Adverse effects of ARVs in pregnancy – prevention of mother to child transmission (PMTCT)
ARVs in pregnancy

Panel presentation

Dr Linda Morfeldt – The EU/US policy
Dr Lizzy Tabane – PMTCT in SA
Dr Karen Cohen – resistance issues in perinatal ART
Dr Rajen N. Misra–The view of the SA Status
The EU/US policy on ART in pregnancy

ART associated adverse events in pregnancy

- Suboptimal efficacy
- Resistance development
- Drug toxicity in child a/o mother
Basic facts

• 800 000 children a year acquire HIV-infection from their mother
The EU/US policy on ART in pregnancy

Basic facts

• 15 – 25 % of children of HIV-infected women risk being infected at birth
The EU/US policy on ART in pregnancy

Indications for ART

• Necessary for the mother herself
• Prevention of HIV transmission to the child
The EU/US policy on ART in pregnancy

Drugs NOT to use!

• Teratogenic: Efavirenz, zalcitabine, hydroxyurea
• Perhaps teratogenic: Newly marketed drugs
• Hyperbilirubinaemia in child: Indinavir during 3rd trimester
Drugs to use with CAUTION

• Stavudine and didansine

Because symptoms of lactic acidosis may easily be mistaken for GI-symptoms of pregnancy
The EU/US policy on ART in pregnancy

Guidelines – when to treat/not to treat

- ART naive woman > 350 CD4 – MTCT prophylaxis during 3rd trimester

- Women already on a successful combination ART most often continue therapy throughout the entire pregnancy
The EU/US policy on ART in pregnancy

MTCT prophylaxis to **ALL** women

- 3-drug combination ART during 3rd trimester – including zidovudine
- To mother at delivery: i.v. Zidovudine until baby is born
- To the child, from 8-12 hours of age: Zidovudine p.o. for 4 weeks
The EU/US policy on ART in pregnancy

Important for successful prophylaxis

• Undetectable viral levels in plasma = HIV-RNA < 50 cc/ml
Breast feeding

- Women are strongly recommended NOT to - and the vast majority don’t.
The EU/US policy on ART in pregnancy

Caesarian section

- With 3-drug combination ART in PMTCT, caesarian section plays a minor role in risk reduction and has been abandoned as a routine procedure in many places, both in US and EU
The EU/US policy on ART in pregnancy

### Incidence of MTCT in Sweden

<table>
<thead>
<tr>
<th>Period</th>
<th>Cases</th>
<th>Total</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985-1993</td>
<td>22/84</td>
<td>26.0%</td>
<td></td>
</tr>
<tr>
<td>1994-1998</td>
<td>5/86</td>
<td>5.8%</td>
<td></td>
</tr>
<tr>
<td>1999-2002</td>
<td>1/112</td>
<td>0.9%</td>
<td></td>
</tr>
</tbody>
</table>
Toxicity problems with present drug regimens

• Zidovudine – anaemia, mother and child
The EU/US policy on ART in pregnancy

Birth defects of NRTIs?

• Zidovudine – no increase has been noticed

Ref.

Birth defects of PIs?

- In 626 of 1200 pregnancies reported to the ”Pregnancy Registry” there was foetal exposure to PI during the first trimester.
- No increase in the incidence of congenital birth defects could be seen.
Long term adverse effects of ART in the child?

Very little is known – long term follow up also of the non-HIV-infected is of great importance
CONCLUSION

In spite of lack of knowledge about potential late onset toxicities in the child, the benefit-risk balance of the present prophylaxis for MTCT of HIV is clearly positive
ARVs in pregnancy

Panel presentation

Dr Linda Morfeldt – The EU/US policy

Dr Lizzy Tabane – PMTCT in SA

Dr Karen Cohen – resistance issues in perinatal ART

Dr Rajen N. Misra–The view of the SA Status
ARVs in pregnancy

Panel presentation

Dr Linda Morfeldt – The EU/US policy
Dr Lizzy Tabane – PMTCT in SA

Dr Karen Cohen – resistance issues in perinatal ART

Dr Rajen N. Misra–The view of the SA Status
What did we know and when did we know it?
Perinatal HIV Clinical Trial Results

- **1994 U.S. AZT Trial (ACTG 076)**
  - 67% reduction in transmission

- **1998 Thai Bangkok short AP/IP AZT trial**
  - 50% reduction in transmission

- **1998 Cote d'Ivoire short AP/IP AZT trials**
  - 37% reduction in transmission (breastfeeding)

- **1999 PETRA AZT/3TC trial (6 wk results)**
  - 50% reduction with longest arm.
  - 38% reduction with the IP/PP arm

- **1999 Uganda 2-dose IP/PP NVP trial (HIVNET 012)**
  - 47% reduction in transmission (breastfeeding)

- **2000 Thai Long vs short AZT regimens**
  - 4% TR in LL (non BF)

- **2002 Cote d'Ivoire DITRAME +**
  - 6.2% TR with AZT & IP/PP NVP

- **2004: PHPT <2% AZT + NVP**

- **1998 Cote d'Ivoire short AP/IP AZT trials**
  - 50% reduction in transmission

- **1999 PETRA AZT/3TC trial (6 wk results)**
  - 50% reduction with longest arm.
  - 38% reduction with the IP/PP arm
Nevirapine for MTCT - background

- Rapidly absorbed and widely distributed in the body
- Crosses the placenta
- Long half life
- Efficacious (~50%) in PMTCT following single doses
- Low genetic barrier to resistance. Single amino acid change confers high level resistance
Potential Selection of NVP Resistant Viruses

- Onset of Labor
- Delivery
- Postpartum
- Replication of NVP Resistant Viruses
- How long does NVP last?

Tim Cressey, PHPT, Bangkok 2004
Acquisition of Antiretroviral Resistance in Mothers Following Antiretroviral Prophylaxis

% with detectable resistance

- NVP
- 3TC
- AZT
Persistence of nevirapine resistance mutations 6 months following single dose nevirapine

Lynn Morris, Neil Martinson, Candice Pillay, Daya Moodley, Claudia Chezzi, Pumla Lupondwana, Schene Beyroo, Matschediso Ntsala, Sarah Cohen, Adrian Puren, John Sullivan, Glenda Gray and James McIntyre

National Institute for Communicable Diseases, Johannesburg, Perinatal HIV Research Unit, University of Witwatersrand
King Edward Hospital, Durban, South Africa
Conclusions

• Cohort of 623 women enrolled, 458 women (with 482 infants) tested at 7 weeks, Those with resistance retested at 6 months.

• Mothers - 38% resistance at 7 weeks
  – 36% of these still had resistance at 6 months - overall rate of 14% persistence at 6 months

• 42% of infants resistance at 7 weeks
  – 62% of these infants still had resistance at 6 months - overall rate of 26% persistence at 6 months

Morris et al, Bangkok 2004
Intrapartum Exposure to Nevirapine and Subsequent Maternal Responses to Nevirapine-Based Antiretroviral Therapy

Gonzague Jourdain, M.D., Nicole Ngo-Giang-Huong, Pharm.D., Ph.D., Sophie Le Coeur, M.D., Ph.D., Chureeratana Bowonwatanuwong, M.D., Pacharee Kantipong, M.D., Pranee Leechanachai, Ph.D., Surabhon Ariyadej, M.D., Prattana Leenasirimakul, M.D., Scott Hammer, M.D., and Marc Lallemant, M.D., for the Perinatal HIV Prevention Trial Group*

PHPT 2 (Perinatal HIV prevention trial)
PHPT 2 (Perinatal HIV prevention trial)

- 1844 women recruited into the study
  - AZT 28 weeks + nevirapine or placebo

- 269 of these women required ART (CD4<250)
  - Median interval between delivery and treatment initiation – 6 months
PHPT 2 (Perinatal HIV prevention trial)
T.O.P.S. (Treatment options preservation study)

Arm 1
- Mother: NVP x1
- Baby: NVP x1

Arm 2
- Mother: NVP x1
- Baby: NVP x1

Arm 3
- Mother: NVP x1
- Baby: NVP x1

McIntyre et al., 2004, Bangkok Conference. Late-breaker
## Interim Results from T.O.P.S.

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>N</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sdNVP</td>
<td>18</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>sdNVP + AZT/3TC x 4d</td>
<td>20</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>sdNVP + AZT/3TC x 7d</td>
<td>23</td>
<td>3 (13%)</td>
</tr>
</tbody>
</table>

- Coadministration of 4-7 days of AZT/3TC with single-dose NVP reduced incidence of NVP resistance
  - 9/18 (50%) vs 4/43 (9.3%); $P = .001$
- Transmission (preliminary data; not primary endpoint)
  - 4/68 infants intrauterine transmission
  - 1 peri/postnatal transmission (single-dose NVP without AZT/3TC)

McIntyre et al. Abstract LbOrB09.
Summary - risk/benefit

- Nevirapine alone
  - Easiest to implement programmatically
  - Resistance

- Combination AZT/NVP regimens- increased transmission reduction, still resistance problems
  - Additional safety concerns- anaemia

- Impact of resistance on future ART unclear- treating within 6 months with an NNRTI-based regimen seems to be less efficacious

- Interim data suggests that covering the nevirapine “tail” with AZT + 3TC may be helpful

- 3 drug ART
  - good prevention of MTCT
  - more complex
  - choice of drugs debated
ARVs in pregnancy

Panel presentation

Dr Linda Morfeldt – The EU/US policy
Dr Lizzy Tabane – PMTCT in SA
Dr Karen Cohen – resistance issues in perinatal ART
Dr Rajen N. Misra–The view of the SA Status
Prevention of Mother To Child Transmission (PMTCT) S.A.
• Media Release 12 July 2004
• MCC no longer recommends the use of monotherapy in preventing mother to child transmission of HIV
• The South African Medicines Control Council reconsidered the merits of nevirapine when used as monotherapy to reduce the risk of transmission of HIV from mother to child during labour. Council believes that the risk-benefit profile of nevirapine monotherapy has changed and therefore no longer recommends its use for the prevention of mother to child transmission (PMTCT) of HIV.
MEDIA RELEASE MCC

• At a recent meeting of the MCC on 2nd July 2004, Council recommended that nevirapine and zidovudine (azt), previously approved for monotherapy in PMTCT, only be used in combination therapy.

• The approval of nevirapine as monotherapy for this indication in April 2001 was conditional upon monitoring of resistance and its impact on efficacy.
In its deliberation the MCC considered the following:

i. Nevirapine leads to significant resistance in mothers and babies when used as monotherapy to reduce the risk of transmission of HIV from mother to child compared to a combination therapy.

ii. Recent studies conducted in South Africa, using nevirapine as a monotherapy for this purpose, show significant resistance of up to 50%.

iii. The clinical significance of these findings needs further investigation as the efficacy of future treatment options in mothers or babies who have nevirapine-resistant HIV may be compromised.

iv. A number of recent studies, including an expert consultation report of the World Health Organisation (February 2004), confirms the view of the MCC that nevirapine monotherapy is less efficacious than combination regimens.
MEDIA RELEASE MCC

• Council’s decision applies to all monotherapy interventions when used to reduce the risk of transmission of HIV from mother to child during labour. Council is of the view that combination therapy should be considered for this indication.

• The Department of Health has introduced a Comprehensive Plan for the Management, Care and Treatment of HIV and AIDS; which introduce ARV’s and the opportunity of combination therapy.
Ministers concluding remarks during the consultative meeting on resistance to nevirapine

• 1. The primary objective and outcome of the programme is to have healthy and HIV negative babies at 24 months when they are weaned

• 2. There must be better coordination of research and clinical trials which must involve the department, the MCC and the MRC.

• 3. We need to examine the impact of the PMTCT programme as a whole, since its inception in September 2001

• 4. We need to examine the financial and health systems implications of these results of resistance to nevirapine when considering other options
Ministers concluding remarks during the consultative meeting on resistance to nevirapine

- 5. The EDL Committee should start doing some work as part of the pharmaco-economic work that is part of their brief.
- 6. There is need to validate and peer review this work as all our decisions must be based on sound scientific evidence.
- 7. We need to diversify research and clinical trials to reflect all races and the demographic profile of our country and the committees need to look critically at this.
- 8. We need to tighten communication with stakeholders and the public.
Ministers concluding remarks during the consultative meeting on resistance to nevirapine

9. I will convene a meeting with the EDL committee, the MCC and the MRC to get a synthesis of the meaning of this information before I take it back to MinMec to decide on the action to be taken, if any.

10. Because of the inadequate size of the sample and the lack of peer review of these results at this stage, we obviously do not have sufficient information to recommend change to policy yet.

11. MinMec listened to the presentations made by the researchers. Questions of clarification were raised with the researchers. In the final analysis it was agreed the the PMTCT programme will be implemented in the current form until there is sufficient data and evidence to warrant a review of the current protocol.
Thank You

Rajen Misra
MbChB;D.For.Med;MFGP;M.ClinPharm
Director :Clinical Evaluations & Trials, MRA,NDOH