Toxicities Linked to ARVs

Non-Nucleoside Reverse Transcriptase Inhibitors (NNTRIs)

Protease Inhibitors (PIs)
Acknowledgements

sources of slide material

Published data
Lynne Moffenson
WHO – progress report 2009
DART study group
Targets for Antiretroviral Drugs in HIV Life Cycle

Reeves & Piefer, 2005
### NNRTIs

<table>
<thead>
<tr>
<th>Name</th>
<th>Originator Trade Name</th>
<th>Originator Company</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine *</td>
<td>Viramune</td>
<td>Boehringer Ingelheim</td>
<td>1996</td>
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<tr>
<td>Efavirenz *</td>
<td>Sustiva / Stocrin</td>
<td>BMS</td>
<td>1998</td>
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<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>Pharmacia, Agouron, Pfizer</td>
<td>1999</td>
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<tr>
<td>Etravirine</td>
<td>Intelence</td>
<td>Tibotec</td>
<td>2007</td>
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</tbody>
</table>
NNRTI Toxicity

Hypersensitivity reactions (all NNRTIs)
   (nevirapine > efavirenz > etravirine)
Hepatotoxicity (Nevirapine)
Neuropsychiatric side effects (Efavirenz)
Concern in women of child bearing age (Efavirenz)

Drug interactions & Resistance
## Nevirapine hypersensitivity

### Most commonly within 6 weeks of Tx

| Grade 1 & 2 rashes in 13.3% of patients |- (compared to 5.8% placebo)  
| Grade 3 & 4 rashes in 1.5% of patients |- (compared to 0.1% placebo)  
| Hepatitis in 4% (range 0% to 11.0%) |- (compared to 1.2% control patients)  
| - risk continues after 6 weeks |

↑ risk: Women (ART naïve & CD4 > 250) 
Men (CD4 > 400)

### Clinical

| Rash (mild – severe forms) + fever, muscle aches, fatigue ± hepatitis, hypotension, nephritis, pneumonitis |
| Hepatitis + fatigue, malaise, anorexia, nausea, .... jaundice, tender liver , ↑ liver |

### Lab: Elevated transaminases

### Management

Dose escalation  
Avoid in risk groups  
Pause or discontinue NVP depending on severity of reaction

### Safety Monitoring

Clinical  
Serum transaminases at baseline (?)  
Symptom driven serum transaminases
Occurrence of SARs in NORA study

- ABC (2.0%)
- NVP (4.7%)

Weeks from randomisation

Proportion SAR-free

DART Trial Team. TIMH 13 (1), 6-16
Efavirenz hypersensitivity

<table>
<thead>
<tr>
<th>Most common within the first 2 weeks</th>
<th>Clinical:</th>
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<tbody>
<tr>
<td><strong>Rash:</strong> new onset rash in 26% of patients (compared to 17% in control groups) median onset within 11 days ↑ rates in children (46% in one study)</td>
<td>itchy skin rash (mild – moderate) ± fever, acute hepatitis and pneumonia</td>
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<tr>
<td><strong>Hepatic enzyme elevation – no symptoms</strong> 3% of patients in clinical trials ↑ to 8% in Hep B or C co-infection</td>
<td>Lab:</td>
</tr>
<tr>
<td></td>
<td>Elevation of hepatic transaminases</td>
</tr>
<tr>
<td>Rash not always treatment limiting - often resolves with continuing EFV Discontinuation rate for rash in clinical trials = 1.7%</td>
<td>Safety monitoring</td>
</tr>
<tr>
<td></td>
<td>Liver enzymes especially recommended in hepatitis</td>
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</tbody>
</table>
Other therapeutic issues with NNRTIs

**PK interaction**
- rifamycins; oral contraceptives

**Low genetic barrier to resistance**

**Prolonged plasma half life (Nevirapine)**
- nevirapine “tail cover” or “staggered stop”
Rate of decay of NVP plasma levels in Ugandan patients after discontinuing NVP containing cART

19 subjects analysed in a PK study
- 5 male, 14 female; median 35 years; median CD4 341 cells/mm³
All had received 52 weeks of prior cART: Combivir + Nevirapine
1 patient had substituted stavudine for zidovudine at week 16 - anaemia

After 1 week: 15/18 (83%) had detectable plasma NVP
- 11 (61%) were above 100 ng/ml
- but only 5 (28%) were >200 ng/ml

By 2 weeks, only 5/19 had detectable NVP

<table>
<thead>
<tr>
<th>200 ng/ml</th>
<th>100 ng/ml</th>
<th>20 ng/ml</th>
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<tbody>
<tr>
<td>7.6 days</td>
<td>9.3 days</td>
<td>13.2 days</td>
</tr>
<tr>
<td>IQR 7.0 – 10.1</td>
<td>IQR 12.3 – 18.4</td>
<td>12.3 – 18.4</td>
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</table>

Data suggest that the optimum period of staggered therapy for patients who discontinue NVP (at steady state) is 7–10 days when covered with NRTIs or with currently licensed (ritonavir-boosted) protease inhibitors.

Kikaire B et al. AIDS 2007, Vol 21 No 6
Issues with Efavirenz in women of reproductive age

Neural tube defects in neonates
Meningomyelocele
Efavirenz Drug Label Information – Pregnancy Category D

Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving SUSTIVA. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of SUSTIVA is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies in pregnant women. SUSTIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

As of July 2008, the Antiretroviral Pregnancy Registry has received prospective reports of 526 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (507 pregnancies). Birth defects occurred in 13 of 407 live births (first-trimester exposure) and 2 of 37 live births (second/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been five retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of SUSTIVA has not been established, similar defects have been observed in preclinical studies of efavirenz.
Issues with Efavirenz and Reproductive-Aged Women

- Highest risk to use is in women who become pregnant while receiving EFV; contraception/family planning critical part of care of HIV-infected women.

- APR prospective and retrospective data indicate possible signal for neural tube defects with 1st trimester EFV exposure, with defects similar to animal data.

- Overall birth defects not increased with EFV, but incidence of neural tube defects is only ~0.1%.

- With available 1st trimester data (~500 patients) can likely rule out 10-fold increase in risk of neural tube defects with EFV (eg, incidence of 1%).

- To rule out lesser increase in risk, need several thousand 1st trimester exposures.

- Based on available data, if risk is present, seems would be likely <1% with 1st trimester EFV exposure.
Issues with Efavirenz and Reproductive-Aged Women

• The risk/benefit of EFV use in reproductive-aged women varies depending on reason for use and availability of alternatives (e.g., benefits of use for treatment vs other alternative available if used solely for PMTCT; benefit of use for treatment with co-existing TB).

• It is probable that EFV can safely be used in pregnant women 2\textsuperscript{nd}-3\textsuperscript{rd} trimester (and probably late 1\textsuperscript{st} trimester). The real concern is use in non-pregnant women who conceive while on EFV.

• Women need to better understand the risks (eg, that they are relatively low) to be able to make educated decisions regarding starting EFV-based treatment.
Efavirenz

Neuropsychiatric side effects
Commonly described in patients taking Efavirenz

- Insomnia
- Dizziness
- Lightheadedness
- Nervousness
- Irritability
- Impaired concentration
- Abnormal / vivid dreams
- Hallucinations

- Last a median of 13 days
- Usually decrease within 2 – 4 weeks

Also reported in patients taking Efavirenz

- Severe depression
- Suicidal ideation
- Aggressive behaviour
- Paranoid reactions
- Manic reactions

But also correlated with:
- Injecting drug use
- History of psychiatric disorders
- Previous psychiatric medication

→ Association with Efavirenz ???

Take EFV on an empty stomach / at bedtime
Eliminate or diminish alcohol
Care with psychoactive drugs
<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
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<tr>
<td>Saquinavir</td>
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<tr>
<td>Indinavir</td>
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<tr>
<td>Ritonavir</td>
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<tr>
<td>Nelfinavir</td>
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<tr>
<td>Lopinavir + Ritonavir</td>
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<tr>
<td>Atazanavir *</td>
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<tr>
<td>Darunavir *</td>
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* Revised Guidelines
Class wide side effects of PIs

**associated with some ↑ risk**

- GI disturbances
- Hepatotoxicity
- Metabolic changes
  - ↑ tryglycerides
  - ↑ cholesterol
- Insulin resistance
- Metabolic changes
- ↑ tryglycerides
- ↑ cholesterol
- hyperglycaemia
- lypodystrophy
- Insulin resistance
- CV Risk
- bleeding disorders (haemophilia)

**4 most common**

- GI disturbances (nausea, vomiting, diarrhoea)
- Lipid abnormalities
- Hyperglycaemia
- Lipoaccumulation

*Atazanavir is comparatively less likely to cause GI disturbances or metabolic abnormalities*
## Protease inhibitors

### Management of ADRs

- **Diarrhoea** often early and transient
  - Symptomatic treatment
- **Metabolic Changes**
  - Life style and risk changes
  - Statins
- **Hepatotoxicity**
  - Other risk factors – e.g Hepatitis
  - Symptom directed treatment

### Safety monitoring

- Baseline serum lipid profiles
- Baseline blood glucose (?)
- Baseline liver enzymes
- Symptom driven testing
Other therapeutic issue with PIs

PK interaction with Rifamycins

↑ Access to Rifabutin
Estimated HIV prevalence (%) among people newly infected with TB, 2007
Incidence of TB during ART in cohort of 404 patients
National ART Programme - Senegal

1820 personnes-années
Médiane de suivi = 73 mois

42 cas
Médiane durée de suivi TB = 19 mois
Taux moyen = 2.3/100 P-A
Test tendance RR = 0,26 (p < 10^{-4})
TB / HIV co-treatment

• Timing of ART / TB treatment

• Common toxicities
  – Neuropathy (INH – NRTIs)
  – Hepatic Toxicity (INH - Rifampicin – NNRTIs - PIs)

• Pharmacokinetic interactions
  – Rifamycins – PIs / NNRTIs
Hepatitis Virus Infections
Hepatitis B

Estimated 370-400 million with chronic HBV globally
  – co-infection with HIV common / common epidemiology

Limited access to diagnostic testing for HBV
  – true prevalence may be underestimated

Effects
  – mortality from liver disease
  – susceptibility to hepatic toxicity
  – differential diagnosis of drug induced hepatic toxicity

Selection & maintenance of ARVs
  – Tenofovir, FTC & 3TC are active against HBV
Hepatitis C

Estimated 180 million globally with chronic HBCV infection

Special accelerated risk in people who use injected drugs
- 92% of injecting drug users in India

Hepatitis C virus 10 x as infectious as HIV and infection is often asymptomatic

Co-infection: HIV increases morbidity /mortality from severe HCV liver disease

Pharmacologic interactions: Ribavirin vs Abacavir/ Atazanavir/Zidovudine/ ddl

Challenges
- Awareness & Prevention programmes
- Access to testing & Access to drugs
- Data to inform guidance on co-treatment