JOHNS HOPKINS
MEDICINE

DIVISION OF
CLINICAL
PHARMACOLOGY

The Time Has Come for Injectable Sparing Treatment Regimens for Multidrug-Resistant Tuberculosis (MDR-TB) in Children

Webinar (Sentinel Project and DR-TB STAT)

April 7th, 2017

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Disclosures: EDW is protocol vice-chair for the below trial. Otsuka, the manufacturer of delamanid, is donating study drug and sharing PK modelling and safety PK data from their ongoing trials in children.

IMPAACT 2005: A Phase I/II Open-label, Single-Arm Study to Evaluate the PK, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in Children with MDR-TB with and without HIV

IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network

New York : National Child Welfare Association : Co-operating with Natl. Assn. for the Study and Prevention of Tuberculosis (1922)

Library of Congress, http://hdl.loc.gov/loc.pnp/ds.06489

“Chains of Habit are too light to be felt until they are too heavy to be broken.”

--The Oracle of Omaha

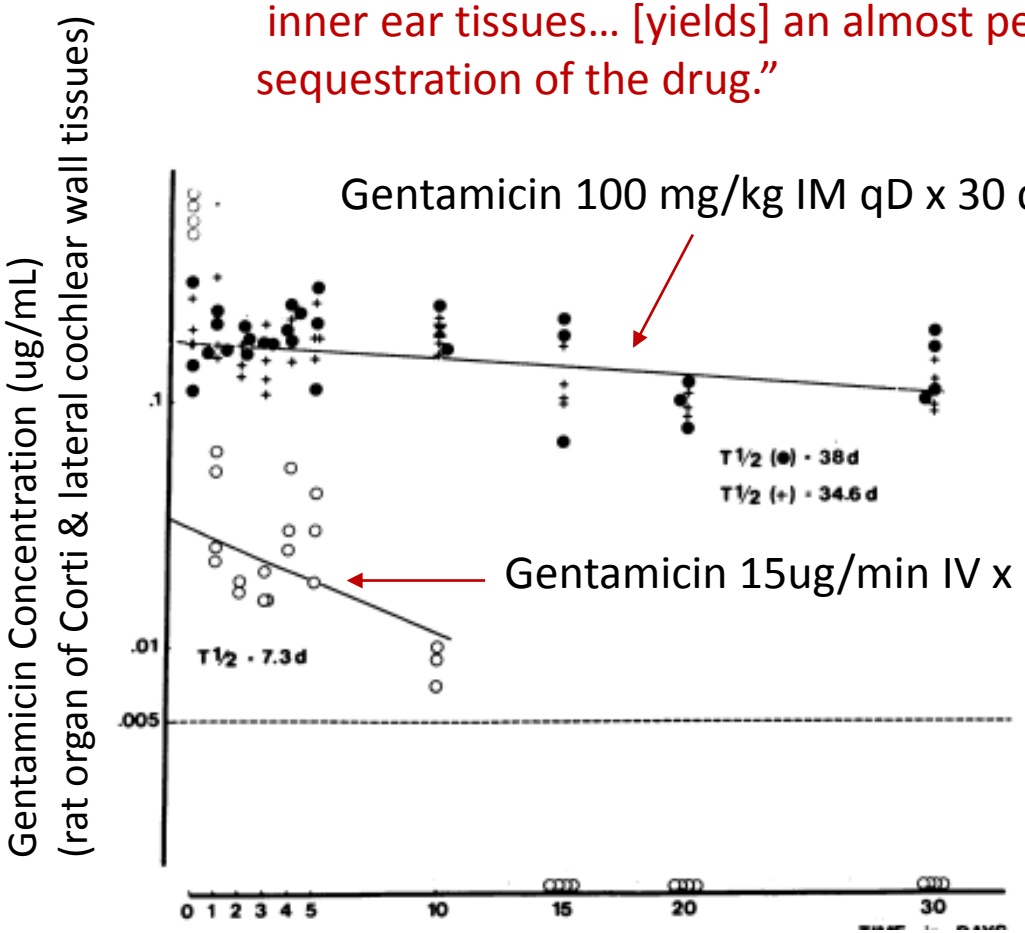
(Warren Buffet)

Objectives

- Review evidence on injectable agents (amikacin, kanamycin, and capreomycin)
  - Toxicities of injectable agents
  - Unclear contribution of injectables to *standard* MDR-TB treatment efficacy
  - Increasing availability of new and repurposed drugs (BDQ, DLM, CFZ, LZD)
- Review evidence on new and repurposed drugs in children with MDR-TB
  - Clinical Pharmacology/ Practical Parameters
  - Efficacy
  - Toxicity
- Rationale for injectable sparing regimen
  - Children have paucibacillary disease & fairly good treatment outcomes
  - Substituting less toxic, more effective drugs for injectables should improve outcomes
  - Ethical aspects

Injectable Ototoxicity

"The extremely slow half-life of disappearance from the inner ear tissues… [yields] an almost permanent sequestration of the drug."



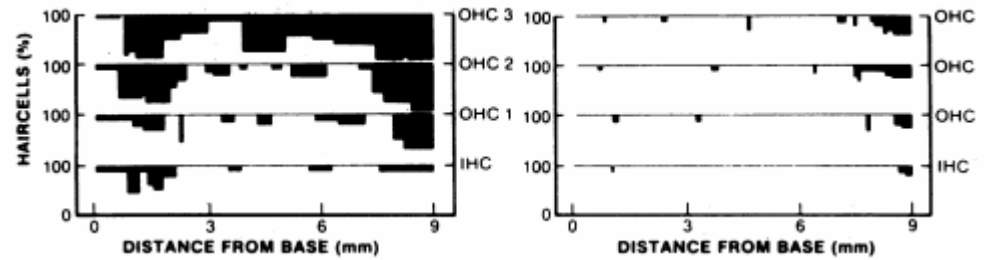
[Tran Ba Huy P *et al.*, *J. Clin Invest.* 1986 (77); 1492-1500.]

Table I. Half-lives of Disappearance (in Days)

Tissues	After 3-h infusion of 30 μg/min (IIIa)	After 30 d of daily 100 mg/kg i.m. injection (IIIb)
Plasma	1–16.9*	2–17.5*
Renal cortex	5.6	14.5
Liver	4.4	10.7
Heart	3.9	14.2
Lung	6.6	18.2
Spleen	4.6	24.1
Cochlear tissues‡	0.25–7.3*	
Organ of Corti		34.6
Lateral wall		38

Half-lives of disappearance of gentamicin from plasma and tissues in group III.
* A bicompartmental analysis was made.
‡ Organ of Corti and lateral wall were pooled.

Cytocochleograms depicting death of hair cells (in black) seen on histology in rats given gentamicin:



100 mg/kg IM qD x 30 days 15ug/min IV x 3 hrs

Sensory cells of the cochlea do not regenerate.

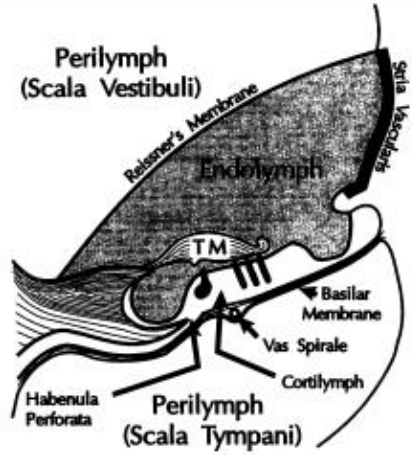
AUC in perilymph correlates w AUC in plasma & predicts ototoxicity in

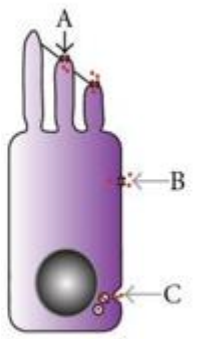
TABLE 1. Amikacin concentrations in plasma and perilymph after different dosing rates and durations

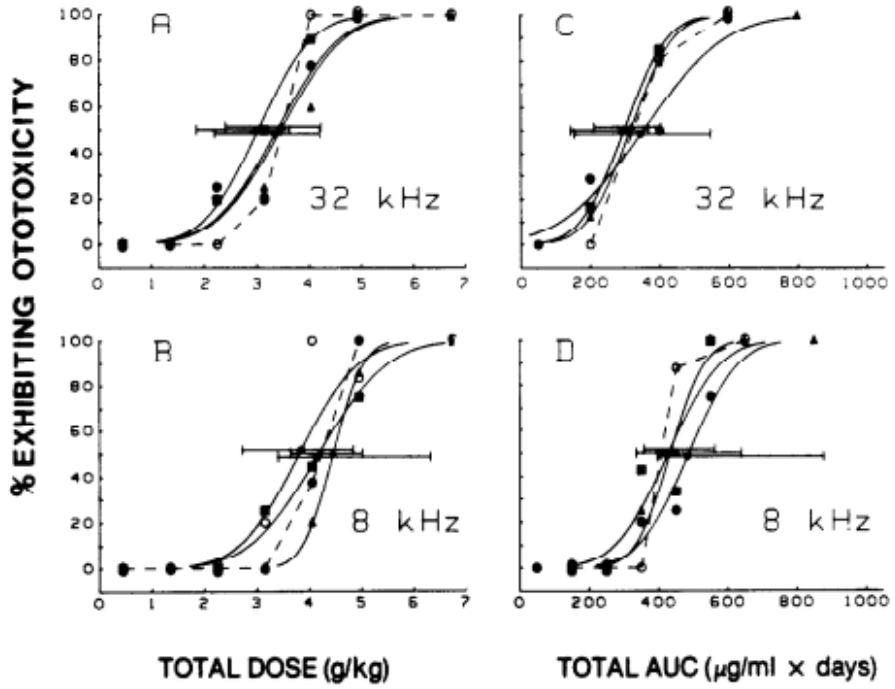
Dosing rate (μg/min)	Duration (days)	Total dose (g)	Amikacin level (μg/ml) in:		Ratio of level in perilymph/ plasma[c]
			Perilymph[a]	Plasma[b]	
47	1	0.07	8.7	21.1	0.41
	2	0.14	9.3	20.2	0.46
	16[d]	*1.09*	*8.4*	*19.3*	*0.44*
	24[e]	***1.63***	***7.7***	***13.4[f]***	***0.57***
94	1	0.14	20.7	38.3	0.54
	2	0.27	19.6	33.8	0.58
	8	*1.09*	*19.8*	*33.5*	*0.59*
	12	***1.63***	***20.1***	***34.7***	***0.58***
188	1	0.27	34.0	69.5	0.49
	2	0.54	28.1	70.4	0.40
	4	*1.09*	*38.0*	*78.3*	*0.49*
	6	***1.63***	***39.0***	***74.9***	***0.52***
377	1	0.54	67.5	133.9	0.50
	2	*1.09*	*72.8*	*159.1*	*0.46*
	3	***1.63***	***75.2***	***157.9***	***0.48***

TABLE 2. Total perilymph AUC at threshold and strongly ototoxic total doses

Dosing rate (μg/min)	Total perilymph AUC (μg · day/ml) at[a]:	
	Total dose of 1.09 g	Total dose of 1.63 g
47	134.4	185.2
94	158.2	241.2
188	152.1	234.2
377	145.5	225.8







[Huth ME *et al., Int. J. Otolaryngol* 2011; 2011]

[Beaubien AR, *et al.*, *Antimicrobial Agents & Chemotherapy* 1991; 1070-1074; Beaubien AR *Am J Otolaryngol*. 1989; 10(4):234-43]

Injectables commonly cause severe, often-irreversible toxicities in

- Injectables for MDR-TB given over prolonged periods (median 4 months→**AUC** ⬆⬆)

- **Ototoxicity**
  - ≥ 25% (25 of 94) of children, often irreversible [Seddon JA et al Thorax 2014;69(5):458-64]
  - Significantly affects neurocognitive development, psychosocial functioning, school performance [Franck C et al, *BMCID* 2014;14:426.]
  - Speech/ language comorbidities
  - Programmatic challenge
    - Can develop before it is perceived (in the high frequency ranges) [Garcia-Prats A et al., *Exp. Opin. Drug Safety* 2016(15); 11]

- Profound source of **physical and emotional suffering** for children and caregivers [Isaakidis P et al, *Trop. Med & Int.* Health, 2013;18(9):1128-33; Seddon JA et al Thorax 2014;69(5):458-64]

II. The contribution of injectables to *standard* MDR-TB treatment efficacy is unclear

for *Mycobacterium tuberculosis*, H37Rv

Drug	*MIC (µg/ml)*	*MBC (µg/ml)*
Isoniazid	0.2	0.4
Amikacin	0.2	0.4
Kanamycin	0.8	0.8
Streptomycin	3.1	3.1

- **In vitro**--amikacin weakly bactericidal; kanamycin bacteriostatic [Sanders WE et al Tubercle 1982;63(3):201-8.]
- **EBA**-- Amikacin 5-15mg/kg/day has ***no early bactericidal activity*** [Donald PR et al IJTLD 2001;5(6):533-8; Jindani A et al Am Rev Resp Dis 1980;121(6):939-49.]

Table 2 Viable counts of colony forming units (cfu) of tubercle bacilli in sputum collections before treatment (S1) and after treatment for 2 days (S3) together with the early bactericidal activity (EBA)

Treatment group	Patients (*n*)	Viable count (log_{10} cfu/ml) S1 (SD)	S3 (SD)	Mean EBA (SD)	95%CI
Amikacin					
5 mg/kg	12	6.873 (0.623)	6.792 (0.729)	0.0405 (0.1004)	−0.0163–0.0973
10 mg/kg	13	7.005 (0.417)	6.914 (0.424)	0.0453 (0.1441)	−0.0432–0.1337
15 mg/kg	15	7.194 (0.601)	7.090 (0.559)	0.0518 (0.0962)	−0.0108–0.1144
Isoniazid 6 mg/kg	9	6.973 (0.723)	5.944 (0.796)	0.5147 (0.1729)	0.4018–0.6276
No drug	10	7.002 (0.757)	6.921 (0.753)	0.0406 (0.113)	−0.0296–0.1108

SD = standard deviation.

Table V. Results of therapy in mice infected with *M. tuberculosis* H37Rv: Effect of streptomycin, kanamycin and amikacin on macroscopic surface lung lesions.

Drug	*Dosage*	*Average number of surface lung lesions per animal*		
		30 Days	*60 Days*	*90 Days*
None	—	50	50	50
Streptomycin	10 mg/kg/da	2	50	50
Kanamycin	10 mg/kg/da	1	50	50
Amikacin	5 mg/kg/da	35	11	12[a]
Amikacin	10 mg/kg/da	7	17	20[a]
Amikacin	15 mg/kg/da	12	1	0

[a]Several animals in these two groups only were devoid of lesions

Table I. Minimum inhibitory (MIC) and minimum bactericidal (MBC) concentrations of drugs for *Mycobacterium tuberculosis*, H37Rv

Drug	*MIC (μg/ml)*	*MBC (μg/ml)*
Isoniazid	0.2	0.4
Amikacin	0.2	0.4
Kanamycin	0.8	0.8
Streptomycin	3.1	3.1

Table IV. Results of therapy in mice infected with *M. tuberculosis* H37Rv: Effect of streptomycin, amikacin and isoniazid on populations of tubercle bacilli in the lungs.

Drug	*Dosage*	*Colony-forming units ($X10^{-5}$) per whole lung (mean and range)*		
		30 Days	*60 Days*	*90 Days*
None	—	15 (0.5–35)	31 (15–43)	25 (1–49)
Streptomycin	25 mg/kg/da	20 (0.2–83)	2.3 (1.6–3.9)	2.5 (0.2–5.3)
Amikacin	10 mg/kg/da	0.5 (0.4–0.6)	0.1 (0.1–0.2)	0.1 (.004–0.2)
Isoniazid	20 mg/kg/da	0.3 (0–0.9)	0.2 (0–0.6)	0 (0)

Clinical Outcomes of Injectables Dubious

- Adults: Large, Individual Patient Data Meta-analysis including 9153 pts, the use of kanamycin, amikacin, or capreomycin vs. no injectable was **NOT associated with a successful treatment outcome** [Ahuja SD et al PloS Med 2012;9(8):e1001300.]
  - Limited by the small number of patients who did not receive an injectable
- Metaanalyses:
  - Treatment success in 64% of patients with MDR-TB, 56% of patients with MDR-TB with additional resistance to injectable agents (MDR-TB+INJr), 48% in patients with MDR-TB with resistance to fluoroquinolones (MDR-TB+FQr), and 40% among patients with XDR-TB. [Falzon D, et al. *Eur Resp. J.* 2013;42(1):156-68.]
  - 337 pts: Baseline FQ-R associated with a 4-fold higher odds of unfavorable outcome whereas **baseline resistance to injectable agents not associated with higher risk of unfavorable outcome** [Jeong B-H et al., *J. Antimicr. Chemother.* 2015.]

- Children: IDP meta-analysis of 842 children: 119 children were treated **without injectables.**
  - **71.9% with culture-confirmed MDR-TB had a successful outcome.**
  - 93.5% children with probable MDR-TB had successful outcome. [A. Hesseling, personal communication]

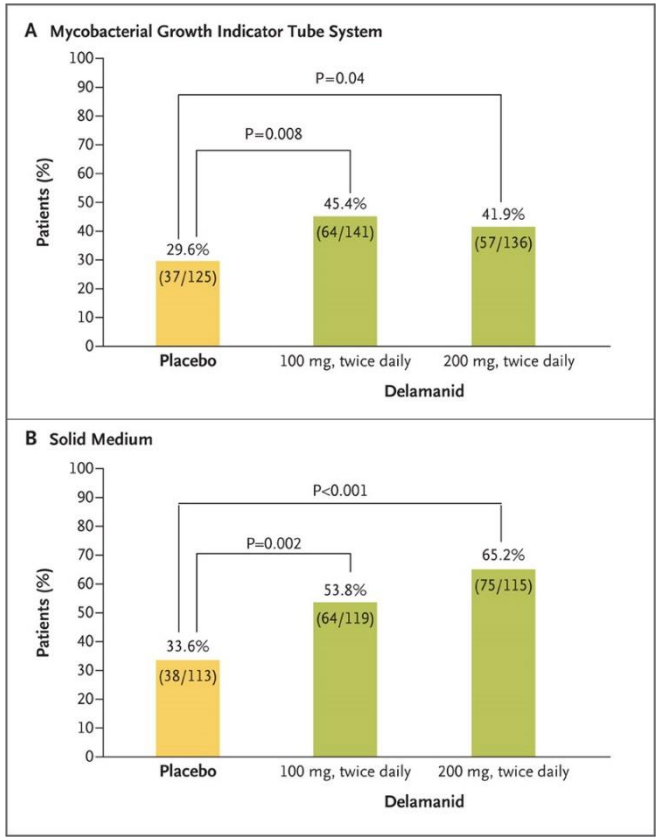
III. Adding *new drug* with proven sterilizing activity to MDR-TB regimen should improve outcomes significantly

- **E.g., Delamanid**
  - Nitroimidazole class, mycobacterial cell wall synthesis inhibitor
  - Bactericidal, with potent sterilizing activity; +EBA
  - First-in-class for MDR-TB; EMA approved; WHO guidance

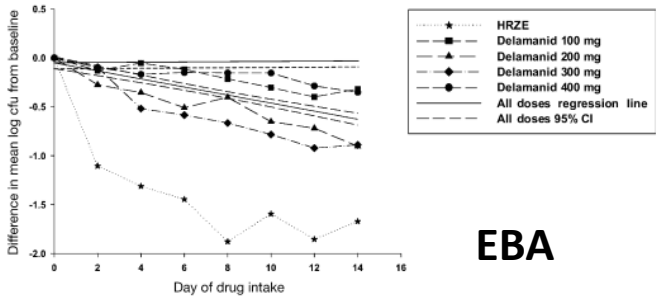
- **Microbiologic efficacy in adults**
  - **RCT: DLM vs. placebo + OBR**
  - N=481 adults (4 HIV+) with PTB
  - DLM 100mg BID vs 200mg BID vs placebo (2 mos on Rx + 1 mo F/U)
  - **Higher 2-month culture conversion (45.4% vs. 29.6%; *p=0.008)*** with DLM c/w placebo

  [Gler MT et al. N Engl J Med 2012;366:2151-2160.]

- **Safety and long-term outcomes in adults**
  - **F/U 24-mo Observational Study in Adults**
  - **lower mortality** in those who received >6 months vs. < 2 months of DLM (1.0% vs 8.3%; *p<0.001)*
  - **74.5% vs 55% favorable outcomes** (*p<0.001)*
  - *QT prolongation but no clinical SAEs*



Proportion of RCT Patients with Sputum Culture Conversion at Day 57.



EBA

Delamanid Pharmacokinetics & Safety

Adult PK highlights

- T_{max} = 4 hours ; $T_{1/2}$ is 30-38 hours; metabolites 150-600 hours
- Increased bioavailability with food & with separating dose from companion drugs; non-linear bioavailability
- No significant DDI with key ARV
- Effects of HIV infection on absorption unknown

Adult safety

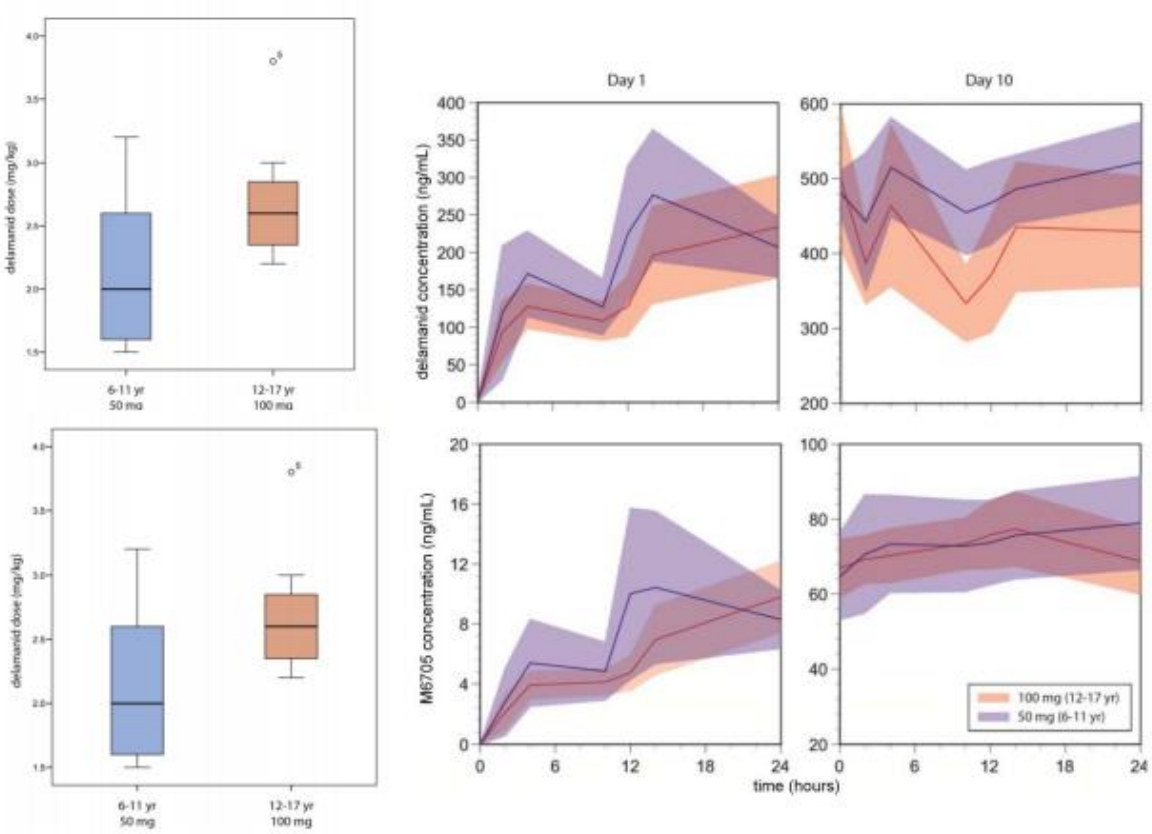
- QT prolongation (maximum 15 ms) , no other cardiac toxicity
- Maximal QT effect at 8 weeks, associated with DM-6705 exposures

Pediatric PK & safety: (Otsuka Trials 232 (14 days) and 233 (24 weeks))

- In small pediatric trial of children with MDR-TB without HIV infection:
  - Age 12-17 (n=7): 100 mg twice daily achieves exposures in range seen in adults with 100 mg twice daily
  - Age 6-11 (n=6): 50 mg twice daily achieves exposures in range seen in adults with 100 mg twice daily
  - Age 3-6 years:
  - Age 0-3 years: Enrolling
- Drug safe and well-tolerated in children (***no QT prolongation***).
- Delamanid Pediatric Formulation (DPF) developed and available
  - bioequivalence study completed: 125mg DPF is bioequivalent to 100mg adult formulation DLM

[Diacon AH et al. Lancet. 2012;380(9846):986-93; Gupta R, et al. NEJM 2015;373(3):291-2; Gler MT, et al. NEJM 2012;366(23):2151-60.]

DLM Dose vs. Exposure Relationships, by Age, in Children in Study 232



[WHO Interim Policy Guidance, “The Use of Delamanid in the Treatment of MDR-TB in Children & Adolescents”. Oct. 25, 2016.]

QT effect & Safety of DLM in children: Trial 233

Category	Cut-off (ms)	Group 1 12-<18yrs (N=7) N	Group 2 6-<12yrs (N=6) n	Group 3 3-<6yrs (N=8) n
New Onset QTcF	>450	0	1	0
	>480	0	0	0
	>500	0	0	0
Change in QTcF from baseline	≥30 and ≤60	2	2	1
	>60	0	0	0

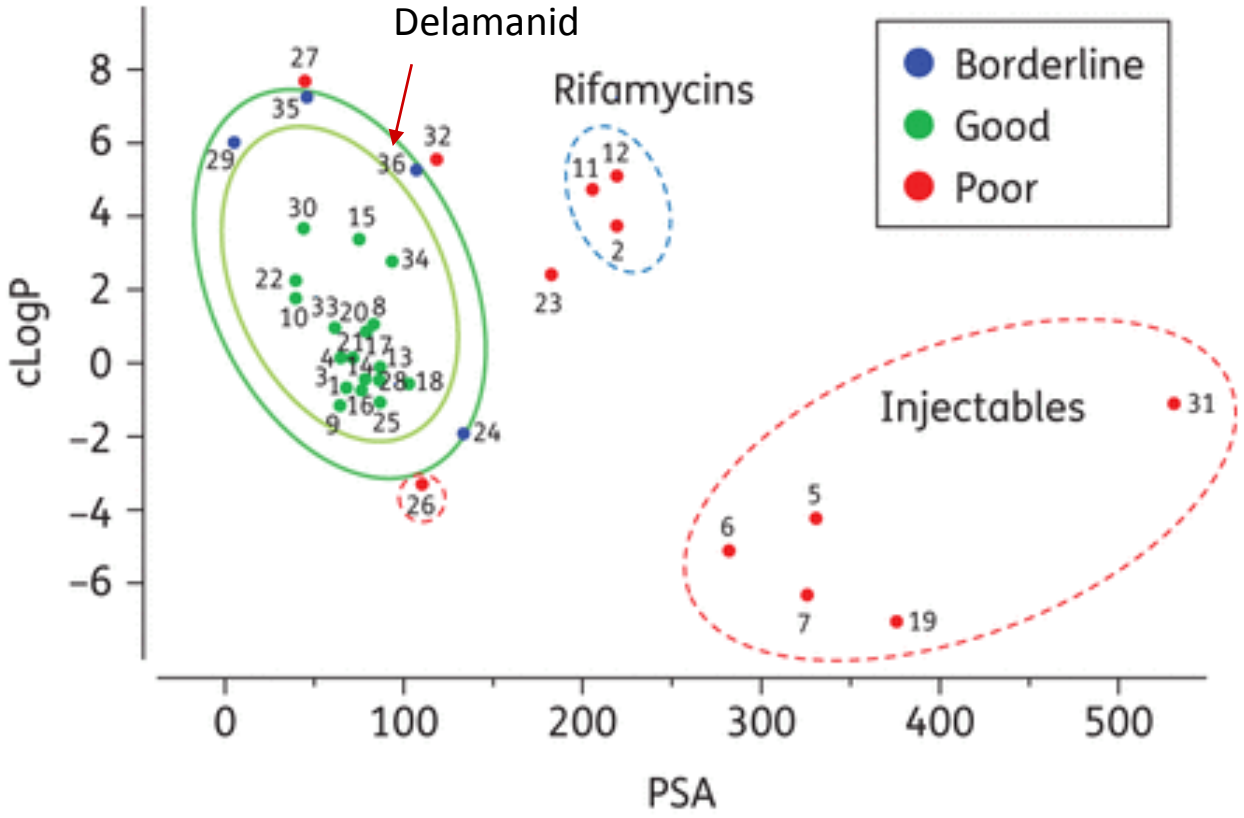
	Group 1	Group 2	Group 3
Week	QTc Mean [SD]	QTc Mean	QTc Mean
Baseline	407.0 [19.2]	411.8	400.9
4	423.4 [11.9]	421.1	413.3
8	417.1 [16.0]	420.0	407.4
12	427.9 [17.1]	416.7	396.2
18	428.6 [13.7]	424.4	393.8
22	423.6 [15.2]	421.0	399.3
26	420.8 [16.8]	420.9	392.0
30	414.2 [8.0]	407.8	400.9

Safety: 21 children have received DLM in trials to date:

- **No serious AE's**
- In Group 3, the youngest group, there were 0 AEs
- In Group 2, 1 case each arthralgia, HA, dizziness.
- In Group 1, 1 case of dizziness.
- (All these children were also on OBR).

[Hafkin J, et al. "Long-term Safety, Tolerability and Pharmacokinetics of Delamanid in Pediatric MDR-TB Patients, Ages 12-17 Years" Poster EP-115-04 at the 46th Union World Conference on Lung Health Cape Town, South Africa; also personal communication.]

DLM bioavailability compared with other anti-TB drugs



Egan Egg analysis of 36 anti-TB compounds. Compounds within ellipsoid have good passive absorption; those outside have poor absorption. [Lakshminarayana SB et al., *J. Antimicrob. Chemother.* (2015) 70 (3): 857-867]

WHO Guidance

- 2014: Interim policy guidance: delamanid (DLM) may be added to a WHO-recommended regimen in **adults** with pulmonary MDR-TB (very low confidence in estimates of effect; conditional upon:
  - Proper patient
  - Adherence to principles of designing a WHO-recommended regimen
  - Close treatment monitoring
  - Active pharmacovigilance (mgmt. AEs)
  - Patient informed consent
- October 25, 2016: New interim policy recommendations (Otsuka 232 & 233; case series of CU in kids; adult comparator values used) that "**DLM may be added to the WHO-recommended longer regimen in children (6-17 years) with MDR/RR-TB who are not eligible for the shorter MDR-TB regimen.**"*
  - ***Very low confidence in estimates of effect***

*Conditional upon: proper patient inclusion, adherence to principles of designing a WHO-recommended longer regimen, close monitoring, active TB drug safety monitoring & management, informed decision-making process.

III. Adding *new drug* with proven sterilizing activity to MDR-TB regimen should improve outcomes significantly

- E.g., bedaquiline (high cure rates in patients with TB resistant to injectables (pre-XDR and XDR TB) [Njeka IJTLD 2015]
- E.g., another nitroimidazole, pretomanid (high potency sterilizer in patients with DS-TB in combination with moxifloxacin, pyrazinamide) [Diacon AH, *Lancet* 2012 Sep 15; 380 (9846):986-93.]
- E.g., clofazimine (emerging PK and safety data in children)
- *Availability of an effective alternative alters the risk-benefit calculus for injectables*

TABLE 1

Principles in designing treatment for a patient with multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB)

Steps	Considerations
1) Diagnosis	Analyse the following information
	Medication history: ≥1 month monotherapy or adding one drug to a failing regimen is a strong predictor of resistance
	D
	F
2) Number of drugs	At l
3) Drug selection	Use cat dru fou con reg
4) Length of TB treatment	Minimum length of treatment is 21 months, divided as follows Intensive phase: 6 months and ≥4 months after culture conversion; longer if three effective drugs are not available during the continuation phase Continuation phase: ≥14 months
5) Surgery	Consider only if few effective drugs are available, localised pulmonary lesions are present and the person has sufficient respiratory reserve
6) Ideal regimen	Standardised: if there has been no use of SLDs in the past Individualised: if there has been use of SLDs in the past or there is a history of contact with an MDR patient who had used them (treat with the effective regimen of the index case)

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WHO: At least 4 drugs: 2 of them core drugs (1 sterilizer, one bactericidal), 2 of them companion drugs to protect action of the core drugs

"Importantly, if a core drug cannot be used because of documented resistance or toxicity, it should be replaced by another with a similar efficacy (bactericidal and sterilizing)" [Caminero JA, *Eur. Resp. Journal* 2015 46: 887-893]

Caminero JA, *Eur. Resp. Journal* 2015 46: 887-893.

Children typically have paucibacillary disease, so generally are easier to treat than adults

- Paucibacillary disease (10^5 bacilli) in theory does not require as many drugs to kill it (from a bacteriologically purist P.O.V.)
  - Less likely to have cavitary disease
  - At <2 yrs old, mostly extrapulmonary dz.

- Treatment failure and relapse are uncommon in children with MDR-TB
  - (Children w HIV coinfection have worse outcomes, higher mortality.)

- Life-altering toxicity from the injectables is common in children with MDR-TB
  - Often providers uncomfortable giving IM injections repeatedly outpatient, so patients hospitalized for duration of their intensive treatment, with grave economic and social consequences for families
  - Monitoring for toxicity is programmatically challenging and often unavailable
  - Toxicity, if detected, can be halted *but not reversed*

Ethical Rationale for Substitution of New/Repurposed Medicines for Injectable in Pediatric MDR-TB Regimens

- Duty to reduce already substantial burdens of suffering for pediatric patients
  - Minimize treatment-related burdens
  - Increase chance of treatment completion by decreasing toxicity
  - Replace injectable with an equally or more effective agent
    - Minimize disease-related burdens
- Priority of justice to ameliorate systematic clusters of disadvantage in childhood [Powers M & Faden R, 2006]
  - **Otherwise they can become entrenched for a whole life**
  - Ototoxicity worst for the pre-verbal/ linguistically developing
- Duty to enable the soonest return of the patient into the world of the child

Simpler, non-injectable, less toxic, shorter

Tony Karumba/ The Guardian

"Tuberculosis [is a] **captain of the men of death**. It is not within the bounds of possibility that the captain of today will become a private; nor is it possible to hope that he will be drummed out of the regiment."
--Sir William Osler

Table 2. Osler's contributions to the literature of infectious diseases and especially that of typhoid fever, tuberculosis, and pneumonia.

Subject	Canadian period (1869–1884)	Philadelphia period (1885–1889)	Baltimore period (1890–1904)	Oxford period (1905–1919)	Totals*
Typhoid fever	3	12	31	8	54
Tuberculosis	12	10	20	18	60
Pneumonia	15	14	7	4	40
All other infectious diseases	36	44	33	31	144
Totals	66	80	91	61	298

NOTE. Numbers indicate published articles. Tabulations are based on [43]. Omitted from the analysis are brief autopsy reports and discussions of other physicians' data. In cases of the co-presence of typhoid fever, tuberculosis, and/or pneumonia, data are tabulated according to the first-mentioned disease.

* From these data, cases of typhoid fever, tuberculosis, and pneumonia accounted for 58% of Osler's papers concerning infectious diseases during the Baltimore and Oxford periods (combined) versus 45% during the Canadian and Philadelphia periods (χ^2 with Yates' correction = 4.31, $P < .05$). After moving to Baltimore, Osler stopped doing autopsies and became increasingly involved in public health issues.

[Bryan CS, *CID* 1996; 23; 1139-49; *Tuberculosis*, Fidelio Ponce de León, 1933]

[*Recovery*, by Anonymous (1950)
Carved single apple tree trunk
70 x 10 inches
American Visionary Art Museum, Baltimore, MD]

Thank You!

[Photo: Jason Beaubien/NPR]

Acknowledgements

Kelly Dooley

Jennifer Furin

Mercedes Becerra

Tony Garcia-Prats

Elin Svensson

Grace Montepiedra

Kate Lypen

Theodore Bailey

NIH UM1 AI068632

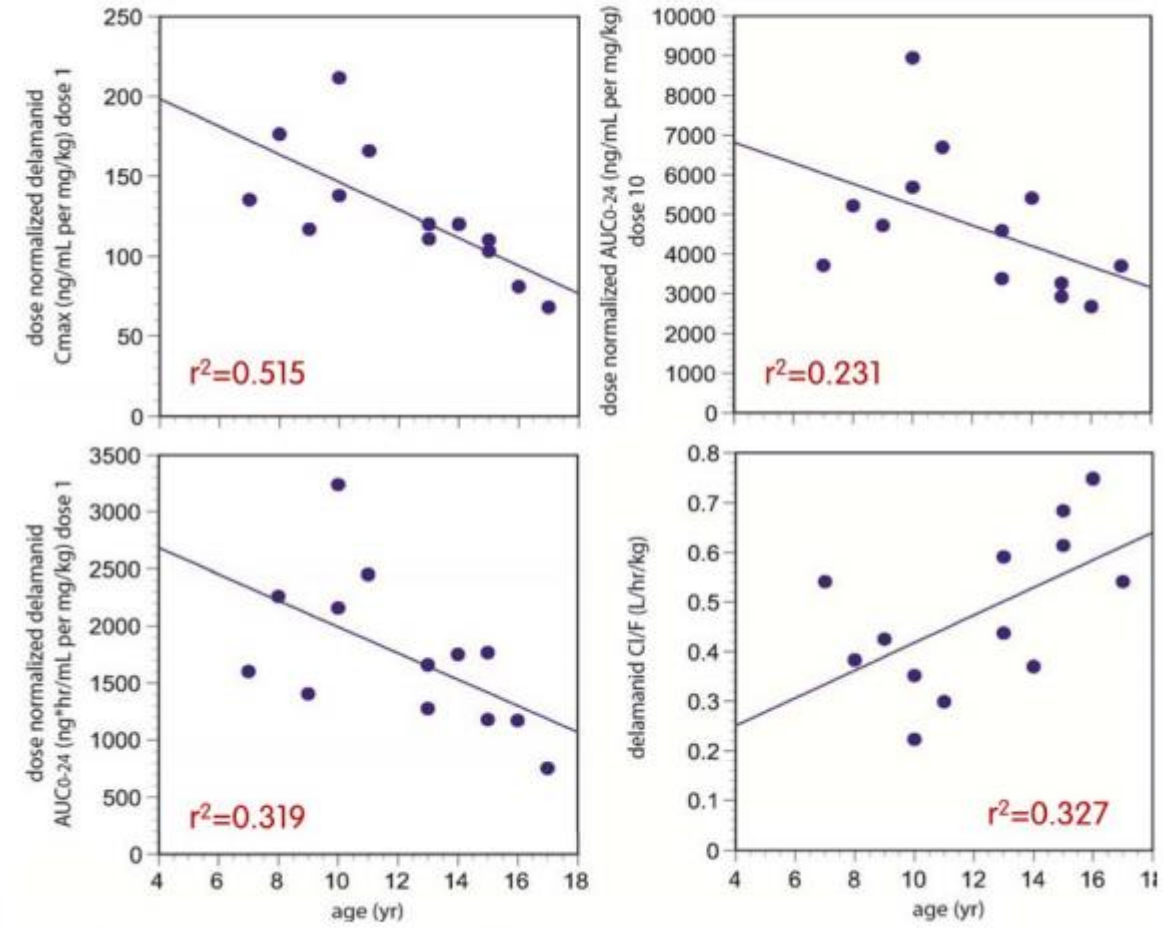
NIH T32 GM066691-11 & GM066691-12, NIGMS

IMPAACT Network

Pearl M. Stetler Research Award for Women Physicians

Edie Nadelhalft, 2012
Mixed media and glass
14 x 4 inches
Baltimore, MD

Fig. 3a. Correlations between the age of children enrolled in Study 242-12-232 and selected disposition parameters for delamanid (n = 13)



AUC, area under the curve; Cl/F, apparent oral clearance; Cmax, maximum plasma concentration; yr, years

Possible explanations:

- Ontogeny of metabolizing enzymes (⇩ as age decreases)
- ?Lower albumin (avg BMI 16), which metabolizes DLM
- Differences in site/ environment
- Differences in pathology
- Age-dependent changes in Cl/F driven by nonlinear bioavailability

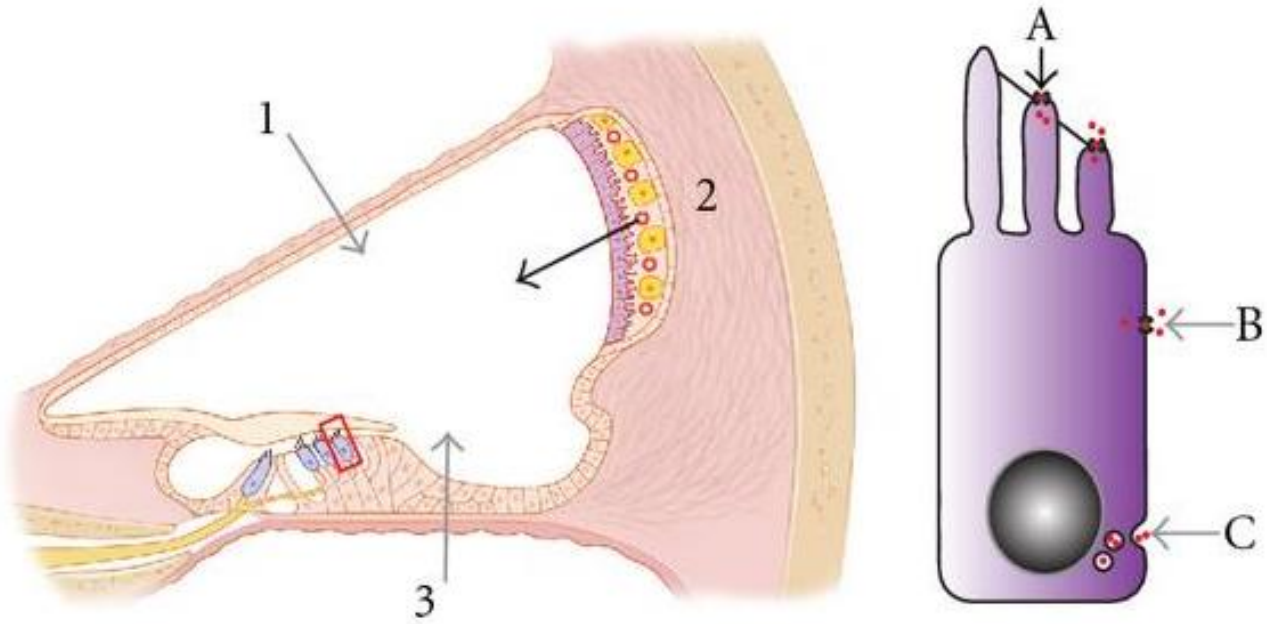


Figure 1: Proposed mechanisms of aminoglycoside transport in the inner ear. Possible entry sites for aminoglycosides into the scala media include via (1) the Reissner's membrane, (2) stria vascularis, and (3) basilar membrane. Published work supports the notion of entry via the Reissner's membrane and the stria vascularis through and between the marginal cells. At the hair cell level, aminoglycosides can potentially enter via mechanotransducer channels located on stereocilia of hair cells (A), endocytosis on the apical or basolateral membranes (A, B, or C), TRP channels (A, B or C), or ATP receptors (A).

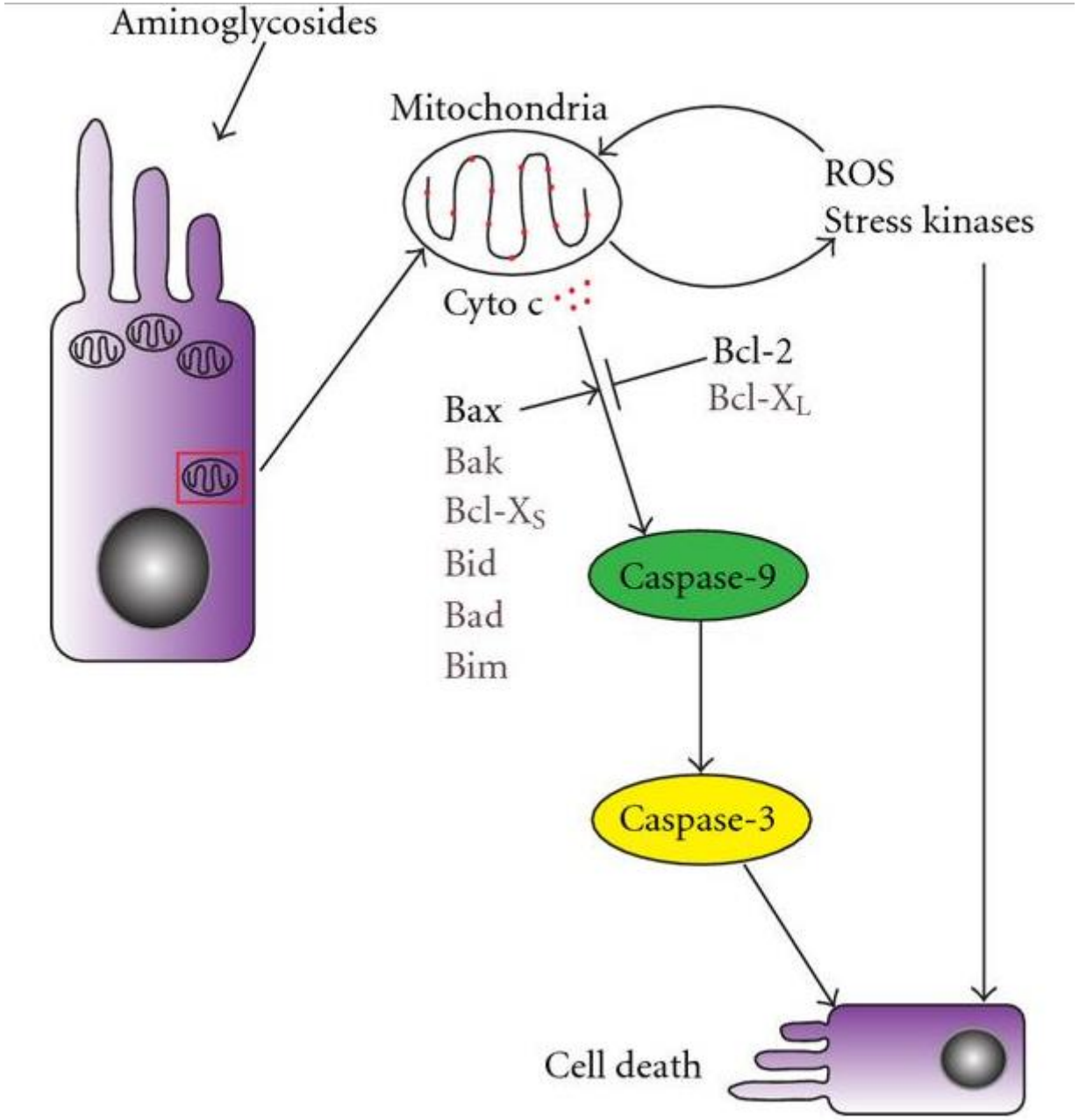
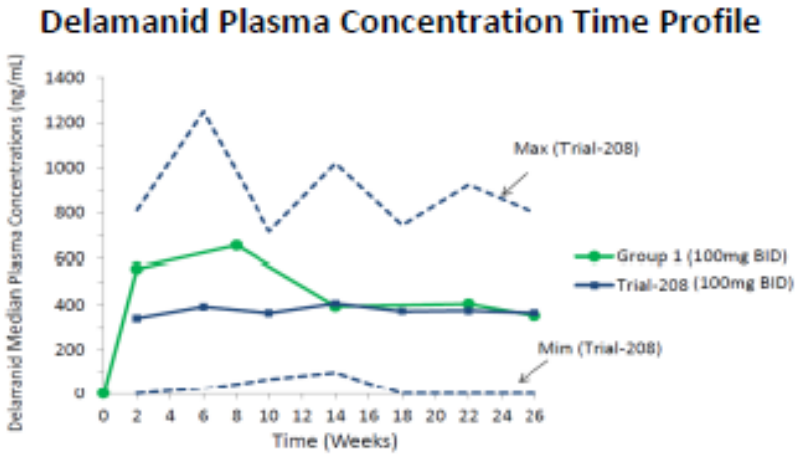
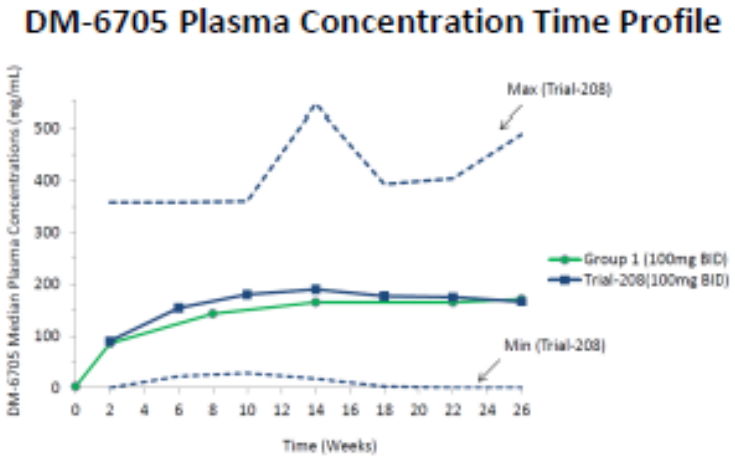


FIGURE 2: A simplified schematic of the cell death cascade in hair cells damaged by aminoglycosides. Reactive oxygen species (ROS), stress kinases, and the caspase family of proteases are activated and mediate hair cell degeneration caused by aminoglycoside exposure, whereas overexpression of Bcl-2 protects against caspase activation and hair cell loss. Aminoglycosides damage the mitochondria and can result in generation of ROS and activation of stress kinases. Both ROS and stress kinases can cause cell death directly as well as amplify insults targeting the mitochondria. The balance between pro-apoptotic and anti-apoptotic Bcl-2 family members determines the integrity of the mitochondria. Cytochrome c leaking out of damaged mitochondria leads to caspase-9 activation, which in turn activates caspase-3 to execute cell death.

[Huth ME, *Int J. Otolaryng.* 2011; 2011:937861]

DLM & Metabolite Levels in Children & Adults





Parameters (DLM)	Group 1 (age 12-17 yrs)		Group 2 (Age 6-11)		Group 3 (Age 3-6)		Adults	
Day	1	10	1	10	1	10	14	56
N	7	7	6	6	6	6	150	144
C_{max} (ng/mL) [Min-Max]	268 [160-420]	557 [304-803]	315 [210-450]	573 [485-682]	202 [164-364]	508 [485-640]	357 [124-1000]	414 (39.9)
AUC_{0-24} (ng*hr/mL) [Range] Or (%CV)	3880 [1800-5300]	9730 [6150-12800]	4100 [3200-6900]	12000 [9770-13300]	3580 [2980-4820]	9520 [8220-10900]	6811 [1669-13325]	7925 (37.5)

Parent drug reaches steady state in 6-7 days

Parameters (DM-6705)	Group 1 (Age 12-17 yrs)				Group 2 (Age 6-11 yrs)		Group 3 (Age 3-6)		Adults		
Day	1	10	56	98	1	10	1	10	14	10*	98 Ω
N	7	7	6‡	6	6	6	6	6	153	ND	100
C_{max} (ng/mL)	8.60 [8.6-15.5]	81.7 [52.9-93.2]			7.68 [6.07-23.1]	90.0 [62.4-112]	7.30 [5.03-8.65]	73.7 [59.1-95.0]	114 [37.3-461]	91.2	
Median Conc. (%CV) or [min-max] (ng/mL)			143 [26.8-205]	165 [25.6-225]							190 (47)
Metabolite: Parent ratio											0.491 (54)
AUC_{0-24} (ng*hr/mL)	113 [89.5-224]	1780 [1210-2010]			122 [81.1-349]	1870 1210-2210]	114 [83.5-139]	1470 [1310-1770]	2404 [782-5792]	1923	

Metabolite reaches steady state in 4-6 weeks

[Hafkin J, et al. "Long-term Safety, Tolerability and Pharmacokinetics of Delamanid in Pediatric MDR-TB Patients, Ages 12-17 Years" Poster EP-115-04 at the 46th Union World Conference on Lung Health Cape Town, South Africa; & Hafkin J, et al. "PK and Safety of Delamanid in Pediatric MDR-TB Patients, Ages 6-17 Years". A-960, ICAAC 2015.]