Treatment of Extensively Drug Resistant Tuberculosis Among Patients with HIV Infection in South Africa

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Outline

1. XDR-TB in KwaZulu-Natal, South Africa
2. Treatment of XDR-TB in South African Patients with HIV Infection
3. Experience from Other South African Provinces
4. XDR-TB among South African Health Care Workers
5. Conclusions

Definition of XDR-TB

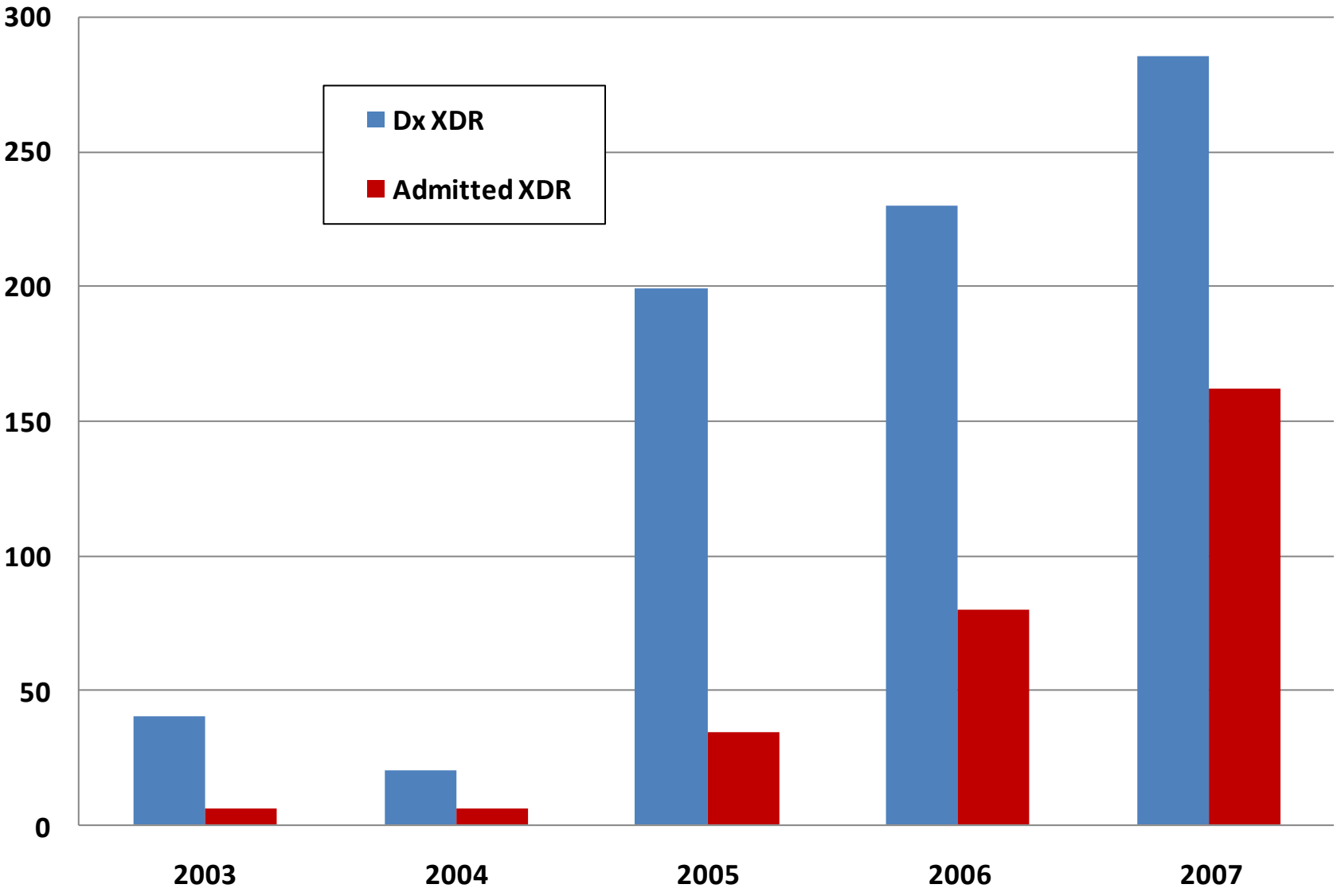
Extensively drug-resistant TB (XDR TB) defined as MDR TB (resistance to INH and RIF) plus any fluoroquinolone and at least one of the three injectable second-line drugs

2006 Tugela Ferry XDR-TB Outbreak

- 53 patients found to have XDR-TB
- 44 patients were tested for HIV; all were found to be infected.
- 51/53 died
- Median survival 16 days from time of sputum collection

Gandhi NR. *Lancet* . 2006

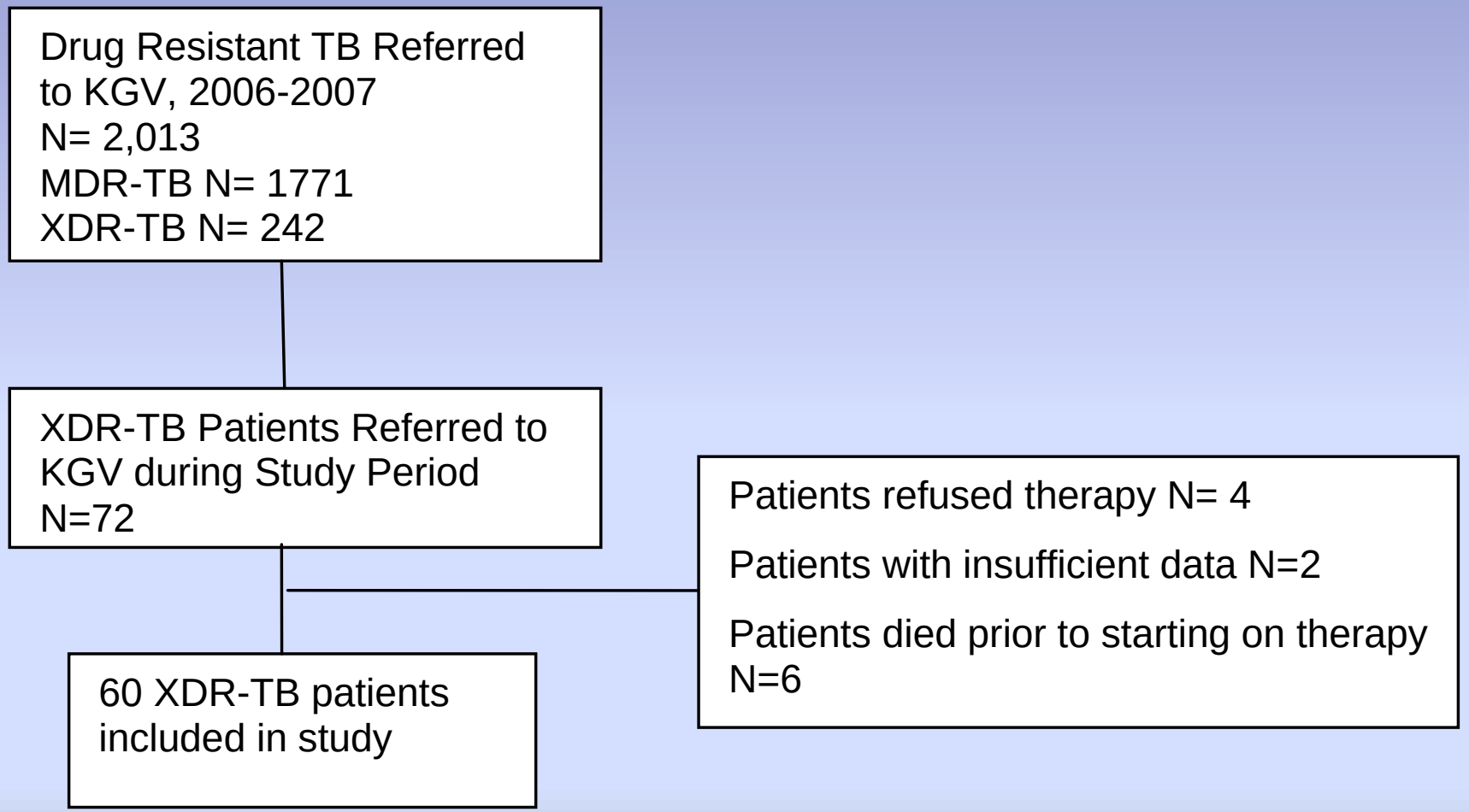
XDR-TB Patients Diagnosed in KZN, South Africa and Admitted with XDR-TB to King George Vth Hospital, Sydenham, KZN. 2003-2007



Methods

- King George V Hospital (KGVH)has been the only public regional MDR TB referral hospital in KZN.
- Capreomycin and PAS became available in KZN Nov. 2006.
- Retrospective cohort of all XDR-TB patients initiated on inpatient treatment at KGVH between December, 2006 and May, 2007.
- Eligible patients had XDR-TB, and agreed to second line tuberculosis treatment.
- Study was approved by Boston University IRB and the University of KwaZulu-Natal Biomedical Research Ethics Committee.

Flow diagram of XDR-TB patients eligible for analysis in study.



Results

- Patients were transferred in from **26** different hospitals or clinics representing **7/11 (64%)** health districts in the province.
- The most common addresses patients reported were Tugela Ferry **(25%),** Durban **(11%),** or Pietermaritzburg **(8%).**
- **16/60 (26%)** were transferred from Church of Scotland Hospital in Tugela Ferry.

Demographic characteristics of extensively drug resistant tuberculosis (XDR-TB) patients initiated on XDR-TB therapy during study period

		XDR-TB Patients (% total)
Sex	Male	26 (43)
Age (years)	Median Age (S.D.)	35.0 (11.6)
HIV Status	Positive Negative Unknown	43 (72) 12 5
CD4 Count (cells/mm^3)	Known Not Determined Mean CD4 Count (S.D.)	29 (48) 14 200.5 (127.4)
On HAART*	Yes No	21(35) 22
Previous TB Treatment	Yes No Unknown	42 (70) 11 7
Previous MDR-TB* Treatment	Yes No Unknown	22 (37) 28 10
Health Care Worker	Yes	3 (5)

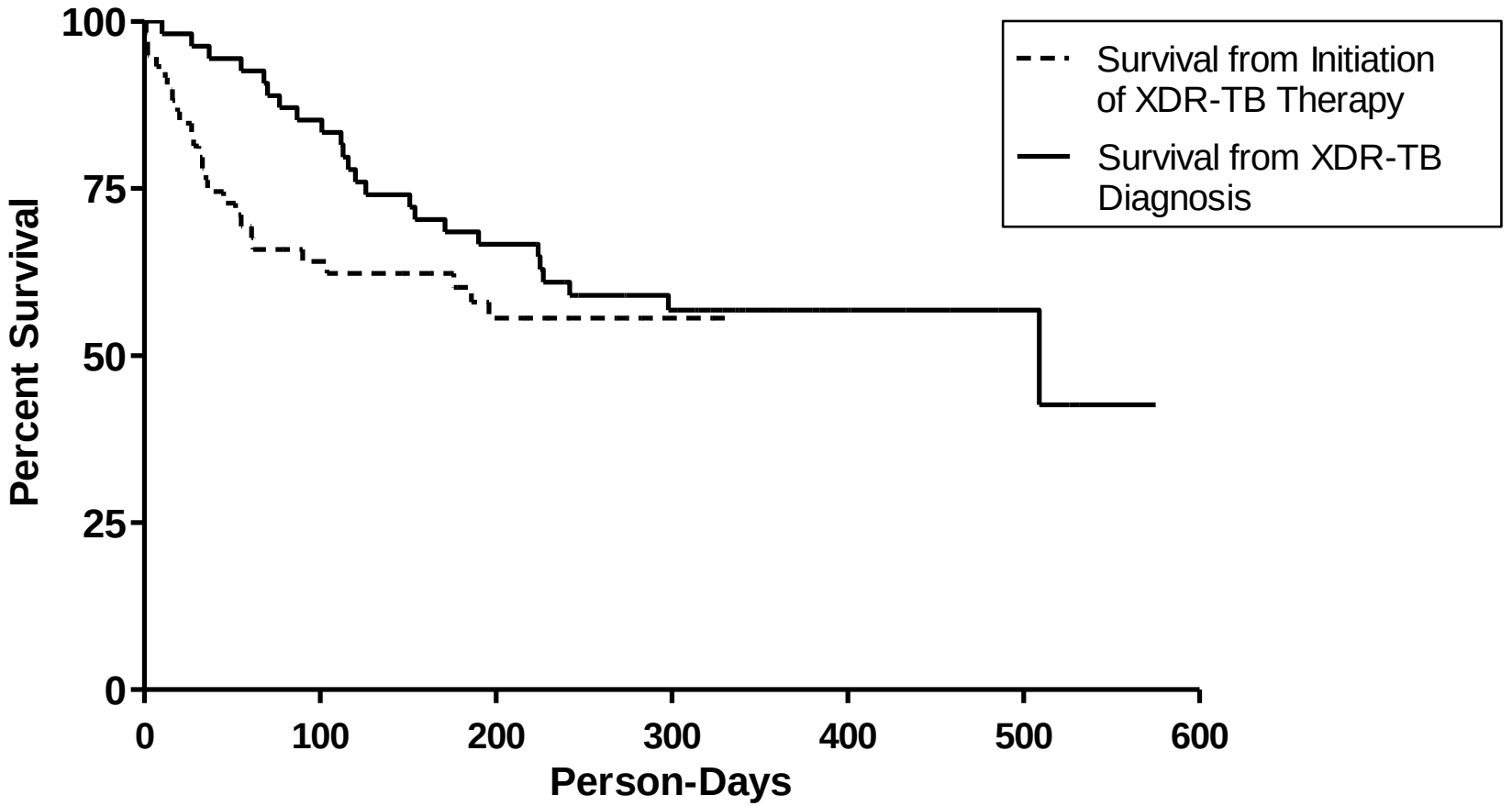
Univariate analysis of predictors of mortality in a treatment cohort of South African XDR-TB patients

		Deceased Number/total (%)	P value	Univariate Hazard Ratio (95% CI)
Sex	Female	13/25 (52)	0.36	0.69 (0.31-1.52)
Age (years)	50+	2/25 (8)	0.66	0.67 (0.11-4.00)
Previous TB Treatment	Yes	17/25 (68)	0.69	0.78 (0.23-2.67)
Previous MDR-TB Diagnosis	Yes	8/25 (32)	0.59	0.89 (0.34-2.32)
HIV Infected	Yes	18/23 (78)	0.90	0.96 (0.52-1.78)
CD4 count (cells/mm^3)	Less than 200	7/9 (78)	0.16	3.07 (0.64-14.79)
On HAART	Yes	8/25 (32)	0.75	0.87 (0.38-2.02)
Severe ADR*	Yes	6/18 (33)	0.94	0.94 (0.35-2.51)

Table 2.
Treatment outcomes in a cohort of South African patients with extensively drug resistant tuberculosis (XDR-TB)

Treatment Outcome	Number (%)
Default	6 (10)
Death	25 (42)
Culture Conversion	12 (20)
Continued Treatment	17 (27)
Median Duration of Follow Up from Initiation of Therapy (interquartile range)	183.5 (44-267)
Median Duration of Period Between XDR-TB Diagnosis and Initiation of Therapy (interquartile range)	83 (61-123)
Median Time to Culture Conversion (interquartile range)	90 (69-118)

Survival of XDR-TB Patients



Initiation of Therapy	**60**	**37**	**23**	**7**		
Date of Diagnosis	**54**	**46**	**36**	**26**	**8**	**4**

Probable* causes of death among XDR-TB patients started on anti-tuberculosis therapy from December 2006 through to October 2007.

Cause of Death	Number of Patients
Respiratory Arrest	8
Unable to Ascertain	7
Adverse Drug Reactions	4
Septic Shock	2
Progression of HIV Disease	2
Massive Hemoptysis	1
Acute Renal Failure	1

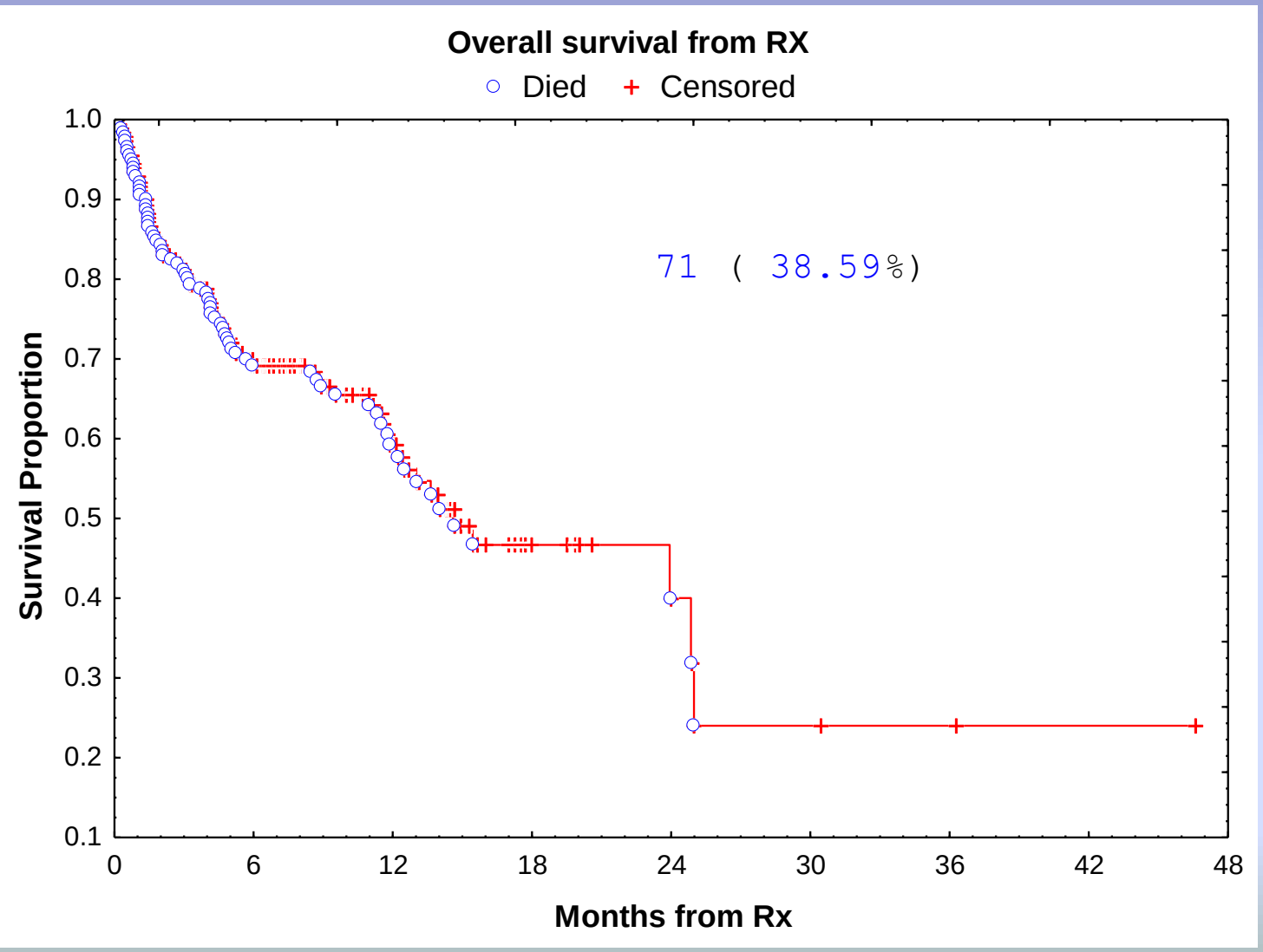
*Based on chart and laboratory review as well as discussion with treating physicians.

XDR-TB Treatment Results from Collaborators at University of Cape Town, South Africa.

- 224 patients diagnosed with XDR- TB from 3 designated treatment facilities (Western Cape, n= 115; Eastern Cape, n=70; Gauteng, n= 39)
- 90% prior TB treatment
- Median age 36 years
- 43% of patients were HIV co-infected
- HIV+ patients had a trend to poorer survival (p= 0.08) but culture converted at the same rate as HIV-ve patients.
- CD4 count not significantly associated with mortality

Dheda, K et al. *Unpublished Data.* Lung Infection and Immunity Unit, Dept of Medicine, UCT & IIDMM, UCT.

XDR-TB Results from Cape Town, South Africa



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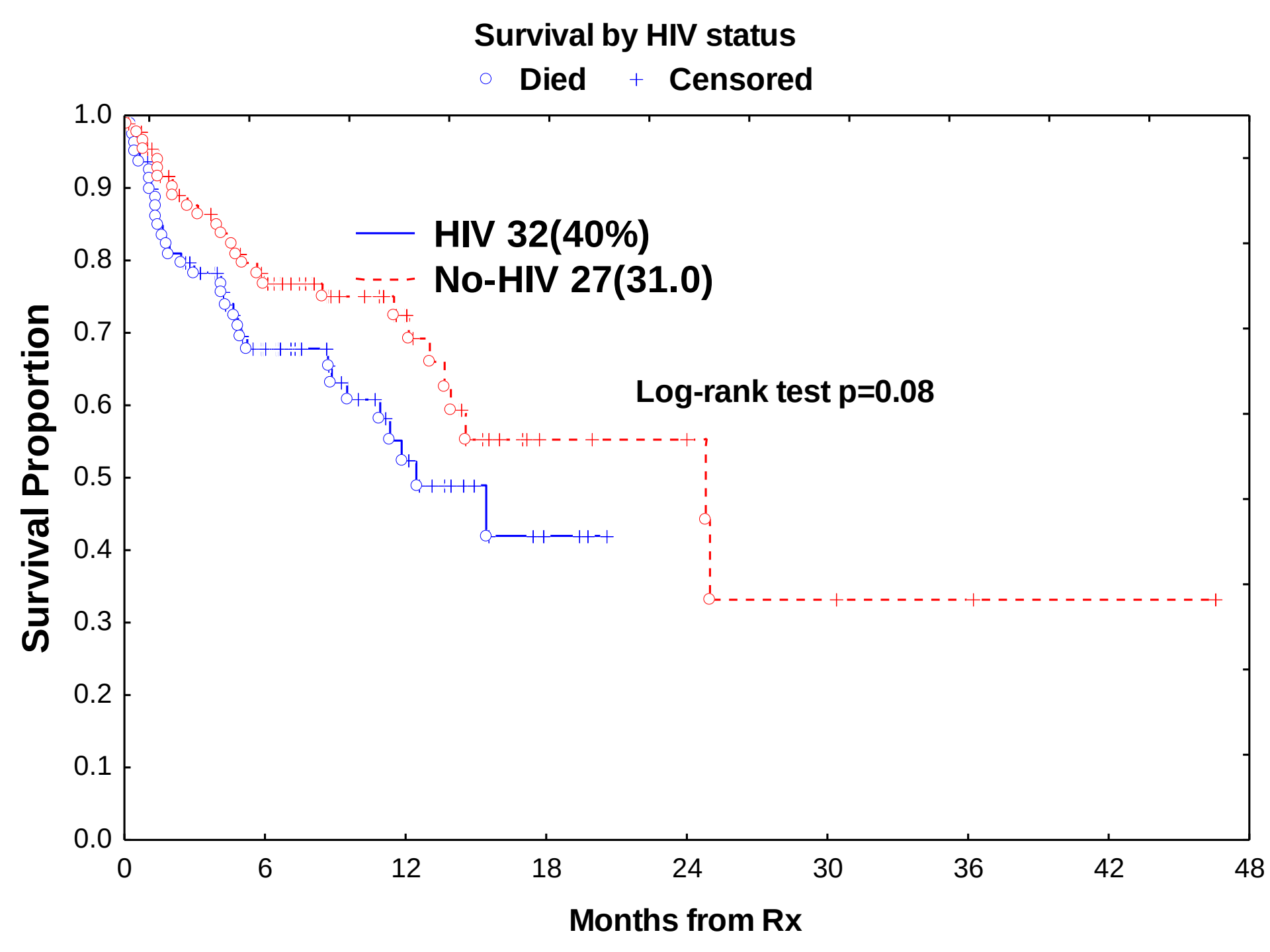
Survival by HIV status
Died
Censored
HIV 32(40%)
No-HIV 27(31.0)
Log-rank test p=0.08
Survival Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
Months from Rx

Nosocomial Transmission

- Data from work by Ghandi et al, Pillay et al, and Andrews, et al. have highlighted endemic transmission of XDR-TB strains either in hospital or community.
- Our own clinical data show high risk for HCW in KZN
- We are following this insight by looking at risk for drug-resistant TB among HCW

Table 1 - KZN HCW Patient characteristics		
	KZN XDR 2003-2008	**KZN MDR 2003-2008**
	n=26	**n=215**
Gender		
Male	6 (23%)	43 (20%)
Mean age in years (range)	36 (20-56)	35 (20-70)
Year of diagnosis		
2008	10	26
2007	6	66
2006	6	40
2005	2	15
2004	0	20
2003	1	20
NR	1*	28**
HIV		
Positive	18 (69%)	114 (53%)
negative	6 (23%)	60 (28%)
unknown	2 (8%)	41(19%)
HIV positive patients on ARVs	14/18 (78%)	71/114 (62%)
Median no. resistant drugs	6	3
Median duration of follow up in months (range)	5 (1-46)	20 (0-71)

Table 3. Annual Incidence of Drug Resistant Tuberculosis Among KwaZulu-Natal Health Care Workers and General Population Patients Referred for Drug-Resistant Tuberculosis to King George V Hospital, 2003-2007.

	HCW	General Population	Odds Ratio (95% C.I.)*
Annual Drug Resistant TB Incidence per 100,000 persons	70.5/100,000	11.7/100,000	5.84 (3.07-11.33)
Annual MDR-TB Incidence per 100,000 persons	63.2 /100,000	10.7/100,000	5.73 (2.93-11.50)
Annual XDR-TB Incidence per 100,000 persons	7.4/100,000	1.04/100,000	7.08 (4.55-10.91)

*All p values <0.0001.

Summary

- XDR-TB is associated with high mortality in South Africa.
- Treatment success for XDR-TB among HIV infected patients is achievable even in resource limited settings.
- HIV disease increases the risk of death among XDR-TB patients but this increase was not statistically significant.
- Treatment of XDR-TB is technically challenging with significant adverse drug reactions and need for close monitoring.
- More effort needs to made to understand why HCW are at increased risk for XDR-TB and to prevent nosocomial transmission of drug resistant disease.

Acknowledgements

King George Vth Hospital: Iqubal Master, Garth Osburn, Veronica Raman

BOSTON UNIVERSITY

Robert Horsburgh, Jussi Saukkonen, John Bernardo

CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA
CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV PREVENTION RESEARCH

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