaginal cancer in daughters

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Alternative

• Study the biological « signature » left on the child by the drug

• Compare drugs with each other

• Choose the least invasive molecules
Conclusions

• The « proof-of-concept » of MTCT has been established for 17 years
• The needs are planet-wide and immense
• The « historical » molecule has a potential toxicity

Work to develop the safest possible prophylaxis should continue
Patients and Families

PHarmacology Jean Marc Treluyer

Fulvio Mavillio (Modena)
Isabelle Schmutz
Emmanuelle Six

EPF Coordination
Josiane Warszawski

Obstetrics Laurent Mandelbrot

Pediatrics Stéphane Blanche

Virology Christine Rouzioux

Marie Laure Chaix

Pharmacology Jean Marc Treluyer

Patients and Families

CD34 Study

Marina Cavazzana
Emmanuelle Six
Isabelle Schmutz-Andre
Fulvio Mavillio (Modena)

French Perinatal Cohort

Hôpital Nord, Amiens (Dechaux N, Douadi Y, Gondry J, Li Thiao Te V, Schmit JL): Hôpital d’Angers (Fournier A); Hôpital Victor Dupouy, Argenteuil* (Allisy C, Braut D); Hôpital Robert Ballanger, Aulnay* (Questiaux E, Zakaria A., Goldenstein C); Hôpital de Bastia (Plencemaille O); Hôpital de la Côte Basque, Bayonne (Bonnal F, Cayla C, Hernandez A); Hôpital Saint Jacques, Besançon (Estravoyé J, Maillet R); Hôpital Avicenne, Bobigny* (Benoist J, Bolle E, Bonier N, Lachassine E, Rodrigues A); Hôpital Pellegrin, Bordeaux (Doudou D, Roux D, Schaeffer V); Hôpital Clémenceau, Caen (Boucher G, Brouard J, Goubin P); Hôpital André Rosemon, Cayenne (Elenge N); Hôpital Beaujon, Clichy* (Ceccaldi-Carp P, Fantin B, Lemaire D, Pariset H); Hôpital de Cluny (Carpentier B, Duval-Arnold M, Kingué-Ekollo C); Hôpital Intercommunal, Créteil* (Garratt V, Lemerel S, Pichon C, Richez C, Touboul C); Hôpital Béclère, Clamart* (Bornarel D, Chambrin V, Chec L, Foix L, Héliaus L, Labrune P, Schoen H); Hôpital Louis Mourier, Colombes* (Crenn-Hebert C, Floch-Tudal C, Mazy F, Hery E, Meier C); Hôpital d’enfants, Dijon (Martha S, Reynaud I); Hôpital le Mix, Evreux (Allouche C, Touré K); Hôpital Francilien Sud, Evry-Corbeil* (Chevjonon P, Devidas A, Granier M, Marchand C, May A, Nguyen R, Turpault I); Hôpital de Fontainebleau (Alissia K, Routier C); Hôpital Victor Fouche, Fort de France (Hatchuel Y, William C); Hôpital Jean Rostand, Ivry (Jault T, Jiao I); Hôpital de Lagney* (Chayon Dernersay A, Froguel E, Gourdel E, Lanty C); Hôpital les Oudairies, La Roche sur Yon (Aubry O, Brossier JP, Esnault J, Leautez S, Perre P, Suard I); Hôpital de la Seyne sur Mer (Chamoulié JM); Hôpital André Magnot, Le Chesnay* (Hentgen V, Messaoudi F); Hôpital de Bègles, Le Kremlin-Bicêtre* (Colmant C, Fourcade C, Fridman S, Peretti D); Hôpital Jeanne de Flandres, Lille (D’angelo S, Hammou Y, Mazine F); Hôpital de Longjumeau* (Gailly-Salin P, Turpault I, Seuma H); Hôpital de la Croix Rousse, Lyon (Browning C, Cotte F, Lavaun J, M Le Thi T, Roussouly M, Tariel O, Therain V); Institut d’hématologie-oncologie pédiatrique, Lyon (Bertrand Y, Kebbi K, Tache N); Centre Hospitalier Lyon-Sud, Lyon (Massardier JY); Hôpital François Quesnay, Mantes la Jolie* (Delanete A, Delnet A, Granier F, Salomon JL); Hôpital la Conception, Marseille (Cravello L); Hôpital la Timone Marseille (Thuret I); Hôpital de Meaux * (Karaoui L, Lefèvre V); Hôpital Marc Jacquet, Melun (Le Lonner B); Hôpital Intercommunal, Montfermeil* (Dehlinger M, Echard M, Mullard C, Talon P); Hôpital Arnaud de Villeneuve, Montpellier (Besoos P, Guigue N, Lalange M); Hôpital Intercommunal, Montreuil* (Heñer-Roussin B, Riehl F, Winter C); Maternité Régionale A. Pinard* Nancy (Hubert C); Hôpital de Nantes (Brunet-Francois C, Meusnier, Réguquet V); Hôpital I* Arche-Fondation Lenval, Nice (Bongain A, Devile A, Gaëbia E, Monpoux F); Hôpital Caremeau, Nimes (Abadie N, Nguyen J); Hôpital Orléans (Arsac S, De Gennes C, Isart V); Hôpital Bichat, Paris* (Bastian H, Bourgeois-Moine A, Matheron S, Raiguru R); Hôpital Cochin-Port Royal, Paris* (Boudjoudi N, Firtion G, Foucher M, Goupil I, Pannier A); Hôpital Lariboisière, Paris* (Ayral D, Cirac-Vincent M, Mouchnino G); Hôpital Necker, Paris* (Bouy S, Blanche S, Maigam A, Parguei F, Rouzioux C, Vier JP, Yamgnane A, Cayol V); Hôpital Pitié Salpêtrière, Paris* (Bois-Chantre M, de Montgolfier I, Quetin F, Edebi N, Lemercier D, Harif M, Naïme-Alix A, Pichard M, Tubiana R); Hôpital Robert Debré, Paris* (De Laizazanne A, Faye A, Gaillon D, Leveillé S, Levine M, Ottenwalder A, Recoules A); Hôpital Saint-Antoine, Paris* (Bui E, Cauneille B, Meychaux M, C, Rodrigues J); Hôpital Paris Est (Laurent C); Hôpital Tenon, Paris* (Hervé F, Lebrete MG); Hôpital Trouseau, Paris* (Duffaut C, Tabone MD, Vaudre G, Wallet A); Hôpital MARECHAL Joffre, Perpignan (Bachelard G, Medus M); Hôpital Les Abymes, Pointe-à-Pitre (Ballou F); Hôpital René Dubos, Pointe-à-Pitre (Ballou F); Hôpital Témoins (Américain, Reims (Munzer M); Hôpital Charles Nicolle, Rouen (Brossard V); Hôpital de Saint-Denis* (Allemont M.C, Bolet P, Ekbouk D, Ghabou S, Gyardeau S, Khoung M.A); Hôpital Nord, Saint Etienne (Biliennak M); Hôpital de Saint Martin (Bissieu F, Walter V); Hôpital de Haute Pierre-Hôpital Civil, Strasbourg (Cheneau M); Hôpital Werle N, Favreau J, Parisian (M); Hôpital Chalucet, Toulouse (Hitinger G); Hôpital Paul-Paule de Viguier, Toulouse (Antras M, Armand E, Berrebi A, Tricorre J); Hôpital Bretonneau, Tours (Brenier J, Nau P); Hôpital Brabois, Vandoeuvre les Nancy (Nejman L); Hôpital de Villeneuve Saint Georges* (Chacque A, Guillot F, Matheron I).