Clofazimine pharmacokinetics in drug-resistant TB

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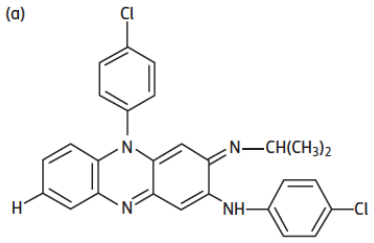
< 10 years

50 years

Everywhere



Lepromatous leprosy

Early 2000's
Small observational studies for MDR-TB
Part of multidrug regimen

2010
Bangladesh
Other observational data

1957
Discovery

Inconsistent activity against Mtb in animal models
Weird PK
Toxicity
Other more potent drugs

1997
"Clofazimine has no place in the treatment of MDR-TB" – WHO

2006 – 2011
No recommended for routine use
Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four.

2015
Small RCT

2017
STREAM-1

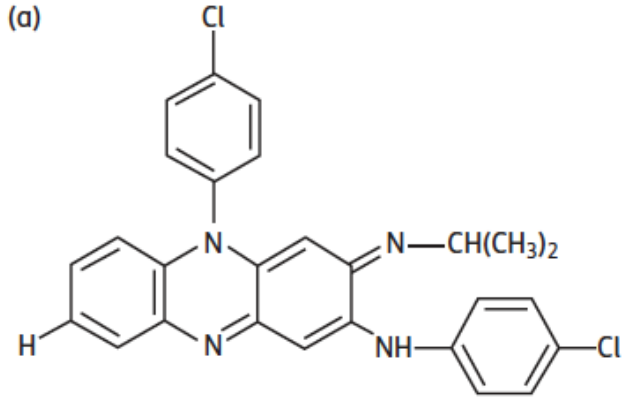
Rapid Communication:

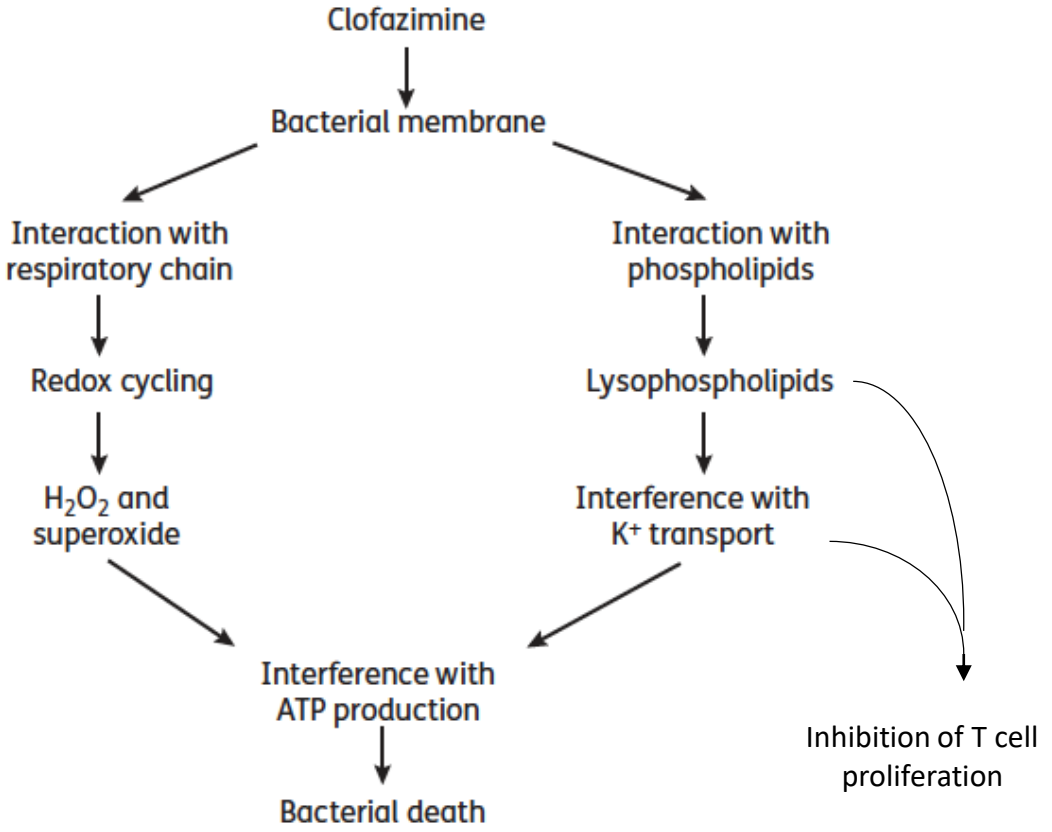
Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Activity

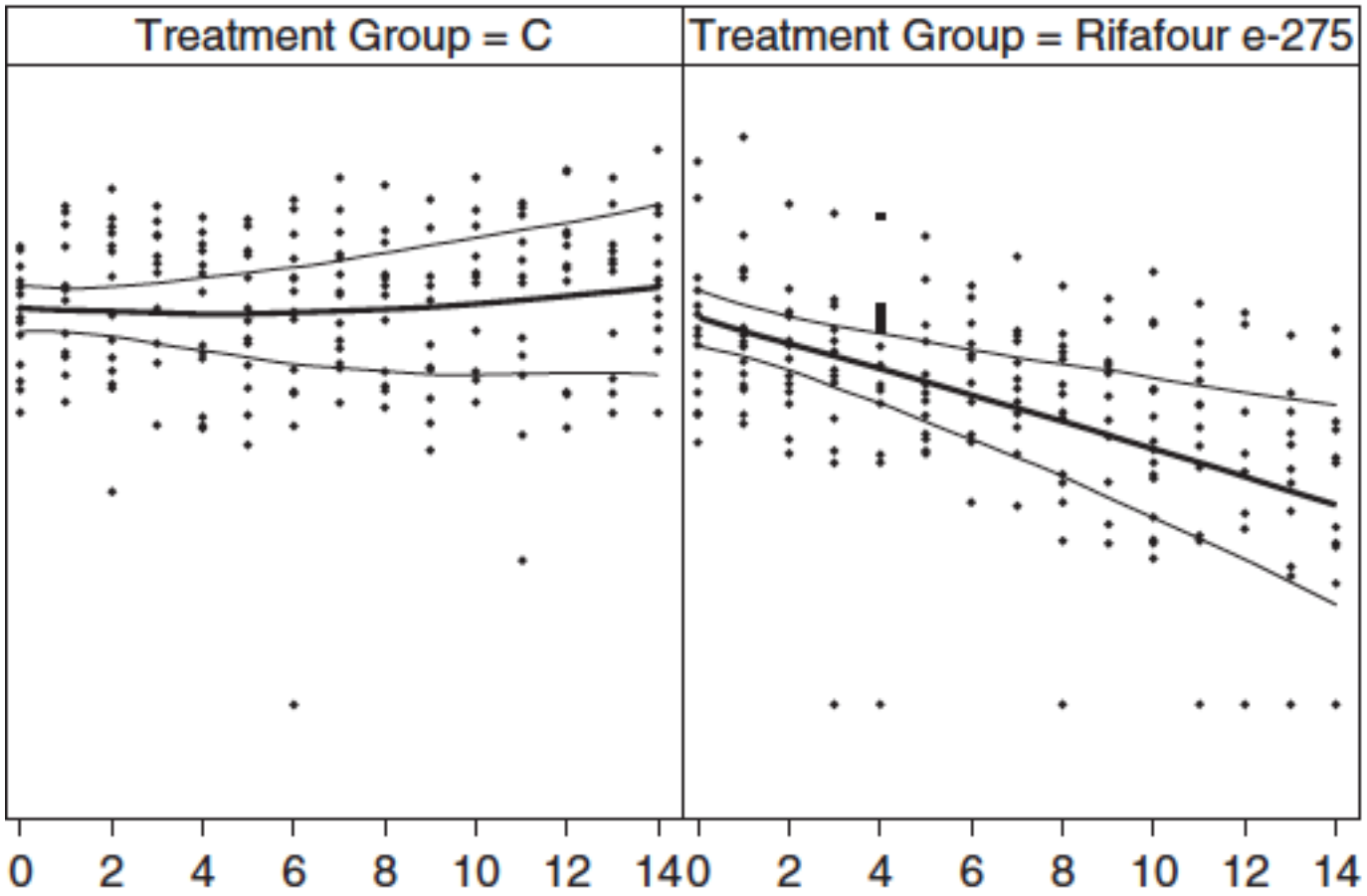
- Riminophenazine pigment derived from lichen
- Likely membrane-destabilizing agent
- *In vitro* activity against Mtb
  - **MIC ≤ 0.25 µg/mL**
  - More potent against slow-growing Mtb
- Anti-inflammatory effects





Cholo JAC 2012

No observed EBA in DS-PTB patients

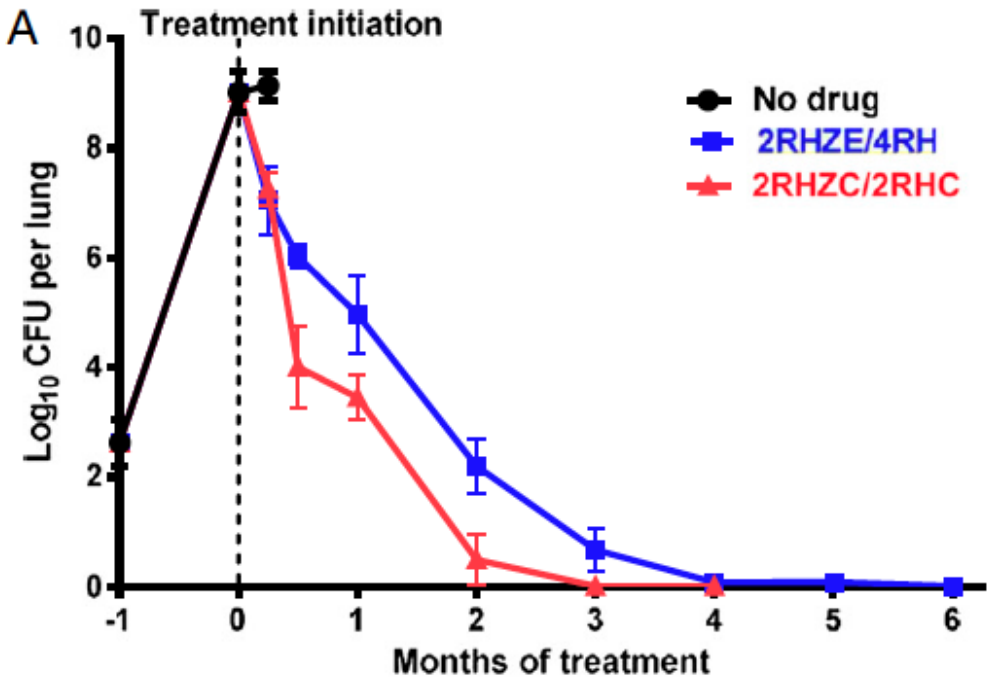


- Is the delay related to the need for depletion of energy stores?
- Does it reflect dominant activity on slow persister phenotypes?
- Limitations of EBA to predict sterilizing ability

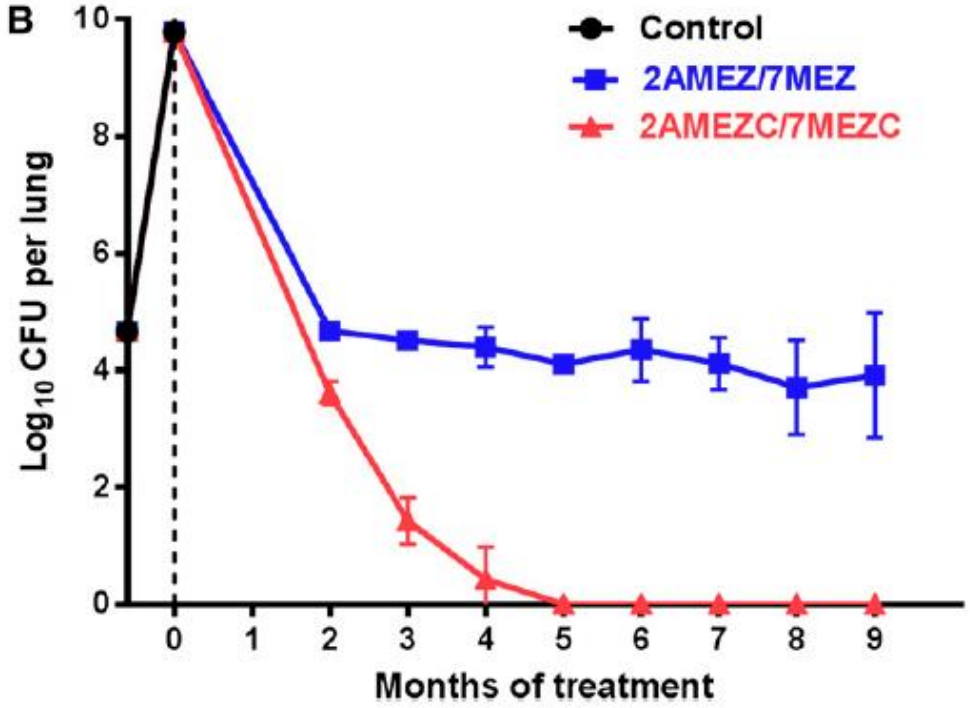
Diacon AJRCCM 2015

Treatment shortening potential and potent sterilizing ability in BALB/c mice

With first line therapy



With second line therapy

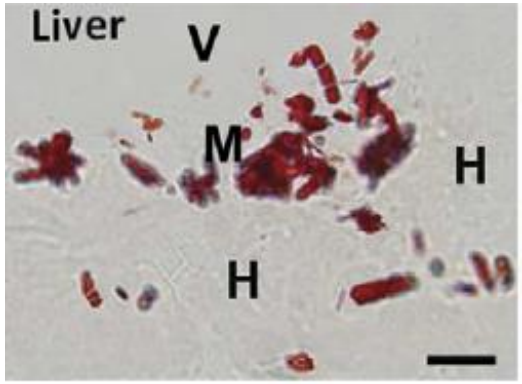


No additive effect in first week, regardless of dose or concentration

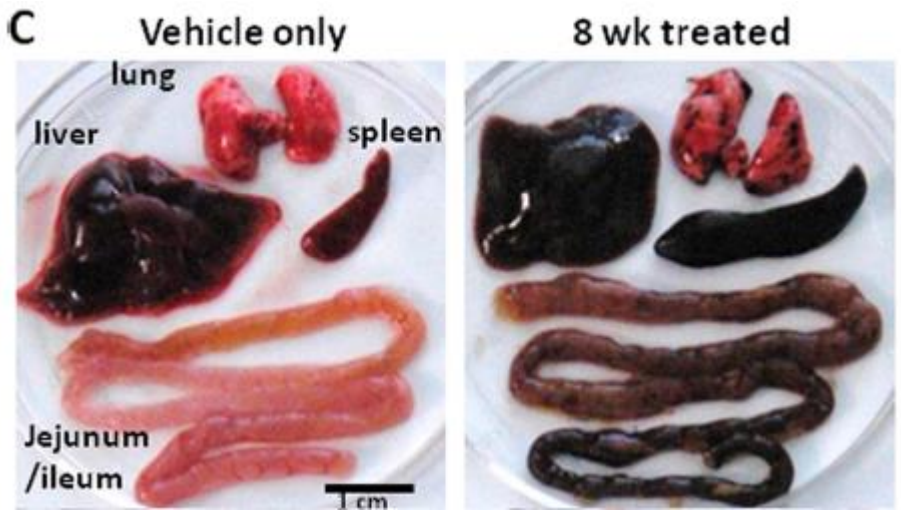
Tyagi PNAS 2015
Grosset Am J Respir Crit Care Med 2013

Unusual PK

- Massive intracellular accumulation in organs (CLDIs)
- Extremely long half-life



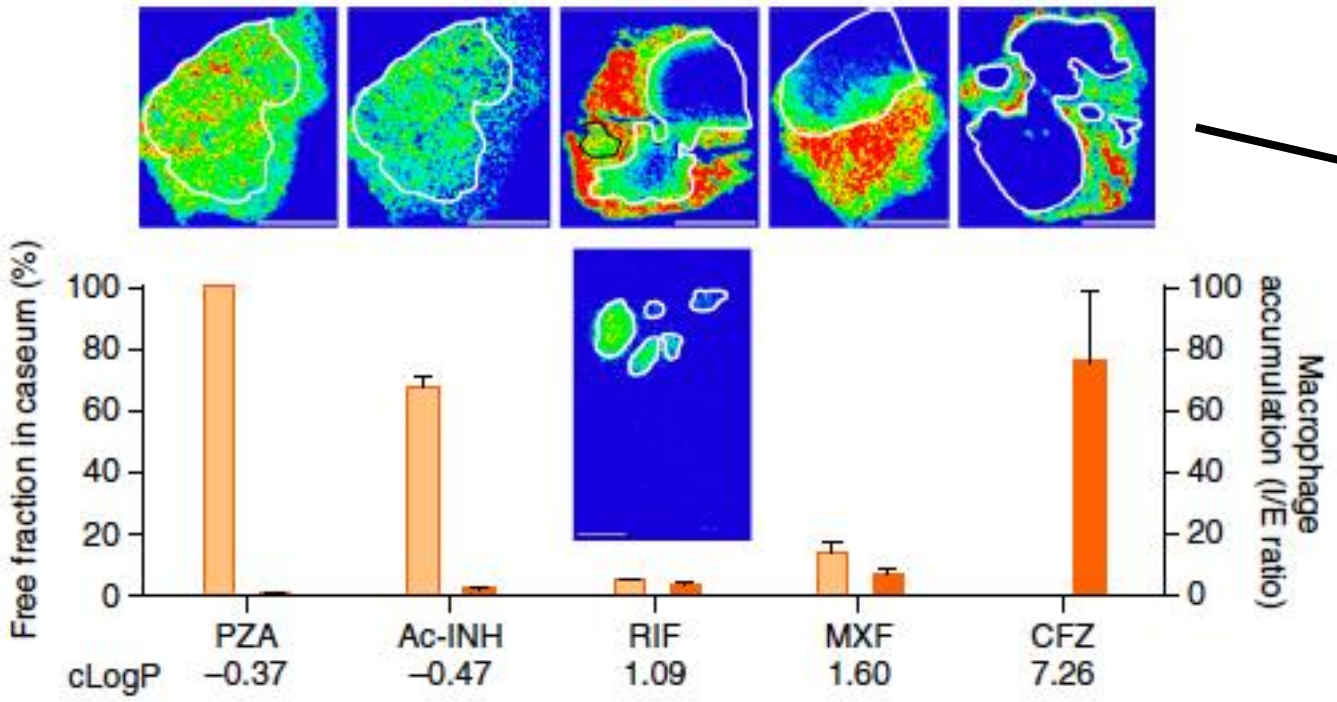
The data of Tables 3 and 4 show that less than 1% of the body's content of B663 is excreted per day. Therefore, the t ½ of B663 in man is greater than 69 days. At this rate of excretion, one may readily calculate that the patient receiving 100 mg B663 daily will accumulate 10 gm of the drug if this dosage is administered indefinitely. The t ½ of B663 for man is probably considerably longer than the minimal estimate of 69 days, and the quantity accumulated proportionately greater than 10 g for a 100-mg daily regimen.

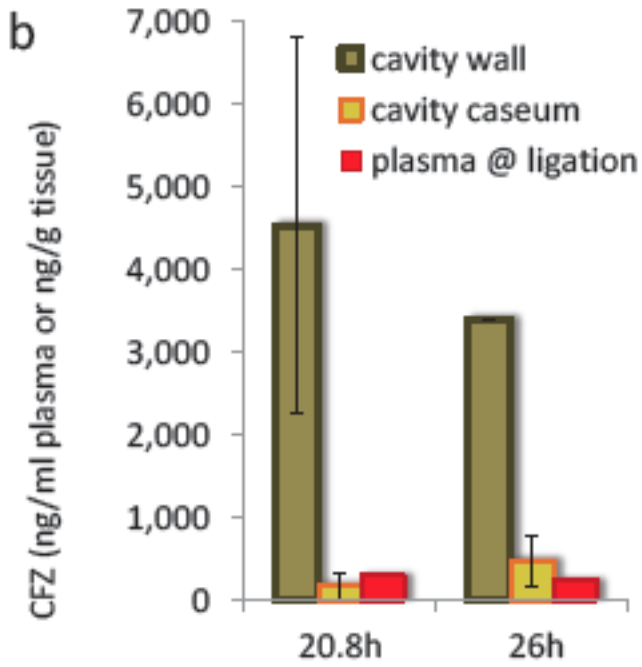


Louis Levy AJTMH 1974

Baik PLOS ONE 2012
Baik AAC 2013

Accumulates in macrophages



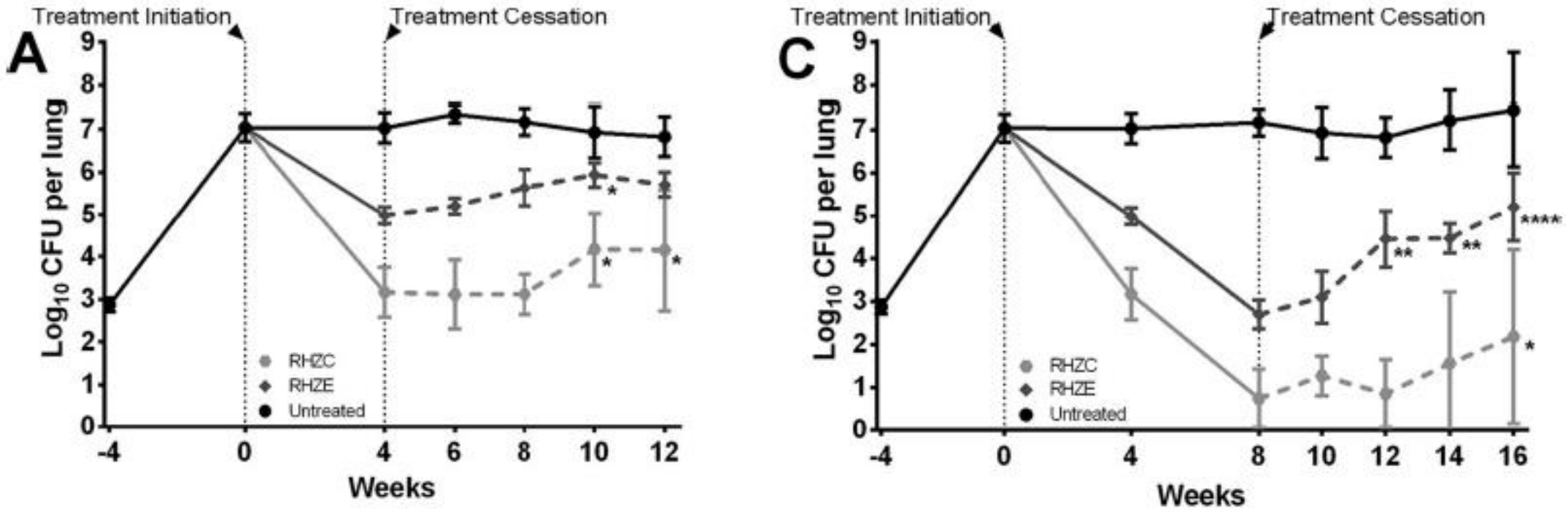


Penetration into macrophages but not caseum

Very low plasma concentrations
Accumulates in macrophages

Prideaux Nature Med 2015

Efficacy could be related to serum concentrations

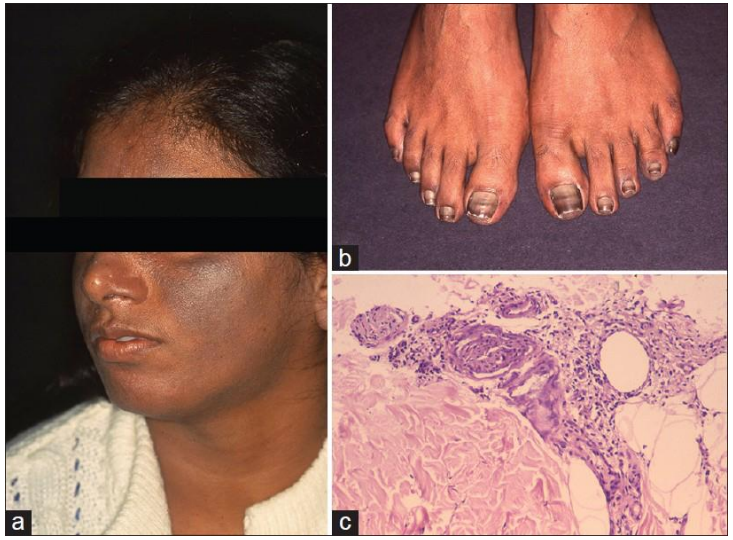


Sustained antimicrobial activity associated with time <u>serum concentration</u> remained ≥ MIC (0.24 µg/mL)

Serum clofazimine levels appear critical to antimicrobial activity

Swanson AAC 2016

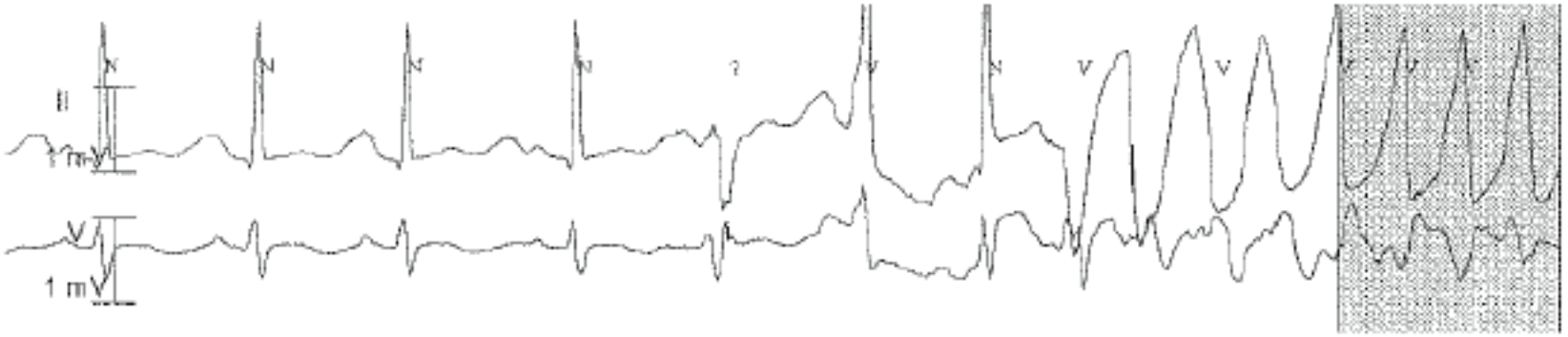
Adverse events: skin changes and potent QT effects



Most frequent AE (universal)

- Can occur within 2 weeks
- Suicides reported as a result of skin changes

How are these related to drug exposures (PK variability)?



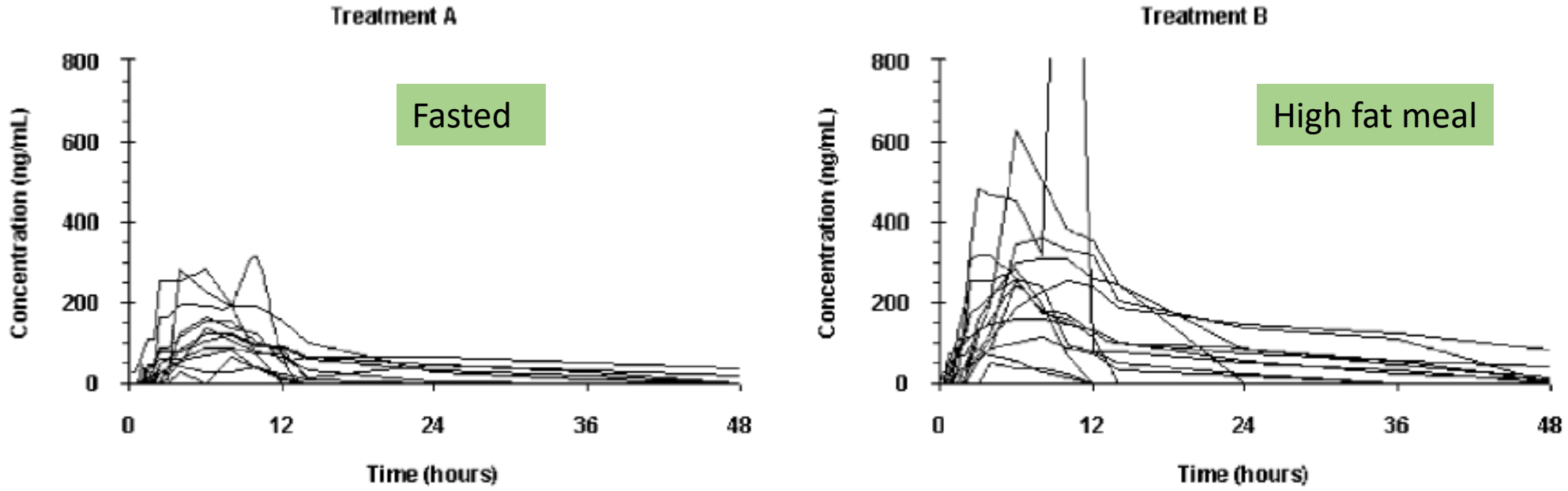
QT prolongation

- Clinical implications?
- Are there PK/PD interactions with other TB drugs?

Hwang 2014 BMJ Open

High PK variability in healthy volunteers

Bioavailability influenced by food
Very low plasma concentrations



Nix Tuberculosis 2004

PK data from patients with drug-resistant TB

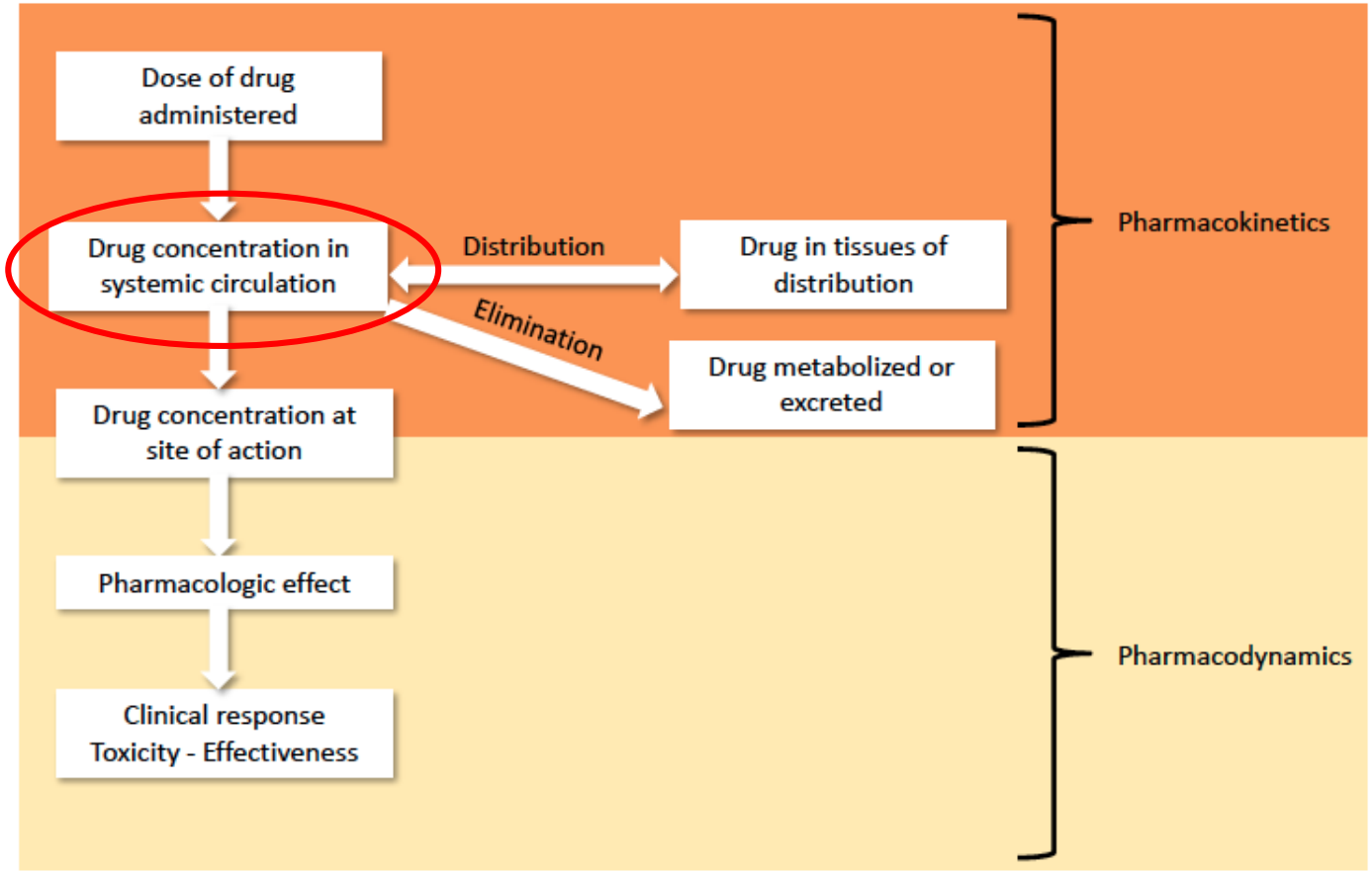
Intentionally blank

Importance of understanding clofazimine PK

- PK variability of antituberculosis agents associated with adverse treatment outcomes and emergent resistance
- Exposures may be different in our population
  - HIV
  - Genetics
  - Clinical factors
  - DDIs
- Estimating probability of achieving PK/PD targets may inform dose optimization

Aims of non-compartmental analysis

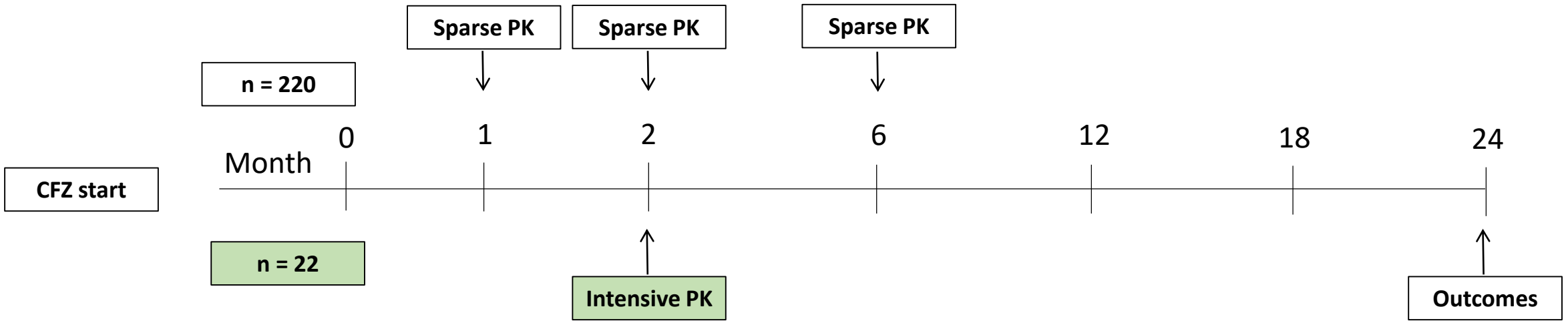
1. Describe the pharmacokinetics of clofazimine in a population of patients with drug-resistant TB in SA
2. Explore effect of key covariates on exposures



Methods

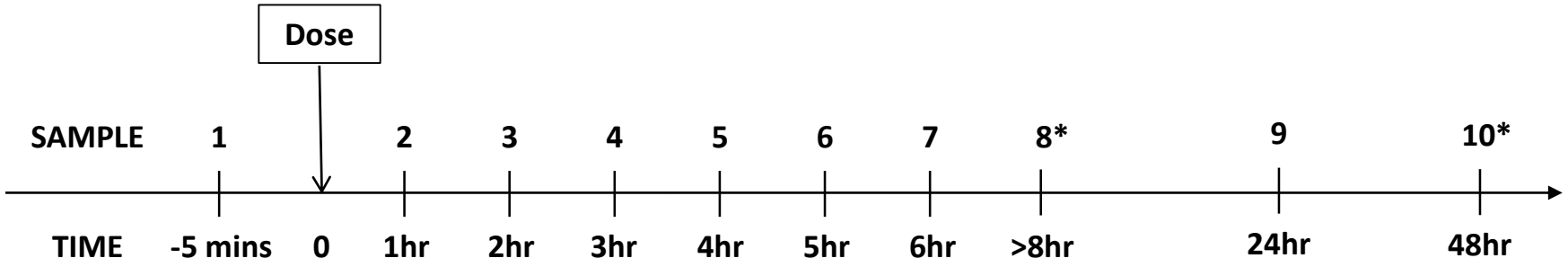
Open-label prospective PK study nested in observational cohort:

PROBeX – James Brust
Safety, PK, and resistance to bedaquiline in pre-XDR, XDR-TB and HIV Age > 18, DR-TB, HIV and pregnancy included 220 participants, followed for 24 months



Methods

Single intensive PK visit at after observed dose and standardized meal



* Some participants

Non-compartmental analysis

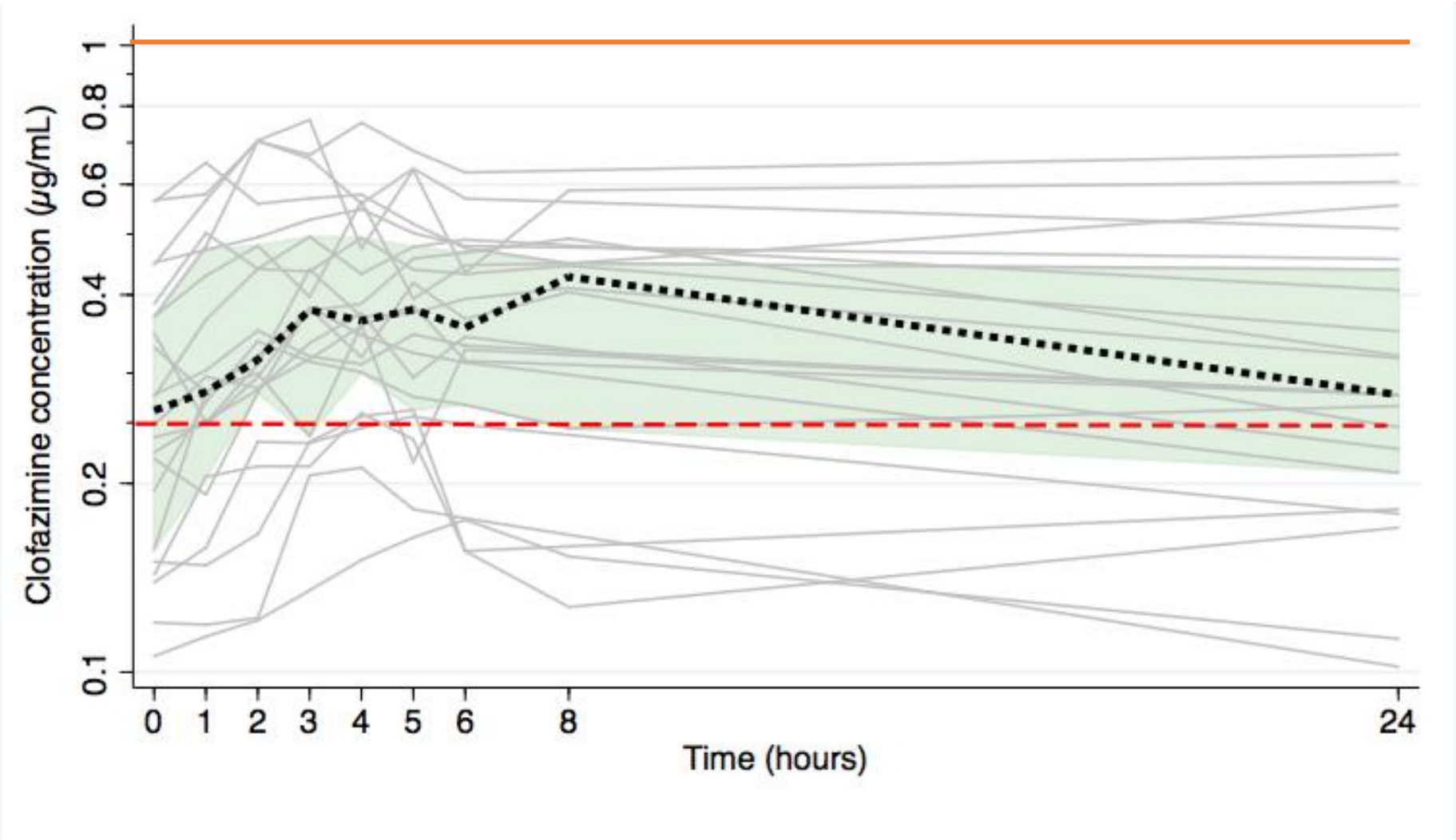
- PK parameters
- Linear regression to determine associations with $AUC_{0\text{-}24}$

Patient characteristics

Variable	**n = 22**
Age, years	29 (25 – 44)
Male sex	11 (50)
Weight, kg	55.2 (48.0 – 64.8)
Fat-free mass, kg	42.0 (38.4 – 47.9)
Percentage fat, %	22.9 (12.4 – 37.2)
BMI, kg/m^2	**19.1 (17.5 – 24.5)**
Albumin, g/L	**38 (35 – 40)**
Ethnicity Black Mixed	 6 (27) 16 (73)
HIV positive	**9 (41)**
Current ART	9 (100)
Current LPV/r	4 (44)
Creatinine, µmol/L	58 (52 – 71)
Creatinine clearance, mL/min	115 (100 – 138)
Duration on clofazimine, days	**71 (62 – 80), range (18 – 97)**
Dose, mg/kg	1.8 (1.5 – 2.1)

Body fat significantly higher in women:
37.1% vs 12.8% in men
$p < 0.0001$

Concentration-time profiles



PK parameters

Parameter	AUC_{0-24} (µg.h/mL)^	$AUC_{0-\infty}$ (µg.h/mL)*	C_{max} µg/mL	T_{max} (h)	$T_{1/2}$ (h)
Number of patients	22	17#	22	22	17#
Median	7.673	28.659	0.401	4	53.5
Interquartile range	6.015 – 10.858	17.605 – 36.801	0.337 – 0.548	3 - 5	31.2 – 75.4
%CV	41.7	171.2	39.3		

^ AUC calculated by trapezoidal method;
*Calculated using an exponential extension from the last point of AUC_{0-24}
Not calculated for patients in whom the clofazimine concentration was either increasing or not decreasing at the last sampling time point

Higher exposures but similar C_{max} to healthy volunteers
Similar absorption but lower weight in TB patients?

Higher exposures compared to EBA study
Longer duration of therapy

Diacon AJRCCM 2015
Nix Tuberculosis 2004

Predictors of AUC_{0-24}: not significant

	Univariable	
$[e^{(ß)} – 1]*100$	**AUC_{0-24} change % (95% CI)**	**P value**
Age Per 10 year increase	-12.0 (-26.5 to 5.3)	0.152
Black African	-18.3 (-48.1 to 28.7)	0.365
HIV positive	**-14.4 (-43.5 to 29.4)**	**0.441**
Current LPV/r	**14.3 (-32.9 to 94.6)**	**0.607**
Creatinine, µmol/L	-0.7 (-2.2 to 0.8)	0.336
Duration on clofazimine Per 30 days	5.8 (-26.9 to 53.0)	0.754

Predictors of AUC_{0-24}: significant

	Univariable	
$[e^{(ß)} – 1]*100$	**AUC_{0-24} change % (95% CI)**	**P value**
Male sex	**65.5 (17.8 to 132.6)**	**0.006**
Weight Per 10 kg increase	**-16.2 (-28.6 to -1.8)**	**0.031**
Percentage body fat Per 10% increase	**-19.4 (-28.8 to -8.7)**	**0.002**
BMI	**-4.9 (-7.9 to -1.7)**	**0.005**
Albumin, g/L	- 3.9 (-7.9 to 0.4)	0.071
Dose, mg/kg	66.2 (-3.0 to 184.9)	0.063

Predictors of AUC_{0-24}

	Univariable		Multivariable	
$[e^{(ß)} – 1]*100$	**AUC_{0-24} change % (95% CI)**	**P value**	**AUC_{0-24} change % (95% CI)**	**P value**
Male sex	65.5 (17.8 to 132.6)	0.006		
Age Per 10 year increase	-12.0 (-26.5 to 5.3)	0.152	-11.4 (-22.3 to 1.1)	0.069
Black African	-18.3 (-48.1 to 28.7)	0.365		
Percentage body fat Per 10% increase	**-19.4 (-28.8 to -8.7)**	**0.002**	**-18.0 (-26.9 to -7.9)**	**0.002**
Albumin, g/L	**- 3.9 (-7.9 to 0.4)**	**0.071**	**-3.3 (-6.5 to 0.03)**	**0.048**
HIV positive	-14.4 (-43.5 to 29.4)	0.441		
Current LPV/r	14.3 (-32.9 to 94.6)	0.607		
Creatinine, µmol/L	-0.7 (-2.2 to 0.8)	0.336		
Duration on clofazimine Per 30 days	5.8 (-26.9 to 53.0)	0.754	23.0 (-5.2 to 59.7)	0.112

Similar findings for C_{max}

Limitations

- Sampling not designed around clofazimine PK
- Single sampling occasion – cannot determine intra-individual variability
- Varying durations on therapy
- Not at steady state (would be around 6 months)
- No observed dosing at 24 hours – uncertain trough concentrations

Conclusions and research priorities

- First PK study of clofazimine in patients with drug-resistant TB and HIV
- High PK variability
- Exposure not influenced by HIV, strongly influenced by body fat
- Plasma exposures of some patients below WT MIC and all below CC: what are the implications?

<u>Next steps</u>

- Integrate sparse PK data into a population PK model
- Explore exposure-response relationships (efficacy and toxicity)
- Understand toxicity better: quantify skin changes, independent effect on QT

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