Treatment of TB Disease in Patients with HIV infection

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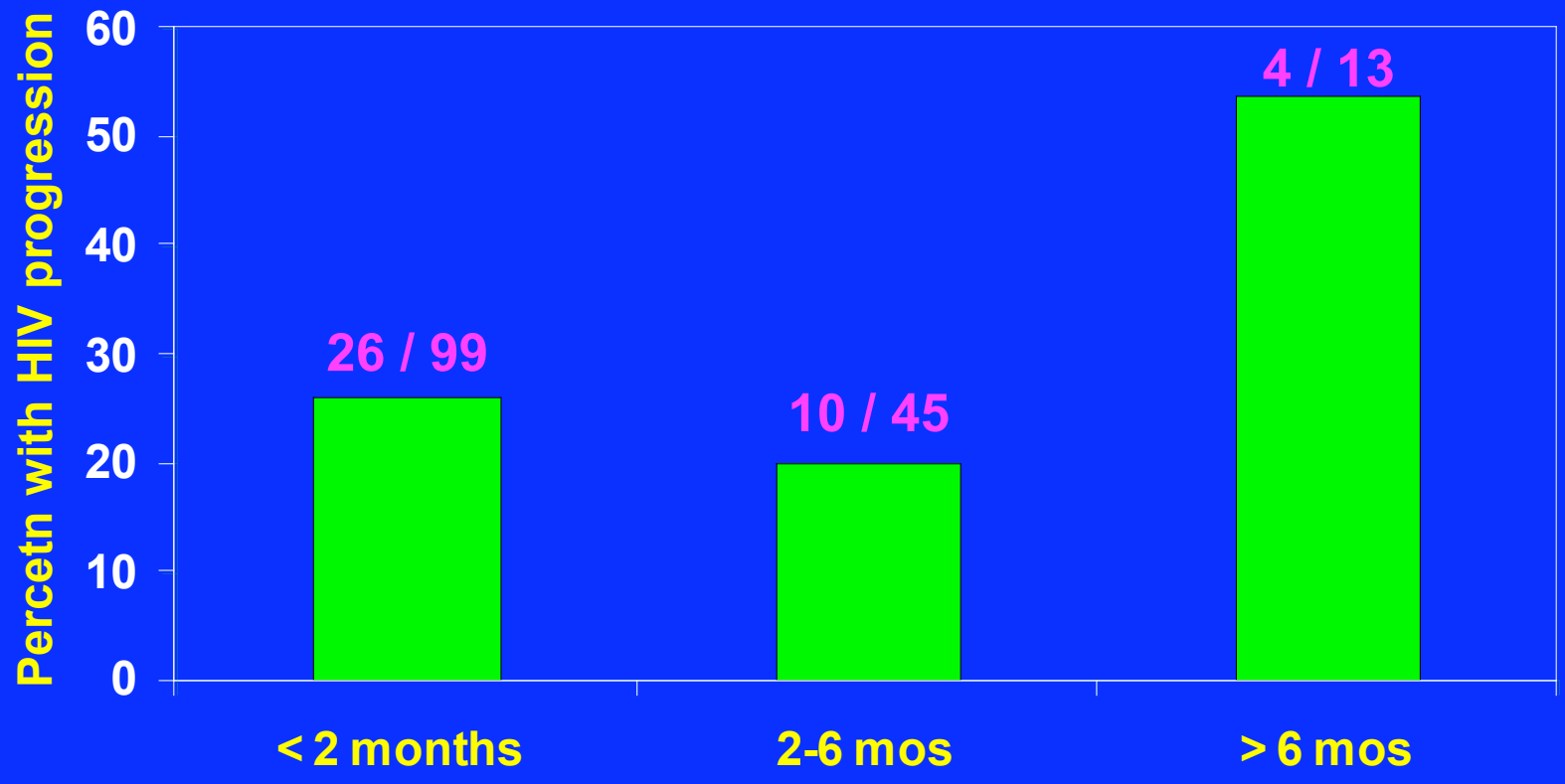
Issues in Therapy for Patients with HIV and TB

- Timing of TB treatment and ART
- Drug interactions
- Drug toxicities
- Adherence
- Paradoxical reactions
- Need to coordinate 2 separate programs

Association between timing of ART during TB therapy and outcomes: results from an observational cohort



12th CROI, abstract 890

Recommendations for use of antiretroviral therapy during TB treatment - WHO

CD4 cell count at TB Dx

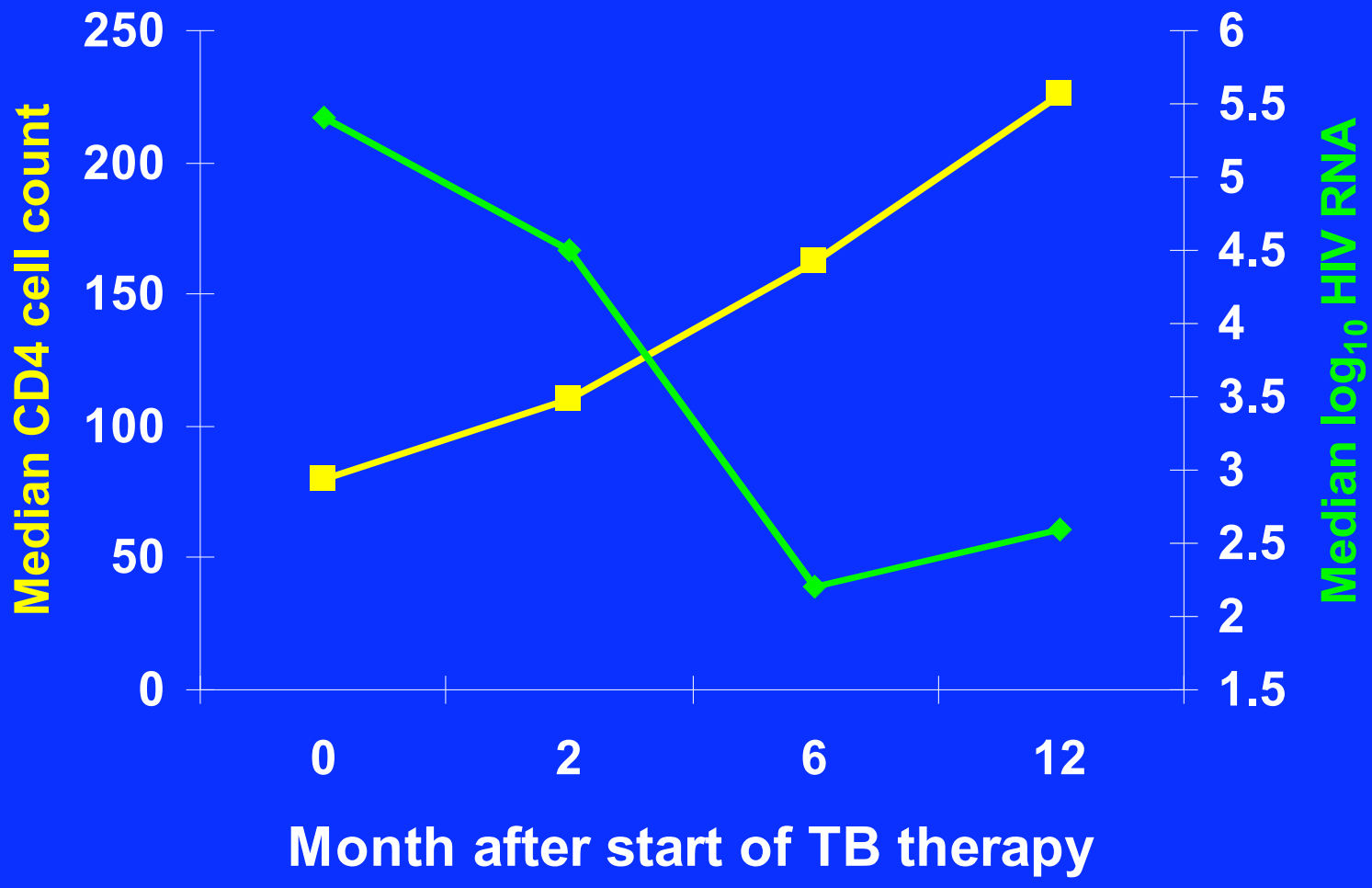
- < 200
  - < 50
  - 50-200
- 200-350
- > 350

- Start ART during TB treatment
  - Within 2 weeks
  - After 2 months
- Monitor, start during TB treatment among those with rapidly-dropping CD4 cell count
- Follow CD4 and clinical status

Starting ART during TB treatment – summary of the steps required

- Start TB therapy, deal with initial side effects
- Help patient deal with the diagnosis of two stigmatizing diseases
- Start cotrimoxazole, deal with initial side effects
- Assess need for and readiness for HAART
- Coordinate start of ART (at least 2 weeks after starting TB therapy, often 2 months)
- Use DOT visits to ↑ adherence with HAART
- Anticipate and manage immune reconstitution events

CD4 cell and viral load response among patients who received HAART during TB therapy – TBTC Study 23



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

RISK FACTORS FOR RELAPSE IN 196 HIV-INFECTED PATIENTS WITH TB

Characteristic	Adjusted Hazards Ratio (95% CI)	p Value
Treated for 6 mo (vs.> 6 mo)	4.33 (1.26-14.8)	0.02
Self-administered therapy	3.11 (0.81-11.9)	0.10
Received therapy intermittently	4.12 (1.09-15.6)	0.04
Hospitalized for tuberculosis	3.60 (0.96-13.5)	0.06
Adverse reaction	0.40 (0.04-4.05)	0.43

AJRCCM 2007; 175:1204

Management of drug interactions: HIV-TB

1. Use a rifamycin-based TB treatment regimen
2. Communicate frequently with HIV care provider
3. Look up dose adjustments
4. Avoid delavirdine, ketoconazole, itraconazole with any rifamycin
5. Avoid within 2 hours of a fluoroquinolone dose: ddI (chewable form), antacids, iron, zinc (or vitamins containing these substances)

Adverse events during treatment of HIV-TB

- 54% (99/167) had adverse events
- 34% interrupted TB or HIV therapy
- Common adverse events
  - Peripheral neuropathy (21%) - more common with use of stavudine
  - Skin rash (17%) - TB drugs (16), co-trimoxazole (7), nevirapine (2), other drugs (4)
  - hepatitis (6%) - TB drugs (6), unknown (5)

AIDS 2002;16:75-83

Overlapping side effect profiles of first-line antituberculosis drugs and antiretroviral drugs

Side effect	Possible causes	
	Antituberculosis drugs	Antiretroviral drugs
Skin rash	PZA, RIF, INH	NVP, DVL, EFV, ABC
Nausea, vomiting	PZA, RIF, RBT, INH	AZT, RIT, AMP, IDV
Hepatitis	PZA, RIF, RBT, INH	NVP, PIs, immune reconstitution
Leukopenia, anemia	RBT, RIF	AZT

Adherence considerations and treatment of TB and HIV

- Increased doses per day
- Increased number of pills per day
- Increased number of kinds of pills

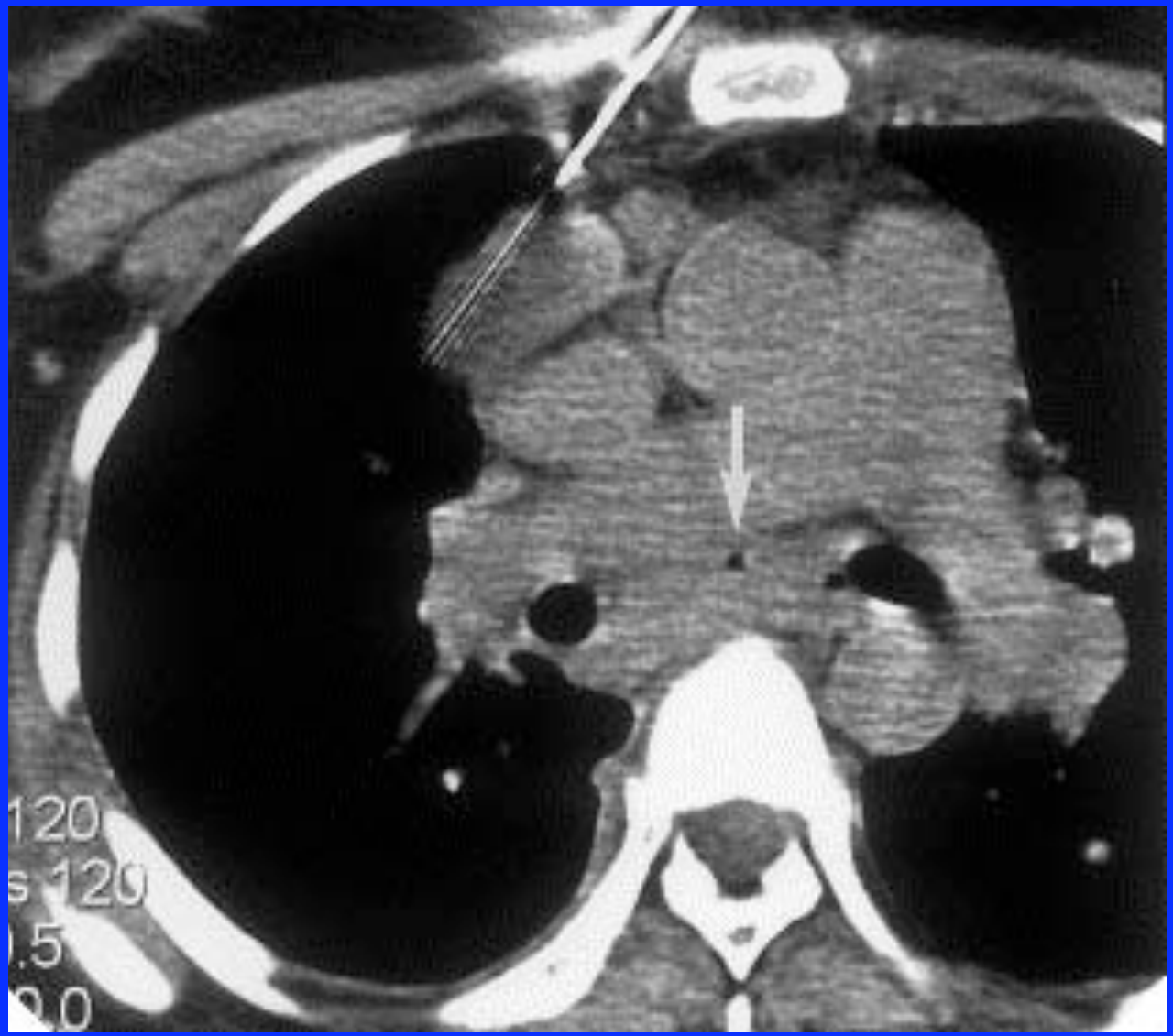
- Clearly decreases adherence
- May decrease adherence
- May decrease adherence

Using ART during TB treatment will be an adherence challenge

Adherence synergy in treatment of TB and HIV

- DOT program for TB builds strong relationships with patients – daily contact, attention to other aspects of care (housing, etc.)
- Once-daily ART now possible
- Provide directly observed ART at the same time as TB medications
- Need to have close working relationships to communicate about about meds, side effects, IRIS (Immune Response Inflammatory Syndrome)

Fever and dysphagia after starting ART



Types of paradoxical (IRIS) reactions in HIV-related TB

- Hectic fever
- New or worsening adenitis - peripheral or central nodes
- New or worsening pulmonary infiltrates, including respiratory failure
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses

Examples of severe paradoxical reactions

- Enlarging adenopathy that compromises function (airway, GI tract)
- Expanding CNS lesion
- Acute respiratory failure
- Acute adrenal insufficiency
- Bowel perforationlarge soft-tissue abscesses

Severity and duration of paradoxical reactions in 169 patients (TBTC Study 23)

NCI toxicity scale	N, %
Grade 1 or 2	7 (4.1%)
Grade 3	9 (5.3%)
Grade 4	8 (4.7%)
Grade 5 (death)	1 (0.6%)
Any	25 (15%)
Hospitalization	12 (7.1%)
Median duration, days (IQR)	7 (3-12)
Severe (grade 4 / 5 or hosp.)	14 (56%)
Median duration of event (IQR)	64 (44 – 99)

IDSA 2004, poster 904

Paradoxical reactions - implications for use of antiretroviral therapy (ART)

- Those who need ART the most (patients with low CD4 cell counts) may be at the highest risk for a paradoxical reaction, including severe reactions
- Delaying ART may decrease risk of severe paradoxical reactions, but may increase risk of another OI or death
- Anticipate paradoxical reactions – discuss beforehand with patient and other care providers
- Schedule early follow-up after starting ARV - detect and manage paradoxical reactions

Treatment of Paradoxical Reactions

Mild: None

Moderate: Prednisone 60 MG QD

Severe: Hold ARV

New TB drugs in Discovery

Bacterial Topoisomerase Inhibitors GlaxoSmithKline, TB Alliance	**Cell Wall Inhibitors** Colorado State University, NIAID	**Dihydrolipoamide Acyltransferase Inhibitors** Cornell University, NIAID
Discovery for Latent Infection Imperial College London, BMGF/Wellcome Trust	**Diphenyl ether based inhibitors of InhA** Stony Brook/ NIH	**Focused Screening** GlaxoSmithKline, TB Alliance
Identification of compounds inhibiting the growth of *M. tuberculosis* – NIH, NIAID, TAACF	**Identification of compounds with in vivo activity against *M. tuberculosis* in animal models –** NIH, NIAID	**InhA Inhibitors** GlaxoSmithKline, TB Alliance
Malate Synthase Inhibitors GlaxoSmithKline, Rockefeller University, Texas A&M	**Multi-Functional Molecules** Cumbre, TB Alliance	**Natural Products Exploration** BIOTEC, California State Univ., ITR, NIAID, TAACF, University of Auckland
Natural Products Exploration NERC Centre, Univ of Strathclyde, Univ of Illinois	**Nitrofuranylamides** NIAID, University of Tennessee	**Nitroimidazole Analogs** TB Alliance, University of Auckland
NM4TB Discovery Portfolio AstraZeneca, European Commission	**Novartis Portfolio** Novartis	**Pleuromutilins** GlaxoSmithKline, TB Alliance
Protease Inhibitors Medivir	**Proteasome Inhibitors** Cornell University/NIAID	**Promazine Analogs** Salisbury University
Quinolones KRICT/ Yonsei University, TB Alliance	**Riminophenazines** Institute of Materia Medica, BTTTRI	**Sanofi-Aventis Portfolio** Sanofi-Aventis
Screening and Target Identification AstraZeneca	**Thiolactomycin Analogs** NIAID, NIH	

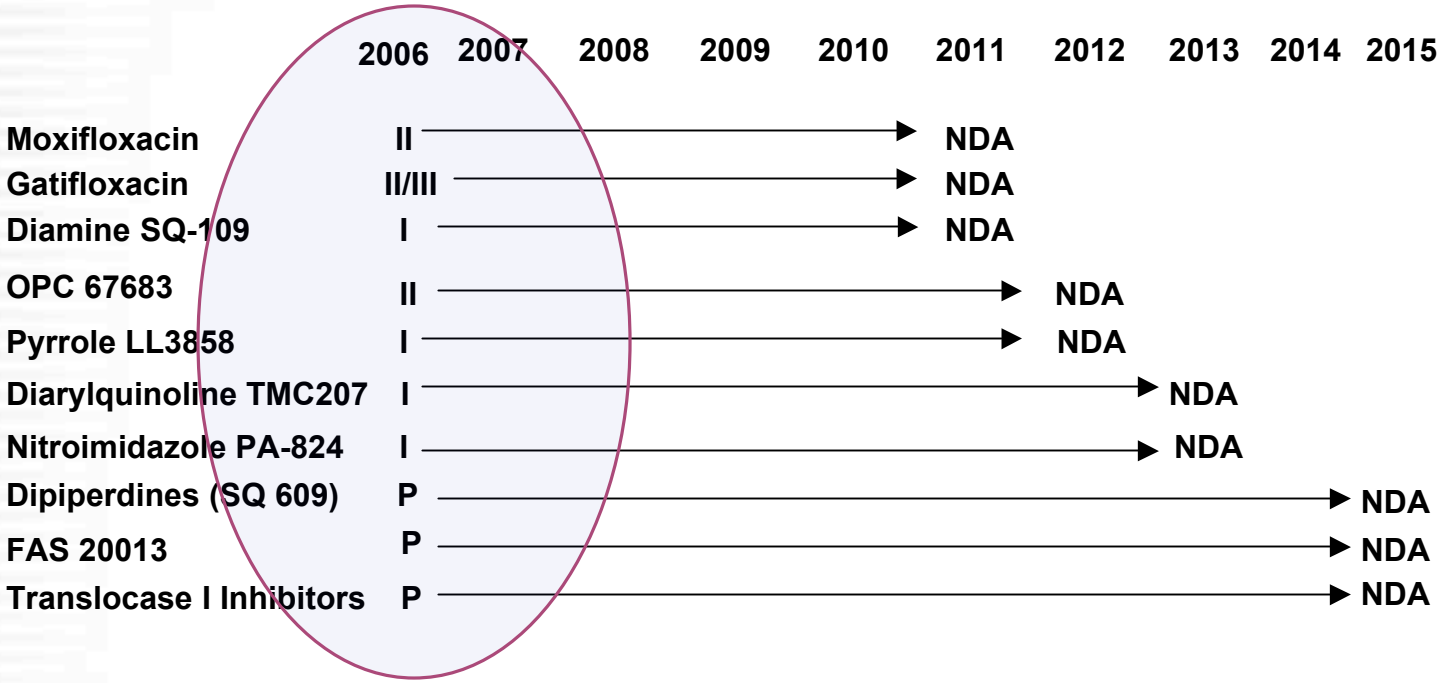
New TB drugs in Preclinical Development

- **FAS Synthase Inhibitor FAS20013**
  FASgen Inc.
- **Nitroimidazole Backup Compound**
  Otsuka
- **Non-Fluorinated Quinolone**
  TaiGen
- **TB Oxazolidinones**
  Pfizer, Inc.
- **Translocase I Inhibitors**
  Sequella Inc., Sankyo

New TB drugs in Clinical Development

Diamine SQ-109 Sequella Inc.	**Diarylquinoline TMC207** Tibotec Pharmaceuticals Limited	**Gatifloxacin** OFLOTUB Consortium: Lupin, NIAID TBRU, Tuberculosis Research Centre, WHO TDR
Gatifloxacin DMID/NIAID/NIH, Case Western	**Levofloxacin** DMID/NIAID/NIH, Case Western	**Linezolid** DMID/NIAID/NIH, TBRU, Case Western, TBTC
Metronidazole for Latent Infection Imperial College London, BMGF/Wellcome Trust	**Moxifloxacin** Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, TB Alliance	**Moxifloxacin** DMID/NIAID/NIH, Case Western
Nitroimidazole PA-824 TB Alliance	**Nitrodihydro-imidazooxazole Derivative OPC-67683** Otsuka Pharmaceutical Co.	**Pyrrole LL-3858 (Sudoterb)** Lupin Limited
SV07 Immune Modulator SciClone Pharmaceuticals		

Expected Timelines to Launch



Treatment of HIV/TB: Conclusions

- When indicated, ART should be started during TB therapy, but not right away
- Use of Efavirenz-containing ART regimen is preferred
- Use standard TB regimen with rifampicin, but consider extending duration of TB treatment
- Pay special attention to adherence and drug toxicities
- New drugs may be coming, but they won't be here soon