ARV pharmacovigilance: moving beyond spontaneous reporting

Karen Cohen

Division of Clinical Pharmacology
UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

Outline

- Limitations of ADR data from clinical trials
- Local example
  - stavudine toxicity
  - data that led to policy change
- Challenges of WHO-recommended approaches in resource limited settings
- Other potential sources of safety data
- Programmatic role for spontaneous reporting

Why programmatic pharmacovigilance?

- Information from clinical trials does not always predict effectiveness and safety in public health programmes
- We need to gather relevant evidence to guide public policy
- The study method chosen should suit the question we are trying to answer

Limitations of existing ARV ADR data

- Short follow up
  - Studies are typically 48 weeks
  - Need long term safety data
- Different population studied
  - Bulk of data from white men in Europe & USA
- Selected populations
  - Exclude comorbidities, coinfections

- Need SA population ADR data
- Need ***incidence*** data

Local example...

A high incidence of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis in HIV-infected patients in a South African context

Rosemary Geddes, Stephen Knight, Mahomed Yunus Suleman Moosa, Anand Reddi, Kerry Uebel, Henry Sunpath

19 (95% CI 9, 29) cases per 1,000 person-years treatment

McCord SAMJ 2006;96:722

A High Incidence of Lactic Acidosis and Symptomatic Hyperlactatemia in Women Receiving Highly Active Antiretroviral Therapy in Soweto, South Africa

M. G. Bolhaar and A. S. Karstaedt

16 cases per 1000 patient-years (female patients)
Chris Hani Baragwanath
CID 2007;45:254

- Higher incidence than previously reported
- Women, particularly obese, at risk

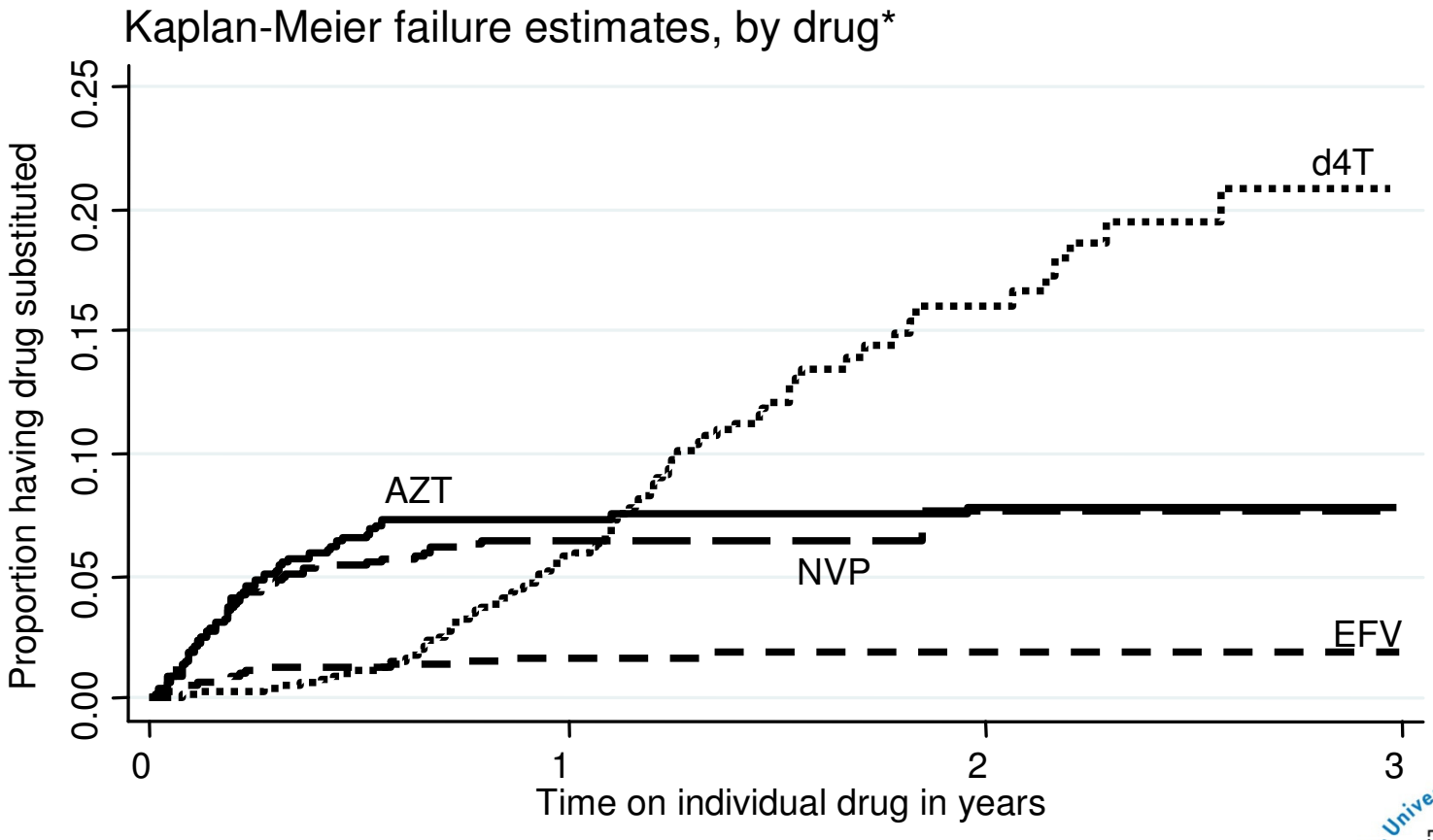
Antiviral Therapy 12:753–760

Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort

Andrew Boulle[1,], Catherine Orrell[2], Richard Kaplan[3], Gilles Van Cutsem[4], Matthew McNally[3], Katherine Hilderbrand[1,4], Landon Myer[1], Matthias Egger[5], David Coetzee[1,3], Gary Maartens[6] and Robin Wood[2] for the International Epidemiological Databases to Evaluate Aids in Southern Africa (IeDEASA) Collaboration*

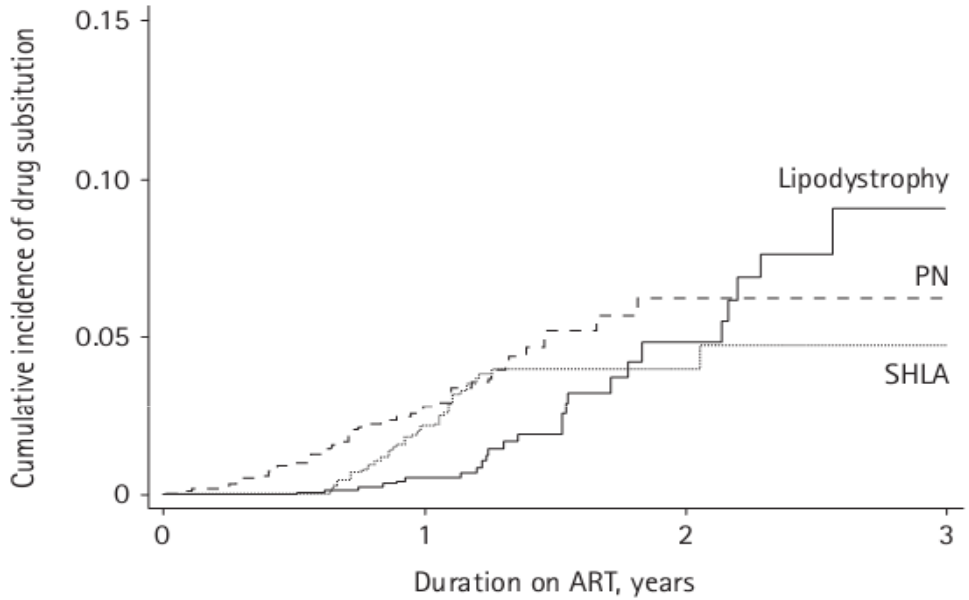
Single ARV substitutions as a marker of toxicity

ARV substitutions for toxicity - first line cART in Cape Town



Boulle A. Antivir Ther 2007;12:753

Reasons for switching d4T



Risk factors

↑lactate	women, obesity
lipodystrophy	women, obesity
peripheral neuropathy	age, advanced disease

Boulle A. Antivir Ther 2007;12:753

Concomitant TB

Tuberculosis Treatment and Risk of Stavudine Substitution in First-Line Antiretroviral Therapy

Daniel J. Westreich,[1,2] Ian Sanne,[2] Mhairi Maskew,[2] Babatyi Malope-Kgokong,[2] Francesca Conradie,[2] Pappie Majuba,[2] Michele Jonsson Funk,[1] Jay S. Kaufman,[1] Annelies Van Rie,[1,2] and Patrick MacPhail[2]

- Themba Lethu Cohort
- Patients with concurrent TB more likely to switch from d4T
- Neuropathy commonest reason for switch

Clin Infect Dis 2009;48:1617

SA response to d4T toxicity reports

- Meta-analysis: lower doses equally effective & less toxic
- Interventions 2007:
  - lower dose d4T
  - point of care lactate meters
  - educate HCWs
  - avoid d4T in obesity

Hill A Expert Opin Pharmacother 2007;8:679
Perez EH Int J Infect Dis. 2008; 553

Impact of changes

Maskew *et al. Journal of the International AIDS Society* 2012, **15**:13
http://www.jiasociety.org/content/15/1/13

JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH **Open Access**

Effectiveness and safety of 30 mg versus 40 mg stavudine regimens: a cohort study among HIV-infected adults initiating HAART in South Africa

Mhairi Maskew[1,2,7*], Daniel Westreich[3], Matthew P Fox[2,4,5], Thapelo Maotoe[6] and Ian M Sanne[1,2,6]

d4T 40 mg vs 30 mg:

Neuropathy	OR 3.1 (95%CI 1.9, 5.3)
Lipoatrophy	OR 11.8 (95%CI 3.2, 43.8)
↑lactate	OR 8.4 (95%CI 3.8, 18.3)
Virologic failure	OR 1.6 (95% CI 0.9, 3.0)

Schutz *et al. AIDS Research and Therapy* 2010, **7**:13
http://www.aidsrestherapy.com/content/7/1/13

AIDS RESEARCH AND THERAPY

RESEARCH Open Access

Reduced referral and case fatality rates for severe symptomatic hyperlactataemia in a South African public sector antiretroviral programme: a retrospective observational study

Charlotte Schutz*[1,2], Andrew Boulle[3], Dave Stead[1,2], Kevin Rebe[1,2], Meg Osler[3] and Graeme Meintjes[1,2,4]

Jooste, Cape Town

Referral rate	2005	20.4/1000py; 2008 1.3/1000py
Acidosis	2003	67% of cases; 2008 13%
Case fatality rate	2004	33%; 2008 0%

d4T spontaneous reporting

- Many reports of ↑lactate received by NADEMC
  - Not informative because no denominator
- Many more reported from provinces
  - Not informative because no denominator
- Spontaneous reporting is valuable to: “Identify signals of previously unidentified adverse reactions to medicines” (WHO)
  - Hyperlactataemia was in package insert

Cohort event monitoring: WHO recommended approach

Two basic requirements:

- establishing a cohort of patients for each medicine and/or medicine combination
- recording adverse events for patients in the cohort(s) for a defined period.

“a cohort with approximately 20 000 patients for each of the main medicine combinations may be needed.”

Setting up cohorts purely for adverse event monitoring is expensive and resource intensive

We have existing cohorts and cohort collaborations

-these can be built on and strengthened.

Other potential sources of safety data

- Records from managed care systems, medical insurance in private sector
- Electronic clinical records

Spontaneous reporting in public health programmes

- Targeted spontaneous reporting (e.g. W Cape)
  - Elicit reports of specific, severe adverse events
  - Increase awareness of ADRs

Mehta 2007
9th Int Conference ADRs and Lipodystrophy in HIV

- Reporting as a facility level clinical governance tool
  - Inclusion in morbidity and mortality reviews
  - Identify preventable harms

- Feedback to prescribers is critical

- Evaluation needed

Conclusions

- Existing cohorts and cohort collaborations should be strengthened to provide ADR incidence data
- Explore electronic managed care databases and clinical records as source of local ADR information
- Encouraging ADR reporting at facility level may be useful as a clinical governance tool and to guide HCW training