# To include or not to include… clinical trial design for HIV-related TB

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# To include or not to include… a case example

Relapse after different treatment durations in the mouse model: rifampin (RIF) vs. rifapentine (RPT)

| Regimen | 8 week | 10 week | 12 week |
|---|---|---|---|
| $RIF_{10}$/INH/PZA | - | - | 15/15 (100%) |
| $RPT_{7.5}$/INH/PZA | - | 9/15 (60%) | 0/15 |
| $RPT_{10}$/INH/PZA | 10/15 (67%) | 0/15 | 0/15 |

In the mouse model, RPT was 4 times as active as RIF

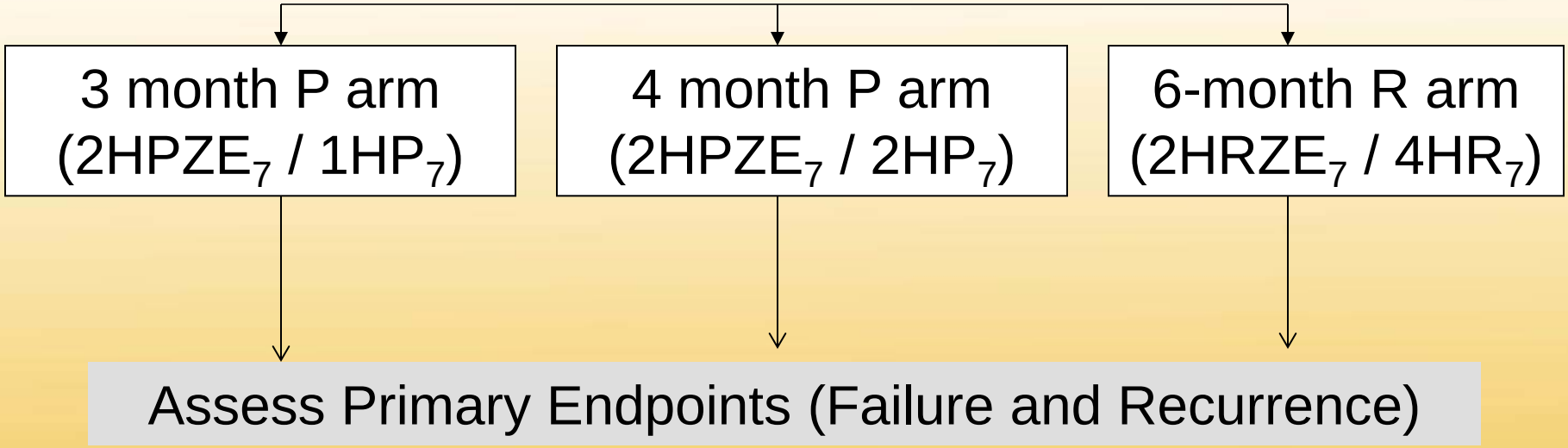
Rosenthal IM, et al. Am J Respir Crit Care Med 2008;178: 989-993

# TBTC Study 31 – Treatment-shortening based on daily RPT

Suspected pulmonary TB, AFB smear+

Should patients with HIV be eligible?

Randomize 1:1:1 (800/arm)



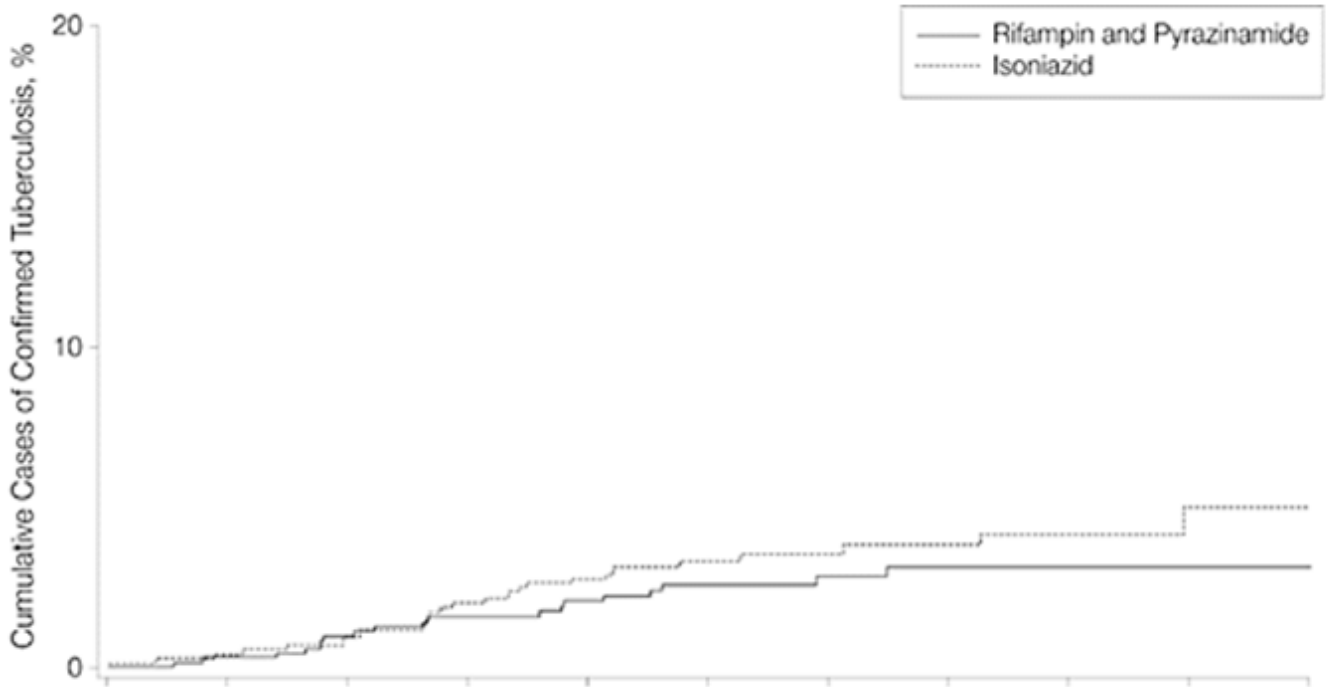
# Pros and cons of including persons with HIV-TB in a Phase 3 trial of treatment-shortening

| Pro | Con |
|---|---|
| Critical subgroup in global TB epidemiology | Drug-drug interactions with ART drugs not fully evaluated |
| Efficacy - high-risk group that may help identify efficacy differences between regimens | Efficacy - increased risk of re-infection may confound the efficacy analysis |
| Tolerability - need to understand tolerability in a major subgroup of TB patients | Tolerability - increased risk of adverse events will lead to regimen discontinuations, thus complicating outcome analysis |

# Broader issue of subgroups in clinical trials

- "Clean trial"
  - Homogeneous population – non-pregnant adults, HIV-negative, no other comorbid diseases
  - Least statistical noise – best chance of seeing the difference caused by the randomization
  - Problems:
    - Uncertainties about generalizability of results
    - Lack of interest in doing follow-up studies in key subgroups
    - Possible result – clinical use of the new regimen in a group that has very different results from those in the trial

# Efficacy results: 12 INH vs. 2RZ for latent TB in persons with HIV




No. of Patients at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Rifampin and Pyrazinamide | 791 | 716 | 591 | 405 | 224 | 71 |
| Isoniazid | 792 | 719 | 575 | 391 | 216 | 66 |

*JAMA.* 2000;283(11):1445-1450

# Tolerability results: 12 INH vs. 2RZ for latent TB in persons with HIV

**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 |

*JAMA*. 2000;283(11):1445-1450

# Response to 2RZ results

Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221--S247.

- 2RZ – recommended for HIV-positive (A2) and HIV-negative persons (B3)*

  * Acceptable alternative, expert opinion

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Weekly

April 20, 2001 / 50(15);289-291

# Fatal and Severe Hepatitis Associated With Rifampin and Pyrazinamide for the Treatment of Latent Tuberculosis Infection --- New York and Georgia, 2000

One of the recommended treatments for latent tuberculosis infection (LTBI) is a 9-month regimen of isoniazid (INH); a 2-month regimen of rifampin (RIF) and pyrazinamide (PZA) is an alternative in some instances. In September 2000, a man in New York died of hepatitis after 5 weeks of RIF-PZA, and in December, a woman in Georgia was admitted to a hospital because of hepatitis after 7 weeks of this regimen. This report summarizes the findings of the investigations of these incidents, which underscore the need for clinical monitoring for adverse effects in all patients receiving treatment for LTBI.

**Case 1**

A 53-year-old incarcerated man received 600 mg (6.7 mg/Kg) RIF and 1750 mg (19 mg/Kg) PZA daily after screening revealed a tuberculin skin test (TST) with 20 mm induration and no radiologic or clinical findings of active tuberculosis (TB). His risk factors for TB included previous work as a medical orderly, homelessness, and multiple incarcerations. He had a history of hypertensive heart disease and alcoholism without evidence of chronic liver disease. He was not known to inject drugs.

The patient died of fulminant hepatitis on day 40, after completing 2RZ

# Hepatotoxicity of 2RZ vs. 6INH in HIV-negative adults: results of a randomized trial

| Hepatotoxicity | RZ (n = 207) | INH (n = 204) |
|---|---|---|
| Grade 1 | 29 (14%) | 27 (13.2%) |
| Grade 2 | 9 (4.3%) | 3 (1.5%) |
| Grade 3 | 7 (3.4%) | 0 |
| Grade 4 | 9 (4.3%) | 2 (1.0) |
| Total | 54 (26.1%) | 32 (15.7%) |
| Drug discontinuation due to hepatitis | 12 (5.8%) | 2 (1.0) |

Other examples of decreased toxicity among persons with HIV

- Nevirapine, rifampin with ritonavir-boosted protease inhibitors

Jasmer R, et al. Ann Intern Med 2002; 137: 640-647

# HIV and acquired rifamycin resistance despite DOT

| HIV status | Acquired drug resistance/all cases of treatment failure or relapse (n) | |
|---|---|---|
| | Twice-weekly rifampin/isoniazid | Once-weekly rifapentine/isoniazid |
| HIV-positive | 0/3 (30) | 4/5 (30) |
| HIV-negative | 1/28 (502) | 0/46 (502) |

Lancet 1999;353:1843-7, Lancet 2002;360:528-34

# Failure/relapse with twice-weekly INH/rifabutin - TBTC Study 23

| Treatment endpoint | N (%) |
|---|---|
| *Failure during treatment* | |
| Culture positive | 2 (1.2%) |
| Event after non-adherence | 1 (0.6%) |
| *Relapse after treatment* | |
| Culture positive | 7 (4.1%) |
| *Overall failure/relapse rate* | 9 (5.3%) |

8 of 9 had acquired rifamycin resistance



Am J Respir Crit Care Med 2006; 173: 350-6

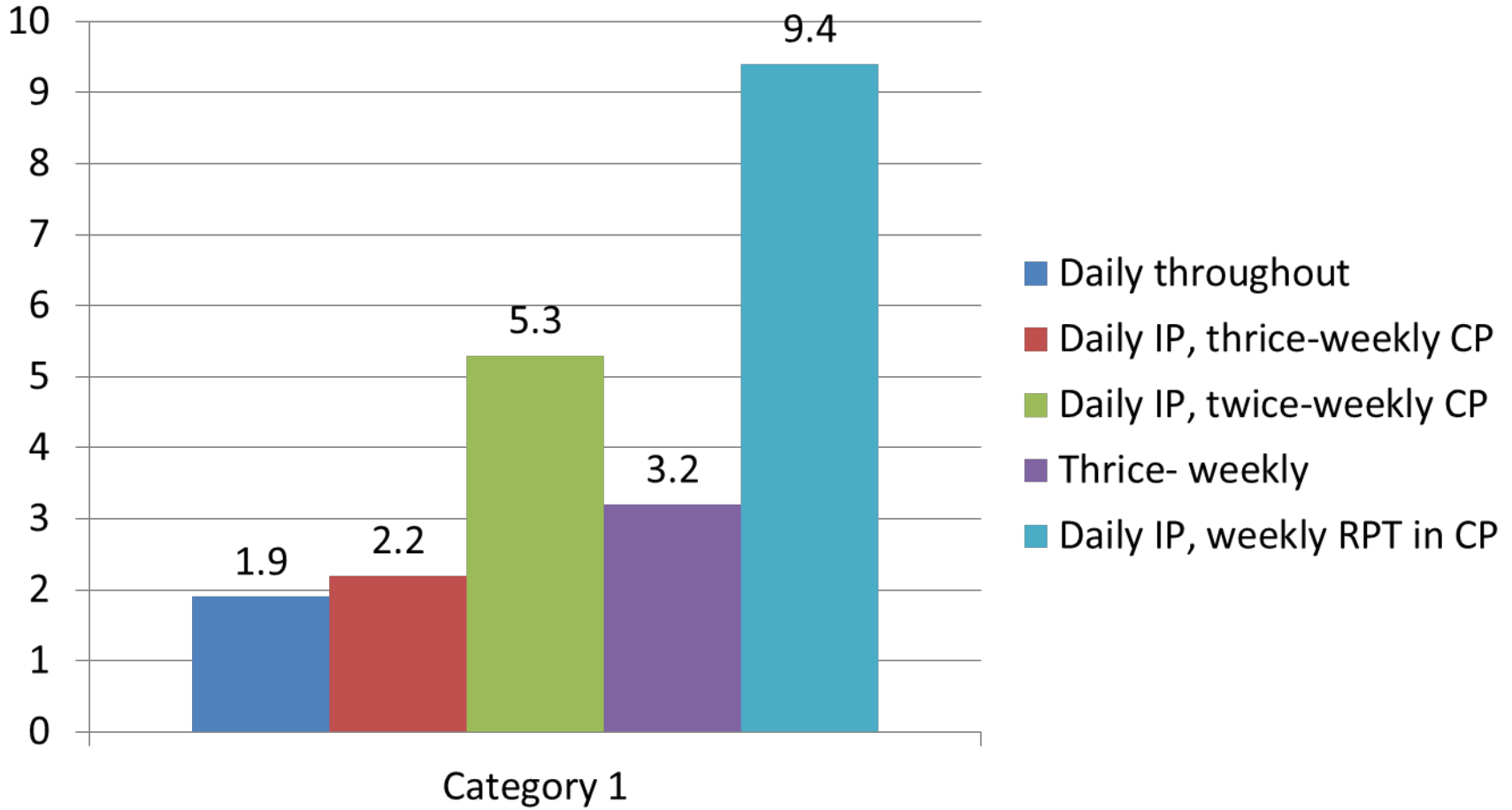
# Responses to acquired rifamycin resistance in HIV-TB

## U.S. guidelines for treatment of active tuberculosis (2003)

| Intensive | Continuation | HIV-negative | HIV positive |
|---|---|---|---|
| $2HRZE_{5-7}$ | $4HR_5$ | A1 | A2 |
| $2HRZE_{5-7}$ | $4HR_2$ | A1 | A2 |
| $2HRZE_{5-7}$ | $4HRpt_1$ | A2 | E1 |
| $2HRZE_3$ | $4HR_3$ | B1 | B2 |

Am J Respir Crit Care Dis 2003; 167: 602-662

# Meta-analysis of the effects of dosing frequency on outcomes of treatment of drug-susceptible TB




Chang KC, et al. Am J Respir Crit Care Med 2006; 174: 1153-8

# Effect of cavitation, 2-month culture status on response to 6-month regimens

| Regimen | Overall recurrence |
|---|---|
| Daily throughout (n = 1554) | 1.9% |
| Daily IP, twice-weekly CP (n = 506) | 5.3% |
| Thrice-weekly throughout (n = 1835) | 3.2% |

Chang KC, et al. Am J Respir Crit Care Med 2006; 174: 1153-8

# Effect of cavitation, 2-month culture status on response to 6-month regimens

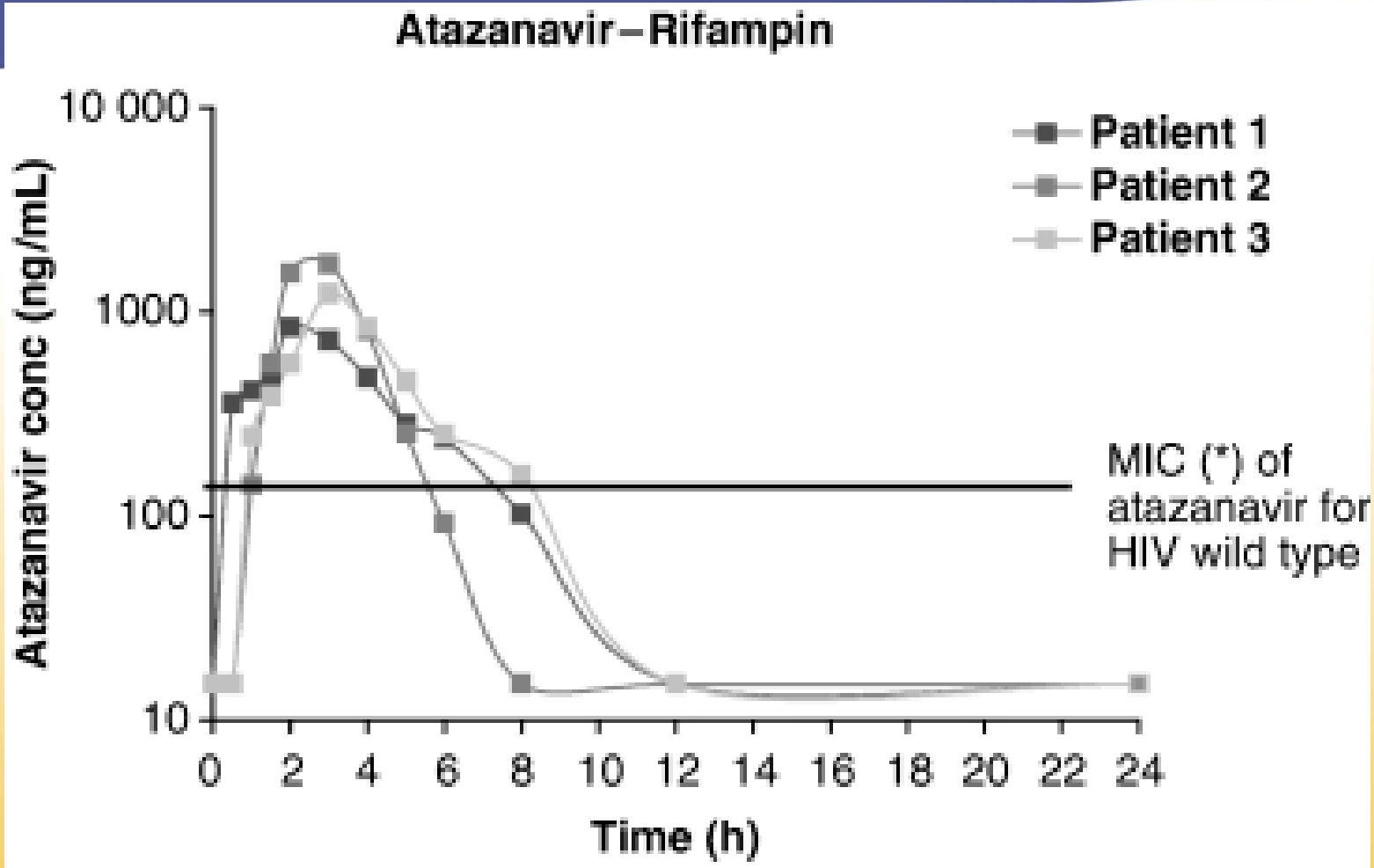
| Regimen | Overall recurrence | Cavitary +, 2-month + | Cavitary +, 2-month _ | Cavitary -, 2-month + | Cavitary -, 2-month - |
|---|---|---|---|---|---|
| Daily throughout (n = 1554) | 1.9% | 6.0% | 2.2% | 1.8% | 0.6% |
| Daily IP, twice-weekly CP (n = 506) | 5.3% | 15.6% | 5.7% | 5.4% | 1.9% |
| Thrice-weekly throughout (n = 1835) | 3.2% | 14.5% | 5.3% | 4.6% | 1.7% |

Chang KC, et al. Am J Respir Crit Care Med 2006; 174: 1153-8

# Thoughts about including patients with HIV in trials of new TB treatment regimens

- Designing a “clean trial” has risks – may miss important tolerability and efficacy findings
- Sample size considerations of including persons with HIV
  - More noise in assessments of tolerability/toxicity
  - Higher percentage of patients who may deviate from protocol (e.g., temporary discontinuation of study drug)
  - Higher risk of failure/relapse would increase power
  - Higher risk of re-infection would decrease power
- My suggestion – be inclusive whenever possible

# Example of drug-drug interactions in HIV-TB care: atazanavir with rifampin

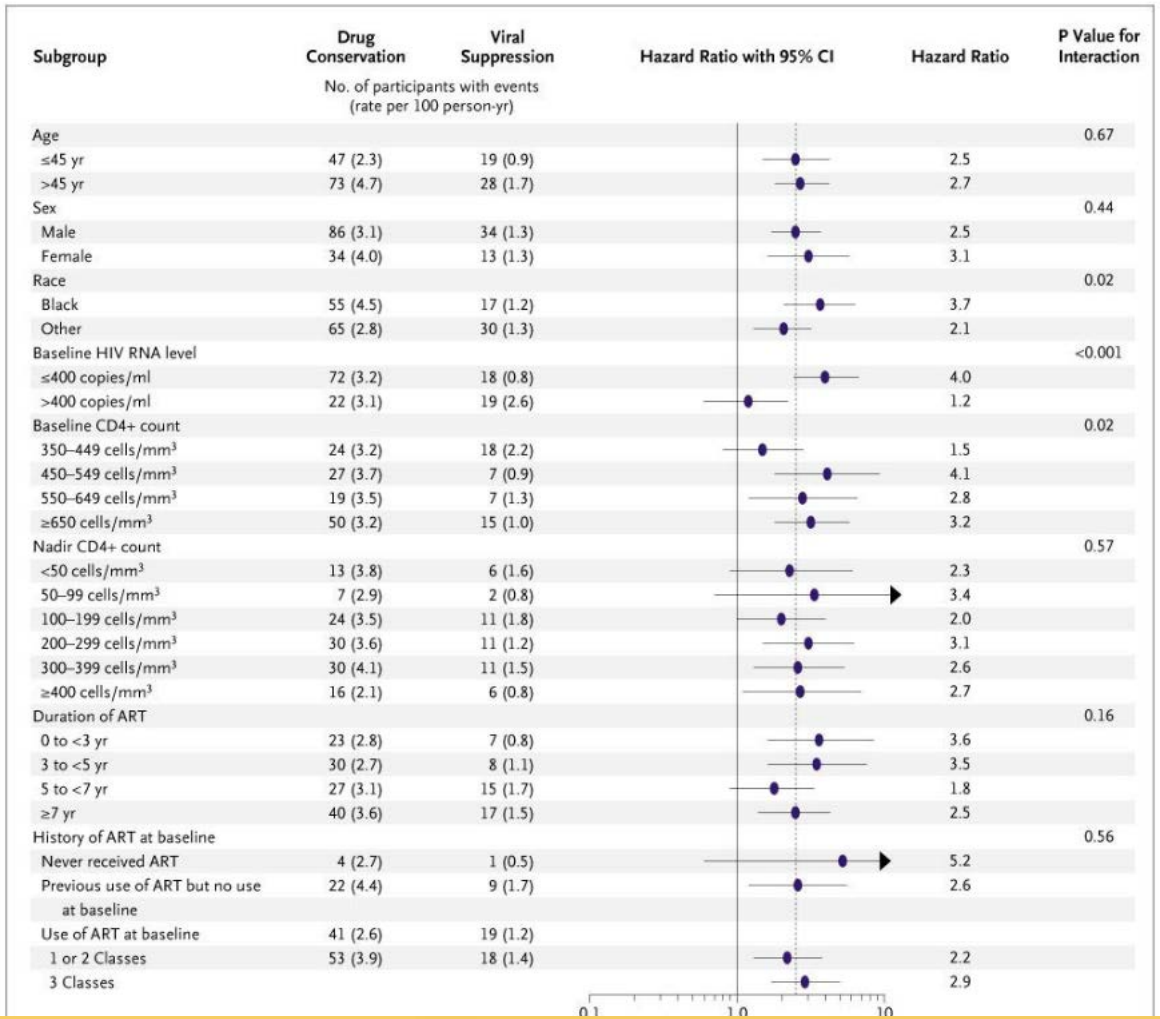



HIV Medicine 2007;8:131-4

# Ways to foster inclusivity in clinical trials

- Evaluate key drug interactions early in drug development
- Staged approach within Phase 3 trials
  - Expand eligibility criteria after initial experience (inclusion of children in PREVENT-TB (TBTC 26)
  - Expand eligibility as drug interaction data becomes available
- Accept the sample size cost of heterogeneity – large, “dirty” trials are the best (SMART study)

# Subgroup analyses of the primary endpoint (AIDS or death) in the SMART trial



| Subgroup | Drug Conservation | Viral Suppression | Hazard Ratio | P Value for Interaction |
|---|---|---|---|---|
| | No. of participants with events (rate per 100 person-yr) | | | |
| Age | | | | 0.67 |
| ≤45 yr | 47 (2.3) | 19 (0.9) | 2.5 | |
| >45 yr | 73 (4.7) | 28 (1.7) | 2.7 | |
| Sex | | | | 0.44 |
| Male | 86 (3.1) | 34 (1.3) | 2.5 | |
| Female | 34 (4.0) | 13 (1.3) | 3.1 | |
| Race | | | | 0.02 |
| Black | 55 (4.5) | 17 (1.2) | 3.7 | |
| Other | 65 (2.8) | 30 (1.3) | 2.1 | |
| Baseline HIV RNA level | | | | <0.001 |
| ≤400 copies/ml | 72 (3.2) | 18 (0.8) | 4.0 | |
| >400 copies/ml | 22 (3.1) | 19 (2.6) | 1.2 | |
| Baseline CD4+ count | | | | 0.02 |
| 350–449 cells/mm³ | 24 (3.2) | 18 (2.2) | 1.5 | |
| 450–549 cells/mm³ | 27 (3.7) | 7 (0.9) | 4.1 | |
| 550–649 cells/mm³ | 19 (3.5) | 7 (1.3) | 2.8 | |
| ≥650 cells/mm³ | 50 (3.2) | 15 (1.0) | 3.2 | |
| Nadir CD4+ count | | | | 0.57 |
| <50 cells/mm³ | 13 (3.8) | 6 (1.6) | 2.3 | |
| 50–99 cells/mm³ | 7 (2.9) | 2 (0.8) | 3.4 | |
| 100–199 cells/mm³ | 24 (3.5) | 11 (1.8) | 2.0 | |
| 200–299 cells/mm³ | 30 (3.6) | 11 (1.2) | 3.1 | |
| 300–399 cells/mm³ | 30 (4.1) | 11 (1.5) | 2.6 | |
| ≥400 cells/mm³ | 16 (2.1) | 6 (0.8) | 2.7 | |
| Duration of ART | | | | 0.16 |
| 0 to <3 yr | 23 (2.8) | 7 (0.8) | 3.6 | |
| 3 to <5 yr | 30 (2.7) | 8 (1.1) | 3.5 | |
| 5 to <7 yr | 27 (3.1) | 15 (1.7) | 1.8 | |
| ≥7 yr | 40 (3.6) | 17 (1.5) | 2.5 | |
| History of ART at baseline | | | | 0.56 |
| Never received ART | 4 (2.7) | 1 (0.5) | 5.2 | |
| Previous use of ART but no use at baseline | 22 (4.4) | 9 (1.7) | 2.6 | |
| Use of ART at baseline | 41 (2.6) | 19 (1.2) | | |
| 1 or 2 Classes | 53 (3.9) | 18 (1.4) | 2.2 | |
| 3 Classes | | | 2.9 | |



Consistent results across multiple subgroups

- ART-experienced
- Prior ART resistance
- ART-naïve
- Different ART regimens
- Baseline CD4
- Baseline VL
- Demographic factors - age, sex, race

New Engl J Med 2006; 355: 2283-2296

# My list of questions in HIV-TB that deserve evaluation in clinical trials

<u>Prevention of active TB among persons with HIV</u>

- What evaluation is needed before starting treatment for latent TB?
- Is there a difference between INH and the rifamycins in terms of the durability of protection against the development of active disease?
- What is the appropriate treatment for the patient exposed to MDR-TB? (combined trial with HIV-negatives)

# My list of questions in HIV-TB that deserve evaluation in clinical trials

## TB treatment among persons with HIV disease

- Dosing frequency – intensive phase, continuation phase?
- Treatment duration – 6 vs. 9 months?
  - Combined trial with other high-risk groups (e.g., smear-positive cavitary pulmonary TB)

## ART initiation during TB treatment

- Can routinely-available clinical and laboratory data substitute for CD4 cell count in making decisions about the timing of ART initiation?

# My list of questions in HIV-TB that deserve evaluation in clinical trials

## Co-treatment of HIV-TB: drug-drug interactions

- Appropriate dosing of raltegravir/dolutegravir when given with rifampin (or rifapentine)
- Optimal management of the interactions between rifamycins and the HIV-1 protease inhibitors
- Optimal co-management regimen for young children (< 3 years of age) with active TB

## HIV-related TB – IRIS events

- Can IRIS events be prevented?
- Optimal management of relatively severe IRIS events

# Summary – challenges in clinical trials of HIV-TB

- Decreasing case rates with broader ART use
- Requirement to use ART during TB treatment in most or all patients
  - Drug interactions (less of a problem with integrase inhibitor-based ART)
  - IRIS events
  - Other adverse events: HIV-related, due to ART or drugs for prophylaxis