Nevirapine-Associated Hepatotoxicity and Rash among HIV-infected Pregnant Women in Kenya: A secondary Analysis from the KEMRI-CDC HIV Research Branch

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KEMRI/CDC HIV Research Branch: An Overview

• Founded in 2001
• World-class ISO-accredited Laboratory
• NIH accredited Clinical Trial Unit
• Study sites in rural & urban Nyanza Province, Kenya:
  – KiBS follow on study (KiBS2)
  – Kisumu Incidence Cohort Study
  – HIV Prevention Trials Network 052: Discordant Couples Study of Treatment as Prevention
  – HIV Sub-Study (HIVSS) in the KEMRI-CDC Health and Demographic Surveillance Survey
  – Evaluating Acute & Recent HIV Infection Longitudinally (EARLY)
  – Kenya Free of AIDS PMTCT Survey (KeFAP2)
  – Unintended Pregnancy (UP) study
HIV Research Branch: Extensive Capacity

- 75-100 KEMRI staff (all GCP trained)
- 4 Americans full-time staff

Sections which support key research functions:
- Regulatory Affairs
- Quality Assurance/Quality Control
- Medical Records
- Data Management
- Pharmacy
- Clinical Affairs
- Laboratory
- Behavioral Sciences and Community Affairs
Background: Nevirapine Use

• Nevirapine (NVP) use reportedly increase risk of hepatotoxicity

• Females and patients with higher CD4 counts are at increased risk of Nevirapine-associated hepatotoxicity (NAH)
  – Women 3X higher risk than men
  – Women with CD4 ≥ 250 cells/ul have 12X higher risk than women with CD4 < 250 cells/ul (11% vs 0.9%)
  – Men with CD4 ≥ 400 cells/ul have 5X higher risk than men with CD4< 400 cells/ul (6.3 % vs 2.3%)

[Baylor, JAIDS 2005]
Nevirapine use cont’d

• Highest risk observed during first 18 wks after initiation of NVP therapy

• Nevirapine related deaths due to fulminant hepatotoxicity including in HIV infected pregnant women have been reported

• Few clinical studies have evaluated use of NVP based ART in HIV infected pregnant women

• Kisumu breastfeeding study can provide insight as it started pregnant women on NVP based triple ARVs prior to the release of the nevirapine toxicity warning
Kisumu Breastfeeding Study (KiBS)

- A single arm clinical trial performed Jul 03 - Feb 09
- Aim: To reduce mother-to-child transmission of HIV among breastfeeding women in a resource limited setting using combination maternal Antiretrovirals (ARVs)

- KiBS Regimens: Triple ARVs from 34 wks gest. to 6 mo. pp.
  - Jul 03-05: All pregnant women: Combivir + Nevirapine
  - Beginning July 2005 in response to Nevirapine toxicity warning:
    - CD4 >250  Combivir +Nelfinavir (NFV)
    - CD4<250  Combivir + Nevirapine (unchanged)
WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY

HEPATOTOXICITY:

Severe, life-threatening, and in some cases fatal hepatotoxicity . . . has been reported in patients treated with nevirapine . . . Female gender and higher CD4+ cell counts at initiation of therapy place patients at increased risk; women with CD4+ cell counts greater than 250 cells/mm^3, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk.
KiBS Schedule of Visits

• Enrollment at 33 wks & ARVs initiated at 34 wks gestation

• Antenatally: Routine antenatal care, assessment of adverse events and CD4, Hb, LFTs & Viral load performed every 2 wks

• Postnatally (Infant): Single dose NVP within 72 hours after birth, evaluations at delivery, 2,6 & 14 wks; & 6,9,12,18 and 24 mo

• Postnatally (Maternal): Evaluations at: delivery, 2,6 & 14 wks; 6,9,12,15,18, and 24 mo
  – Each visit: CD4, Hb, LFTs, Viral load performed
Serious Adverse Effects

• Defined by National Institute of Health/Division of AIDS (NIH DAIDS) Toxicity Tables (version 1.0 Dec 2004)

• Trial criteria for stopping Nevirapine was:
  – Persistent nevirapine-attributable Grade 3 or 4 toxicity
  – Rash -Grade 2B or higher
  – Hepatotoxicity:
    • Grade 1 with clinical symptoms of hepatic toxicity or evidence of hypersensitivity reaction
    • Grade 2
    • Clinical hepatitis
KiBS Major findings

• HIV-transmission rates at birth, 6 weeks, and 6, 12, and 24 months were 2.5%, 4.2%, 5.0%, 5.7%, and 7.0%, respectively.

• Cumulative HIV-transmission or death rate at 24 months was 15.7% (95% CI 12.7%–19.4%).

• KiBS showed that a maternal triple-antiretroviral regimen from late pregnancy through 6 mo of breastfeeding for PMTCT is safe and feasible in a resource-limited setting.
Outcomes for this analysis

• **Primary**
  – Severe Hepatotoxicity defined as:
    • Grade 3/Severe (ALT elevation 5.0 – 9.99 x ULN) or
    • Grade 4/life threatening (> 10.0 x ULN) toxicity.
    • Upper limit of normal (ULN) for ALT was 42 U/L
  – Rash-Associated Hepatotoxicity (rash with ≥ grade 2 hepatotoxicity as long as the two were diagnosed at same study visit)

• **Secondary:**
  – Severe Rash defined as:
    • Grade 3 or 4 rash
    • Grade 2 rash with urticaria, systemic symptoms or evidence of progression to grade 3 rash

All adverse events were graded using NIH DAIDS toxicity tables (version 1.0, Dec 2004)
Analysis performed using SAS software (version 9.1)
Results: Maternal ART initiation in KiBS

522 HIV-infected pregnant women

First antiretroviral period: July 2003 – January 2005
n = 254

CD4 ≥ 250 cells/μL
n = 195
ART regimen
Nevirapine = 195
Nelfinavir = 0

CD4 < 250 cells/μL
n = 59
ART regimen
Nevirapine = 59
Nelfinavir = 0

Analysis #1 – Table 2
(CD4 ≥ 250 vs < 250 cells/μL)

Analysis #2
(nevirapine vs. nelfinavir)

Second antiretroviral period: July 2005 – November 2006
n = 268

CD4 ≥ 250 cells/μL
n = 208
ART regimen
Nevirapine = 207
Nelfinavir = 5*

CD4 < 250 cells/μL
n = 60
ART regimen
Nevirapine = 55
Nelfinavir = 5*

* These 5 women had hepatitis B virus co-infection
Table 1: Hepatotoxicity and Rash outcomes

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>First Enrollment Period*</th>
<th>Second Enrollment Period*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4 &lt; 250 cells/uL n= 59</td>
<td>CD4 ≥ 250 cells/uL n= 195</td>
</tr>
<tr>
<td>Severe hepatotoxicity (grade 3 or 4 ALT elevation)</td>
<td>2 (3%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Any hepatotoxicity (grade 2 – 4 ALT elevation)</td>
<td>6 (10%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>Rash-associated hepatotoxicity (rash with grade 2 – 4 ALT elevation)</td>
<td>1 (2%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Severe rash (with or without hepatotoxicity)</td>
<td>4 (7%)</td>
<td>12 (6%)</td>
</tr>
</tbody>
</table>
Table 2: Associations with severe Hepatotoxicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe Hepatotoxicity</th>
<th>No Severe Hepatotoxicity</th>
<th>Adjusted* Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=11 (4%)</td>
<td>n=243 (96%)</td>
<td></td>
</tr>
<tr>
<td>CD4 &lt; 250 cells/mL</td>
<td>2 (3%)</td>
<td>57 (97%)</td>
<td>ref</td>
</tr>
<tr>
<td>CD4 ≥ 250 cells/mL</td>
<td>9 (5%)</td>
<td>186 (95%)</td>
<td>1.6 (0.4 – 6.0)</td>
</tr>
<tr>
<td>BMI &gt; 20 kg/m²</td>
<td>9 (4%)</td>
<td>227 (96%)</td>
<td>ref</td>
</tr>
<tr>
<td>BMI ≤ 20 kg/m²</td>
<td>2 (11%)</td>
<td>16 (89%)</td>
<td>6.5 (1.3 – 31.8)</td>
</tr>
<tr>
<td>Preceding rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No severe rash</td>
<td>6 (3%)</td>
<td>232 (97%)</td>
<td>ref</td>
</tr>
<tr>
<td>Severe rash</td>
<td>5 (31%)</td>
<td>11 (69%)</td>
<td>17.3 (5.2 – 58.1)</td>
</tr>
</tbody>
</table>
Results summary

• Among women who initiated NVP at any CD4, baseline CD4 ≥ 250 cells/ul was not associated with:
  – Severe hepatotoxicity (4.6% vs. 3.4%; aRR = 1.6; p = 0.52) or
  – Rash associated hepatotoxicity (4.1% vs. 1.7%; RR = 2.4; p = 0.69)

• Among women with a CD4 ≥ 250, those who initiated NVP had higher rates of the primary outcomes compared with those who initiated NFV (Table 1);
  – Severe hepatotoxicity (5% vs. 1%; p=0.03)
  – Rash associated hepatotoxicity (4% vs.0%; p=0.003)

• These events were managed with single drug substitution to Nelfinavir (NFV) and no toxicity event resulted in fulminant hepatotoxicity or death
Limitations

- Relatively small, sample size to detect rare events which limited our ability to assess risk
- Incomplete data of Hepatitis B and Hepatitis C co-infection
- This analysis is retrospective and was not part of the original study objectives
Conclusions

- Severe hepatotoxicity, rash associated hepatotoxicity, and severe rash occurred in 4-6% of HIV-infected pregnant Kenyan women after initiating therapy with nevirapine-based triple antiretroviral prophylaxis but risk for these outcomes was not predicted by a CD4 cell count $>250$ cells/ul.

- Our data support the continued use of NVP-based ART in women with a CD4 $\geq 250$ cells/ul when safer options are unavailable.

- Routine, scheduled monitoring for rash and ALT elevations may have improved clinical outcomes and should be considered for pregnant women receiving NVP-based ART.
Acknowledgements

KiBS Participants
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Thank you!

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.