Pharmacokinetics and Resistance in MDR-TB

Russell Kempker, MD, MSc

TB PK Workshop

September 5th, 2014

Multidrug-Resistant Tuberculosis (MDR-TB)

WHO: MDR-TB Control "Off-track"

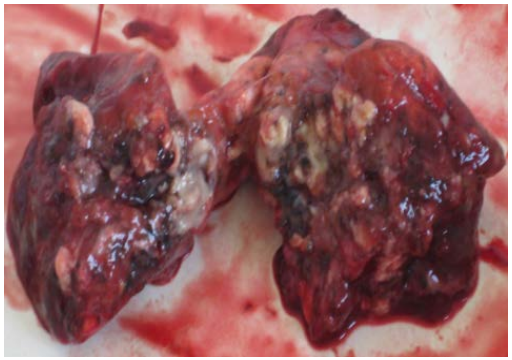
- ~450,000 new cases; 170,000 deaths (2012)
- Highest rates in E. Europe/former Soviet Republics
- Favorable Treatment Outcomes → 62% (36-79%)[1]

Can optimizing TB Pharmacokinetics help?

- First-line drug (FLD) concentrations related to outcomes[2]
- FLD variability assoc. with acquired drug resistance[3]
- Limited data on second-line drug (SLD) pharmacokinetics

[1]Orenstein et al. Lancet ID 2009
[2] Pasipandoya at al. JID 2013
[3] Pasipandoya at al. CID 2012

Tuberculous Cavitary Lesion



Classic TB Lesion

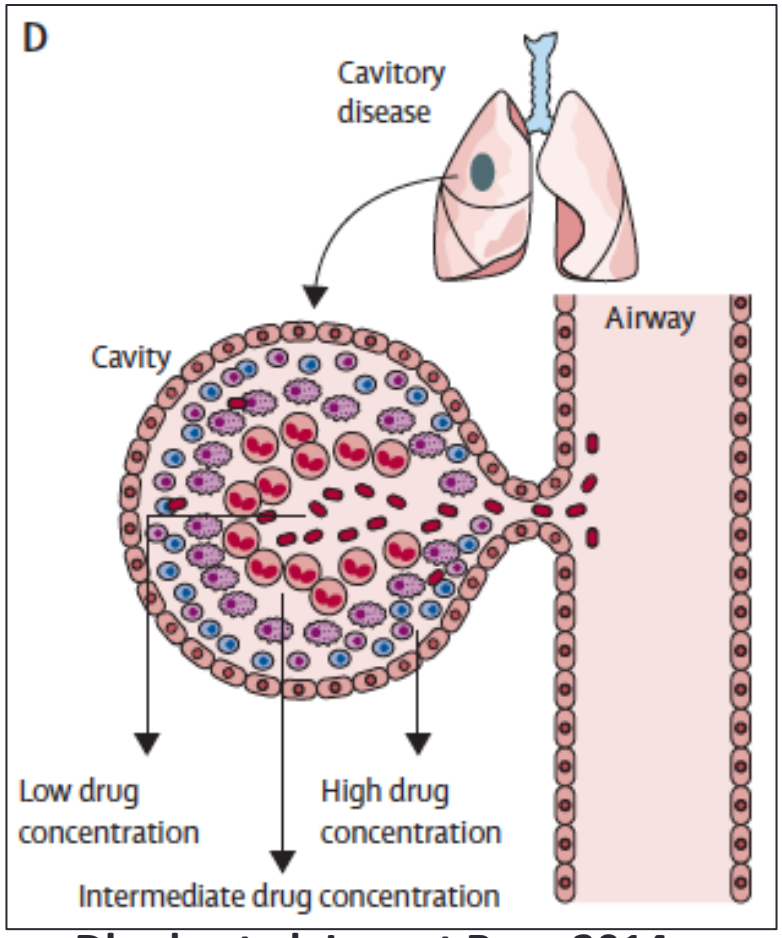
- High AFB burden
- Heterogeneous; varying levels of fibrosis & vascularity
- SLD drug penetration not clear but…

Cavities correlated with

- Acquired drug resistance[1]
- Poor treatment outcomes and relapse[2]

[1]Kempker et al. CID 2012,2014
[2] Kim at al. CID 2007

TB Drug Penetration into Cavity



Dheda at al. Lancet Resp 2014

Human Data

- FLD studies from 1950-80s[1]
- Case report for SLDs[2]

Animal Data

- Good moxifloxacin penetration into granulomas[3]

[1]Dartois et al. Curr Clin Pharm 2010
[2] Akkerman at al. ERJ 2013
[3] Prideaux at al. Anal Chem 2011

Study Question

How well do second-line TB drugs penetrate into Cavitary Lesions?

↓

AIM

Measure the intra cavitary concentration of levofloxacin utilizing microdialysis

Methods

I. Setting

- National Center for TB and Lung Diseases in Tbilisi, Georgia

II. Patients

- MDR-TB cohort undergoing adjunctive surgical resection

III. Pharmacokinetics

- Serum samples at 0, 2, 4 & 8 hours & time of resection (HPLC)
- µD performed for intra cavitary samples (HPLC-MS/MS)
- Tissue samples for total drug concentrations (HPLC)
- All LEVO concentrations done at U. of Florida

Why we chose Levofloxacin

FQs cornerstone of MDR treatment; good tissue penetration

↓

LEVO

- Best early bactericidal activity of FQs[1]
- Generic; most commonly used FQ in study setting

PK Parameters[2]

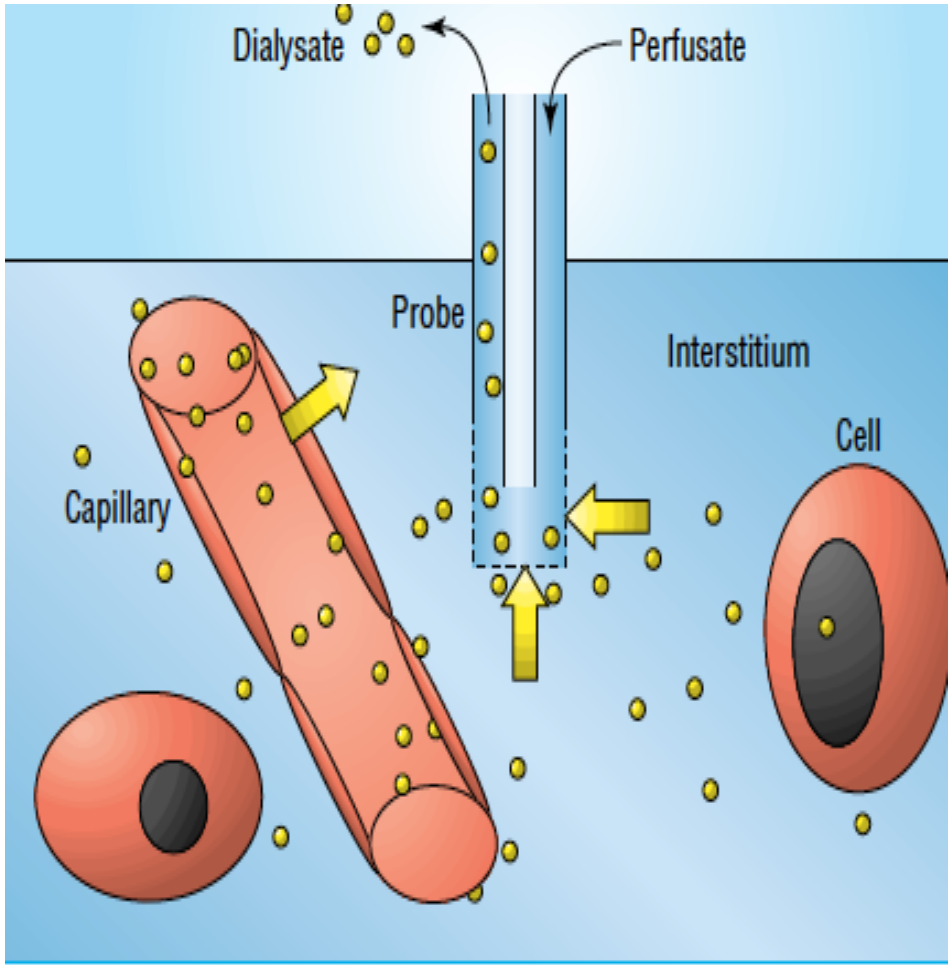
- Bioavailability ~100%
- $T_{½}$ = 7.4 hours
- T_{max} = ~ 1 hour

[1]Johnson et al. Int J TB Lung Dis 2006

[2] Peloquin at al. Antimicrob Agent Chemo 2013

Microdialysis (µD)

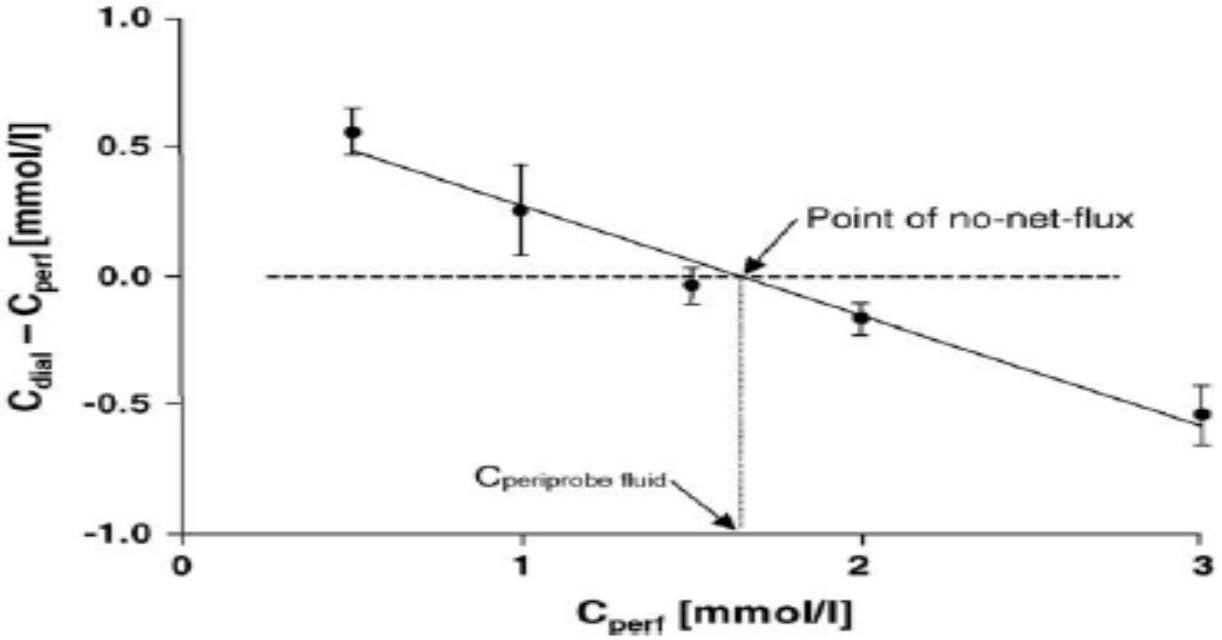
- Measures extracellular, unbound drug
- Must account for less than 100% recovery rate (calibration)



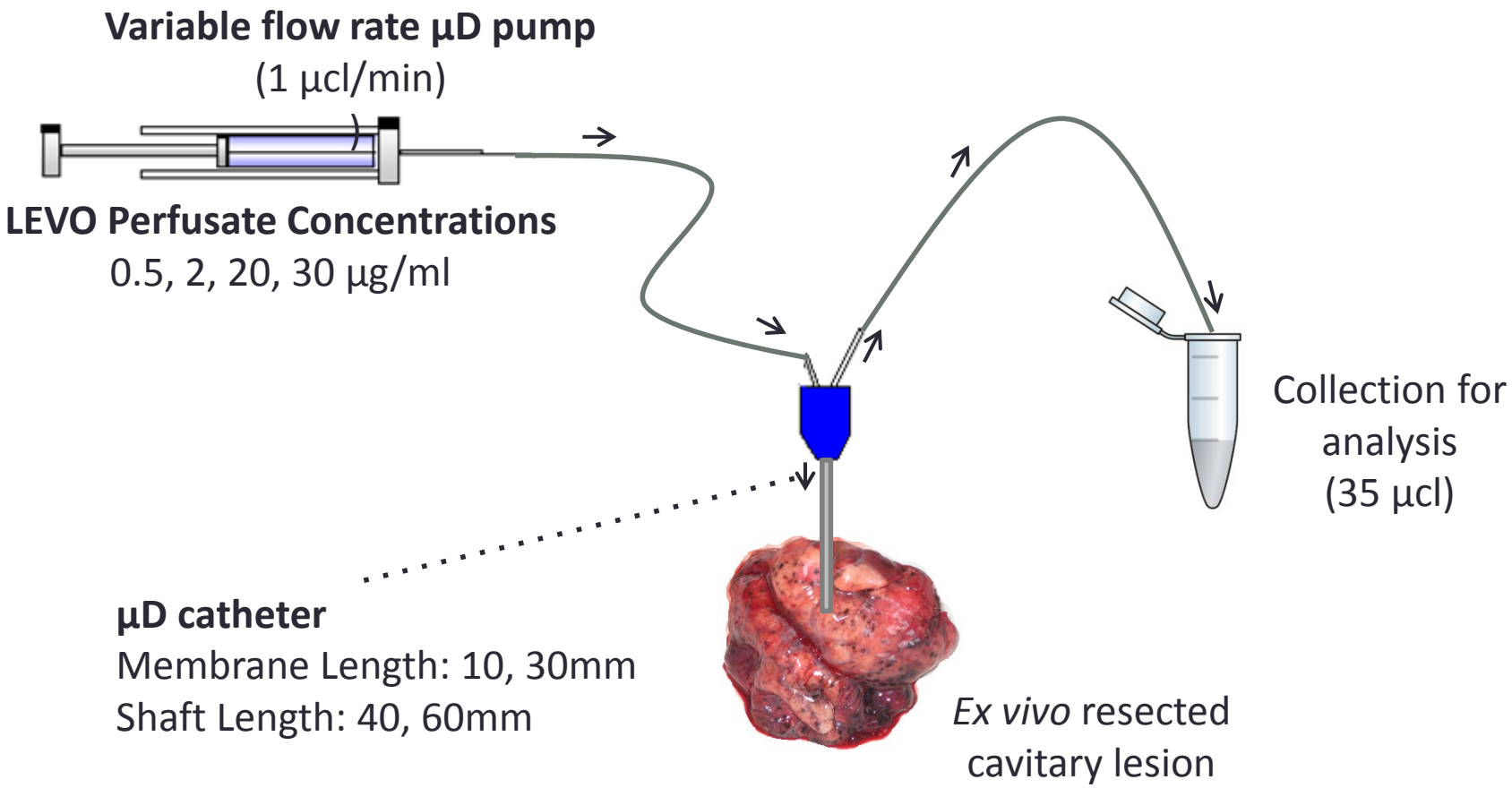
Muller et al. BMJ 2012

No-Net-Flux Calibration Method

- Using different perfusate concentration while the extracellular concentration of analyte in vivo is constant.



µD using No-Net Flux Method



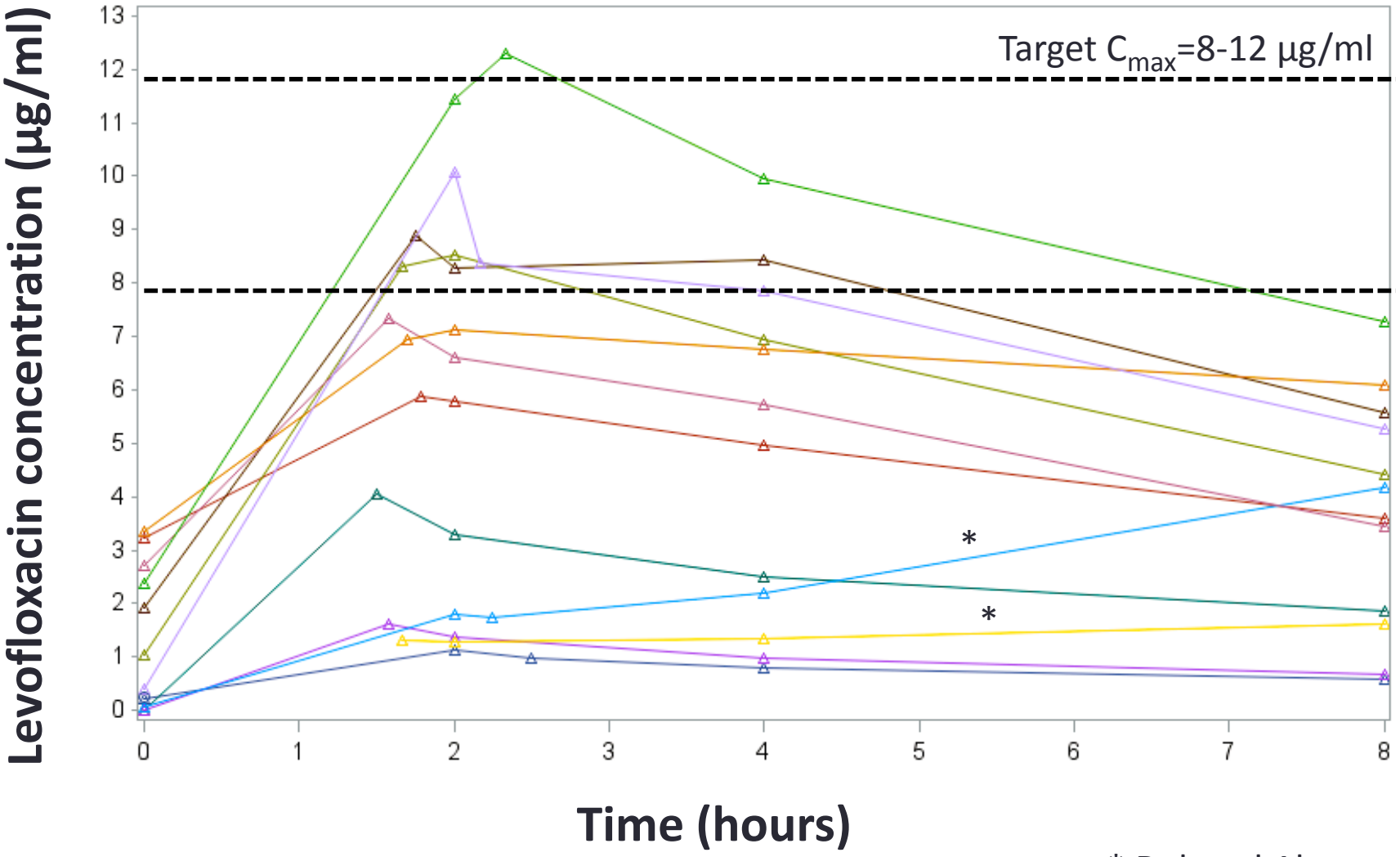
PHARM-TB STUDY

Study Results: Table 1 (n=12)

Characteristic	Result	Characteristic	Result (N=12)
Male	11 (92)	Creatinine (mg/dl)*	0.89 (0.66-1.26)
Georgian	10 (84)	CrCl (ml/min)*	118 (81-143)
Age*	34 (17-54)	Albumin (g/dl)*	4.4 (3.5-4.9)
Diabetes	2 (17)	Hemoglobin (g/dl)*	12.8 (12.1-13.5)
Hepatitis C	5 (42)	ALT*	30.5 (10-125)
Weight (kg)*	68 (49-100)	LEVO 750 mg	10 (83)
BMI (kg/m^2)*	22.6 (17-33)	LEVO (mg/kg)	11.8 (7.5-15.3)
New TB case	9 (75)	LEVO Days	372 (15-810)
Cavity diameter (cm)	2.8 (2.1-10)		

* Median value (range)

LEVO Concentration Time Graph (n=12)



* Delayed Absorption

Non-Compartmental Analysis*

PHARM-TB STUDY

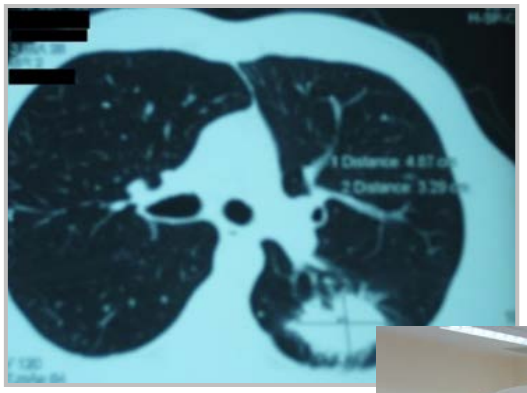
Parameter	All (n=12)
K_e $(h^{-1})^+$	0.09 (.03-.12)
$T_{1/2}$ $(h)^+$	7.6 (5.9-26.6)
T_{max} (h)	2 (1.5-8)
C_{max} (µg/ml)	6.5 (1.1-12.3)
AUC_{last}*(h•µg/ml)	39.4 (5.9-70.8)
$AUC_{0-\infty}$*$(h•µg/ml)^+$	86.2 (12.2-284)
CL/F $(L/h)^+$	10.1 (5.7-69.6)
V/F $(L)^+$	140.5 (63-754)

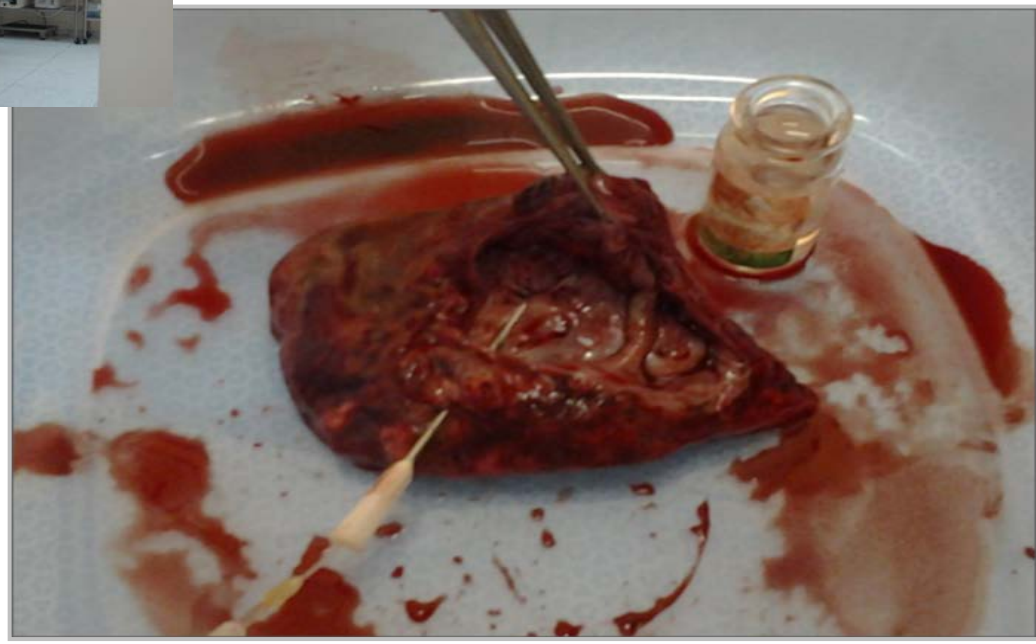
*Median values (range)

$^+$Two patients not included 2nd delayed absorption

Microdialysis

PHARM-TB STUDY





I. Serum/Cavitary LEVO Concentrations

PHARM-TB STUDY

ID	$C_{resection}$* (µg/ml)	$C_{cavitary}$ (µg/ml)	$C_{cavitary}/C_{resection}$
1	0.74	0.46	0.63
2	4.40	9.59	2.18
3	3.03	5.31	1.75
4	6.66	8.82	1.32
5	1.21	2.85	2.36
7	1.31	2.07	1.58
8	5.50	2.7	0.49
9	5.21	5.55	1.07
10	9.23	7.83	0.85
11	6.28	4.36	0.69
12	0.99	1.78	1.80

* Free concentration (LEVO*0.75)

II. Serum/Cavitary LEVO Concentrations

PHARM-TB STUDY

Group	Serum (µg/ml)*		Cavity (µg/ml)	Cavity/Serum
	Total LEV	Free LEV	Free LEV	Free LEV
All (n=11)	5.87 (0.98-12.3)	4.40 (0.74-9.23)	4.36 (0.46-9.59)	1.33 (0.49-2.36)

* At time of surgical resection

Serum vs. Cavitary Comparison (p=0.38)
Serum & Cavitary Correlation (r=0.71)

Cavitary LEVO Concentrations: Microdialysis vs. Whole Tissue

ID	Free Cavitary Concentration (µg/ml)	Total Cavitary Concentration (µg/g)
1	0.46	5.30
2	9.59	40.25
3	5.31	12.85

PHARM-TB STUDY

Conclusion

- **Summary**
  - Wide range of LEVO concentrations (C_{max} 1.1-12.3)
  - LEVO good cavitary penetration: Median Cavitary/Serum Ratio= 1.33 (0.49-2.36)
  - Optimal LEVO serum concentration → optimal tissue levels
- **Next Steps**
  - Correlate tissue pathology & radiology characteristics (CT) with cavitary LEVO concentrations
  - Year 2 Cohort: Evaluating Moxifloxacin & PZA

Acknowledgements

NCTLD

Sergo Vashakidze
Ketino Nikolasihvili
Irina Sabulua
Nestani Tukvadze
Nino Bablishvili

University of Florida

Hartmut Derendorf
Chuck Peloquin
Aline Barth
Ravi Singh

Emory University

Henry Blumberg
Jeanette Guarner

Grant Support

NIH NIAID K23AI103044