Assessing Pharmacokinetics in Clinical Studies

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Disclaimers

No industry conflicts of interest.

Dr. Peloquin directs a not – for – profit clinical laboratory that performs TDM.

Dr. Peloquin's salary is not paid by the clinical lab, and he does not work on commission in any fashion.

How Do Antibiotics Work ?

A drug must enter the organism,

bind to a specific target,

and produce an inhibitory or lethal effect.

Unless the drug is delivered to the site of infection (PK), nothing happens (PD).

Where are we now ?

I thought we just gave " THE DOSE "

Giving THE DOSE implies that every patient is THE PATIENT (aka, " the average Joe ").

That is the same as saying there is no such thing as inter‑individual variability (I I V in POP PK language).

We have definitive proof that this is **false.**

So why do we keep giving THE DOSE ?

Same as it ever was...
Yeah, the twister comes
Here comes the twister
Same as it ever was...

—*Once in a Lifetime*, Talking Heads

Same as it ever was...Same as it ever was...Same as it ever was...
Same as it ever was...Same as it ever was...Same as it ever was...
Same as it ever was...Same as it ever was...

SPECIAL ARTICLES

Using Personalized Medicine in the Management of Diabetes Mellitus

Nina Elk and Otito F Iwuchukwu

PHARMACOTHERAPY

The Journal of Human Pharmacology and Drug Therapy

Standardized Doses of TB Drugs

Standardized Doses of TB Drugs

Original BMRC Dose	Current Dose	Rel. %
RIF 600 mg / 48 kg = 12.5 mg / kg	RIF 600 mg / 80 kg = 7.5 mg / kg	60%
INH 300 mg / 48 kg = 6.25 mg / kg	INH 300 mg / 80 kg = 3.75 mg / kg	60%
PZA 35 mg / kg	PZA 20 – 25 mg / kg	≤ 71%
EMB 25 mg / kg	EMB 15 mg / kg	60%

Fixed doses of INH and RIF are too small

Full

48 kg

RIF 600 mg in Original patients

80 kg

Not Full

RIF 600 mg in Current patients

Like putting 10 gallons of gasoline in each of these vehicles ...

Full

Not Full

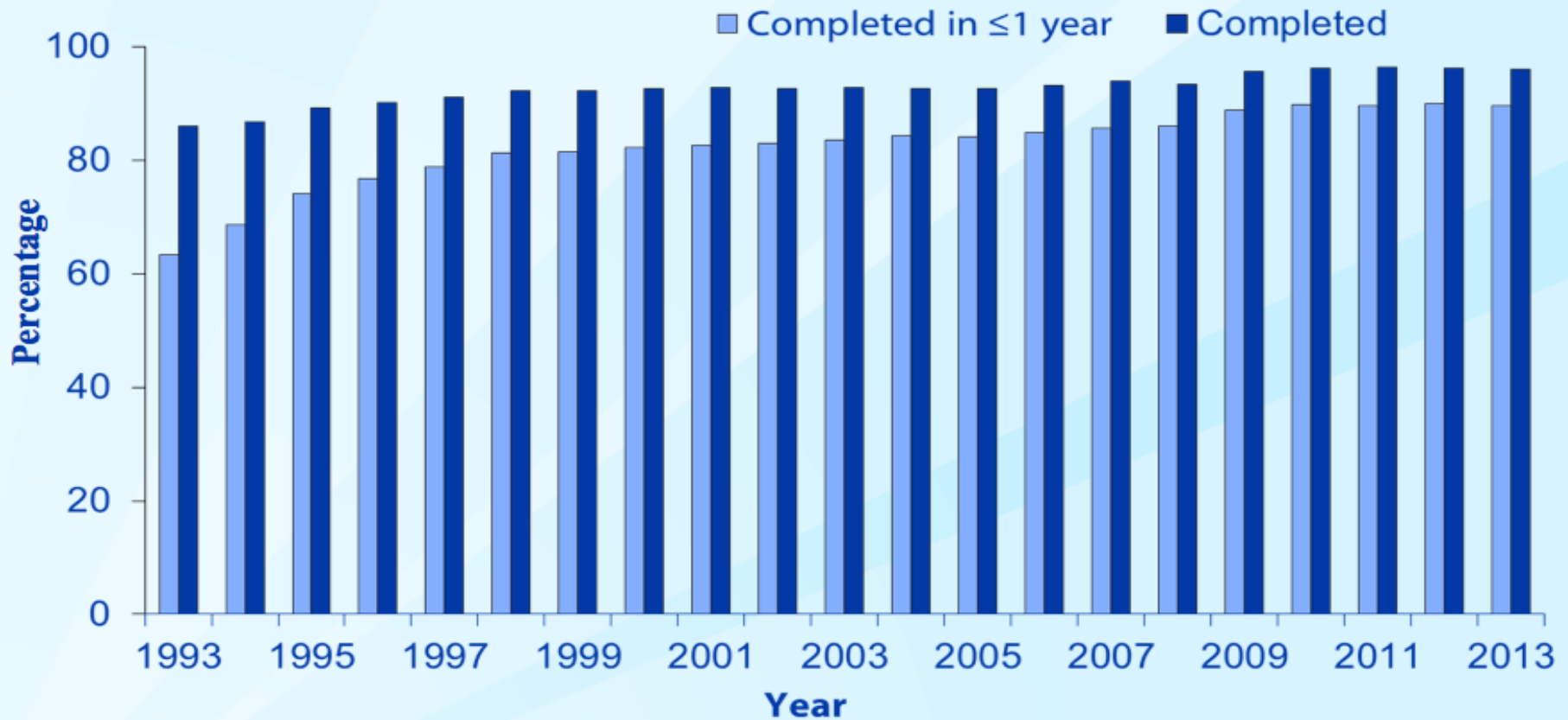# " But TB Treatment is only 6 months long and it is > 95 % effective "

This is TB dogma.

The BMRC did show, using per protocol analyses, that rifampin – based regimens were > 95 % effective.

However, the other 20 % of the patients not in those analyses are still in your clinic.

Thus, you might predict 0.95 * 80 % = 76 % efficacy at 6 months in your clinic. Right ?

Completion of TB Treatment Therapy, United States, 1993–2013*

Legend: ■ Completed in ≤1 year ■ Completed

Y-axis: Percentage (0, 20, 40, 60, 80, 100)

X-axis: Year (1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009, 2011, 2013)

* As of June 9, 2016; data available through 2013 only.

Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die within one year of initiating treatment; excludes persons with initial rifampin-resistant isolate, patients with bone and joint disease, meningeal disease, or disease of the central nervous system, or pediatric patients (ages 0–14 years) with miliary disease or positive blood culture or a positive nucleic acid amplification test on a blood specimen, and those who moved out of the country within one year of initiating treatment.

Percentage of Tuberculosis Cases Completing Therapy by Month of Completion Among Persons for Whom Therapy Was Indicated for ≤1 Year, United States, 2013
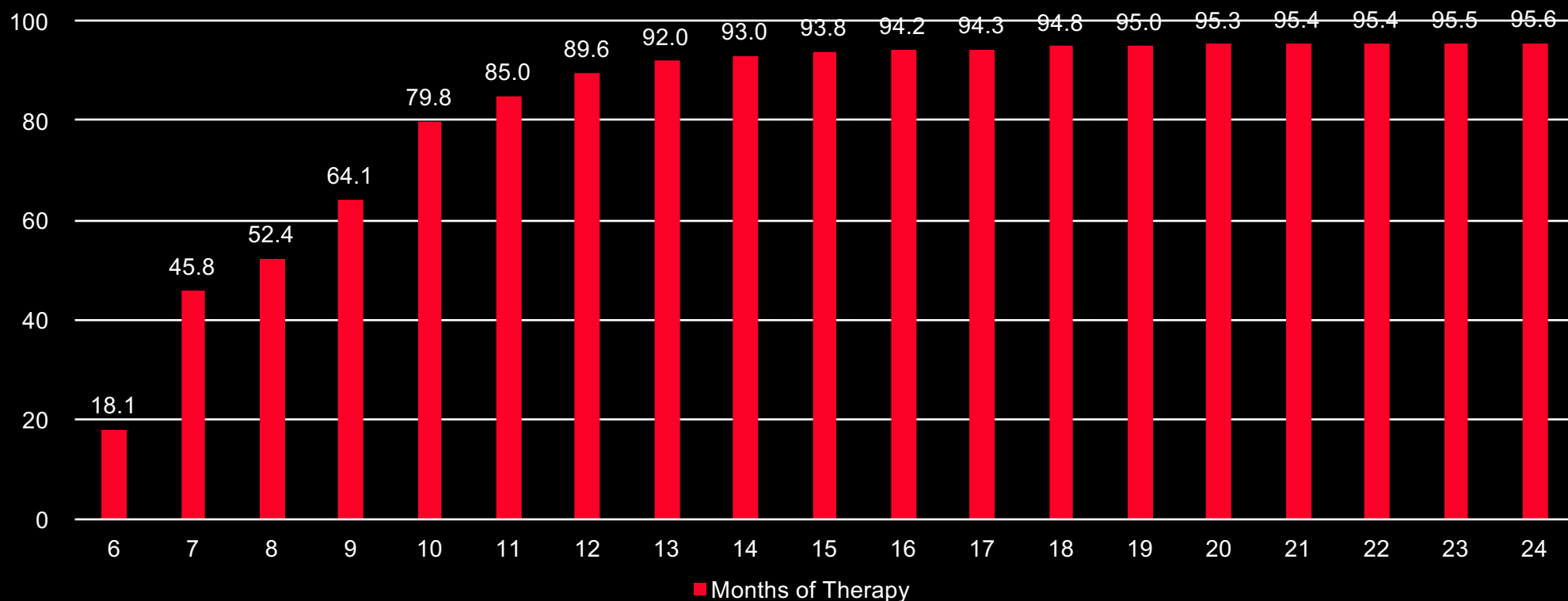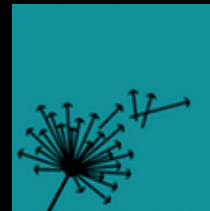
Source: CDC, National Tuberculosis Surveillance System, 2013

Standardized Doses of TB Drugs

Phil Hopewell, MD

CURRY
INTERNATIONAL
TUBERCULOSIS
CENTER

" There is a fine line between dogma
and dog manure. "

Standardized Doses of TB Drugs

For the current regimen, we should only claim the efficacy actually delivered.

In the US, the RIPE regimen is ~ 90 % effective at 12 months.

It is < 20% effective at 6 months, and < 46 % effective at 7 months.

Where are we going ?

Key Question 1

Bridging pre-clinical data to clinical data :

Focus on determining the pharmacodynamically (PD) – linked parameter : f AUC / MIC, f Cmax / MIC, or f Cmin / MIC (as an alternative to % f T > MIC) .

Then, determine the dose and frequency likely to achieve a high rate of target attainment, be that for bacterial cell kill or suppression of resistance.

Bridging Pre - Clinical Data to Clinical Data

The **PD – linked parameter is conserved** for each drug and organism pair, although the organism may display various growth states (log – phase growth, slow growth, non – replicating persisters).

The PD driver for **cell kill** may not be identical to the PD driver for **suppression of resistance.**

Pharmacokinetics and Dosing of Levofloxacin in Children Treated for Active or Latent Multidrug-resistant Tuberculosis, Federated States of Micronesia and Republic of the Marshall Islands

Sundari R. Mase, MD, MPH,* John A. Jereb, MD,* Daniel Gonzalez, PharmD, PhD,†‡§ Fatma Martin, MBBS,¶ Charles L. Daley, MD,‖ Dorina Fred, MBBS,** Ann M. Loeffler, MD,†† Lakshmy R. Menon, MPH,* Sapna Bamrah Morris, MD,* Richard Brostrom, MD,* Terence Chorba, MD,* and Charles A. Peloquin, PharmD, FCCP‡‡
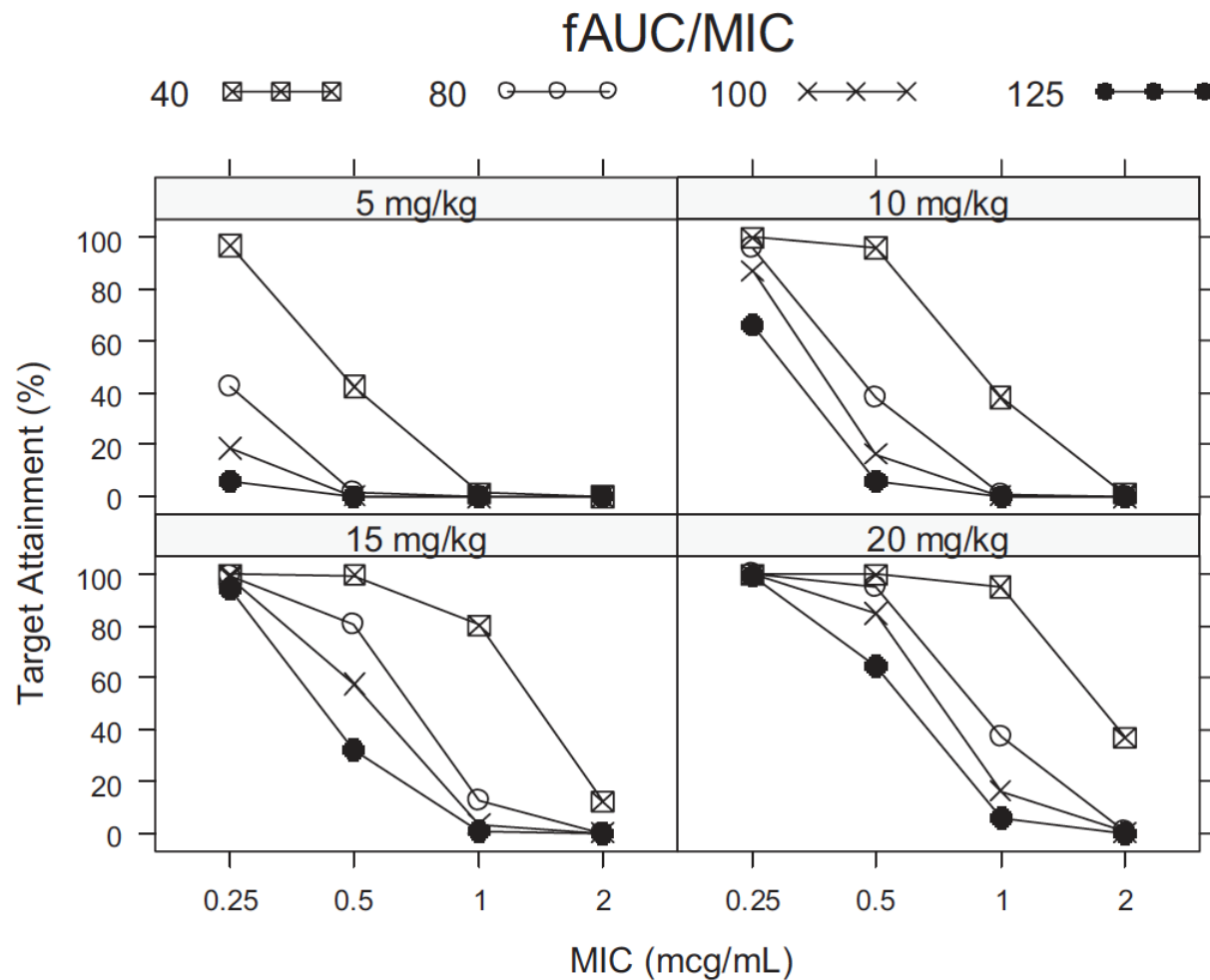
FIGURE 4. Target attainment analysis performed by applying the developed PK model to simulate 10,000 virtual children (50 children/data set × 200 simulations) and calculate likelihood of attaining various *f*AUC/MIC targets (40, 80, 100 or 125) after steady-state dosing of levofloxacin (5, 10, 15 or 20 mg/kg).

Key Questions 2 & 3

How to fine tune in patients ?

Answer : Measure serum concentration and adjust doses for each individual patient,
a.k.a personalized medicine

Do TB patients metabolize drugs differently ?

Answer : No, but their PK is more variable.

Key Question 4

Discuss PK variability / considerations across populations ?

Answer : There is no single predictor of poor drug absorption. Certain patients may be *more* likely than others to malabsorb drugs, but there are many exceptions.

Examples: HIV / AIDS patients, diabetic patients, acutely ill and cachectic patients

The Clinical Pharmacokinetics of Rifampin and Ethambutol in HIV-Infected Persons with Tuberculosis

David C. Perlman,[1] Yoninah Segal,[2] Susan Rosenkranz,[2] Petrie M. Rainey,[3] Rory P. Remmel,[4] Nadim Salomon,[1] Richard Hafner,[5] and Charles A. Peloquin,[6] for the AIDS Clinical Trials Group 309 Team

[1]Beth Israel Medical Center, New York, New York; [2]Statistical and Data Analysis Center/Harvard School of Public Health, Boston, Massachusetts; [3]University of Washington, Seattle; [4]University of Minnesota, Minneapolis; [5]National Institute of Allergy and Infectious Disease, Bethesda, Maryland; and [6]National Jewish Medical and Research Center, Denver, Colorado

Rifampin Plasma Concentrations
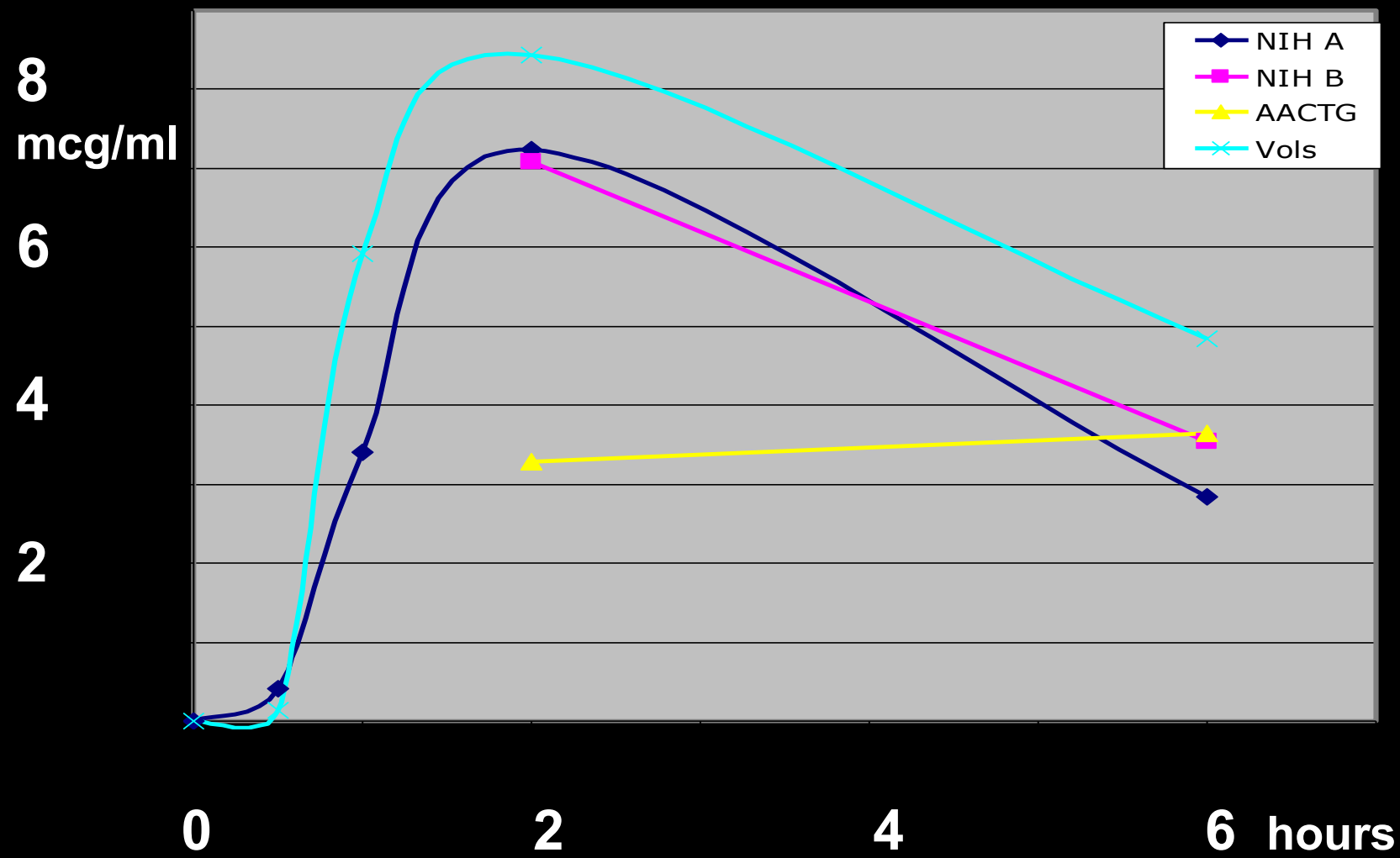
Rifampin 2 hour Sample Variability, 2016

Sample Result
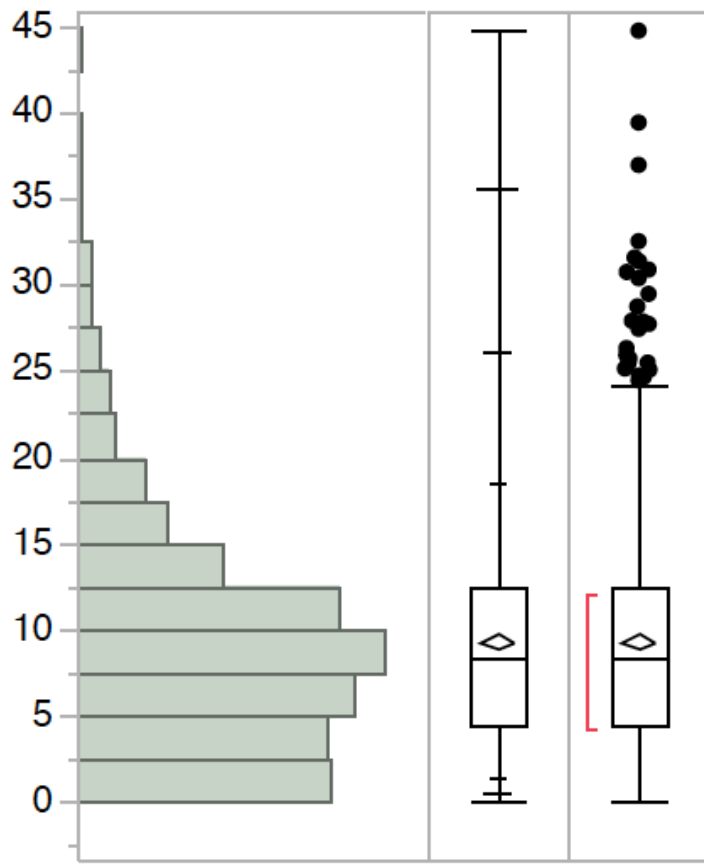
Quantiles

100.0%	maximum	44.72
99.5%		35.62
97.5%		26.11
90.0%		18.50
75.0%	quartile	12.40
50.0%	median	8.43
25.0%	quartile	4.41
10.0%		1.46
2.5%		0.51
0.5%		0.00
0.0%	minimum	0.00

Rifampin 2 hour Sample Variability, 2016
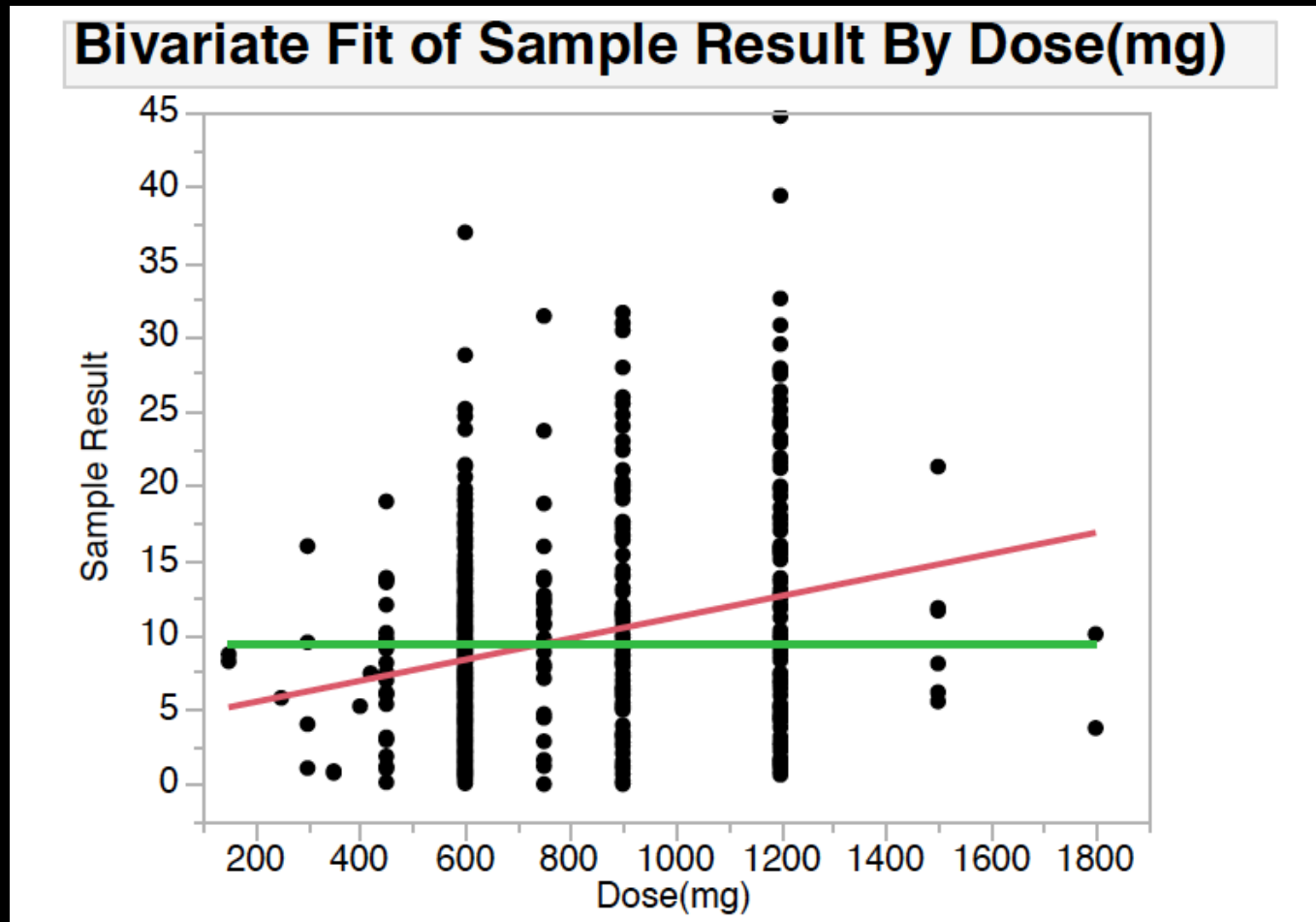
Therapeutic Drug Monitoring (TDM)

The decision to use TDM is the same as

the decision to check a CBC with diff. ,

or the decision to get a CT or MRI.

None of these guarantees the outcome of Tx.

However, all of these inform the clinician

prior to making clinical decisions.

The Role of Therapeutic Drug Monitoring in Mycobacterial Infections

CHARLES PELOQUIN[1]

[1]Infectious Disease Pharmacokinetics Lab, College of Pharmacy, Emerging Pathogens Institute, University of Florida, Gainesville, FL 32610

Why Use TDM ?

In the end, knowing is better than guessing.

Determine the individual MIC.

Determine the individual PK.

Optimize the individual treatment.

Smart Bomb

Dumb Bomb

Key Question 5

How does PK change in TB patients over the course of months, esp. considering drug toxicities, etc. ?

Answer :
- Rifamycins undergo auto - induction
- Isoniazid absorption can improve once the patient starts improving
- Ethambutol, levofloxacin, cycloserine vary with renal function

Key Question 6

How much confidence in Epithelial Lining Fluid (ELF) data ?

Answer : Not well studied with TB drugs. The alternative is to measure drug in cavitary lesions.

Cavitary Penetration of Levofloxacin among Patients with Multidrug-Resistant Tuberculosis

Russell R. Kempker,[a] Aline B. Barth,[b] Sergo Vashakidze,[c] Ketino Nikolaishvili,[c] Irina Sabulua,[c] Nestani Tukvadze,[c] Nino Bablishvili,[c] Shota Gogishvili,[c] Ravi Shankar P. Singh,[b] Jeannette Guarner,[e] Hartmut Derendorf,[b] Charles A. Peloquin,[b] Henry M. Blumberg[a,d]

Division of Infectious Diseases Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA[a]; University of Florida, College of Pharmacy, Gainesville, Florida, USA[b]; National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia[c]; Departments of Epidemiology and Global Health, Emory Rollins School of Public Health, Emory University, Atlanta, Georgia, USA[d]; Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia, USA[e]

TABLE 3 Comparison of free serum and cavitary levofloxacin concentrations among patients with multidrug-resistant pulmonary tuberculosis

Subject[a]	Serum concn at time of resection[b] (μg/ml)	Cavitary concn (μg/ml)	Cavitary/serum concn ratio
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	2.70	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
Median	4.40	4.36	1.33

[a] No cavitary concentration was available for subject 6.
[b] Free serum concentration = measured levofloxacin concentration × 0.75.

Key Questions

PK specific predictors for drug dosages from previous TB trials

Low Isoniazid Concentrations and Outcome of Tuberculosis Treatment with Once-Weekly Isoniazid and Rifapentine

Marc Weiner, William Burman, Andrew Vernon, Debra Benator, Charles A. Peloquin, Awal Khan, Stephen Weis, Barbara King, Nina Shah, Thomas Hodge, and the Tuberculosis Trials Consortium

University of Texas Health Science Center and South Texas Veterans Health Care System, San Antonio, TX; Denver Public Health and Department of Medicine, University of Colorado Health Science Center and National Jewish Medical and Research Center, University of Colorado Schools of Pharmacy and Medicine, Denver, CO; Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA; VAMC and George Washington University Medical Center, Washington, DC; and University of North Texas Health Sciences Center, Fort Worth, TX
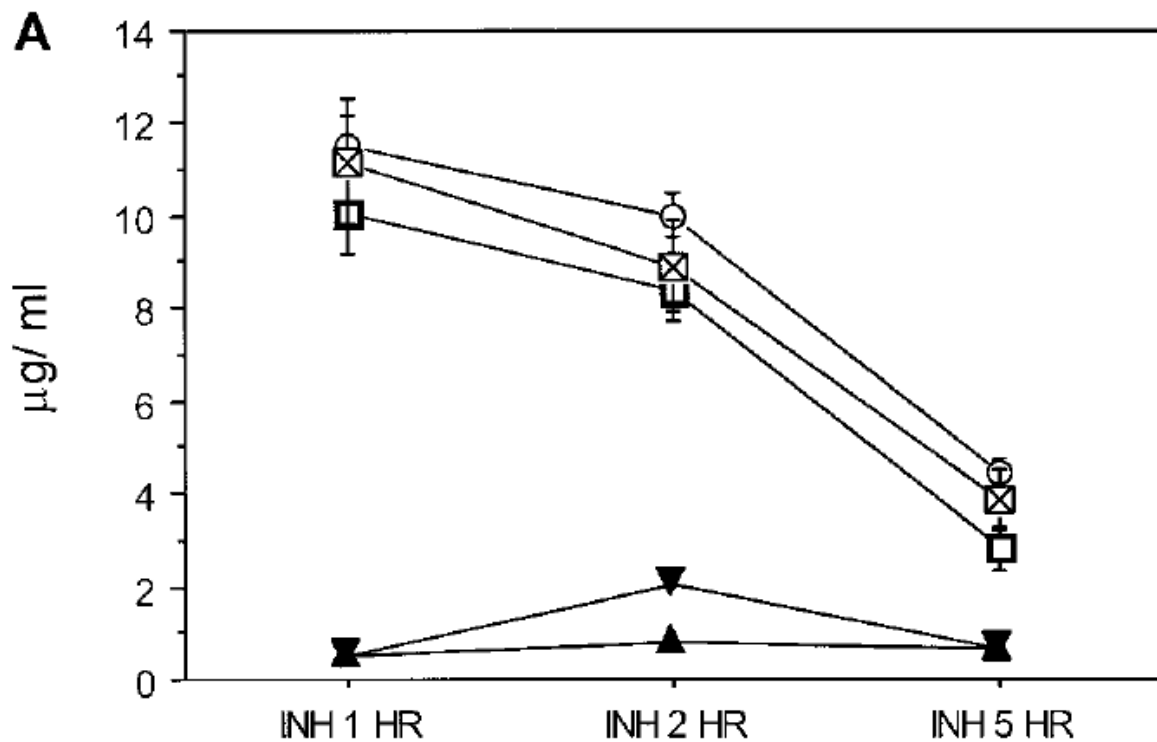
Lowest INH concentrations associated with acquired rifamycin resistance.

Figure 1. Drug concentrations in 154 patients with failure/relapse or cure compared with 2 patients with acquired rifamycin-resistant relapse. (*A*) Mean isoniazid concentrations (± SE µg/ml) are depicted 1, 2, and 5 hours after oral dosing from patients (n = 111) with cure (*open circle*); with drug-susceptible failure/relapse (n = 24) treated once per week with rifapentine/isoniazid(*square*); with drug-susceptible failure/relapse (n = 17) treated twice per week with rifampin/isoniazid (*square with X*); and from two patients with acquired rifamycin-resistant relapse (*triangle*, human immunodeficiency virus (HIV)–seropositive and *inverted triangle*, HIV-seronegative). (*B*) Mean rifampin concentrations (±

Association between Acquired Rifamycin Resistance and the Pharmacokinetics of Rifabutin and Isoniazid among Patients with HIV and Tuberculosis

Marc Weiner,[1] Debra Benator,[2] William Burman,[3] Charles A. Peloquin,[4] Awal Khan,[5] Andrew Vernon,[5] Brenda Jones,[6] Claudia Silva-Trigo,[6] Zhen Zhao,[5] Thomas Hodge,[5] and the Tuberculosis Trials Consortium[a]

[1]University of Texas Health Science Center San Antonio and South Texas Veterans Health Care System, San Antonio, Texas; [2]Veterans' Affairs Medical Center and George Washington University Medical Center, Washington, D.C.; [3]Denver Public Health and Department of Medicine, University of Colorado Health Science Center, and [4]National Jewish Medical and Research Center and University of Colorado Schools of Pharmacy and Medicine, Denver, Colorado; [5]Division of TB Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia; and [6]Los Angeles County/University of Southern California Medical Center, Los Angeles, California

Lower rifabutin AUC associated with failure, relapse, and acquired rifamycin resistance
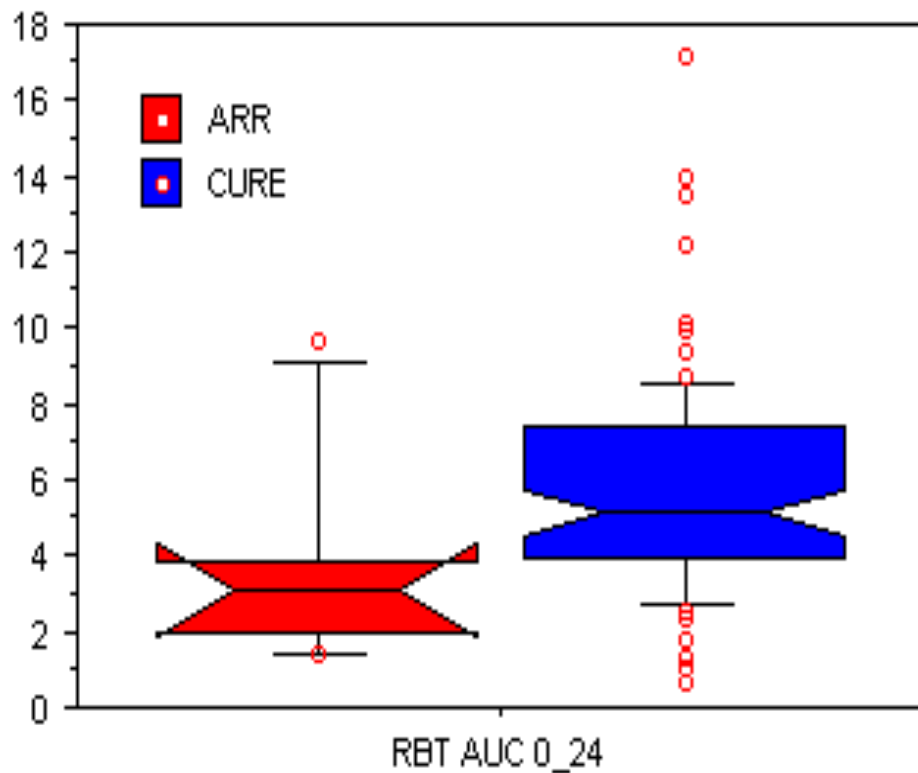
Group	No.	Dose mg/kg Med (IQC)	AUC$_{0-24}$ Med (IQC)	P-Value*
ARR	6	4.6 (3.5 - 5.7)	3.1 (2.0 - 3.8)	
CURE	82	4.8 (4.2 – 6.2)	5.1 (4.0 - 7.4)	0.04

- P for RBT AUC ARR vs. cure, Mann-Whitney
- Odds ratio for CD4 count 1.01
- Odds ratio for RBN AUC 23

Clin Infect Dis 2005; 40: 1481 - 1491., slide by Dr. Weiner

Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis, United States, 2005–2007

Suzanne M. Marks, Jennifer Flood, Barbara Seaworth, Yael Hirsch-Moverman, Lori Armstrong, Sundari Mase, Katya Salcedo, Peter Oh, Edward A. Graviss, Paul W. Colson, Lisa Armitige, Manuel Revuelta, Kathryn Sheeran, and the TB Epidemiologic Studies Consortium

Cost of Developing MDR - TB

Direct costs, mostly covered by the public sector,
averaged $134,000 per MDR TB,
and $430,000 per XDR TB patient.

In comparison, estimated cost per non-MDR TB patient
is $17,000.

Drug resistance was extensive, care was complex,
treatment completion rates were high,
and treatment was expensive.

A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis

Martin J. Boeree[1,2], Andreas H. Diacon[3,4], Rodney Dawson[5,6], Kim Narunsky[5,6], Jeannine du Bois[4], Amour Venter[3], Patrick P. J. Phillips[7], Stephen H. Gillespie[8], Timothy D. McHugh[9], Michael Hoelscher[10,11], Norbert Heinrich[10,11], Sunita Rehal[7], Dick van Soolingen[12,13], Jakko van Ingen[12], Cecile Magis-Escurra[1], David Burger[14], Georgette Plemper van Balen[1], and Rob E. Aarnoutse[14]; on behalf of the PanACEA Consortium

[1]Department of Lung Diseases, [12]Department of Medical Microbiology, and [14]Department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands; [2]University Centre for Chronic Diseases Dekkerswald, Groesbeek, the Netherlands; [3]DST/NRF Centre of Excellence for Biomedical Tuberculosis Research and MRC Centre for TB Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa; [4]TASK Applied Sciences, Cape Town, South Africa; [5]Department of Respiratory Medicine, University of Cape Town, Cape Town, South Africa; [6]The Lung Institute, Cape Town, South Africa; [7]MRC Clinical Trials Unit and [9]Centre for Clinical Microbiology, University College London, London, United Kingdom; [8]The Medical School, University of St. Andrews, St. Andrews Fife, United Kingdom; [10]Department for Infectious Diseases and Tropical Medicine, University of Munich, Munich, Germany; [11]German Centre for Infection Research DZIF, Munich, Germany; and [13]National Institute for Public Health and the Environment, National Mycobacteria Reference Laboratory, Bilthoven, the Netherlands

Dose Ranging Trial to Optimize the Dose of Rifampin

Maximum tolerated dose study :

RIF 10, 15, 20, 25, 30, 35 mg / kg for 14 days

in patients with drug – susceptible TB

[70 kg * 35 mg / kg = 2,450 mg, round to 2,400 mg]

More – than proportional increases in Cmax

and AUC occurred as doses increased.

Am J Respir Crit Care Med 2015; 191: 1058 - 1065.

Dose Ranging Trial to Optimize the Dose of Rifampin

Maximum tolerated dose study :

High inter –individual variability in Cmax and AUC within any given dose (an argument for TDM).

Greatest reduction in sputum colony counts of Mtb were seen with the highest AUC.

Daily Rifapentine for Treatment of Pulmonary Tuberculosis
A Randomized, Dose-Ranging Trial

Susan E. Dorman[1], Radojka M. Savic[2], Stefan Goldberg[3], Jason E. Stout[4], Neil Schluger[5], Grace Muzanyi[6], John L. Johnson[6,7], Payam Nahid[2], Emily J. Hecker[4], Charles M. Heilig[3], Lorna Bozeman[3], Pei-Jean I. Feng[3], Ruth N. Moro[3,8], William MacKenzie[3], Kelly E. Dooley[1], Eric L. Nuermberger[1], Andrew Vernon[3], Marc Weiner[9], and the Tuberculosis Trials Consortium

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]University of California, San Francisco, San Francisco, California; [3]Centers for Disease Control and Prevention, Atlanta, Georgia; [4]Duke University School of Medicine, Durham, North Carolina; [5]Columbia University Medical Center, New York, New York; [6]Uganda–Case Western Reserve University Research Collaboration, Kampala, Uganda; [7]Case Western Reserve University School of Medicine, Cleveland, Ohio; [8]CDC Foundation Research Collaboration, Atlanta, Georgia; and [9]University of Texas Health Science Center at San Antonio and the South Texas VAMC, San Antonio, Texas

Daily Rifapentine for Treatment of Pulmonary Tuberculosis

High inter –individual variability in Cmax and AUC within any given dose (an argument for TDM).

High RPNT exposures (AUC) were associated with high levels of **sputum sterilization** at the completion of 8 weeks of treatment (end of intensive phase)

Dorman et al. Am J Respir Crit Care Med 2015; 191: 333 - 343.

Role for PK in Treating TB

TDM allows you to <u>individualize</u> therapy.

TDM allows you to <u>optimize</u> the pharmacodynamically - linked variable [typically Cmax or AUC].

" But that is SO EXPENSIVE "

10,000 patients times (> all US TB patients)

$70 per test times

8 tests per patient

_____

$5,600,000

Compare … Sports at Univ. Florida

WHAT DOES THE UAA'S RECORD $128 MILLION BUDGET ENTAIL?

Savanna Collins   June 12, 2017   Feature Sports News, Gator Sports   105 Views

GAINESVILLE, Fla. — The University of Florida Athletic Association has approved their budget for the 2017-2018 at $218 million on Monday—up $6 million from last financial year.

- Football – Expense: $25.46 million Revenue: $82.55 million
- Men's Basketball – Expense: $6.88 million Revenue: $13.48 million

- All other sports- Expense: $17.6 million Revenue: $3.19 million

Thanks to our top team of researchers ...

Thanks

- **<u>The University of Florida IDPL Team</u> :**
  TJ Zagurski, Kyung Mee Kim, Emily Graham,
  Yasuhiro Horita, Stacy Stoneberger

- **<u>The University of Florida IDPL Students</u> :**
  Wael Alghamdi, Mohammad Alshaer, Yang Zhao
  Toni Tablante, Carlos Alemán, Maggie Kudlinski

http://idpl.pharmacy.ufl.edu