

Therapeutic Drug Levels for Tb: When and Why

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The Problem

- Slow response to tuberculosis (TB) treatment leads to prolonged infectiousness, may increase the likelihood of acquired drug resistance and extends treatment duration
- Our assumption is low drug levels is a contributor to slow response, at least in some patients
- Since 2007, initiative for patients slow to respond to TB therapy to have therapeutic drug level monitoring

Methods

- All adults treated for pulmonary TB from 3/1/07-5/1/09
- ≥ 18 years, culture-positive, started on first-line TB regimen; excluded if drug monitoring for other reasons, or if TB isolate resistant to one or more first-line drugs
- Slow response- After 4 weeks of therapy: two or more of the following-
 - 1. persistent TB symptoms, 2. positive sputum smear, 3. no improvement in chest x-ray
- Drug levels drawn at 2 hrs after observed morning dose of all medications, serum separated and sent on ice to referral laboratory in Florida for HPLC.

350 patients treated for drug-susceptible PTB

37 patients with initial TB isolate resistant to one or more first-line agents

2 patients with TDM performed for reasons other than slow response

311 patients included

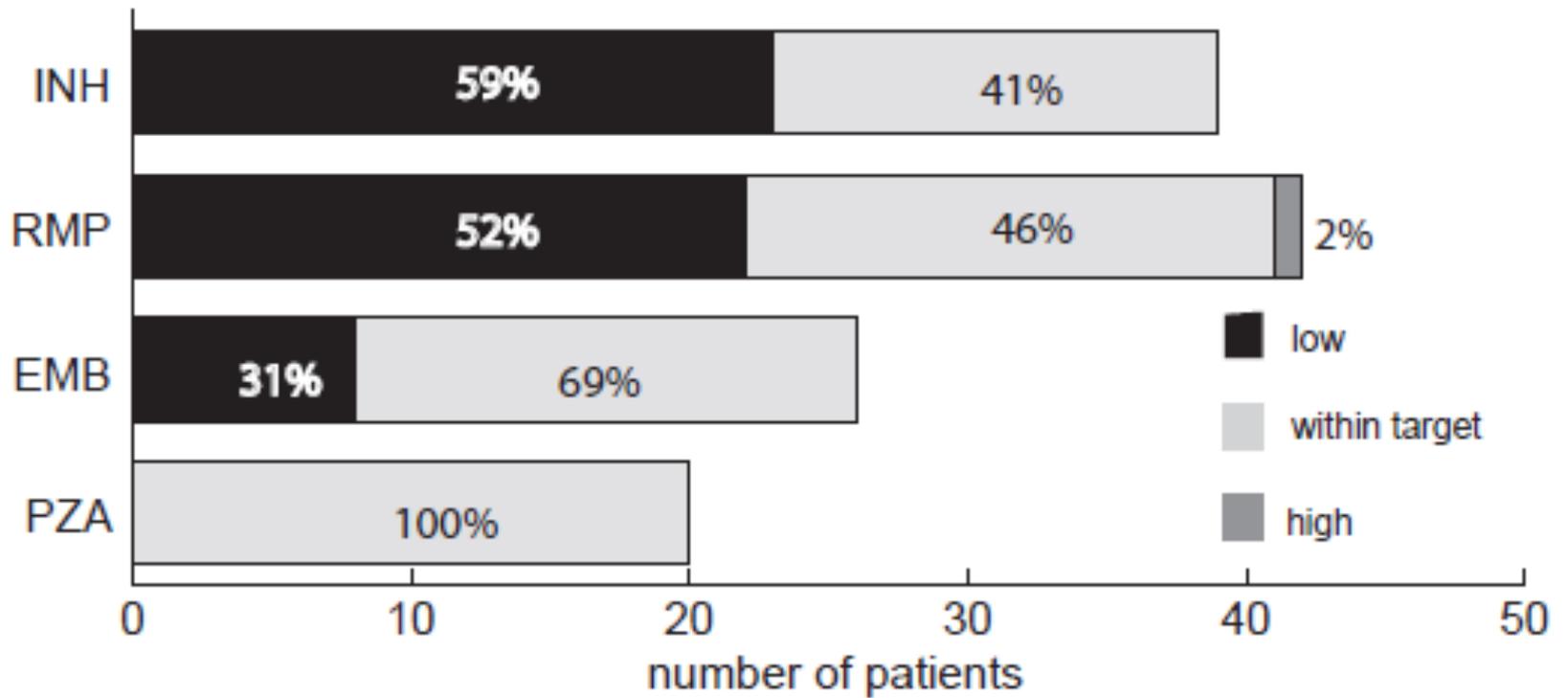
42 (14%) met criteria for slow response

Diabetes is a risk factor for slow response

	Total N= 311 (%)	Slow response N=42 (%)	Normal response N= 269 (%)	Risk Ratio [95% CI] p-value
Age 18-39	151 (49)	16 (38)	135 (50)	referent
40-64	90 (29)	13 (31)	77 (29)	1.4 [0.65-3.1] p=0.38
≥65	70 (22)	13 (31)	57 (21)	1.9 [0.87-4.3] p=0.11
Female	107 (35)	13 (31)	94 (35)	0.84 [0.42-1.7] p=0.61
Race/Eth				referent
Asian	102 (33)	19 (45)	83 (31)	0.67 [0.30-1.5] p=0.34
Hispanic	82 (26)	11 (26)	71 (26)	0.45 [0.19-1.1] p=0.07
Black	86 (28)	8 (19)	78 (29)	0.47 [0.15-1.5] p=0.20
White	41 (13)	4 (10)	37 (14)	
Foreign-born	228 (73)	33 (79)	195 (72)	1.4 [0.64-3.0] p=0.41
HIV				p>0.99
Yes	11 (3)	0	11 (4)	1.1 [0.39-2.9] p=0.90
Unk.	34 (11)	5 (12)	29 (11)	
Alcohol abuse	35 (11)	4 (9)	31 (11)	0.81 [0.27-2.4] p=0.70
Diabetes	41 (13)	17 (40)	24 (9)	6.9 [3.3-14.6] p<0.001*
Initial smear				
Positive	193 (62)	30 (72)	163 (61)	1.7 [0.79-3.8] p=0.17
Unavailable	24 (8)	3 (7)	21 (8)	1.3 [0.34-5.4] p=0.67
Chest x-ray				
abnormal	173 (56)	19 (45)	154 (57)	0.86 [0.18-4.1] p= 0.85
Cavitary	122 (39)	21 (50)	101 (38)	1.5 [0.31-6.8] p=0.64

Majority of slow responders had low C_{2hr} levels of INH and rifampin

A.

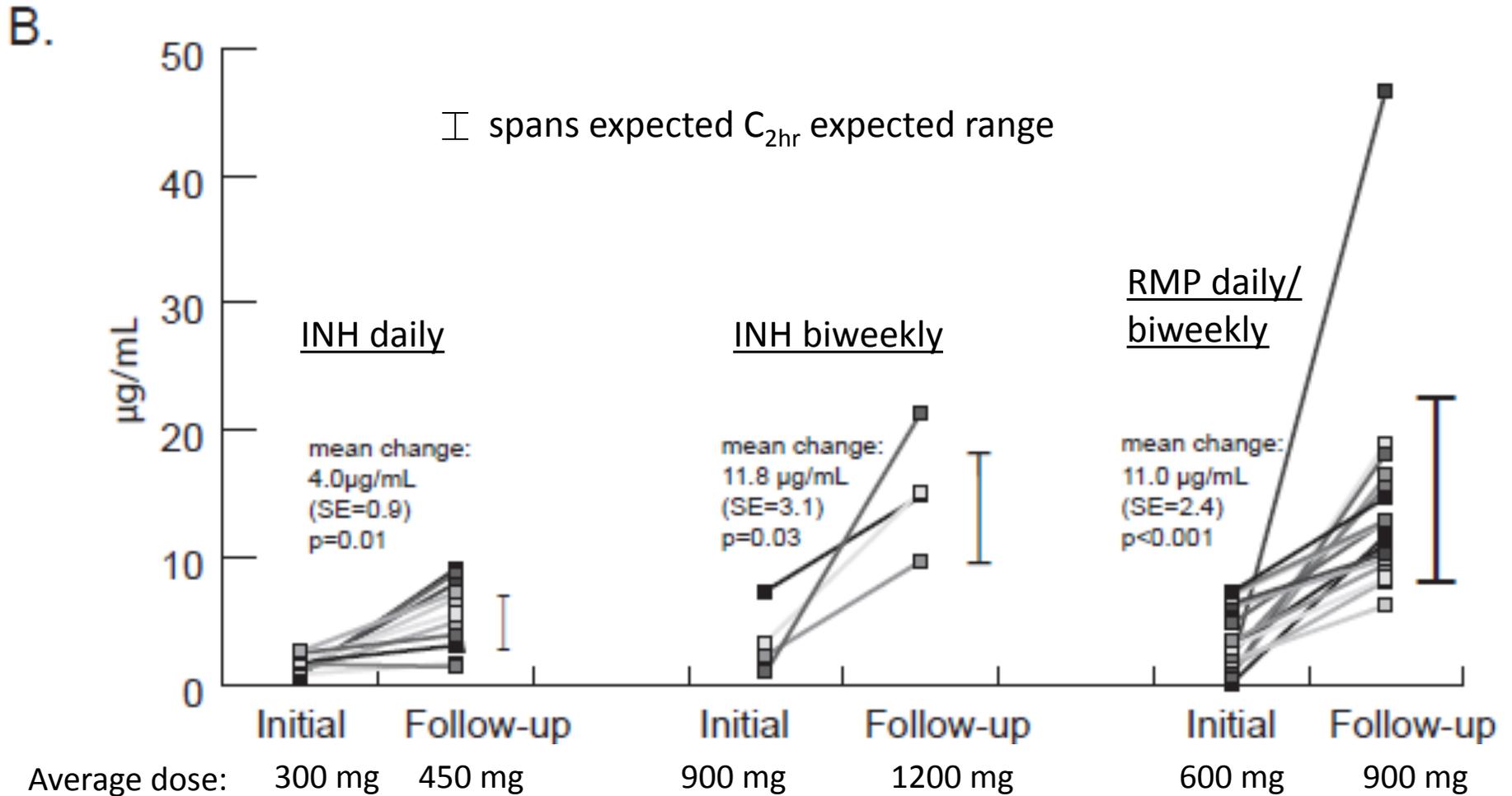


82% had low levels to one of INH or RMP

Diabetes was a significant risk factor for low rifampin levels

	Normal INH N=16 (%N)	Low INH N=23 (%N)	Risk Ratio [95% CI] p-value	Normal RMP N=20 (%N)	Low RMP N=22 (%N)	Risk Ratio [95% CI] p-value
Age 18-39	4 (25)	8 (35)	referent	5 (25)	10 (46)	referent
40-64	7 (44)	8 (35)	0.57 [0.12-2.8] p=0.49	8 (40)	7 (32)	0.44 [0.10-1.9] p=0.27
≥65	5 (31)	7 (30)	0.70 [0.13-3.7] p=0.67	7 (35)	5 (22)	0.36 [0.07-1.7] p=0.20
Female	5 (31)	8 (35)	1.2 [0.30-4.6] p=0.82	7 (35)	7 (32)	0.87 [0.24-3.1] p=0.81
Race/Eth						
White	1 (6)	3 (13)	1.9 [0.16-22.3] p=0.61	3 (15)	1(5)	0.37 [0.3-4.2] p=0.42
Asian	7 (44)	11 (48)	referent	10 (50)	9 (41)	referent
Hispanic	6 (38)	4 (17)	0.42 [0.09-2.1] p=0.43	3 (15)	8 (36)	3.0 [0.60-14.7] p=0.18
Black	2 (12)	5 (22)	1.6 [0.24-10.6] p=0.63	4(20)	4 (18)	1.1 [0.21-5.8] p=0.90
Foreign-born	13 (81)	17 (74)	0.65 [0.14-3.1] p=0.59	14 (70)	19 (86)	2.7 [0.58-12.8] p=0.21
Diabetes	6 (37)	10 (43)	1.3 [0.35-4.7] p=0.71	4 (20)	13 (59)	5.8 [1.4-23.1] p=0.01*
EtOH use	1 (6)	1 (4)	0.69 [0.4-11.7] p=0.79	2 (10)	2 (9)	0.90 [0.12-7.1] p=0.92
Dose interval						
Daily	8 (50)	19 (83)	referent	11 (65)	16 (73)	referent
Biweekly	8 (50)	4 (17)	0.21 [0.05-0.9] p=0.04 [†]	6 (35)	6 (27)	0.88 [0.23-3.3] p=0.85

INH and rifampin levels correct easily after first dose adjustment



No drug related toxicities associated with dose increase

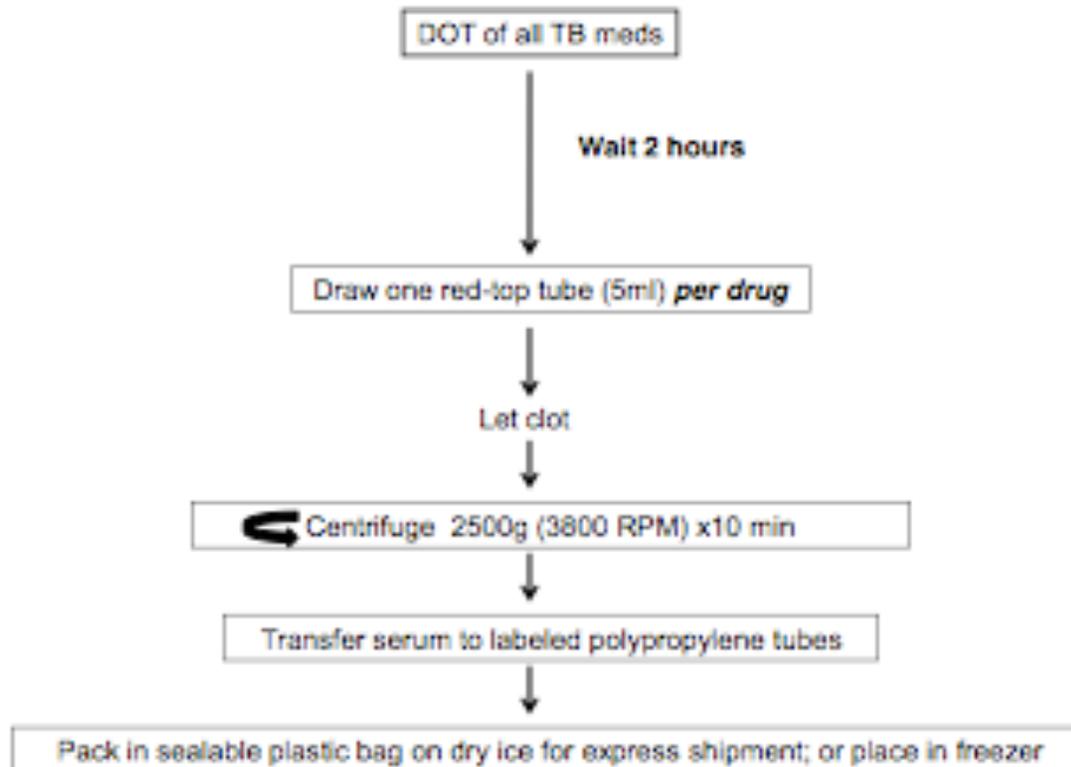
**Patients with low>corrected rifampin levels finished treatment 7 wks earlier
(than those with normal levels)**

	Total, N= 42 (%)	Low>corrected RMP, N=22 (%)	Normal RMP, N=20 (%)
Death	3 (7)	1 (5)	2 (10)
Acquired resistance	0	0	0
Moved out of state	2 (5)	1 (5)	1
Remains on treatment	10 (24)	6 (27)	4 (20)
Treatment duration*, median weeks [IQR]	45 [40-51]	40 [38-48]	47 [44-55] Log-rank p=0.17

Summary-1

- Drug level monitoring for INH and RMP may be a useful adjunct in Tb patients who are responding slowly to treatment

Figure 1. Obtaining a sample for TDM



Summary-1

•Drug level monitoring for INH and RMP may be a useful adjunct in Tb patients who are responding slowly to treatment

•We expect to find low levels to INH or RMP in many, and thus have created guidelines

Table 1. Indication and timing of therapeutic drug monitoring (TDM) in clients slow-to-respond

Reason for TDM	Drugs to check
<p>1. In any client with slow response at 4-6 weeks of treatment suggested by either or both of the following:</p> <ul style="list-style-type: none">a. For clients with smear positive pulmonary TB, sputum smear (+) not decreasing [adequate decrease is 4+ to 2+; 3+ to 1+; or 2+/1+ to smear negative]b. no improvement in TB symptoms (e.g. no weight gain, no reduction in cough, persistent fever, or worsening of chest x-ray if performed)	Isoniazid, Rifampin

Summary-2

- If levels are low:

Table 2. Isoniazid and Rifampin expected peak concentrations and usual dose adjustment*

Medication (expected C _{max} range in µg/ml)	Client Serum Result	Dose adjustment
▪ Isoniazid / daily (3-6) / biweekly (9-18)	If client is on daily therapy and serum level is <2 If client is on biweekly therapy and serum level is <7	Increase daily dose to 450 mg from 300 mg Increase biweekly dose to 1200 mg from 900 mg
▪ Rifampin (8-24)	If serum level is <6 (for both daily and intermittent therapy)	Increase dose to 900 mg from 600 mg (both daily and intermittent therapy)

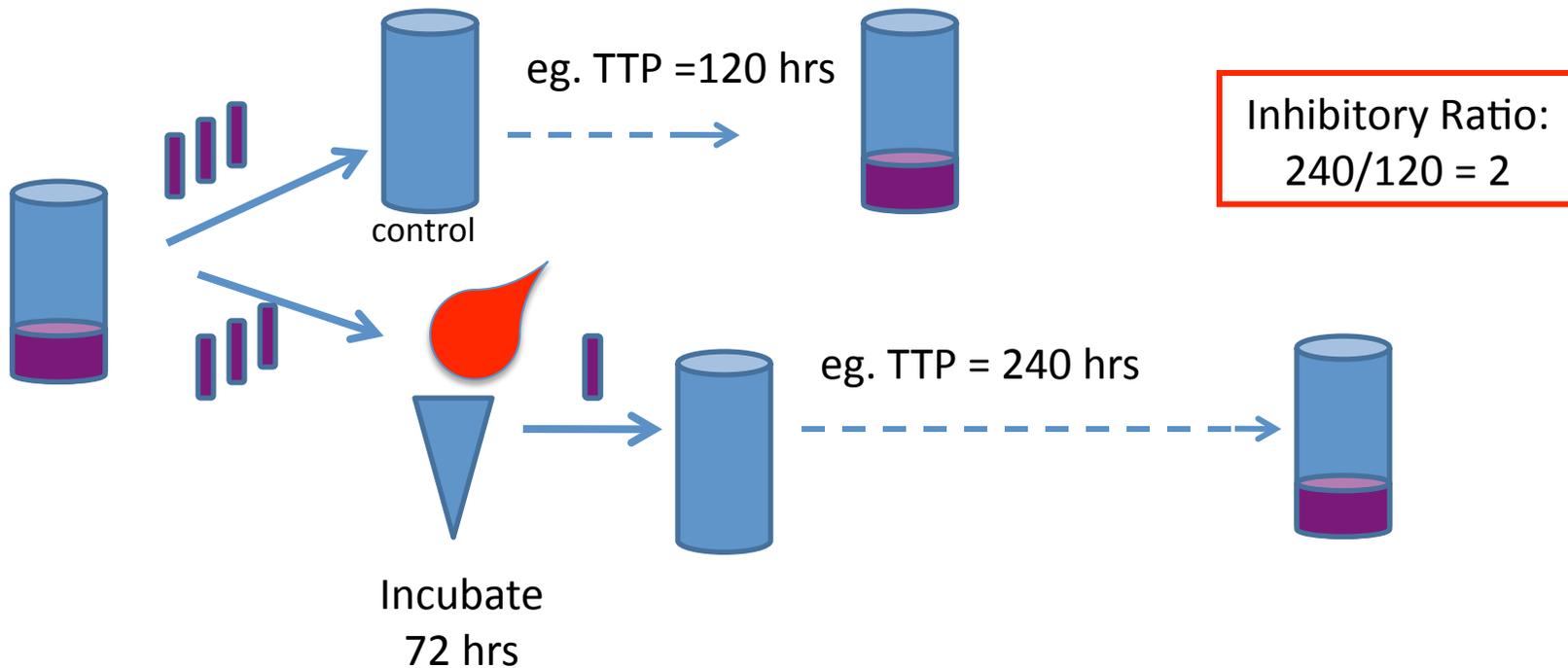
Summary-3

- Additionally, we are now starting an initiative to collect INH/RMP levels on all diabetics at the start of therapy (2 weeks)

Summary-4

- Finally, we are trying to understand why serum drug levels are not perfectly predictive
 - many individuals with low levels will do fine
 - not all slow responders will have low levels

Part of this is likely because the blood tells you the about the drugs, but not the bug



Summary-4

- Finally, we are trying to understand why serum drug levels are not perfectly predictive
 - many individuals with low levels will do fine
 - not all slow responders will have low levels

Part of this is likely because the blood tells you the about the drugs, but not the bug

Thus, we have an approved protocol to receive from Florida left-over serum, and to receive from DCLS the Tb isolate

We need to get permission from the client, during or after you collect the serum

Will not affect their care, no extra blood draw, etc.

Summary-5

GUIDELINES FOR SLOW RESPONDERS

1. Client observed to have slow response as defined by VDH Guidelines for Therapeutic Drug Level Monitoring (approx 6 weeks of treatment)
2. Drug levels drawn for isoniazid and rifampin per VDH Guidelines and single dose increase with repeat levels following dose adjustment

DIABETES

1. Diabetes documented upon client registry:
2. Client identified for early drug level monitoring per VDH initiative (approx 2 weeks of treatment)
3. Drug levels drawn for isoniazid and rifampin per VDH Guidelines and single dose increase with repeat levels following dose adjustment

1. VDH Nurse/Staff completes drug level request form which includes written confirmation that client releases his/her name and contact information to UVA research staff to be contacted for possible enrollment in the study [IRBs VDH (#40110) and UVA (#14771)] using leftover serum from drug level measurement and a portion of their *M. tuberculosis* isolate from DCLS.
2. Release form includes client's first language allowing appropriate telephone interpreter service if/when contacted by UVA staff