Clinical Management of Tuberculosis Disease in the Context of Immunosuppression

Christopher Spitters, MD, MPH
christopher.spitters@doh.wa.gov
CITC Intensive Course
July 14, 2023

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Disclosures

- No relevant relationships or interests in commercial entities to disclose
- Financial ties: WA DOH only
- Off-label uses that may be mentioned:
  - NAAT on non-respiratory specimens
  - Rifabutin as an alternative to rifampin
  - One month isoniazid-rifapentine for LTBI
  - BPaL for rifampin-resistant or –intolerant TB
  - Boosted protease inhibitors with rifampin
  - TNF alpha blockers or thalidomide for IRIS

Learning Objectives

- Anticipate drug-drug interactions involving anti-mycobacterials, HIV medications, and immunosuppressants to optimize outcomes.
- Recognize and diagnose immune reconstitution inflammatory syndrome (IRIS) to improve patients' safety and quality of life during therapy.
- Address timing of antiretroviral or immunomodulatory therapy during TB treatment to improve outcomes related to other conditions.

TB & Immunosuppression: Agenda

- Relevant conditions: HIV, TNF-alpha blockade, solid organ transplant
- Diagnosis
- Regimens
- Anti-retroviral therapy initiation
- Drug drug interactions
- Adverse effects
- IRIS
- Resuming interrupted immunosuppressants
- Exiting from treatment

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Clinical Presentation of TB
Severe Immunosuppression

- Atypical presentations more common
  - Extrapulmonary
  - Disseminated
- Urgency greater
  - CNS involvement
  - Systemic illness and abnormal vital signs

Clinical Presentation of TB in Immunosuppressed Patients

Immunosuppressed	Immunocompetent
• Adenopathy	• Pulmonary
• Effusions	• Reactivation type
• Dissemination	• Cavitation
• Extrapulmonary sites	• Less extrapulmonary
• Smear-negative more common	• Smear positive more common
• More IRIS	• Less IRIS

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Diagnosis

- **Imaging: lower threshold for CT and MRI**
- **Sample all relevant sites**
  - Respiratory *always*
  - Other sites of involvement
  - **Urine and blood merit consideration**
- Molecular
- AFB smear and culture
- Chemistries
- Cell counts and differential
- Cytology/pathology
- TST and/or IGRA (reduced sensitivity)

Treatment Regimens

- Is 2HRZE + 4HR adequate? In many/most cases, yes.
- **Preference for daily therapy throughout**
- Extend duration of therapy? Often, yes.
  - **HIV: 9 months increasingly common**
  - Consider extended durations for
    - Severe disease (e.g., disseminated, cavitary, late conversion)
    - Severely immunosuppressed
    - Not on ART
- 2HPMZ+2HPM ok if CD4>100 and using efavirenz AND low-burden disease
- Rifamycin resistance-or-intolerance: expert consultation
- Corticosteroids:
  - CNS
  - some pericarditis

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

TB& HIV
Initiating Antiretroviral Therapy

- During TB treatment better than after
- Baseline CD4 ≤50: start <2 weeks
- Baseline CD4 >50: start at ~8 weeks
- TB meningitis—"uncertain"
  - Pre-2018: "wait until TB disease well controlled"
  - Current: "consider immediate if CD4<50 and able to monitor"
- Typical regimens
  - 2NRTI + integrase inhibitor (double dosed bid)
  - 2NRTI + EFV

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Drug-Drug Interactions
Common Contributors

Antiretrovirals

- Protease inhibitors
- NNRTIs
- Tenofovir alafenamide (TAF)
- Integrase inhibitors

Anti-mycobacterials

- Rifamycins
- Rifabutin
- Rifapentine
- Isoniazid

Immunosuppressants

- Corticosteroids
- Mycophenolic acid
- Tacrolimus
- Cyclosporine

Other antimicrobials for OIs

- Azoles

Chronic Disease Medications

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Drug-Drug Interactions
ART-Rifamycin Strategies

- Alternatives to standard regimens:
  - Protease inhibitor + rifabutin half-dose (add therapeutic drug monitoring)
  - Boosted protease inhibitor + rifampin (hepatotoxicity)
  - Rifamycin-free treatment regimen (18 months?!)
- Manage rifamycin interactions rather than avoiding them

Drug-Drug Interactions
Contraindications to Use with Rifamycins

- Rilpivirine
- Etravirine
- Doravirine
- Bictegravir
- Elvitegravir+cobicistat
- Cabotegravir
- Tenofovir alafenamide (TAF [TDF is ok])

Other Drug-Rifamycin Interactions

- Tacrolimus and cyclosporine
  - Avoid rifamycin

  OR
  - Rifabutin + therapeutic drug monitoring
- Corticosteroids may require higher doses
- Azoles
  - Rifamycins reduces azole levels
  - Azoles increase rifamycin levels
  - Options
    - avoid rifamycins
    - half-dose rifabutin and check levels

Washington State Department of HEALTH

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Adverse Effects of Treatment for TB

- **More common in HIV-TB**
- Mild: treat the adverse effect and monitor
- Moderate-to-severe:
  - Interrupt or change therapy
  - **Explore other causes**
  - Serial challenge
- **Less margin of error for holding TB meds in…**
  - Severe disease
  - Severe immunosuppression
  - Early in therapy

Washington State Department of HEALTH

CURRY INTERNATIONAL TUBERCULOSIS CENTER

IRIS

Immune Reconstitution Inflammatory Syndrome

- **Unmasking** is a new presentation of tuberculosis that is emerges in the weeks following initiation of ART (less common)
- **Paradoxical worsening** after the start of ART in patients initially responding to tuberculosis treatment
  - Typically presents as
    - Worsening at original site of disease
    - LNs most common
    - CNS tuberculomas, pulm infiltrates, effusions
    - Granulomatous hepatitis
- Typical onset: 1-4 weeks after starting ART or stopping immunosuppressants
- Typical duration: 2-3 months
- Usually self-limited in HIV; more persistent following TNF-alpha blockade withdrawal

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Paradoxical IRIS--Overview

- HIV
  - Incidence ~20-30% overall
  - Risk factors
    - Immediate ART start
    - Extrapulmonary disease
    - Lower baseline CD4 or higher viral load
    - Larger change in CD4 or viral load on ART
- TNF-alpha blockade
  - Common following interruption of TNF-alpha blockade
  - Often severe and of long duration
- SOT
  - Anecdotally: not so common
  - Case reports: "…becoming more common…"
  - Risk factors include use of rifampin, EPTB

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Paradoxical IRIS Evaluation & Management

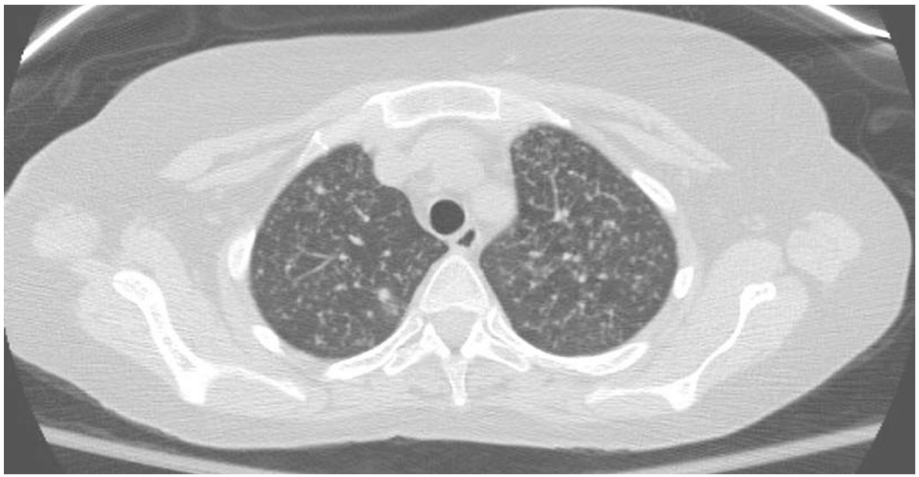
- Differential diagnosis
  - Treatment failure (adherence, drug resistance, poor absorption)
  - Another opportunistic infection or malignancy
- Evaluation
  - Sample affected site(s)
  - Repeat molecular drug susceptibility testing
- Management
  - NSAIDs
  - Drainage of LNs/effusions in some cases
  - Corticosteroids
    - Treatment
    - Prevention (<30d ART start AND CD4 <100)
  - TNF-alpha blockers? Thalidomide?

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Paradoxical IRIS: Case Presentation

- 28 y/o HIV negative-woman
- RA; TNF-alpha blockade x 6 months. Last dose 3 wks.
- 2 weeks of fever, dyspnea, dry cough, and anorexia
- T102F, P120, BP 90/60, O2 sat 92%



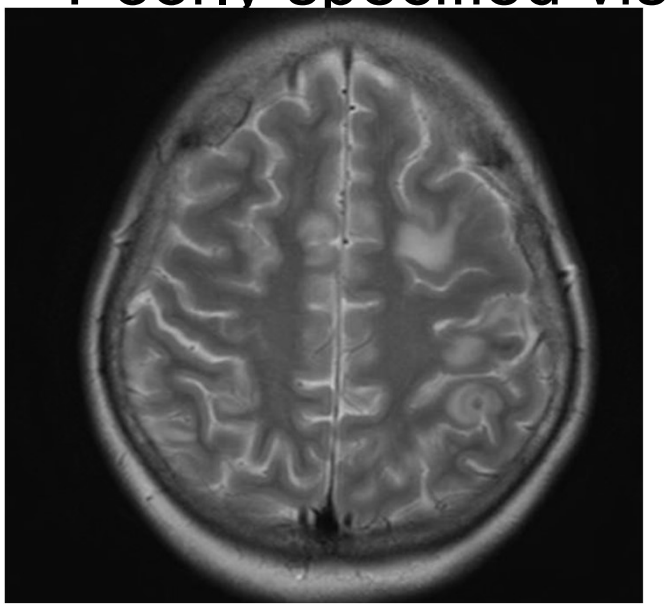
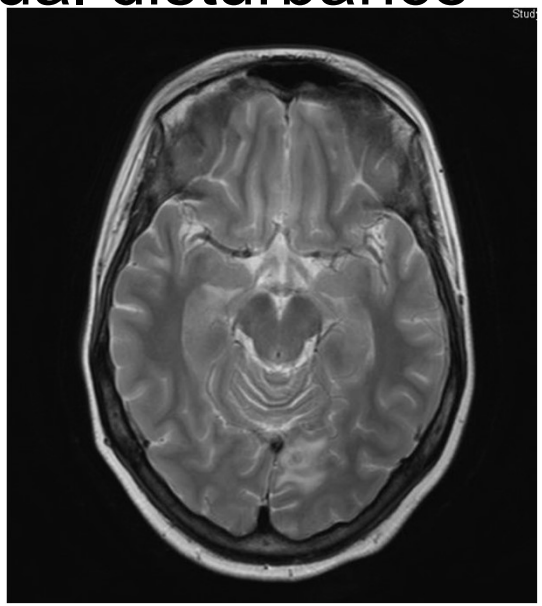
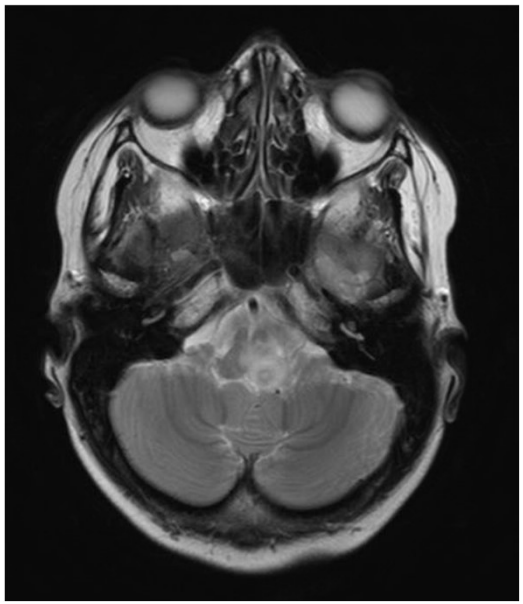
- Sputum AFB smear neg; PCR neg
- BAL 2+ and PCR+, no rifampin resistance mutations
- Starts HRZE

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Paradoxical IRIS: Case Presentation--2

- Initial improvement in fevers and appetite
- 2 weeks into therapy: headache, dizziness, gait problems, fell twice.
- Poorly specified visual disturbance

- CSF: 0 WBC, protein 27, glucose 84

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Case Presentation—2
Interactive Question

A reasonable next step for this patient would be:

A. Brain biopsy

B. Expand regimen to cover MDR

C. Hold TB therapy until neurologic symptoms improve

D. Continue TB therapy and add dexamethasone

Timing of Return to TNF-alpha blockade

- Preferred: after completion of TB therapy
- Alternative:
  - When disease is “well-controlled”
  - At least 2 months into therapy
- Last line of therapy for severe/recalcitrant IRIS

  -off label

  -expert-guided
- Note: LTBI rx and starting TNF-alpha blockade
  - Ideally: >1 month after starting LTBI treatment
  - Alternative: tolerant, adherent to LTBI treatment

    (e.g., 2wks)

CURRY INTERNATIONAL TUBERCULOSIS CENTER

Washington State Department of HEALTH

Terminating Therapy

- Plain imaging of chest (+/- other imaging)
- Educate patient about risk of relapse and symptoms to watch for
- Give patient a copy of their treatment record
- **Trigger necessary post-rx dose adjustments for medications interacting with rifamycins**
- **Consider post-rx surveillance, either directly or delegated to managing clinician for immunosuppressing condition**
- No post-rx isoniazid in low burden settings

Summary
TB & Immunosuppression--1

- Easier to treat LTBI than active disease
- Clinical presentation can be atypical and/or severe
- Err on the side of over-imaging and over-sampling rather than under-doing diagnostics
- Lean toward lower threshold for starting empiric treatment once evaluation is complete
- Manage mild adverse effects, interrupt for more severe or systemic adverse effects
- Look and adjust for drug-drug interactions
- Consider therapeutic drug monitoring

Summary
TB & Immunosuppression--2

- Pay attention to starting/stopping other rx
  - Starting ART in HIV at 2-8 weeks, depending on CD4/TBM
  - Stop TNF-alpha blockade immediately and individualize resumption after disease is treated or at least well controlled
  - Don’t stop tacrolimus or cyclosporine; adjust TB rx instead
  - Gentle slopes on corticosteroid tapers for CNS, pericardial, post-TNF blockade IRIS
- Anticipate, evaluate and manage IRIS for patient safety and comfort
- Trigger dosing revisions at end of therapy for rifamycin-interacting drugs
- Work closely with clinician managing other condition

TB & Immunosuppression Recommended Reading

- Mycobacterium tuberculosis Infection and Disease, in *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*. US DHHS: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/mycobacterium-tuberculosis-infection-and?view=full
- 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care & Research* (2015): DOI 10.1002/acr.22783.
- Horne D, et al. Challenging Issues in Tuberculosis in Solid Organ Transplantation. *Clin Infect Dis* (2013); 57(10):1473–82. DOI: 10.1093/cid/cit488

Drug Interaction Checkers

- Curry International TB Center Rifamycin Drug-Drug Interactions Guide

  https://www.currytbcenter.ucsf.edu/products/view/rifamycin-drugdrug-interactions-a-guide-for-primary-care-providers-treating-latent-tuberculosis
- University of Liverpool:

  https://www.hiv-druginteractions.org/checker
- HIV-Insite Database of Antiretroviral Drug Interactions:

  http://hivinsite.ucsf.edu/InSite?page=ar-00-02
- DHHS Adult and Adolescent ARV Guidelines:

  https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/367/overview
- Lexi-Comp via Up-to-Date (proprietary)

CURRY
INTERNATIONAL
TUBERCULOSIS
CENTER

Washington State Department of
HEALTH

LTBI & Immunosuppression
An Ounce of Prevention…1

- Diagnosis:
  - Low-mitogen indeterminate results are not negative results in this context.
  - In the absence of symptoms (including cough of *any* duration), a normal CXR is sufficient to exclude active TB.
- HIV
  - Preferred regimen options
    - 3HP 1/7 (ok with efavirenz, dolutegravir, raltegravir)
    - 3HR 7/7 (recommended only for efavirenz-based regimens)
  - Alternative
    - 9H 7/7
    - 4R 7/7
    - 1HP 7/7
  - Not recommended
    - 4-Rifabutin 7/7 (lack of data, but that's also the case for active TB)
    - 2RZ (unacceptable hepatotoxicity incidence)
  - If "not infected" and CD4<200, re-test when CD4>200
- TNF-alpha blockade
  - *Pre-blockade* evaluation and treatment
- Solid organ transplant
  - Preferred: evaluate and treat prior to immunosuppression

LTBI & Immunosuppression
An Ounce of Prevention…2

- Avoid exposure!
- Limited sensitivity of tests for cell mediated immunity to TB
- Consider dual testing to maximize sensitivity (e.g., TST+IGRA or both IGRAs)
- Consider chest imaging regardless of TST/IGRA results
- Close contacts: default is to treat for LTBI regardless of results