

Incidence of Sub-Therapeutic Tuberculosis (TB) Drug Concentrations and Associated Treatment Outcomes among Predominantly HIV-infected TB Patients — Botswana, 1997–2001

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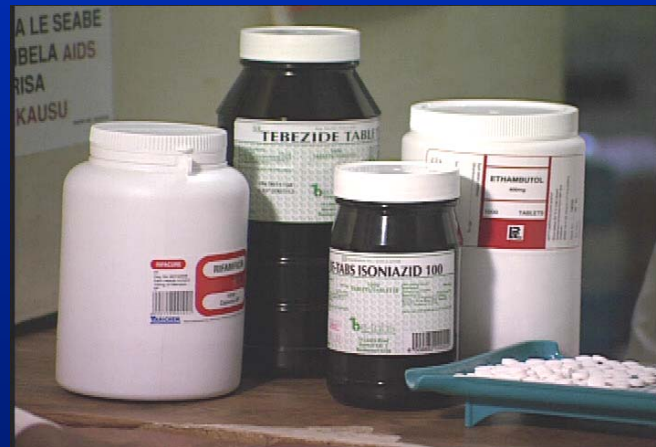
Division of Tuberculosis Elimination

U.S. Centers for Disease Control and Prevention



Tuberculosis Chemotherapy

- Tuberculosis (TB) is a life-threatening disease caused by *Mycobacterium tuberculosis*
 - Leading cause death of people living with AIDS
- Current treatment:
 - Isoniazid (INH)
 - Rifampin (RIF)
 - Ethambutol (EMB)
 - Pyrazinamide (PZA)
- Pharmacokinetic profiles established on healthy adults



Low TB Drug Levels

- Lower-than-expected TB drug levels
 - Gastrointestinal illnesses
 - Drug-drug interactions
 - Patient demographics
 - HIV infection

Sequelae of Low TB Drug Levels

- Poor TB treatment responses
 - Prolonged symptoms and infectiousness
 - Treatment failure
 - Death
- Development drug-resistant *M. tuberculosis*

Public Health Importance

- Population-specific pharmacokinetic norms relatively unknown
 - PLWHA
 - Sub-Saharan Africans
- Emergence of extensively drug-resistant (XDR)-TB
- Few studies on pharmacokinetics, outcomes

Study Objectives

- Determine frequency of low serum levels of isoniazid, rifampin, ethambutol & pyrazinamide among adults with TB in Botswana
- Identify associations between patient risk factors and low drug levels
- Investigate associations between low drug levels and poor treatment outcomes

Study Methodology

Patients at Gaborone
public outpatient clinic



- Age \geq 18 years
- Cough \geq 2 weeks
- Abnormal chest x-ray
- Agree to HIV testing
- + sputum smear or culture
- TB treatment in past 7–13 days

Study Methodology

Patients at Gaborone
public outpatient clinic

Consent obtained
& enrolled

- Age ≥ 18 years
- Cough ≥ 2 weeks
- Abnormal chest x-ray
- Agree to HIV testing
- + sputum smear or culture
- TB treatment in past 7–13 days

Hospitalized;
Fasted ≥ 8 h

Study Methodology

Patients at Gaborone
public outpatient clinic

Consent obtained
& enrolled

All 4 study drugs
given simultaneously

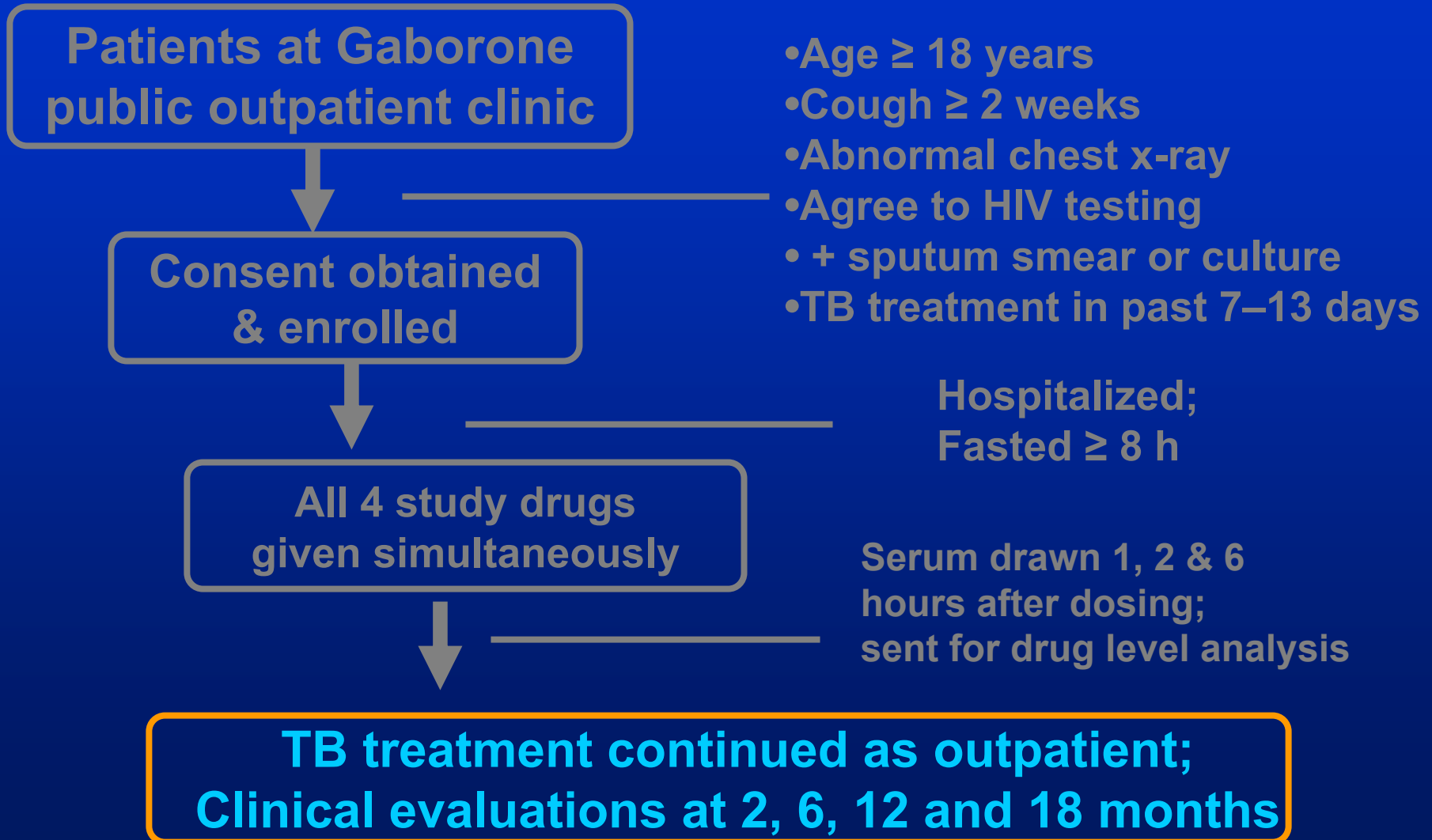
- Age ≥ 18 years
- Cough ≥ 2 weeks
- Abnormal chest x-ray
- Agree to HIV testing
- + sputum smear or culture
- TB treatment in past 7–13 days

Hospitalized;
Fasted ≥ 8 h

Serum drawn 1, 2 & 6
hours after dosing;
sent for drug level analysis



Study Methodology



Pharmacokinetic Definitions

“Low” maximum serum drug levels (C_{max})
using previously published* reference
points

- Isoniazid: $< 3 \mu\text{g/ml}$
- Rifampin: $< 8 \mu\text{g/ml}$
- Ethambutol: $< 2 \mu\text{g/ml}$
- Pyrazinamide: $< 35 \mu\text{g/ml}$

* Peloquin CA, et al. *Antimicrob Agents Chemother* 1997 (41): 2670-9

Poor Treatment Outcome

- **Treatment failure:**

- Sputum positive after 6 months treatment

or

- No clinical improvement after 6 months treatment

----- or -----

- **Death during treatment:**

- Death before TB treatment completion

Data Analysis

1. Univariate analyses of risk factors versus “Poor Treatment Outcome”



2. Forward logistic regression “Poor Treatment Outcome” and risk factors with $p < 0.1$ on univariate analysis

- **Exact methods used for cell sizes < 5**

Results



Patient Sample Size

Screened patients at Gaborone
public outpatient clinic
N=442

Consented, enrolled and
TB drugs administered
N=250

Treatment & monitoring
for 18 months

Final Analysis
N=225

192 ineligible, excluded:

- Normal CXR
- Cough < 2 weeks
- Refused HIV testing
- Refused consent
- Other

25, data not used:

- drug levels not done
- missing drug, CD4 data
- non-TB on cultures

Patient Characteristics (N=225)

Characteristic	n
Male sex	143 (64%)
Median age (range)	32 years (18–87)
Infected with HIV	155 (69%)
Taking ARVs	0
Cavitations on chest x-ray	71 (32%)
Median CD4 count (range)	269 cells/ μ L (1–1327)
Not HIV-infected	606 (234–1327)
HIV-infected	189 (1–984)

Median C_{max} Values ($\mu\text{g/mL}$)

Drug	Not HIV-infected n=70	HIV-infected CD4 \geq 200 n=71	HIV-infected CD4 < 200 n=84	p
INH	4.1 (1.3–10.3)	4.2 (0.9–10.8)	4.3 (0.4–9.0)	0.8
RIF	4.6 (1.2–13.4)	5.7 (1.1–15.0)	4.4 (0.7–12.7)	<.04
EMB	2.2 (1.0–7.2)	2.4 (0.8–5.1)	2.1 (0.4–6.9)	0.5
PZA	52.3 (29.9–84.4)	49.9 (29.4–108)	46.9 (25.8–119)	<.04

“Low” Serum Drug Levels

Drug	Not HIV-infected n (%)	HIV-infected CD4 \geq 200 n (%)	HIV-infected CD4 < 200 n (%)
INH	24 (35%)	27 (39%)	33 (39%)
RIF	56 (82%)	55 (80%)	77 (93%)
EMB	27 (39%)	23 (33%)	37 (45%)
PZA	3 (4%)	4 (6%)	4 (5%)

“Low” Serum Drug Levels

Drug	Not HIV-infected n (%)	HIV-infected CD4 \geq 200 n (%)	HIV-infected CD4 < 200 n (%)	p
INH	24 (35%)	27 (39%)	33 (39%)	.77
RIF	56 (82%)	55 (80%)	77 (93%)	.005
EMB	27 (39%)	23 (33%)	37 (45%)	.11
PZA	3 (4%)	4 (6%)	4 (5%)	.84

Treatment Outcomes

Characteristic	Not HIV-infected n (%)	HIV-infected CD4 \geq 200 n (%)	HIV-infected CD4 < 200 n (%)
Poor treatment outcome	7/66 (11)	8/67 (12)	21*/77 (27)
Treatment failure	6/61 (10)	7/58 (12)	11/61 (18)
Death during treatment	1/66 (2)	1/67 (2)	12/77 (16)

* Two patients experienced both treatment failure and, later, death during treatment

Treatment Outcomes

Characteristic	Not HIV-infected n (%)	HIV-infected CD4 \geq 200 n (%)	HIV-infected CD4 < 200 n (%)	p
Poor treatment outcome	7/66 (11)	8/67 (12)	21*/77 (27)	.01
Treatment failure	6/61 (10)	7/58 (12)	11/61 (18)	0.4
Death during treatment	1/66 (2)	1/67 (2)	12/77 (16)	<.001

* Two patients experienced both treatment failure and, later, death during treatment

Risk Factors for Poor Treatment Outcome

	Univariate		Multivariate	
	<u>Odds Ratio (95% CI)</u>	<u>p</u>	<u>Odds Ratio (95% CI)</u>	<u>p</u>
HIV-infected	13.0 (1.7–98.8)	.002	-----	.08
CD4 < 200	3.0 (1.4–6.2)	.003	3.2 (1.1–11.7)	.03
PZA low	5.4 (1.5–19.6)	.005	7.7 (1.8–33)	.003

Pyrazinamide and Treatment Outcomes

Low PZA associated* with

Treatment Failure RR 5.7, 95% CI (1.5–20.7)

Death during treatment RR 4.5, 95% CI (1.5–13.3)

*after controlling for HIV and CD4 count

Strengths and Limitations

- **Strengths**

- Prospective cohort
- Relatively large sample size

- **Limitations**

- High mortality rate, no autopsies
- Pharmacokinetic testing done once

Conclusions

- Low TB drug levels occurred frequently
- Immunosuppression was associated with pharmacokinetic aberrations
- Low PZA levels may increase risk of
 - Treatment Failure
 - Death during TB treatment

Future Steps

- Establish TB drug pharmacokinetic norms for
 - People living with HIV/AIDS
 - People of color
 - Women
- Investigate
 - Pyrazinamide's role in TB treatment
 - Relationship TB drug pharmacokinetics and acquired drug-resistance
 - ARV's effects on TB drug levels

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Study Staff and Patients



TB Drug Administration (N=225)

Characteristic	HIV-infected	Not HIV-infected	p
Time fasted (range)	12 h (8–19)	12 h (8–20)	.60
Dose (mg/kg)			
Isoniazid	6.8 (5.1–9.3)	6.8 (5.2–8.5)	.74
Rifampin	10.2 (7.6–14.0)	10.2 (7.8–12.8)	.97
Ethambutol	21.3 (15.3–29.4)	21.8 (15.6–29.3)	.10
Pyrazinamide	34.0 (17.5–46.5)	34.1 (26.0–42.6)	.96

