Malignancies in HIV children

Dr Elena Chiappini, MD, PhD
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- Cancers in children with HIV infection in the HAART era: who gets them, and which ones

- Recent pathogenetic findings

- Cancer risk in children exposed to antiretroviral drugs in utero
- Cancers in children with HIV infection in the HAART era: who gets them, and which ones

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- Cancer risk in children exposed to antiretroviral drugs in utero
# Cancers in HIV Disease

## AIDS-Defining
- Kaposi’s Sarcoma: HHV-8
- Non-Hodgkin’s Lymphoma (systemic and CNS): EBV, HHV-8
- Invasive Cervical Carcinoma: HPV

## Non-AIDS Defining
- Anal Cancer: HPV
- Hodgkin’s Disease: EBV
- Leiomyosarcoma (pediatric): EBV
- Squamous Carcinoma (oral): HPV
- Merkel cell Carcinoma: MCV
- Hepatoma: HBV, HCV
In HIV+ children < 5 ys the incidence of NHL was about 2500 times greater than expected in the UK child population. NHL tends to occur in advanced HIV disease.

Among children with AIDS 2.5% were identified as having cancer. Mean age was 4.5 ys (median 3 ys.)
- NHL: 81%
- KS: 8%
- Leiomyosarcoma: 3%
- HDG 2%

boys > girls
Caucasians> blacks

Primary brain lymphomas in 25% of all NHL in pediatric HIV patients

Among the 156 tumors captured in the CDC AIDS definition in children.

A conservative estimate is that children with HIV infection appear to have at least a 100-fold higher incidence of cancers.

The incidence of neoplasms in children with AIDS was of 1.47% if compared to healthy non-HIV-infected children who developed cancer in approximately 130 cases per million children (0.013%) per year.


The Italian Register for HIV infection in children
(coordinators: de Martino M and Tovo PA)

It is a nationwide multi-centre study of children born to HIV-1 infected mothers instituted in 1985 by the Italian Society of Paediatrics.

- 106 paediatric Centres in Italy
- >9,000 children enrolled between 1985-2011
- 42 studies published in peer-review journals from 1988 to 2011 (cumulative impact factor: 352)

- Performs teaching activity for participating Centres
- Centre of epidemiological surveillance of the Italian Health Ministry
- Collaborative centre of WHO, MRC, CDC, COHERE, NIH, EPPICC
Clinical event rates in HIV-infected children


Clinical event rates in HIV-infected children


*P<0.0001

*Poisson regression adjusted for age and repeated events in the same subject
Cancer Rates After Year 2000 Significantly Decrease in Children With Perinatal HIV Infection: A Study by the Italian Register for HIV Infection in Children

Elena Chiappini, Luisa Galli, Pier-Angelo Tovo, Clara Gabiano, Catiuscia Lisi, Carlo Giaquinto, Osvalda Rampon, Guido Castelli Gattinara, Giulio De Marco, Patrizia Osimani, Mariano Manzionna, Angela Miniaci, Carlo Pintor, Raffaella Rosso, Susanna Esposito, Alessandra Viganò, Icilio Dodi, Anna Maccabrini, Carlo Fundarò, and Maurizio de Martino
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Total observation time, years</td>
<td>4,688.9</td>
<td>2,688.1</td>
<td>2,646.4</td>
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<tr>
<td>Observation time per child, years</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median</td>
<td>4.3</td>
<td>3.98</td>
<td>3.48</td>
</tr>
<tr>
<td>Range</td>
<td>0.01-9.98</td>
<td>0.0-3.99</td>
<td>0.02-4.01</td>
</tr>
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<td>CDC category</td>
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</tr>
<tr>
<td>N</td>
<td>31</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>A</td>
<td>116</td>
<td>164</td>
<td>174</td>
</tr>
<tr>
<td>B</td>
<td>272</td>
<td>315</td>
<td>333</td>
</tr>
<tr>
<td>C</td>
<td>546</td>
<td>275</td>
<td>213</td>
</tr>
<tr>
<td>Deaths during the study period</td>
<td>321†</td>
<td>84†</td>
<td>9†</td>
</tr>
<tr>
<td>HAART-treated children</td>
<td>23</td>
<td>223</td>
<td>568</td>
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</table>
# Cancer rates in HIV+ children

<table>
<thead>
<tr>
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<tr>
<td>Observation years</td>
<td>4689</td>
<td>2688</td>
<td>2646</td>
</tr>
<tr>
<td>HAART (%)</td>
<td>2.4</td>
<td>27</td>
<td>72</td>
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<tr>
<td>Cancers (n)</td>
<td>22</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>1000/PY</td>
<td>4.49</td>
<td>4.09</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>(2.73-6.64)</td>
<td>(1.69-6.50)</td>
<td>(0.0-1.80)</td>
</tr>
<tr>
<td>P</td>
<td>0.08</td>
<td>0.0001</td>
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</table>

*Poisson regression adjusted for age and repeated events in the same subject

Italian Register for HIV infection in children
Table 2. Cancer Rates in HIV-Infected Children by Calendar Period

<table>
<thead>
<tr>
<th>Calendar Period</th>
<th>NHL</th>
<th>Kaposi’s Sarcoma</th>
<th>CNS Lymphoma</th>
<th>Hepatoblastoma</th>
<th>Vulva Carcinoma</th>
<th>Splenic Sarcoma</th>
<th>Leiomyoma of Gallbladder</th>
<th>ALL</th>
</tr>
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<tr>
<td>1985-1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Patients, No.</td>
<td>13</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rate, events per 1,000 children/yr</td>
<td>2.77</td>
<td>0.21</td>
<td>1.07</td>
<td>0.21</td>
<td>—</td>
<td>0.21</td>
<td>0.21</td>
<td>—</td>
</tr>
<tr>
<td>95%CI, events per 1,000 children/yr</td>
<td>1.27 to 4.28</td>
<td>0.00 to 0.63</td>
<td>0.13 to 2.00</td>
<td>0.00 to 0.63</td>
<td>—</td>
<td>0.00 to 0.63</td>
<td>0.00 to 0.63</td>
<td>—</td>
</tr>
<tr>
<td>1996-1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No.</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rate, events per 1,000 children/yr</td>
<td>2.60</td>
<td>—</td>
<td>0.37</td>
<td>—</td>
<td>0.74</td>
<td>—</td>
<td>—</td>
<td>0.37</td>
</tr>
<tr>
<td>95%CI, events per 1,000 children/yr</td>
<td>0.68 to 4.53</td>
<td>—</td>
<td>0.00 to 1.10</td>
<td>—</td>
<td>0.00 to 1.77</td>
<td>—</td>
<td>—</td>
<td>0.00 to 1.10</td>
</tr>
<tr>
<td>2000-2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients, No.</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rate, events per 1,000 children/yr</td>
<td>0.38</td>
<td>0.38</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>95%CI, events per 1,000 children/yr</td>
<td>0.00 to 1.12</td>
<td>0.00 to 1.12</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: NHL, non-Hodgkin’s lymphoma; ALL, acute lymphoblastic leukemia.
However malignancies in HIV are a growing concern

The number of malignancies occurring in HIV positive children rises as the prevalence of HIV increases in the population.

The scale of the problem is potentially immense.
Given the figures by the Italian Register and other Western Cohorts

Of 2,100,000 children < 15 years living with HIV in 2007, 1,800,000 (85.7%) were residing in sub-Saharan Africa and 280,000 (13.3%) in South Africa.

Only 35% of children in sub-Saharan Africa and 61% of children in South Africa who need ART are receiving treatment.

We should be seeing at least 1,000 cases of HIVRM per year.

A study of HIV and childhood malignancy from four of South Africa’s nine academic sector-based paediatric oncology units showed only 131 cases of HIV-related malignancy and 48 cases of incidental malignancy since the start of the epidemic. (Davidson A. Pediatric Blood Cancer 2009;53:719)
Epidemiologic Trends of Cancer Diagnoses Among HIV-infected Children in Spain From 1997 to 2008

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate (95% CI)</td>
<td>No.</td>
<td>Rate (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>AIDS-defining cancer</td>
<td>50</td>
<td>3.8 (2.8; 4.9)</td>
<td>31</td>
<td>9.1 (5.9; 12.3)*</td>
<td>13</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>200</td>
<td>3.8 (2.8; 4.9)</td>
<td>31</td>
<td>9.1 (5.9; 12.3)</td>
<td>13</td>
</tr>
<tr>
<td>Non–AIDS-defining cancer</td>
<td>73</td>
<td>5.6 (4.3; 6.9)</td>
<td>2</td>
<td>0.6 (0.0; 1.4)</td>
<td>18</td>
</tr>
<tr>
<td>Malignant neoplasm of liver and intrahepatic bile ducts</td>
<td>155</td>
<td>3 (0.0; 0.5)</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Malignant neoplasm of bone and articular cartilage</td>
<td>170</td>
<td>20 (1.5; 2.2)</td>
<td>20</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>Malignant neoplasm of brain</td>
<td>191</td>
<td>3 (0.2; 0.5)</td>
<td>0</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>201</td>
<td>2.4 (1.5; 3.2)</td>
<td>31</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>Other malignant neoplasms of lymphoid and histiocytic tissue</td>
<td>202</td>
<td>4 (0.3; 0.6)</td>
<td>1</td>
<td>0.29 (0.00; 0.87)</td>
<td>3</td>
</tr>
<tr>
<td>Lymphoid leukemia</td>
<td>204</td>
<td>9 (0.7; 1.1)</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms of unspecified nature</td>
<td>239</td>
<td>3 (0.0; 0.5)</td>
<td>1</td>
<td>0.29 (0.00; 0.87)</td>
<td>2</td>
</tr>
<tr>
<td>All cancer diagnoses</td>
<td>123</td>
<td>9.4 (7.8; 11.1)</td>
<td>33</td>
<td>9.7 (6.4; 13.0)</td>
<td>31</td>
</tr>
</tbody>
</table>

ICD-9-CM, data are coded according to the International Classification of Diseases (Ninth revision, Clinical Modification); Rate, cancers per 1000 HIV-infected children/yr.

*Significant differences between AIDS-defining cancers and non–AIDS-defining cancers within a calendar period (P < 0.05).

*Significant differences between calendar periods (1997–1999 vs. 2000–2002) within a cancer category (P < 0.05).

*Significant differences between calendar periods (1997–1999 vs. 2000–2002) within a cancer category (P < 0.05).
HIV-infected children had a dramatic decrease in the rate of ADM diagnoses and an increase in the rate of non-ADM diagnoses.

The overall cancer diagnosis rate has not decreased during the past decade and the incidence of cancer still remains high in HIV-infected children in Spain.
Long term cancer risk among people diagnosed with AIDS during childhood


Data from the U.S. HIV/AIDS Cancer Match Study

5,850 children diagnosed with AIDS in 1980-2007 and followed up to 10 years

standardized incidence ratios (SIR) was calculated to compare cancer risk to the general population.

106 cancers observed

significantly elevated risks for the two major AIDS-defining cancers:
- Kaposi sarcoma (incidence declined of 87% in the HAART era)
- non–Hodgkin lymphoma (incidence declined of 60% in the HAART era)

- no decline in non-AIDS-defining cancers and CNS lymphoma
- leiomyosarcoma risk was elevated during both time periods

SIR : 863 (235 to 2,211) → 533 (173 to 1,243).
People diagnosed with AIDS during childhood remain at elevated risk for KS, NHL, and leiomyosarcoma in the HAART era


<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>SIR</td>
</tr>
<tr>
<td>All cancer</td>
<td>69</td>
<td>40</td>
</tr>
<tr>
<td>AIDS-defining cancers overall</td>
<td>58</td>
<td>441</td>
</tr>
<tr>
<td>KS</td>
<td>17</td>
<td>1,694</td>
</tr>
<tr>
<td>NHLa</td>
<td>41</td>
<td>338</td>
</tr>
<tr>
<td>– DLBCL</td>
<td>7</td>
<td>280</td>
</tr>
<tr>
<td>– Burkitt lymphoma</td>
<td>10</td>
<td>304</td>
</tr>
<tr>
<td>– CNS lymphoma</td>
<td>5</td>
<td>1,994</td>
</tr>
<tr>
<td>Other/unspecified NHL</td>
<td>24</td>
<td>378</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non–AIDS-defining cancers overallb</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissue (other than leiomyosarcoma)</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>4</td>
<td>863</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytic leukemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Poorly specifiedc</td>
<td>3</td>
<td>86</td>
</tr>
</tbody>
</table>

NOTE: Bold values are significant at P < 0.05.
• AIDS-defining cancers accounted for the majority of cancers

• there was a notable decline in the incidence of AIDS-defining cancers in the HAART era but no decline in non-AIDS-defining cancers

• many of the malignancies observed are related to EBV (CNS lymphoma and leiomyosarcoma did not decrease over time)

• Children may be especially vulnerable to EBV-related malignancies

- Cancers in children with HIV infection in the HAART era: who gets them, and which ones

- Some pathogenetic findings

- Cancer risk in children exposed to antiretroviral drugs in utero
Why in the HAART era rates of EBV related malignancies in children are still sustained?
HIV and MALIGNANCIES

- IMMUNEDEPRESSION

• Children may be especially vulnerable to EBV-related malignancies, because primary EBV infection can occur in the setting of marked immunosuppression, and subsequent HAART may not be effective in allowing control of EBV replication

- IMMUNE ACTIVATION

- ONCOGENIC PROPERTIES OF VIRAL PROTEINS
About 15-20% of HIV-infected patients on HAART showed an immunological response (i.e. increase in peripheral CD4+ lymphocytes) without a virological response (i.e. lack of HIV suppression).

Patients with such a dissociated response to HAART show an increase in B cell stimulation and EBV load. As these parameters are both predictive of lymphoma, these patients might represent a new risk group for lymphoma development over time.
156 HIV-1-infected patients.

1) EBV types 1 and 2 were quantified PBMCc by PCR.

2) Plasma levels of cytokines and LPS were determined by immunoenzymatic assays.

3) B-cell activation was analyzed by flow cytometry.
Relationship between EBV load and activated B-cells.

A role of these cytokines in driving B-cell stimulation in the development of lymphoma (IL-6)
• strong association between HIV-1 viremia, markers of immune activation and EBV load

• regardless of peripheral CD4 cell depletion/repopulation

• persistence of HIV-1 viremia and immune activation, may favor expansion of EBV-infected cells and onset of EBV-related malignancies.
It is likely that immune activation preferentially promotes the expansion of EBV-infected B-cells
EBV-RELATED LYMPHOMAGENESIS IN THE CONTEXT OF IMMUNODEPRESSION

Oligoclonal EBV+ B cell expansion

Ag-driven B cell-stimulation

LMP-2+ EBNA1+

LMP-1,2+ EBNA1-6+ EA, VCA

Ig levels

EBV specific CTL

EBV spread and load

IMMUNEDEPRESSION

IMMUNE ACTIVATION

Monoclonal EBV+ expansion
EBV-DRIVEN LYMPHOMAGENESIS IN THE CONTEXT OF HIV INFECTION

**HIV DIRECT ROLE**

- HIV-driven B cell-stimulation
- **LMP-2+ EBNA1+**
- **LMP-1,2+ EBNA1-6+ EA, VCA**
- **T CD4+ HIV-1+**

**Uncontrolled proliferation of EBV+ lymphoblasts**

- **Ig levels**
- **EBV spread and load**
- **EBV specific CTL**

Viral factors?
• Hundreds of human host factors have been identified as necessary during viral infection and replication.

• Thousands of protein-protein interactions between HIV and human host proteins have been reported in the literature.

• HIV infection shares common molecular mechanisms with certain signaling pathways and cancers.

• Interference in apoptosis pathways and the long-term suppression of immune system functions by HIV infection might contribute to tumorigenesis.
TAT activates AKT1 and NF-κB, and led to the expression of anti-apoptotic genes.

Chen KC. PlosONe 2012;7:e3240

The pancreatic cancer pathway
TAT and Malignancies

Tat was consistently found in the neoplastic cells of B-NHL arising in HIV-infected patients
(Lazzi et al, Hum Pathol 2002; 33:723)

Tat modulates DNA-repair β-polymerase enzyme
(Srivastava et al, AIDS 2001; 15:433)

Tat transgenic mice developed lymphomas of B-cell origin
(Kundu et al, Blood 1999;94:275)

Tat accelerated Kaposi's Sarcoma
(Chen X et al, Neoplasia 2009;11:1272)

Tat inhibits apoptosis and accelerated tumorigenesis in nude mice
(Huynh et al, Curr HIV Res 2007;5:403)

Tat plays an oncogenic role in the development of KSHV-associated neoplasms
TAT and B-NHL

Tat was consistently found in the neoplastic cells of B-NHL arising in HIV-infected patients.

Tat prevents cell cycle arrest triggered by serum withdrawal.

Tat modifies cell adhesion properties.

Tat promotes cell migration/invasion through an alternative/additional pathway.

B cells expressing Tat may have growth advantage among the EBV-driven cell proliferation and may originate B cell clones with more oncogenic potential.

De Rossi et al, Exp Cell Res 2004
- Cancers in children with HIV infection in the HAART era: who gets them, and which ones

- Recent pathogenetic findings

- Cancer risk in children exposed to antiretroviral drugs in utero
AZT remains the reference molecule
Use of Antenatal and Postnatal Prophylaxis and Rates of Mother-to-Child Transmission of Human Immunodeficiency Virus (HIV), by Birth Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>1998–2000 (Proportion)</th>
<th>2001–2003 (Proportion)</th>
<th>2004–2008 (Proportion)</th>
<th>Proportion (% [95% CI]) of Infants with HIV infection</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antenatal ART (any type)</strong></td>
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<tr>
<td>Yes</td>
<td>915/1018 (89.9)</td>
<td>1024/1074 (95.3)</td>
<td>1306/1472 (88.7)</td>
<td>42/3203 (1.3 [0.92–1.71])</td>
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<tr>
<td>No</td>
<td>103/1018 (10.1)</td>
<td>150/1074 (14.7)</td>
<td>166/1472 (11.3)</td>
<td>53/366 (12.6 [10.88–18.09])</td>
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<tr>
<td><strong>Elective Caesarean delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
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<tr>
<td>Yes</td>
<td>836/1018 (82.1)</td>
<td>1032/1160 (89.0)</td>
<td>1291/1447 (89.2)</td>
<td>52/3107 (1.6 [1.22–2.12])</td>
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<tr>
<td>No</td>
<td>182/1018 (17.9)</td>
<td>128/1160 (11.0)</td>
<td>156/1447 (10.8)</td>
<td>43/423 (9.2 [7.29–13.05])</td>
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<tr>
<td><strong>Neonatal prophylaxis (any type)</strong></td>
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<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>805/1021 (78.8)</td>
<td>1080/1176 (91.8)</td>
<td>1429/1473 (97.0)</td>
<td>74/3321 (2.2 [1.73–2.73])</td>
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<tr>
<td>No</td>
<td>216/1021 (21.2)</td>
<td>96/1176 (8.2)</td>
<td>44/1473 (3.0)</td>
<td>20/345 (5.8 [3.33–8.26])</td>
<td></td>
</tr>
<tr>
<td><strong>Neonatal prophylaxis ≥6 weeks</strong></td>
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<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>687/1021 (66.3)</td>
<td>922/1176 (78.4)</td>
<td>1138/1473 (77.3)</td>
<td>49/2689 (1.8 [1.32–2.33])</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>343/1021 (33.6)</td>
<td>254/1176 (21.6)</td>
<td>335/1473 (22.7)</td>
<td>46/932 (4.9 [3.54–6.33])</td>
<td></td>
</tr>
<tr>
<td><strong>No of drugs in neonatal prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1</td>
<td>797/1021 (78.1)</td>
<td>1072/1176 (91.2)</td>
<td>1388/1473 (94.2)</td>
<td>69/3188 (2.1 [1.66–2.67])</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8/1021 (0.8)</td>
<td>5/1176 (0.4)</td>
<td>19/1473 (1.3)</td>
<td>1/31 (1.1 [0.00–9.45])</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0/1021 (0)</td>
<td>3/1176 (0.3)</td>
<td>22/1473 (1.5)</td>
<td>2/23 (2.1 [0.00–20.21])</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Crude mother-to-child transmission rates were 3.8% in 1998–2000 (39 of 1021 infants; 95% CI, 2.6–5.0), 2.4% in 2001–2003 (28 of 1176 infants; 95% CI, 1.5–3.2), and 1.9% 2004–2008 (28 of 1473 infants; 95% CI, 1.2–2.6; P<.001). ART, antiretroviral therapy; CI, confidence interval.

<sup>a</sup> P value for cumulative mother-to-child transmission rates for all 3 periods.

<sup>b</sup> P = .01.

<sup>c</sup> P<.001, by multivariate logistic regression.
AZT is a nucleoside analogue

3’-azido-3’deoxy-thymidine

mt DNA
n DNA
Mechanisms of genotoxicity of nucleoside reverse transcriptase inhibitors.

NRTI exposure is associated with both mutagenesis and other forms of DNA damage.


AZT

- is incorporated into DNA
- causes mutations in the hypoxanthine-guanine phosphoribosyl-transferase (HPRT) and thymidine kinase (TK) genes,
- induces micronuclei, chromosomal aberrations, sister chromatid exchange, shortened telomeres, and other genotoxic effects in cultured cells.

Genomic instability would be predicted as a consequence of these events
NRTI-drug pair zidovudine–didanosine is highly cytotoxic and mutagenic


Fewer infants had detectable AZT-DNA incorporation levels in the group exposed to AZT (71%; n = 7) compared with those receiving AZT-3TC (100%; n = 21),

the mean AZT-DNA incorporation for AZT-exposed infants (14.6 +/- 6.3 AZT/10^6 nucleotides) was significantly lower than that in AZT-3TC exposed infants (51.6 +/- 10.2 AZT/10^6 nucleotides; P = 0.028).

Low levels of 3TC-DNA incorporation found in a few AZT-3TC-exposed newborns correlated with AZT-DNA incorporation values in the same samples

Limited clinical data are reassuring regarding the risk of malignancy in the short term (to age 5-10 years)
Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. 

TO DATE NO INCREASED RISK

Benhammou V, et al. AIDS 2008;22;2165-77

9127 AZT exposed children

Median age: 5.4 years

> 53 000 patient-year

The overall incidence did not differ significantly from that expected for the general population:

10 cases observed vs. 9.6 expected
Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors.

Benhammou V, et al. AIDS 2008;22;2165-77

However, 5 cases of central nervous system cancer were observed compared with 1.6-2.1 expected cases; a higher cancer risk was observed with exposure to didanosine lamivudine-containing regimens compared with exposure to zidovudine alone, although only 4% of women received such regimens.
Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data

Hankin, Claire; Lyall, Hermione; Peckham, Catherine; Tookey, Pat
Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data.

*Hankin C et al. AIDS 2007;21:867-9*

- Data on children reported through national HIV surveillance were linked to routinely collected cancer and death data: a process known as "flagging".
- 95% (2612) of reported children born in 2001-2004 in England or Wales who were uninfected or of indeterminate infection status were flagged.
- By the end of 2005, no cancers and 14 deaths (three uninfected and 11 indeterminate) had been notified.
The PACTG 219/219C study found no increase in early childhood cancer associated with antiretroviral exposure, when comparing HIV-uninfected children with or without exposure to any antiretrovirals. 

Brogly S et al. JAIDS 2006;41:535-6

<table>
<thead>
<tr>
<th>In Utero ART Exposure</th>
<th>No. Children</th>
<th>No. Cancer Cases</th>
<th>Person-Years</th>
<th>IR/1000 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>2077</td>
<td>1</td>
<td>7871.2</td>
<td>0.127 (0.003 to 0.708)</td>
</tr>
<tr>
<td>Any ART</td>
<td>1859</td>
<td>0</td>
<td>6792.1</td>
<td>0.000 (0.000 to 0.543)</td>
</tr>
<tr>
<td>NRTI</td>
<td>1847</td>
<td>0</td>
<td>6758.1</td>
<td>0.000 (0.000 to 0.546)</td>
</tr>
<tr>
<td>No NRTI/ART</td>
<td>184</td>
<td>1</td>
<td>988.4</td>
<td>1.012 (0.000 to 5.637)</td>
</tr>
</tbody>
</table>

IR indicates incidence rate.

The children's median age at last study visit was 3.1 years (range: 0.5 months to 14.9 years).
• Limited data are reassuring regarding the risk of malignancy in the short term (to age < 5-10 years)

• Follow-up of children with exposure to ARVs should continue into adulthood when the effect on the promotion of malignancies are more likely to be observed

BUT

TO DATE NO reports available with follow up into adolescence or young adulthood –

• Long term follow-up of not-ill children is almost impossible

• The cohort may be not representative of the whole population

• Under or over declaration bias may occur
Thanks