Pharmacovigilance to inform policy in South Africa

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South African context

- Largest ARV treatment programme in the world
  - 3.7 million people on ART
- High rates of concomitant HIV and TB treatment
- Growing burden of non-communicable diseases

The need to for ongoing, locally relevant pharmacovigilance

Pharmacovigilance: "Detection, assessment, understanding and prevention of short and long term adverse effects of medicines"

- Clinical studies short
- Co-morbidities, concomitant medicines, genetic variability
- Risk versus benefit:
  - early treatment initiation
  - prevention
- Focus on **serious adverse drug reactions (ADRs)**
  - Resulting in hospitalisation and death
  - Treatment limiting ADRs- drug substitutions

Pharmacovigilance methods

- Hospital-based surveys
  - ADRs resulting in admission
  - ADRs resulting in death
  - ADRS presenting to emergency units
- Sentinel Cohorts
- Spontaneous reporting
  - Targeted
  - ADR queries from HCW

Hospital-based ADR surveys

Hospital-based surveillance

- 4 South African hospitals in 2013
- 8.4% medical admissions in SA due to ADR (164/1951)
  (Worldwide 5.3% of admissions)
  - ART, TB treatment and/or co-trimoxazole implicated in 34%
  - 45% of ADRs were preventable
- In 16% of in-hospital deaths ADR implicated (56/357)
  - Most commonly implicated: tenofovir, rifampicin, co-trimoxazole
- ADR contributed to death of 2.9% of medical admissions
  (Europe, UK, USA 0.05 to 0.32% of admissions)

Mouton et al 2015 *Br J Clin Pharmacol* 80(4); Mouton et al 2016 *Medicine* 95(9);Kongkaew Ann Pharmacother. 2008; 42: 1017 ; Juntti-Patinen et al 2002 *Eur J Clin Pharmacol* 58; Davies et al 2009 *PloS ONE* 4:e4439; Pirmohamed et al 2004 *BMJ* 329 ; Lazarou et al 1998 *JAMA* 279: 1200

ADRs resulting in admission

(1951 admissions)

	Renal impairment (n=24)	Hypoglycaemia (n=22)	Liver injury (n=20)	Haemorrhage (n=19)
Median age (yrs)	41	61	35	67
HIV infection	**71%**	5%	**90%**	16%
Commonly implicated drugs	**tenofovir (46%)** ACE-I (38%)	insulin (64%) sulfonylureas(50%)	**TB drugs (60%) efavirenz (20%)**	warfarin (68%) NSAIDs (32%)
Mortality	**46%**	18%	**35%**	16%
Median stay	9 days	6 days	10 days	6 days
Preventable	46%	77%	15%	58%

- ADRs in HIV patients- high mortality, prolonged admission
- Importance of looking at all drug exposures

Mouton et al Medicine 2016, 95 e3437

ADR-related adult admissions

TABLE 3. Generalized Estimation Equation Model of Associations With Adverse Drug Reaction-Related Admission (n = 1711 Admissions in 1669 Patients), Excluding Patients Documented to Have Had Zero Drug Exposure Before Admission

	n	Crude OR (95% CI)	Crude Wald *P*	Adjusted* OR (95% CI)	Adjusted* Wald *P*
Sex					
Male (referent)	724	1.00		1.00	
Female	987	1.54 (1.09–2.17)	0.01	1.51 (1.06–2.14)	0.02
Age†	1711	1.04 (0.95–1.13)	0.39	1.02 (0.91–1.14)	0.73
HIV and ART					
HIV-negative/unknown (referent)	1211	1.00		1.00	
HIV-infected, not on ART	186	0.85 (0.46–1.55)	0.59	1.15 (0.59–2.22)	0.68
HIV-infected, on ART	314	2.11 (1.46–3.04)	<0.001	1.92 (1.17–3.147)	0.009
Antituberculosis therapy					
Not on ATT (referent)	1524	1.00		1.00	
On ATT	187	2.05 (1.33–3.17)	0.001	1.22 (0.73–2.06)	0.45
Drug count‡	1711	1.20 (1.15–1.25)	<0.001	1.14 (1.09–1.20)	<0.001
Comorbidity score§	1711	1.29 (1.15–1.45)	<0.001	1.23 (1.07–1.41)	0.004

ART = antiretroviral therapy, ATT = antituberculosis therapy, CI = confidence interval, OR = odds ratio.
*Adjusted for other factors in the model.
†Included in the model as a continuous variable. The reported odds ratio is for each 10-year increment.
‡Included in the model as a continuous variable. The reported odds ratio is for each additional drug.
§Included in the model as a continuous variable. The reported odds ratio is for each additional point on the modified Charlson comorbidity score.

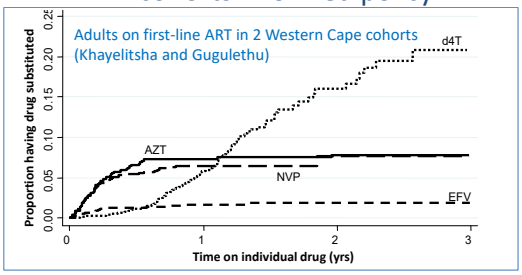
Mouton et al Medicine 2016, 95 e3437

Sentinel cohorts

Sentinel cohorts

- Valuable resource for ADR surveillance
  - Requires fewer resources than setting up cohorts solely for toxicity surveillance (Cohort event monitoring)
- Robust denominator data
  - Can determine incidence of treatment-limiting ADRs
  - Can identify risk factors

Data on stavudine toxicity from sentinel cohorts informed policy

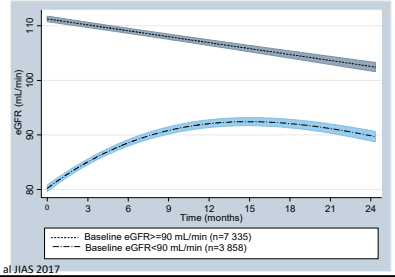


2007: 30 mg all weights, point of care lactate meters, avoidance in obesity, education HCW
Dramatic decrease referral rates, severity at admission, mortality

Boulle et al 2007 *Antivir Ther*;12:753; Schutz 2010 *AIDS Res Ther*, 7:13

Tenofovir and renal function

- Tenofovir (TDF)- modest decline in eGFR over time
- Clinically significant kidney dysfunction uncommon:
  - higher risk with TDF compared to other ARVs
- 15156 adults commencing TDF-Themba Lethu and Khayelitsha
  - 34.5% commenced ART with CKD eGFR<90 mL/min



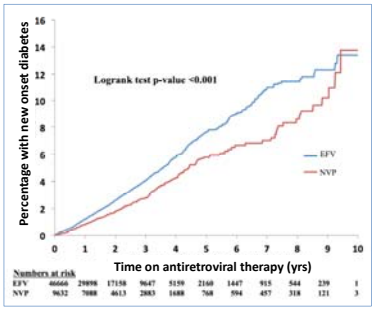
De Waal et al JIAS 2017

Tenofovir and renal function

- 1.9% of patients develop eGFR<30mL/min
- **Risk factors:**
  - age, advanced disease (CD4<200) , baseline eGFR<60 mL/min, weight<60 kg, protease inhibitor.
- **Implication for guidelines:**
  - Monitor patients with risk factors
  - Tenofovir cessation in acutely ill patients

De Waal et al JIAS 2017; 20: 1, De Waal et al SAMJ 2016 : 106(4) 369

ARV exposure and diabetes



Diabetes incidence: 13.24 per 1000 PYFU

Associations with diabetes:
- Older age
- Higher BMI
- Efavirenz, zidovudine and stavudine exposure
- Other diabetogenic meds

Karamchand *et al* 2016 *Medicine* 95(9) e2844

Spontaneous reporting

Spontaneous reporting

- Does not give prevalence/incidence
- Signal detection
  - e.g Interstitial nephritis lopinavir/r
- ADRs that trouble HCWs
  - Guide HCW training and clinical support
  - Nurse-driven services
- Need accessible and responsive systems
  - Telephonic and online reporting in addition to paper-based
  - Prompt, individualised feedback and clinical support

Chugley et al 2015 *AIDS* 29:503. Njuguna et al 2015 *Drug Saf* doi:10.1007/s40264-015-0359-8

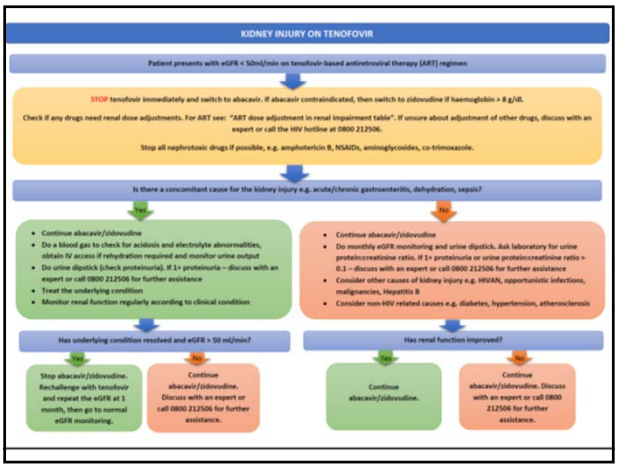
Western Cape ARV and TB pharmacovigilance programme

- Started in 2005, collaboration:
  - Western Cape Provincial Health Department
  - Medicines Information Centre (University of Cape Town)
- Targeted spontaneous reporting system
  - Serious ADR reporting form with case definitions for specific events
  - Follow up by pharmacist
  - Panel for causality assessment of deaths
- Goals:
  - Increase drug safety awareness
  - Identify signals
  - Inform policy and training
- Feedback
  - Information to reporter
  - Reports
  - newsletters

ADRs Reported to HIV & TB hotline

- SA National HIV & TB HCW hotline most frequent ADRs:
  - Rash (efavirenz)
  - Liver injury (tuberculosis treatment and efavirenz)
  - Kidney injury (tenofovir)
  - Gynaecomastia (efavirenz)
  - Neuropsychiatric (efavirenz)

Njuguna et al 2015 *Drug Saf* doi:10.1007/s40264-015-0359-8



Conclusions

- Pattern of serious ADRs in SA reflects colliding epidemics of infectious and non-communicable diseases
- Large burden of serious ADRs due to treatment of HIV and/or TB infection
  - ADRs due to ARVs AND concomitant medicines
- Resource limited settings
  - Create systems that can address multiple questions
- Repeated surveys to see changing patterns

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- AfA
- Patients
- Health care workers who report

How can we help you?

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