Adverse drug reactions (AEs) and Monitoring of MDR and XDR Treatment (Oct 2012; UCT)

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Conflict of interest: none

Overview

- AEs to 2nd line drugs

1. How frequent are AEs
2. How do AEs differ by HIV status
3. Do AEs impact on outcomes

- Monitoring of MDR and XDR treatment

1. What parameters can be used to assess response to treatment and what to monitor?

2. Frequency of AEs- MDR-TB

- Important: impact compliance and may cause serious morbidity or death
- AEs to second line drugs more frequent than 1st line drugs
- Very common:

  73.3% in Tomsk, Russia

  69,2% in Istanbul Turkey

  Suspension of any drug:

  Peru (14%),

  Multicentric study= 30%;

  Turkey 55%.

Torun T, IJTLD, 2005

Shin SS, IJTLD, 2007

Nathanson E, IJTLD, 2004

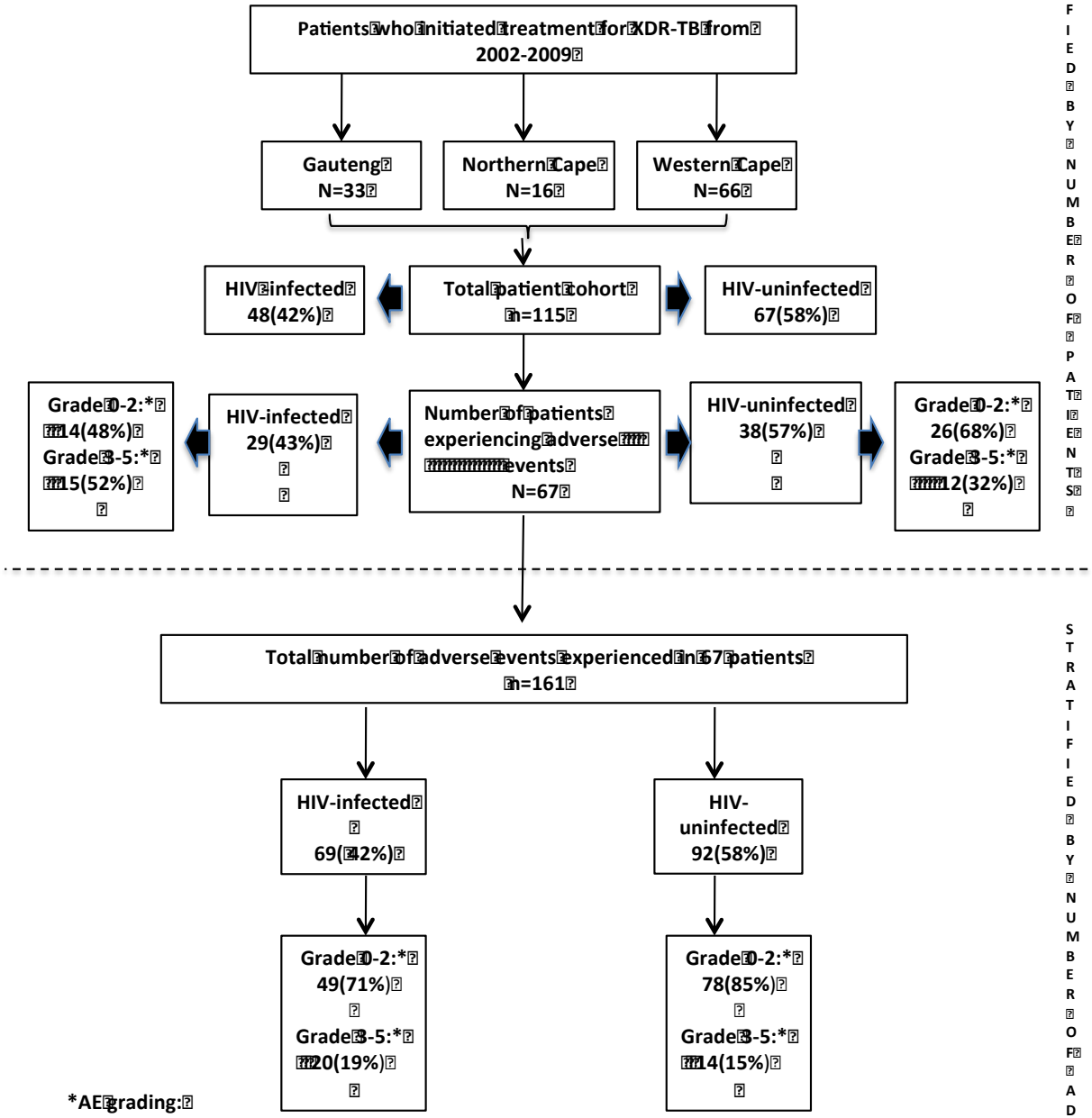
Frequency of AEs- XDR-TB

- Study submiited- 115 patients with XDR-TB had AEs (Shean K and Pietersen E)
- AE's were graded according to severity [mild to moderate (grade 1-2) and severe (grade 3-5: drug stopped, life-threatening or death)].
- 161 AEs were experienced by 67/115 (58%) patients
- 17/67(25%) patients required no intervention;

  24/67(35%) required modification of treatment,

  the offending drug was discontinued in 19/67(28%) of patients;

  reactions were life-threatening in 2/67(3.0%) and 6(9.0%) died.


Patients who initiated treatment for XDR-TB from 2002-2009
Gauteng N=33
Northern Cape N=16
Western Cape N=66
Total patient cohort n=115
HIV-infected 48(42%)
HIV-uninfected 67(58%)
Number of patients experiencing adverse events N=67
HIV-infected 29(43%)
Grade 0-2:* 14(48%)
Grade 3-5:* 15(52%)
HIV-uninfected 38(57%)
Grade 0-2:* 26(68%)
Grade 3-5:* 12(32%)
STRATIFIED BY NUMBER OF PATIENTS
Total number of adverse events experienced in 67 patients n=161
HIV-infected 69(42%)
HIV-uninfected 92(58%)
Grade 0-2:* 49(71%)
Grade 3-5:* 20(19%)
Grade 0-2:* 78(85%)
Grade 3-5:* 14(15%)
STRATIFIED BY NUMBER OF ADRS
*AE grading:
0-2 Mild to moderate
3-5 Severe

2. Do AEs impact on outcomes (n= 115 from 3 Provinces)

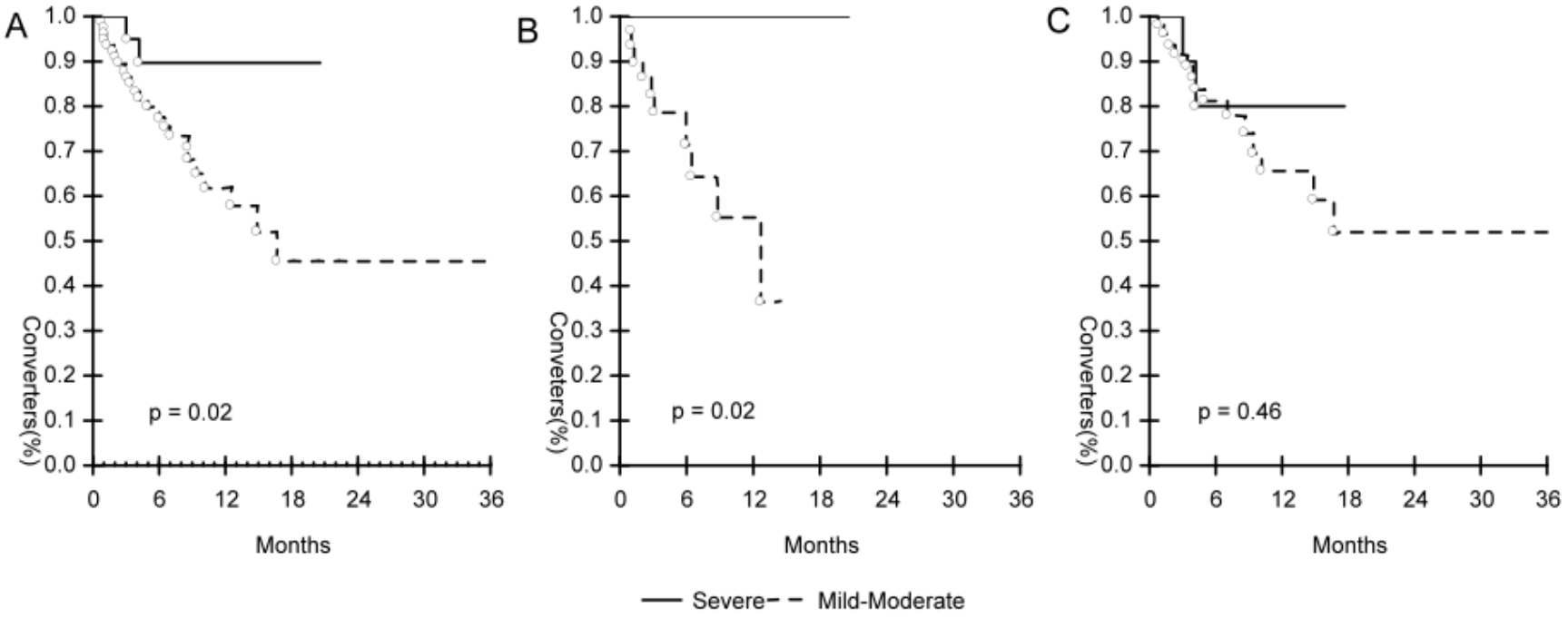
- Russian MDR-TB study- no impact on outcomes

Shin SS, IJTLD, 2007

- Those with severe AEs failed to culture-convert

2/28(7.1%) vs. 24/87(27.5%); p=0.02

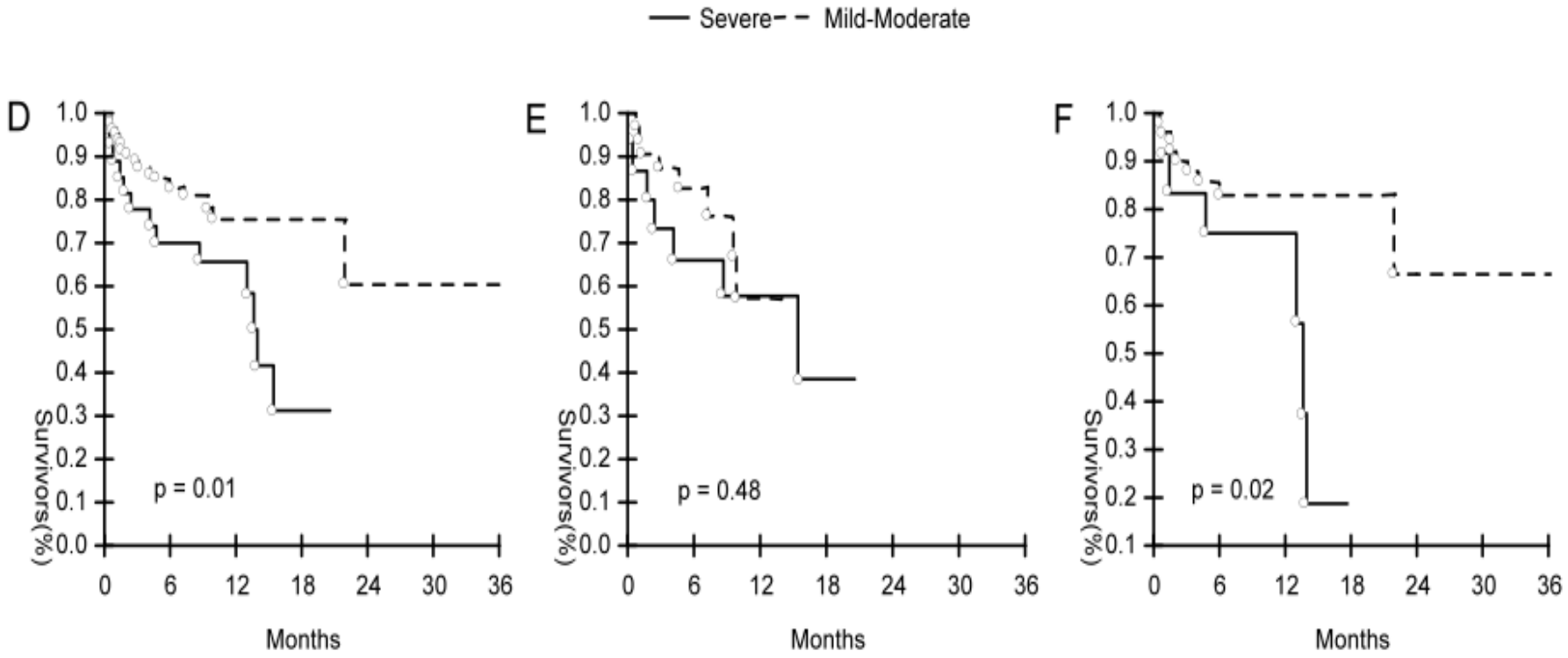
All HIV infected HIV-uninfected



All

HIV infected

HIV-uninfected



- Mortality higher in those with severe AEs

13/28(46%) vs. 17/87(19.5%); p=0.004

Univariate and multivariate analysis of factors associated with mortality in 115 patients with XDR-TB

Factor	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95%CI)	P-value	Hazard Ratio (95%CI)	P-value
Adverse event				
Grade 3-5	2.39(1.14-4.97)	0.02	1.43(0.67-3.05)	0.35
Grade 0-2	1		1	
Previous MDR TB				
Yes	3.27(1.32-8.03)	0.01	2.91(1.16-7.35)	0.02
No	1		1	
6 month culture conversion				
Yes	0.09(0.01-0.63)	0.02	0.10(0.01-0.747)	0.03
No	1		1	

- No specific parameter predicted of who would get ADR
- Those with severe ADRs more likely to have had previous MDR-TB

2. ADRs by HIV status

- HIV-infected patients were more likely to die from a severe ADR compared to uninfected patients [5/6(83.3%) vs. 1/6(16.6%), p=0.01)]
- The type, frequency and severity of AEs was similar in HIV-infected and uninfected patients

Profile of drugs withdrawn

N (%)	Drug dosages used	No. of patients who were prescribed a specific drug as part of XDR-TB regimen n=115(%)	Withdrawn due to side effects N-=34(%)
Amikacin	15-20mg/kg/daily*	3(2.6)	1/34(2.9)
Ethionamide	15-20mg/kg/daily	66(57.3)	7/34(20.6)
Capreomycin	15-20mg/kg/daily*	104(90.4)	15/34(44.1)
Para-aminosalicylic acid	8g (400mg BD)	101(87.8)	8/34(23.5)
Terizadone/Cycloserine	500-750mg daily	104(90.4)	2/34(5.9)
Amoxicillin-clavulanate	375mg	65(56.5)	2/34(5.9)

Capreomycin

- Capreomycin was withdrawn in 15/104(14%) of patients
- Comprised 44% of total drug withdrawals- median of 73 days
- 6/13(41%) deaths in the severe group were ascribable to capreomycin-related AEs (renal failure in five patients and hypokalemia in one)- median of 14 days

Conclusion of AEs in XDR-TB

- Drug-associated AEs occur commonly with XDR-TB treatment, are often severe, frequently interrupt therapy, and negatively impact on culture conversion outcomes.
- Less toxic drugs and standardised strategies (including pre-treatment counselling, early detection, monitoring, and follow-up) are needed to optimally manage patients with XDR-TB

Aminoglycosides

- Can cause hypoK+, hypoCa++ and hypoMg++ (PCT cell affected- reversible)
- Clinical renal failure is rare

- Ototoxicity occurs in less than 5% of patients (not reversible and cumulative dose important)
- D/T oxidative damage and apoptosis of cochlear hair cells/ neurons and mitochondrial dysfunction- genetic mutation predisposes

May occur rapidly and within hours (high frequency)

- Vestibular cell toxicity is reversible

Aminoglycosides

- ? asprin protective

- Need to decide on risk benefit ratio in the individual patients when deciding to stop AG because of renal impairment or ototoxicity (can also reduce the dose or give 3 to 5 times per week).

Can also check levels

- Should perform audiology tests monthly whilst on AG

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- Arthralgia- NSAIDS, anti-gout agents do not help

Cycloserine/ teridizone

- Seizures- well controlled epilepsy not a C/I,
  Exclude other causes of seizures by CT scan, LP etc, start anti-convulsant, reduce dose, pyridoxine, stop drug (FQ)

- Peripheral N (AG, C, INH, E, FQ)- increase dose of pyridoxine to 200mg, exclude other causes, use NSAIDS, TAD and gabapentin for pain, reduce dose or stop drug

- Psychosis: stop drug, use anti-psychotics if necessary, exclude other causes

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- PAS- use with food is fine for absorbtion, reduce dose, anti-emetics

2. Monitoring of ADRs

- Baseline: exclude neuropathy,
  perform eye test (ethambutol),
  HIV, pregnancy test, check LFT,
  creatinine, audiometry if using kanamycin,
  TFT (ethionamide, PAS)

2. What to monitor?

- Capreomycin- Cr, Mg, K 2X monthly for 3 months then monthly

  AG- Cr monthly, audiometry monthly

  ethionamide or PAS- TST 6 monthly,

  LFTS- when clinically indicated or every 3 months if on PZA or pre-existing hepatitis

2. What parameters can be used to assess response to treatment?

- Symptoms: fever, night sweats, appetite, cough
  (all improved by 1 to 2 months)
- Signs: weight
- Blood tests: haemoglobin
- Imaging: chest x ray
  (lags behind clinical improvement; no data; 3 to 6 months should see significant improvement)

2. What parameters can be used to assess response to treatment and what to monitor?

- Monthly weight, smear and culture (if still culture positive after 4 to 6 months get 2nd line DST), neuropathy check
- CXR- baseline, 4 months, 6 months, 9 months and end Rx

Summary

- ADRs with second line drugs common
- Impact on outcomes
- Capreomycin must be monitored carefully
- Treat symptomatically, stop drug if required
- Consider risk benefit ratio
- Careful monitoring and counseling required
- Watch for treatment failure and assess HIV status, compliance, consider alternative diagnosis, consider surgery, and then possible XDR-TB treatment (hetero-resistance)


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STOP
TB

Funding Agencies:

EUFP7

Discovery

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