Clinical trials: optimal use of new and existing medications

Bill Burman

Denver Public Health

© 2014 Denver Public Health

Presenter disclosures

- Chair - Data Safety and Monitoring Boards for TMC207 studies, ad hoc advisor for Tibotec for the development of bedaquiline
- Tibotec paid Denver Public Health for my time

© 2014 Denver Public Health

Presenter disclosures

- Chair - Data Safety and Monitoring Boards for TMC207 studies, ad hoc advisor for Tibotec for the development of bedaquiline
- Tibotec paid Denver Public Health for my time
- Recovering clinical trialist – TBTC
- Now a public health bureaucrat

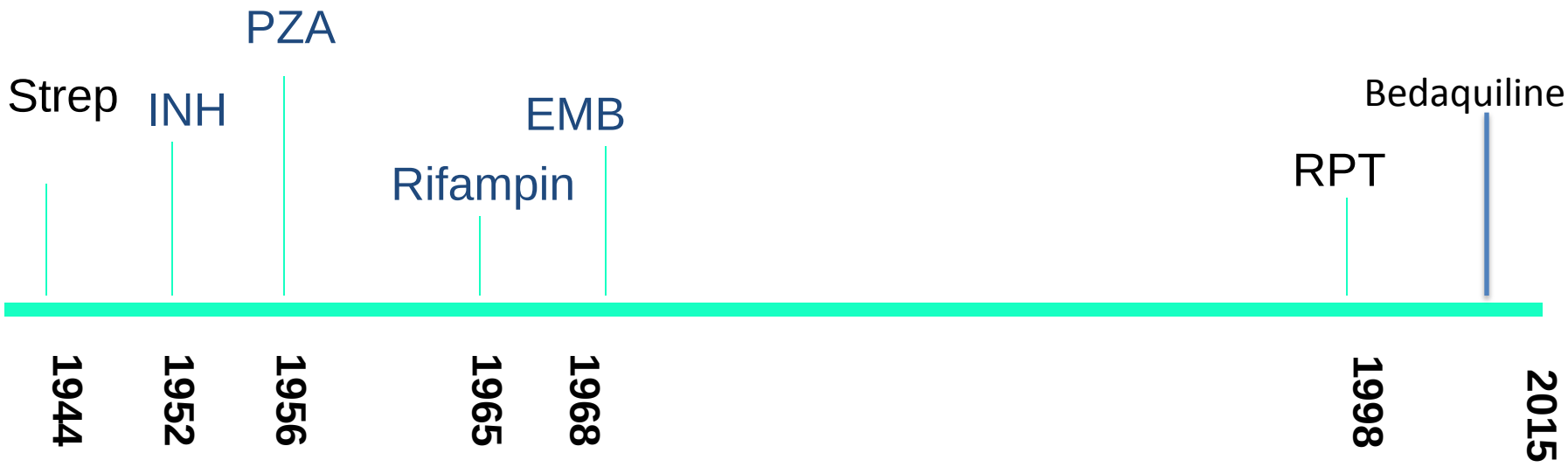
© 2014 Denver Public Health

Presentation outline

- High-level overview of clinical trials during the resurgence of TB trial activity
  - Successes
  - Lessons learned
- Key clinic questions that aren't being addressed in clinical trials

© 2014 Denver Public Health

Tuberculosis drug development



© 2014 Denver Public Health

Treatment of LTBI – a mis-step, followed by success

Table 4. Proportion of Patients Who Developed Reportable Adverse Events*

Adverse Event	Rifampin and Pyrazinamide (n = 791)	Isoniazid (n = 792)	*P* Value
At least 1†	12.3	10.5	.27
At least 1 at grade 4 or higher	5.6	7.3	.18
Study drug permanently discontinued	9.5	6.1	.01
Abnormal liver function tests	1.4	3.3	.02
Hepatitis	0.8	0.4	.34
Peripheral neuropathy	0.1	0.5	.37
Skin rash	1.4	0.6	.14
Neutropenia	0.8	0.4	.34
Nausea and/or vomiting	1.9	0.1	<.001
Narcotic withdrawal	1.5	0.0	<.001

Gordin F, et al. JAMA 2000; 283:1445-50

© 2014 Denver Public Health

Treatment of LTBI – a mis-step, followed by success

Table 4. Proport

Advers
At least 1†
At least 1 at grade
Study drug permar
Abnormal liver func
Hepatitis
Peripheral neuropa
Skin rash
Neutropenia
Nausea and/or vor
Narcotic withdrawa

Table 2. **Hepatotoxicity in 411 Patients for Whom Follow-up Liver Enzyme Test Results Were Available***

Hepatotoxicity†	Rifampin and Pyrazinamide Group (*n* = 207)	Isoniazid Group (*n* = 204)	*P* Value
	n (%)		
Grade 1	29 (14)	27 (13.2)	.34
Grade 2	9 (4.3)	3 (1.5)	.37
Grade 3	7 (3.4)	0 (0)	.14
Grade 4	9 (4.3)	2 (1.0)	.34
Total	54 (26.1)	32 (15.7)	<.001
Discontinuation of study medications owing to hepatotoxicity	12 (5.8)	2 (1.0)	<.001

Gordin F, et al. JAMA 2000; 283:1445-50

Jasmer R, et al. Ann Intern Med 2002; 137: 640-7

© 2014 Denver Public Health

Treatment of LTBI – a mis-step, followed by success

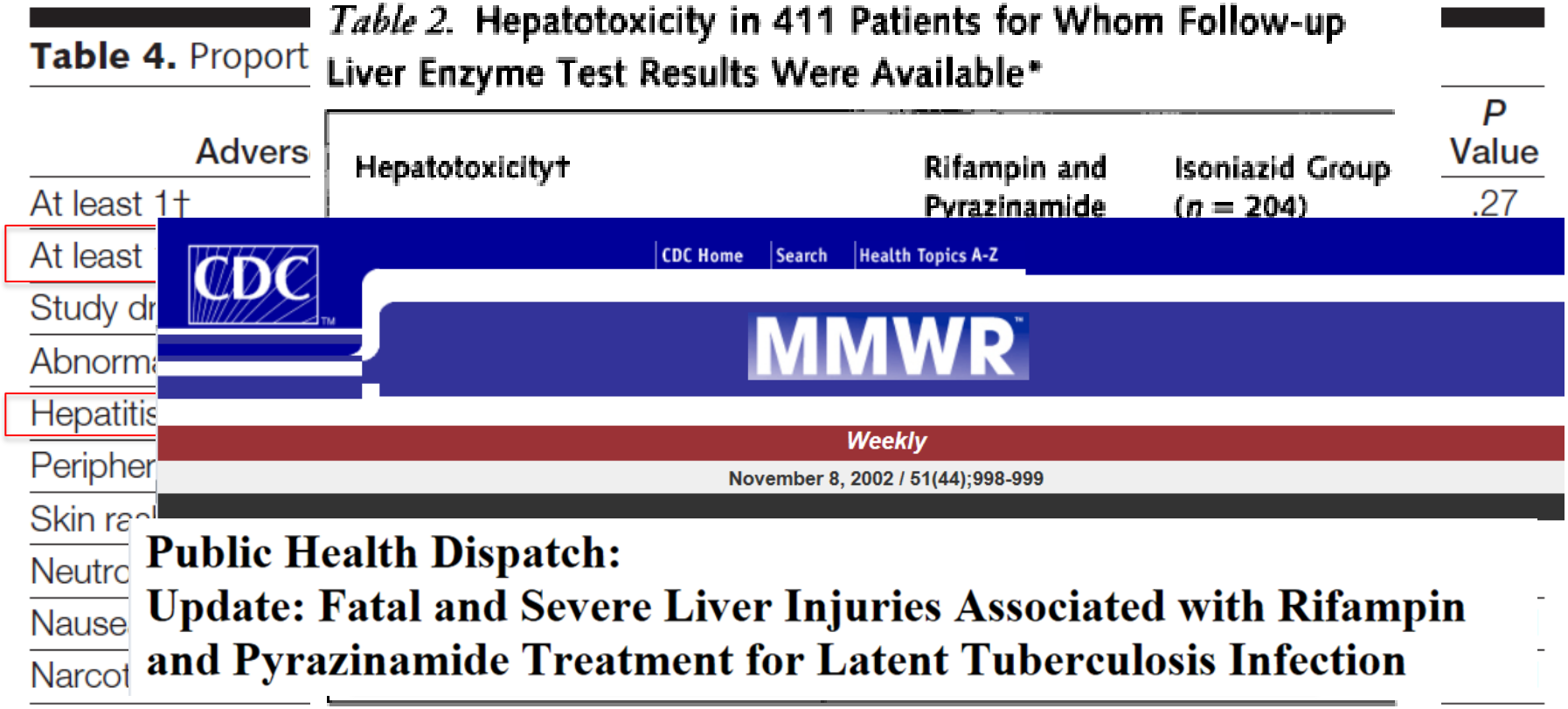


Table 4. Proport

Advers

At least 1†

At least

Study dr

Abnorma

Hepatitis

Peripher

Skin ra

Neutro

Nause

Narcot

Table 2. **Hepatotoxicity in 411 Patients for Whom Follow-up Liver Enzyme Test Results Were Available***

Hepatotoxicity†	Rifampin and Pyrazinamide	Isoniazid Group (*n* = 204)	*P* Value

CDC Home | Search | Health Topics A-Z

CDC

MMWR

Weekly

November 8, 2002 / 51(44);998-999

Public Health Dispatch:
Update: Fatal and Severe Liver Injuries Associated with Rifampin and Pyrazinamide Treatment for Latent Tuberculosis Infection

Gordin F, et al. JAMA 2000; 283:1445-50

Jasmer R, et al. Ann Intern Med 2002; 137: 640-7

© 2014 Denver Public Health

Treatment of LTBI – a mis-step, followed by success

- Lessons of RIF/PZA for latent TB treatment trials
  - Safety is paramount in the treatment of latent TB infection
  - Beware of homogeneity in clinical trial design – evaluate safety in all major patient subgroups that will receive the intervention
  - Rare serious side effects may be missed in clinical trials – need “post-market surveillance”

© 2014 Denver Public Health

Treatment of LTBI – RPT/INH vs. INH

Table 3. Safety End Points Among Children Who Received at Least 1 Dose of Study Medication

Characteristic	Patients, No. (%)		*P* Value[a]	Difference (95% CI)[b]
	Isoniazid (n = 493)	Rifapentine Plus Isoniazid (n = 539)		
AEs attributed to treatment				
Grades 1 and 2	5 (1.0)	11 (2.0)	.21	-1.0 (-2.5 to 0.5)
Grade 3	1 (0.2)	3 (0.6)	.63	-0.4 (-1.1 to 0.4)
Grade 4	0	0	NA	NA
Grade 5, death	0	0	NA	NA
Serious AEs	0	0	NA	NA

TB outcomes

- 0 cases in RPT/INH arm
- 3 cases in INH arm

Villarino ME, et al. JAMA Pediatrics, on-line first

© 2014 Denver Public Health

Treatment of LTBI – RPT/INH vs. INH

Table 3. Safety End Points Among Children Who Received at Least 1 Dose of Study Medication

Characteristic	Patients, No. (%)		*P* Value[a]	Difference (95% CI)[b]
	Isoniazid (n = 493)	Rifapentine Plus Isoniazid (n = 539)		
AEs attributed to treatment				
Grades 1 and 2	5 (1.0)	11 (2.0)	.21	-1.0 (-2.5 to 0.5)
Grade 3	1 (0.2)	3 (0.6)	.63	-0.4 (-1.1 to 0.4)
Grade 4	0	0	NA	NA
Grade 5, death	0	0	NA	NA
Serious AEs	0	0	NA	NA

TB outcomes

- 0 cases in RPT/INH arm
- 3 cases in INH arm

Evaluation of safety and efficacy in patients with HIV – similar results (2 vs. 6 TB cases)

Villarino ME, et al. JAMA Pediatrics, on-line first
Sterling T, et al. CROI 2014, abstract 817

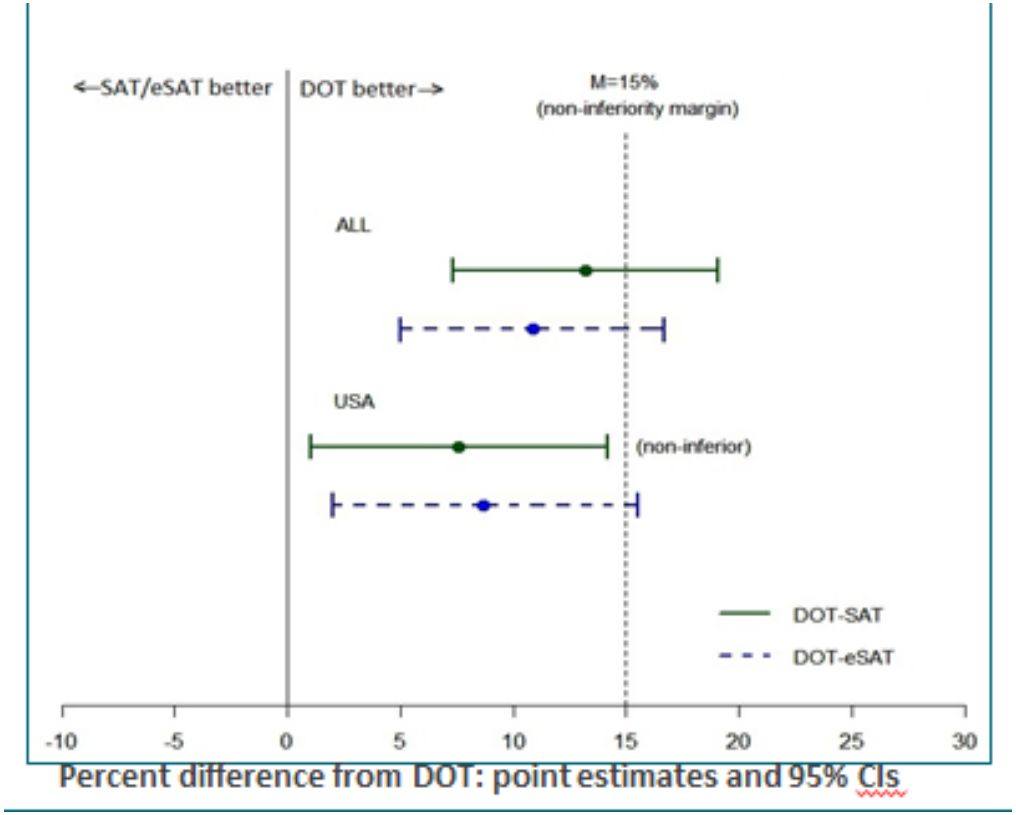
© 2014 Denver Public Health

Treatment of LTBI with RPT/INH: need for DOT

Randomized trial of RPT/INH: DOT, SAT, eSAT

Completion of therapy at US sites

- DOT – 85%
- SAT – 78%
- eSAT – 76%



Belknap R, et al. 2015 CROI

© 2014 Denver Public Health

4 RIF vs. 9 INH

	4 Months of Rifampin (n = 420), n (%)	9 Months of Isoniazid (n = 427), n (%)
Drug-related adverse events subtotal	16 (3.8)	24 (5.7)
Grade 3 or 4 adverse events		
Subtotal	7 (1.7)	17 (4.0)
Hepatotoxicity	3 (0.7)	16 (3.8)
Hematologic	2 (0.5)	1 (0.2)
Drug interaction	1 (0.2)	0 (0)
Rash	1 (0.2)	0 (0)
Grade 1 or 2 adverse events		
Subtotal	9 (2.2)	7 (1.7)
Rash	8 (1.9)	5 (1.2)
Gastrointestinal intolerance	1 (0.2)	2 (0.5)

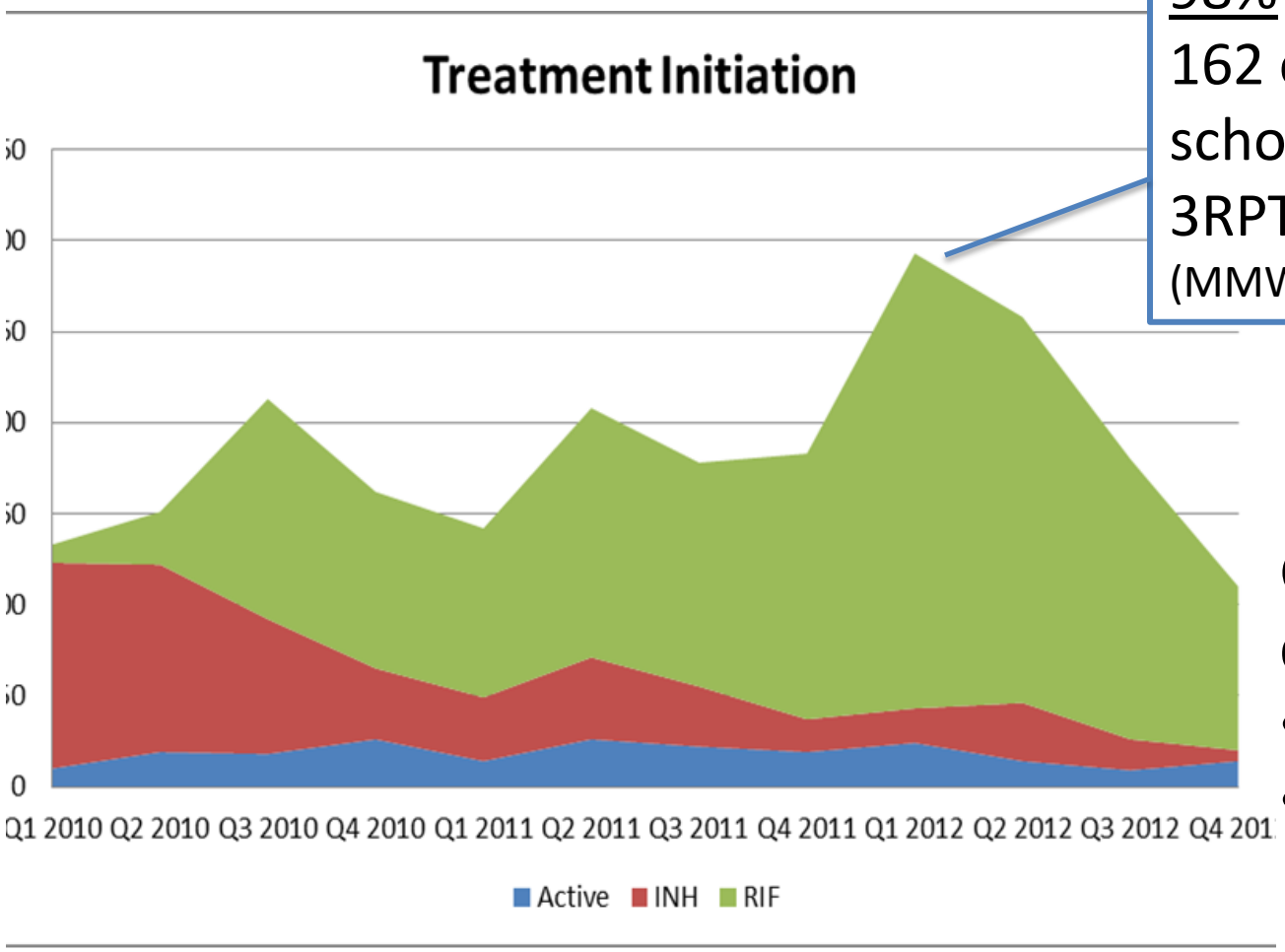
Menzies R, et al. Ann Intern Med 2008; 149: 694

Overall trial progress

- Efficacy cohort (~ 6000) enrolled and in follow-up
- Parallel pediatric study enrolled and in follow-up

© 2014 Denver Public Health

LTBI Treatment at the Denver TB Clinic



98% completion among 162 contacts of a high school case, using 3RPT/INH and 4RIF (MMWR 2013; 62: 805-9)

Overall completion:

- 9 INH: 60%
- 4RIF: 80%

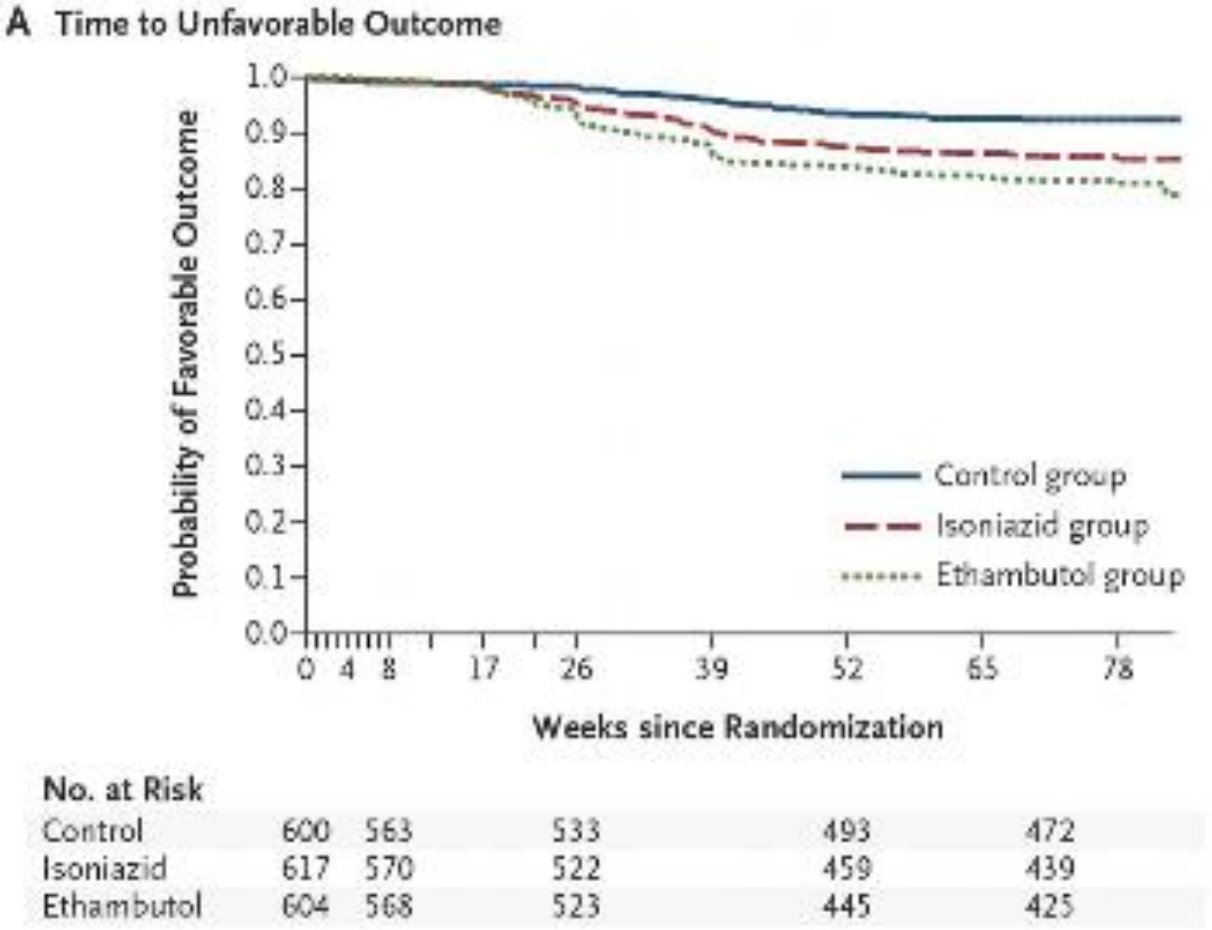
© 2014 Denver Public Health

Treatment of LTBI – current status

- Rifamycin-based regimens – solid progress that helps programs (shorter, safer, better completion, trend toward greater efficacy)
  - Clinical trials completed in children, persons with HIV
- Post-marketing surveillance needed
  - Look for rare serious side effects from RPT, RIF
  - Risk of selection for RIF resistance in programmatic settings
- Trials in progress
  - Daily RPT/INH for 1 month (vs. INH)
  - Levo for contacts of MDR

© 2014 Denver Public Health

Treatment-shortening using moxifloxacin for drug-susceptible active disease



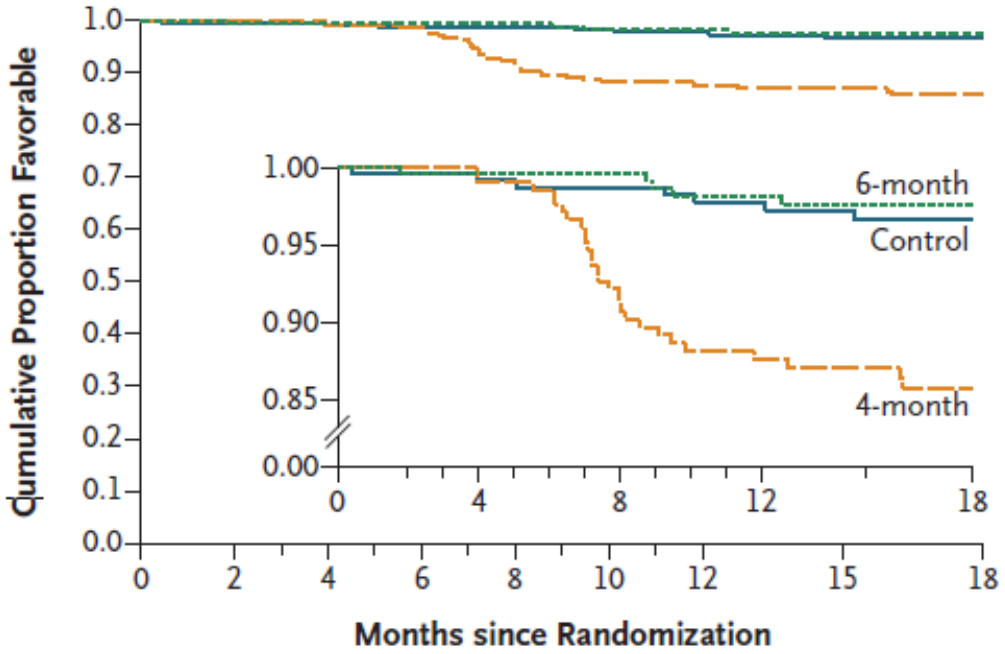
Relapses

- IRZE – 12 (2%)
- IRZ<u>M</u> – 46 (9%)
- <u>M</u>RZE – 64 (12%)

Gillespie S, et al. N Engl J Med 2014; 371: 1677-87

© 2014 Denver Public Health

Treatment shortening with moxifloxacin and high-dose RPT



No. at Risk									
Control	240	232	227	213	210	203	195	175	142
4-month	239	223	211	202	185	172	169	147	127
6-month	251	234	224	217	212	207	205	180	153

Relapses

- Control – 4 (2%)
- 6 (weekly RPT/Moxi) – 4 (2%)
- 4 (biweekly RPT/moxi) – 19 (13%)

27% HIV+
65% cavitation

Jindani A, et al.New Engl J Med 2014; 371: 1599-608

© 2014 Denver Public Health

TB clinical trials: drug-susceptible TB

- Summary
  - Moxi/gati do not allow meaningful treatment-shortening
  - Continuation-phase weekly moxi/RPT (1200 mg) – not ready for prime time; more data needed on safety and efficacy
- Current generation of trials
  - High-dose RIF or RPT(with or without moxi) for treatment-shortening (to 4 months of daily therapy)

© 2014 Denver Public Health

TB clinical trials: drug-susceptible TB

- Lessons from the past decade
  - Mouse model of TB treatment is not perfect, though still very useful
  - Don’t start Phase 3 trials of treatment-shortening without compelling results from Phase 2
    - Increase in 2-month culture status from RIF – 20%, from PZA – 13%)
  - Regimens for drug-susceptible disease should be applicable to women of child-bearing age and children
  - Is treatment-shortening to 4 months “worth the squeeze”, particularly if it requires daily dosing throughout?

© 2014 Denver Public Health

What is it like to be treated for TB with current therapy?

- Cohort treated in the Denver Metro TB clinic, side effects from chart review
  - Any side effect – 32%
  - Nausea – 14%
  - Hepatitis – 7%
  - Peripheral neuropathy – 0.5%

- Multidrug therapy for drug-susceptible TB is not “well-tolerated”

© 2014 Denver Public Health

Prospective study of tolerability of treatment for pulmonary TB

- Multicenter prospective study – 4 regions of China, sampling scheme to assure representative sample of patients with pulmonary TB
- Baseline survey and labs
- Treatment: IRZE for initial treatment, Strep added for re-treatment
- Symptom diary during treatment
- Repeat labs at 2 months
- Adverse events and TB treatment outcomes evaluated using standardized criteria

© 2014 Denver Public Health

Demographic and clinical characteristics of the cohort

Parameter	Number (% of 4304)
Median age (IQR)	42 (29 – 55)
Male/female	3082 / 1227
TB treatment history	
Primary	3556 (83%
Re-treatment	748 (17%)
Hep B S Ag positive	469 (11%)
History of drug reaction	118 (3%)
Hepatobiliary disease	23 (0.5%)
Gastroenteropathy	40 (1%)
Diabetes	51 (1%)
Other medical illnesses	103 (2%)

Lv Z, et al. PLoS One 2013

© 2014 Denver Public Health

Adverse drug reactions

- Frequency
  - 766 (17%) had an adverse reaction, 1.4% had a serious adverse reaction, 1% hospitalized
  - Liver dysfunction – 6.3%, 0.6% had serious hepatotoxicity
- Effect of TB treatment regimen
  - 43% of those with adverse reaction had regimen changed, 5% stopped all TB treatment
- Effect on TB treatment outcomes
  - 2.8% with adverse reaction had unsuccessful TB treatment (vs. 1% of those without an adverse reaction)
  - 19% of all unsuccessful outcomes attributed to adverse reactions

© 2014 Denver Public Health

Comparison of hepatotoxicity risk among antimicrobial agents

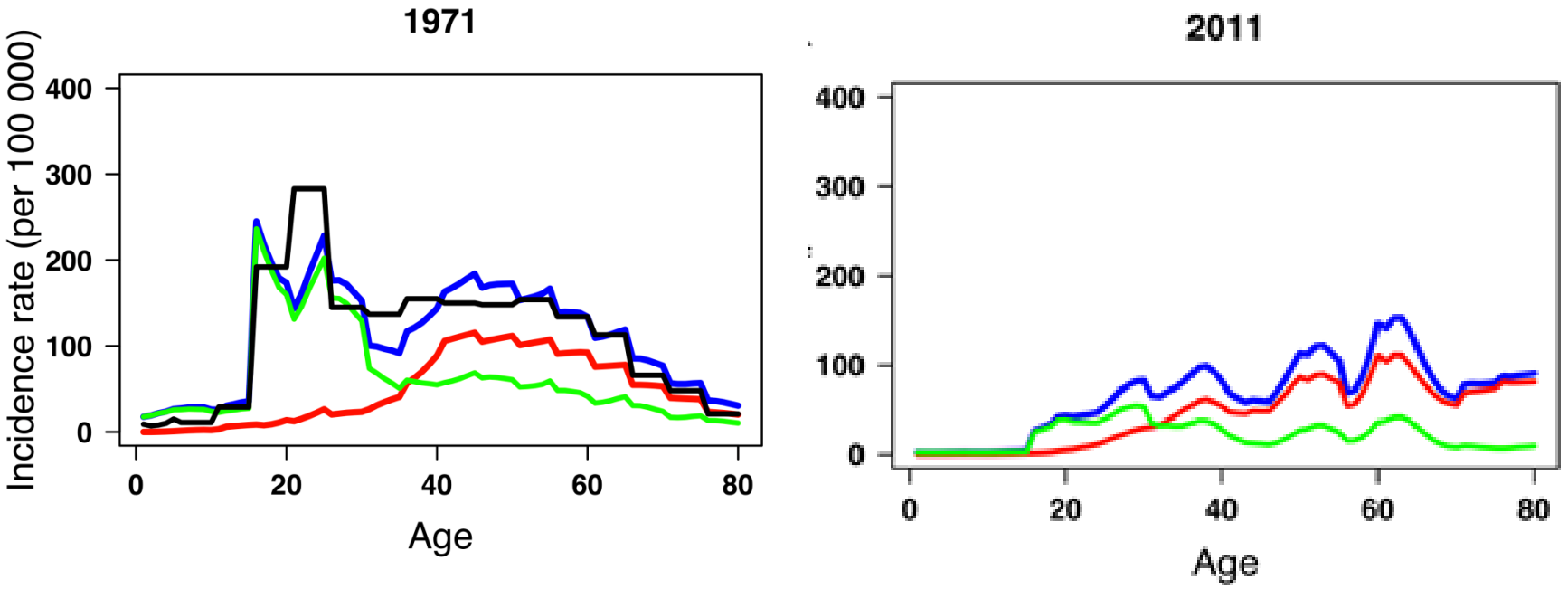
Drug	Hepatotoxicity incidence per 100,000 courses	Comments
Amox-clav *	1-17	Generally benign
Telithromycin *	17	Withdrawn from the market
Levofloxacin *	0.02	
Trovofloxacin *	6	Withdrawn from the market
Rifampin	70	Annals Intern Med 2008; 149: 694
Isoniazid	380	Annals Intern Med 2008; 149: 694
Pyrazinamide	430	Ann Intern Med 2002; 137: 640-7

* Andrade R, Tulkens PM. J Antimicrob Chemother 2011; 66: 141-6

In population-based studies, TB drugs are among the most common causes of serious drug-related hepatotoxicity (Aliment Pharmacol Ther 2010;31:1200, Gastroenterol 2008;135:1924)

© 2014 Denver Public Health

Changes in age-distribution among cases of active TB (Hong Kong)

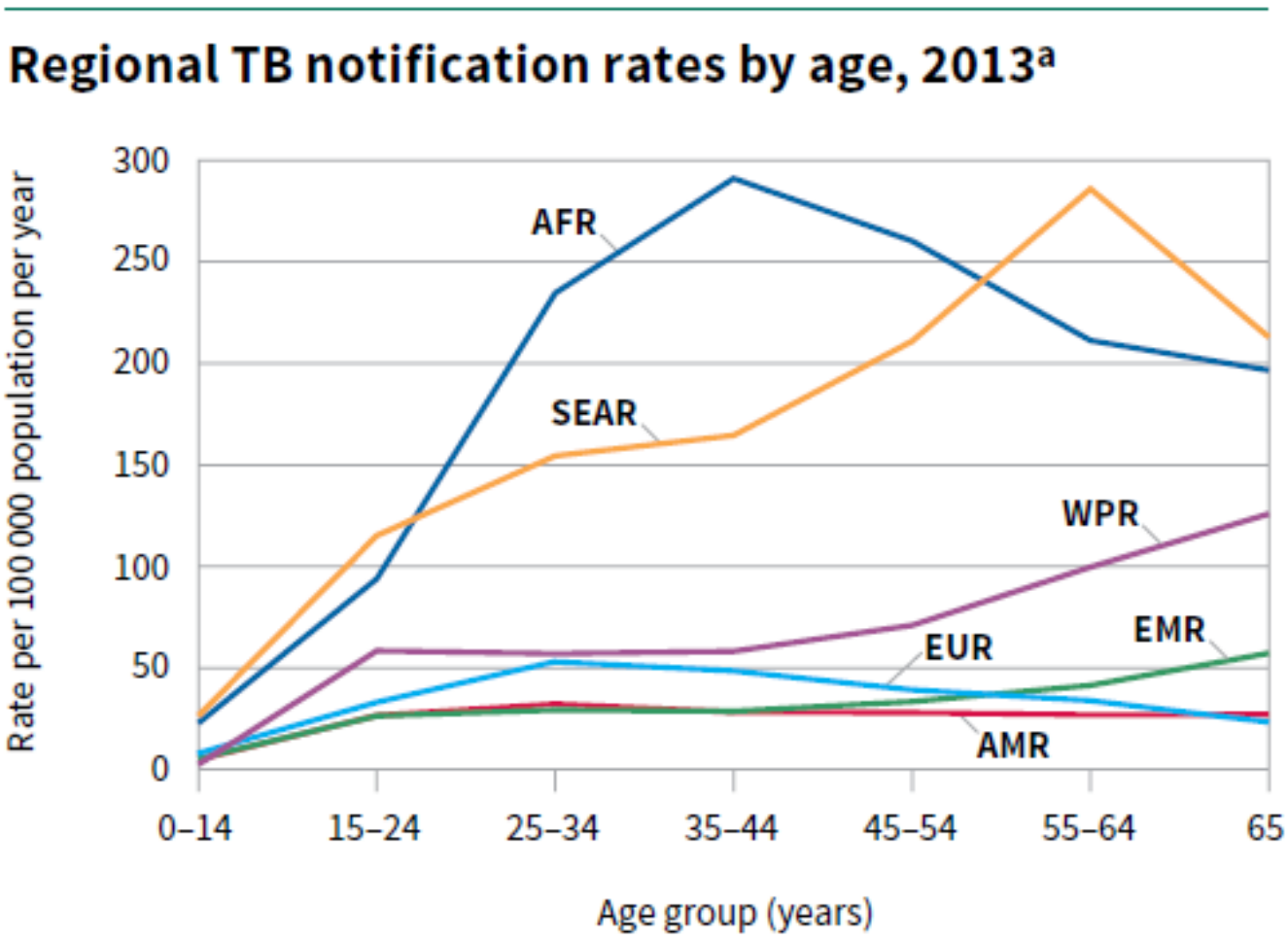


As transmission decreases, active TB becomes increasingly a disease of the elderly

Wu P, et al. PLoS One, 2010

© 2014 Denver Public Health

Age-specific rates of active TB, by WHO region



http://www.who.int/tb/publications/global_report/en/

© 2014 Denver Public Health

Toxicity considerations in treatment of drug-susceptible disease

- INH and PZA are much more hepatotoxic than antibiotics that have been removed from the market
- Concerns about moxi safety in adults: 2-fold increased risk of CVD death (compared to amox/clav) in a recent large observational study (Clin Infect Dis 2015; 60: 566-77)
- The new norm of TB – elderly, increased comorbid disease – who have higher risk of adverse effects, including hepatitis
- Encourage enrollment of elderly and "complicated patients" into TB clinical trials
- Is it time for trials comparing interventions for toxicity avoidance?

© 2014 Denver Public Health

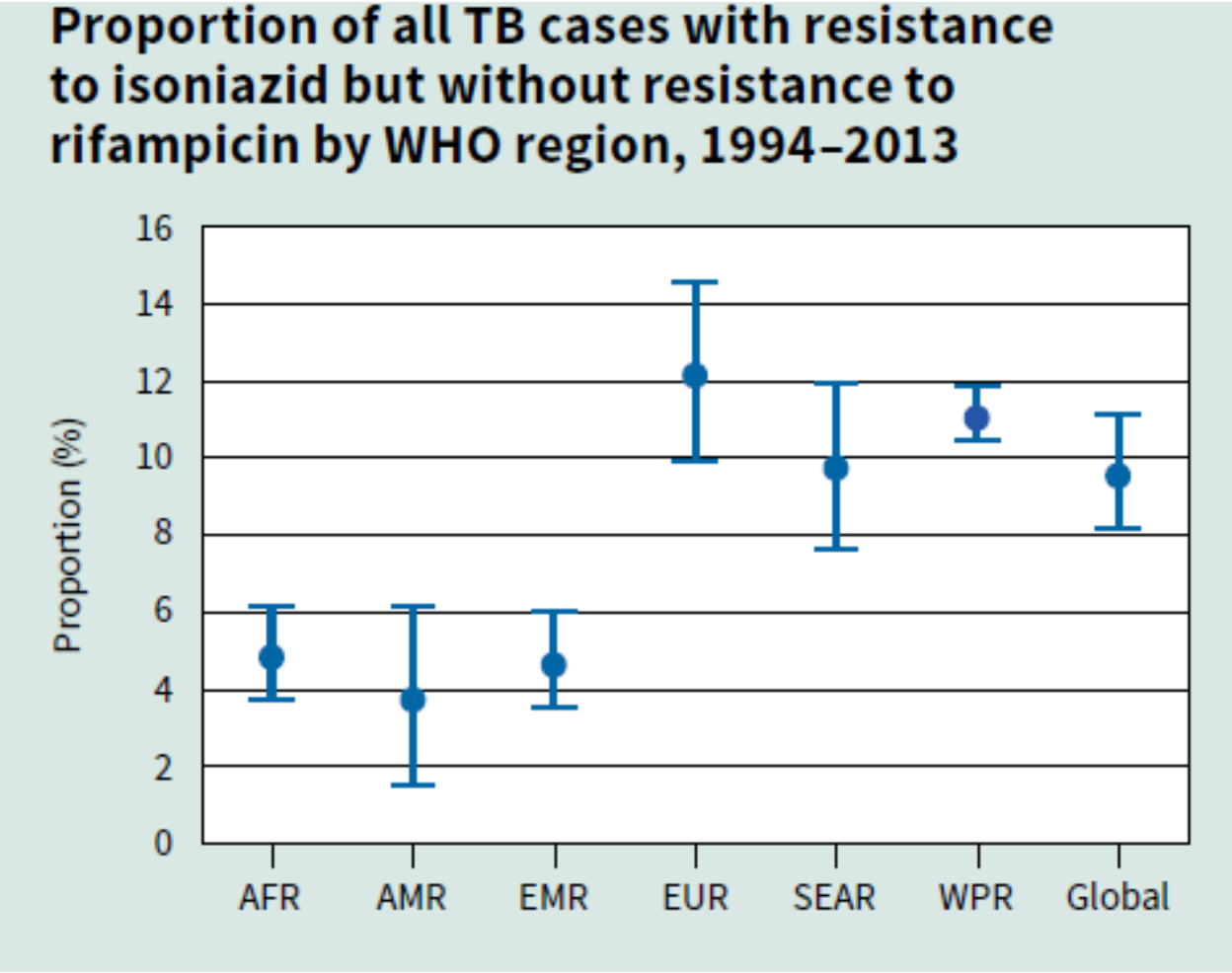
Treatment outcomes of INH-resistant TB, South Africa (2008-9)

- 155 patients with INH-monoresistant isolates
  - 23% new cases, 75% prior TB treatment
  - 21% HIV-positive
- Treatment
  - 26% - standard IRZE
  - 74% - re-treatment regimen with high-dose INH
- Outcomes
  - 15% - treatment failure – 14/23 developed MDR
  - 16% defaulted

Jacobson KR, et al. Clin Infect Dis 2011; 53: 369-72

© 2014 Denver Public Health

Prevalence of initial INH resistance, without RIF resistance



http://www.who.int/tb/publications/global_report/en/

© 2014 Denver Public Health

Effect of initial INH resistance on treatment outcomes

Initial resistance	Failure *	Relapse *	Acquired resistance *
Susceptible	0.3%	3.7%	0.3%
INH	2.8%	11.4%	2.4%
INH/Strep	8.3%	10.1%	5.7%

* Pooled event rates from meta-analysis of trials and cohorts using RIF-based regimens

- INH resistance is clinically relevant, and is not reliably managed with contemporary DOTS regimens
- The data behind current recommendations for managing INH resistance is a “dog’s breakfast” of inadequate trials and cohort studies

Menzies R et al. , PLoS Med. 2009 : 6: 1-14, Menzies R, et al. PLoS Med 6: 1000146

© 2014 Denver Public Health

Summary – role of clinical trials in improving treatment in the clinic

- Latent TB infection
  - Solid progress that is making a difference in the clinic
  - Inclusion of key sub-groups in clinical trials
  - Key remaining issue – managing the many drug interactions of RIF and RPT
- Drug-susceptible TB
  - Overly focused on increasing regimen potency
  - We need clinical trials evaluating interventions to improve tolerability
- Drug-resistant TB
  - Don’t forget INH resistance – the source of new MDR cases

© 2014 Denver Public Health