Definitions of AE related to ARVs: What are we talking about?
What we don’t know

What we know about safety from trials

The case for ensuring pharmacovigilance

Evans and Waller, MCA 2002
Enthusiasm for a treatment as a function of time since first entering clinical testing

Enthusiasm

Time since initiation of phase I trials (years)
Disentangling a drug effect

Drug(s) A

Non-drug factors

Risk of outcome "X"

Drug(s) B

Non-drug factors
ART naïve patients: Mean lactate values at 48 weeks (Δ from BL)

Kumar P, et al. 9th CROI 2002; Abs 33
Time to first severe drug-related AE

Saquinavir/r

Indinavir/r

P = 0.0002 (log rank test)
Time to first severe drug-related AE

Proportion of subjects without a grade 3/4 AE

Saquinavir/r

Indinavir/r

Diarrhoea (ritonavir)

P = 0.0002 (log rank test)

MaxCmin1: Dragsted et al, JID, 20
**Time to first severe drug-related AE**

- **Saquinavir/r**
- **Indinavir/r**

**Proportion of subjects without a grade 3/4 AE**

- **Retinoid-like toxicity** + kidney stones

**Time (weeks)**

- 0
- 4
- 12
- 24
- 36
- 48

**P = 0.0002 (log rank test)**

MaxCmin1: Dragsted et al, JID, 2021
Stavudine but not abacavir associated with depletion of limb fat

Changes in limb fat by dexa scan

<table>
<thead>
<tr>
<th>Weeks</th>
<th>d4T/3TC/EFV (n=32)</th>
<th>ABC/3TC/EFV (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>48</td>
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<tr>
<td>96</td>
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</table>

Grams

- d4T/3TC/EFV: +686 (p=0.001) to +913 (p<0.001)
- ABC/3TC/EFV: -1164 to -1579

Nº pts: 57, 57, 57

* 95% CI

ITT= intent-to-treat analysis

FIRST: Shlay et al. JAIDS 2005;38:147
Abacavir hypersensitivity reaction (HSR) and HLA haplotype

- Presence of HSR and HLA-B*5701 status:
  - B*5701 pos: 14/18 (78%)
  - B*5701 neg: 4/167 (2%)
- Reduction of prevalence of HSR by denying patients with HLA-B*5701, HLA-DR7, HLA-DQ3 abacavir:
  - 9% to 2.5%

Mallal et al, Lancet 2002
Time to Onset of *Asymptomatic* ALT or AST >5 x ULN on NVP in Controlled Trials

**0-12 Months**

<table>
<thead>
<tr>
<th>Months of Treatment</th>
<th>NVP (n = 1731) Probability (%)</th>
<th>Control (n = 1912) Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>2</td>
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</tr>
<tr>
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<tr>
<td>10</td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td></td>
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</table>

**3-12 Months**

<table>
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<tr>
<th>Months of Treatment</th>
<th>NVP (n = 1731) Probability (%)</th>
<th>Control (n = 1912) Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>4</td>
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<td>10</td>
<td></td>
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<tr>
<td>12</td>
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</tbody>
</table>

Stern JO et al. XIV IAS Conference, 2002
The "conundrum" of using cART

- Allow persons to get older
  - De-masking other HIV-associated disease processes
    - eg. HBV, HCV
  - Allow the normal aging process to manifest itself clinically
    - dementia, cancers, CVD, hypertension, diabetes, body shape changes, etc
  - Exacerbate AEs of cART that interacts with the normal aging process
Incidence of DM and exposure to stavudine

Exposure to stavudine

D:A:D study: deWit et al. Diabetes Care 200
Relative Rate of MI according to PI Exposure – Adjusted for NNRTI

Adjusted RR* per year of PI: 1.16 [1.10-1.23]

*: Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body-mass index, NNRTI exposure

D:A:D study: Friis-Møller et al, NEJM 200
NRTIs and risk of myocardial infarction
cumulative and current/recent use

- Zidovudine
- Didanosine
- Stavudine
- Lamivudine
- Abacavir

Adjusted relative rate of myocardial infarction (95% CI)

Cumulative (l/yr, adjusted for recent) vs Recent (adjusted for cumulative)

D:A:D: Sabin et al, 15th CROI 200
Disentangling a drug effect

Risk of outcome "X"

Drug(s) A

Drug(s) B

Non-drug factors

Non-drug factors
Deaths in D:A:D
Multivariable relationships with death rate
Latest CD4 count

All-cause mortality

Liver-related mortality

Relationship between combination antiretroviral therapy and liver-related deaths: benefits and potential harm

Calendar time trends*

Risk per year of exposure to ART in recent years**

Univariable
- All CD4 cell strata
- CD4 cells above 200/µL
- CD4 cells below 200/µL

Multivariable
- Nadir CD4 cells
- Latest CD4 cells

** EuroSIDA study: Mocroft et al, AIDS 2005
Glomerular filtration rate (GFR) over time by baseline GFR: Impaired baseline GFR improved

Mean GFR change (ml/min/1.73m²)

Weeks

Baseline GFR
- grade 2
- grade 1
- grade 0

Glomerular filtration rate (GFR) over time by baseline GFR:
Impaired baseline GFR improved

DART: Reid et al. XVI IAC (2006). Abst. THAB0105
Risk of major CVD events in SMART: intermittent (DC) vs continuous (VS) ART

% with a major CVD event

Relative hazard:
1.57 (1.00 – 2.46)
\( p = 0.05 \)

SMART/CVD-lipid: Phillips et al, AVT 2008
Subgroup in SMART either naïve or not currently on ART: early versus deferred

Serious Non-AIDS

Hazard Ratio = 7.05 (95% CI: 1.58–31.5) p = 0.01

<table>
<thead>
<tr>
<th>Months</th>
<th>Def. ART (DC)</th>
<th>Imm. ART (VS)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>228</td>
<td>249</td>
</tr>
<tr>
<td>4</td>
<td>189</td>
<td>210</td>
</tr>
<tr>
<td>8</td>
<td>159</td>
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<td>128</td>
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<td>27</td>
<td>44</td>
</tr>
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No. at risk
Def. ART 228 189 159 128 96 73 59 36 27 24
Imm. ART 249 210 180 145 125 106 80 58 44 36

# of events
Deferred ART (DC) 12
Immediate ART (VS) 2

Serious non-AIDS events:
complication of using ART but also from untreated HIV

- Decompensated liver disease
- End-stage renal disease
- Cardiovascular disease
- Non-AIDS defining cancers
Disentangling a drug effect
Adjusted incidence rate ratios of new AIDS/death, AIDS, HIV or non-HIV death after starting HAART

Adjusted for Age, AIDS, prior ARV treatment, HAART regimen started, Hepatitis C status, date started HAART and both CD4 and viral load as time-updated variables

EuroSIDA: Mocroft et al, AIDS 2005
Disentangling a drug effect

Risk of outcome "X"

Drug(s) A

Drug(s) B

Non-drug factors

Non-drug factors
Young age makes adverse influence on risk of myocardial infarction from using PI trivial

* Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD

D:A:D study: Friis-Møller et al, NEJM, 2
Laboratory based AEs
Laboratory defined adverse effect endpoints: grading

Time since starting drug X

ALT

ULN

1

2

3
Time to Onset of Asymptomatic ALT or AST >5 x ULN on NVP in Controlled Trials

0-12 Months

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3-12 Months

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<td>Control</td>
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Stern JO et al. XIV IAS Conference, 2002
Laboratory defined adverse effect endpoints: already abnormal (e.g. viral hepatitis)
Laboratory defined adverse effect endpoints:
timing of measurement

ALT

Time since starting drug X
Laboratory defined adverse effect endpoints: clinical detectable consequences

ALT

Time since starting drug X

Level of clinical detection "Toxic hepatitis"
Critical issues in pharmacovigilance

- Prioritize collection of well defined events
  - Clear & simple case definition
  - Easy to ascertain & clinically important (to patient, his/her provider and treatment programme)
    - Severe clinical disease (fatal or non-fatal)
    - Reasons for treatment switch
    - (laboratory defined endpoints)
  - Keep track of emergence relate to starting drug (early vs late)
- Have procedures in place to capture emerging problems
  - Spontaneous reporting (UMC)
  - Causes of death
Serious non-AIDS events:
complication of using ART but also from untreated HIV

- Decompensated liver disease
  - Liver (pre)coma or transplantation
- End-stage renal disease
  - Permanent dialysis or kidney transplantation
- Non-AIDS defining cancers
  - Pathology reports or clinical obvious
- Cardiovascular disease
  - Dundee classification (WHO Monica)
Changes to a first combination ART regimen

- Off all antiretrovirals
- Any change to original HAART regimen, remaining on treatment
- On original cART regimen

N: 1198, 1108, 1015, 931, 822, 665, 505, 381, 286

EuroSIDA: Mocroft et al, AIDS Research Hum Retro, 2005
Quality versus quantity

Quality of data

Volume of questions/work required
Summary

- ARVs = millions of life-years gained
- All ARV induces AEs
- All AEs are not induced by ARVs
- PV system
  - Events: Clinical important, easy to define & ascertain
    - Keep it simple but consistent and harmonised
  - Keep things in perspective
    - Frequency
    - Benefits