HIV Update for the Internist

Jonathan Vilasier Iralu, MD, FACP
Indian Health Service Chief Clinical Consultant for Infectious Diseases
Disclosures
A 26 year-old male come in to the office to establish primary care after moving to the area. Review of his social history reveals that he drinks < 7 servings of alcohol per week but has had multiple male sexual partners in the last 12 months. He has a normal physical exam. Routine screening labs are sent for syphilis, HIV, gonorrhea, chlamydia (urine, pharyngeal swab and rectal swab) and all three come back negative.
Which of the following is most likely to decrease this man’s risk of acquiring HIV?

1. Recommend Condoms
2. Recommend Sexual Abstinence
3. Prescribe Daily Tenofovir/Emtricitabine Pre-Exposure Prophylaxis (PrEP)
4. Recommend Sero-concordant dating
Background: HIV Prevention

- Approximately 50K Americans acquire HIV annually.
- Adolescent and Young adult Men who have Sex with Men (MSM) age 13-24 are at especially high risk for HIV acquisition.
- Condoms are 90-95% effective with consistent use but only 60-70% effective in meta-analyses including all users.
Pre-exposure Prophylaxis - What is it?

- HIV anti-retroviral therapy taken to prevent acquisition of HIV
  - Zidovudine taken during pregnancy and for 6 weeks after by the baby decreases transmission by 68%
  - Zidovudine taken within 72 hrs of an occupational needle-stick injury decrease HIV acquisition rates by 81%
- Animal studies suggested PrEP might be efficacious
- Human Studies have focused on the combination pill Tenofovir difumarate-Emtricitabine
PrEP-The evidence

- iPrEx-
  - 1224 MSM given daily TDF/FTC
    - 44% reduction in HIV acquisition
    - No transmission of resistant virus

- Partners PrEP-
  - 1572 heterosexual men and women given TDF and 1568 given TDF/FTC
    - 66% reduction in women getting both drugs
    - 84% reduction in men getting both drugs
    - No transmission of resistant virus
Who Should get PrEP?

- MSM:
  - Adult man
  - No evidence for acute or established HIV infection
  - Any male partners in the past six months
  - Not in a monogamous partnership with a recently tested HIV – negative man
  - And at least one of the following
    - Anal sex without condoms in the last six months
    - STI in the last 6 months
    - In a sexual relationship with an HIV positive male partner
Who Should get PrEP?

- Heterosexual Men and Women
  - Adult
  - No sign of acute or established HIV infection
  - Not monogamous with a recently tested HIV negative partner
  - And at least one of the following:
    - Man who has sex with both men and women
    - Infrequently uses condoms with sex with one or more partners of unknown HIV status who are at high risk (IDU or bisexual)
    - HIV positive partner
Who Should get PrEP?

- Injection Drug Users
  - Adult
  - No sign of acute or established HIV infection
  - Any injection of un-prescribed drugs in last 6 months
  - And at least one of the following
    - Sharing of injection equipment in last 6 months
    - Been in a methadone, buprenorphine or suboxone Rx program in last 6 months
    - Risk of sexual transmission
What baseline evaluation should be done?

- Document negative antibody test within 1 week of starting PrEP
  - Serology
  - Rapid oral test
- Review for signs/symptoms of Acute HIV infection in prior 4 weeks
  - Fever, fatigue, myalgia, HA, pharyngitis, adenopathy, arthralgia, night sweats, diarrhea
  - If ROS positive, send HIV antibody/antigen test and HIV viral load test
- Other tests
  - Renal function (don’t prescribe if eCrCl < 60)
  - Hepatitis serologies
  - Other STDs
How do you prescribe PrEP?

- Tenofovir difumarate/ Emtricitabine (Truvada™) 1 po daily
  - Tenofovir alafenamide/Emtricitabine trials are underway

- Interactions
  - Acyclovir, valacyclovir, cidofovir, ganciclovir, aminoglycosides, NSAIDS

- Side Effects
  - Start-up syndrome: HA, Nausea, Flatulence
  - Nephrotoxicity
  - Decreased bone mineral density (1% decline), no fragility change at 1-2 years
How do you follow-up PrEP patients?

- **Quarterly**
  - HIV testing and Review for signs and symptoms
  - Pregnancy testing
  - Give a 90 day supply with no refills
  - Review side effects and adherence
  - Answer new questions

- **Semi-annually**
  - Monitor eCrCl
    - Stop if eCRCl < 60, monitor if > 60
  - Screen for syphilis, gonorrhea, chlamydia (urine, rectal, pharyngeal)
PrEP Reference

A 29 year-old man comes in to the clinic complaining of one week of fever, myalgias and sore throat. On review of symptoms he denies cough but notes watery diarrhea. He drinks alcohol socially, does not inject drugs and is married with 2 children. On exam he has a temperature of 100.7 degrees F. Exam is notable for pharyngeal erythema, posterior cervical lymphadenopathy and a faint macular rash on the chest. Routine laboratory tests are notable for WBC 4.1K, platelets 135, Creatinine 0.7 and ALT 67.
Which test is likely to reveal the diagnosis?

- a. Monospot
- b. Fourth Generation HIV Ag/Ab assay
- c. RPR
- d. HIV Viral load
- e. B and D
Acute HIV Infection

- **Background**
  - Acute febrile illness occurring 2-4 weeks after HIV exposure
  - 40-90% of persons acquiring HIV experience this syndrome
  - 80% of transmissions occur via mucosal surfaces
  - 20% of transmissions are percutaneous or intravenous
Acute HIV Infection Pathogenesis

- Virus crosses the mucosal barrier
- Infects dendritic cells and macrophages in anogenital submucosa
- HIV infected cells fuse with CD4 cells
- Massive proliferation in gut mucosa with CD4 depletion
- Dissemination to rest of body
Acute HIV Infection
Differential Diagnosis

- HIV
- Secondary Syphilis
- EBV
- RMSF
- Measles
- Drug rash
- Lupus
Acute HIV infection
Clinical Presentation

- Symptoms
  - Fever
  - Fatigue
  - Myalgia
  - Rash
  - Headache
  - Pharyngitis
  - Cervical adenopathy
  - Arthralgia
  - Night Sweats
  - Diarrhea
Acute HIV Infection: Diagnosis

- You have to think of it.

- What to order:
  - Fourth Generation HIV Antigen/Antibody test
    - Screen for Ag and Ab
    - Differentiation assay for HIV 1 vs HIV 2
    - HIV viral load
  - HIV Viral load

Order Both!
Acute HIV Infection: Treatment

- Treat immediately!
  - Improves symptoms especially if there is meningoencephalitis or neuropathy
  - Makes the biomarkers look good
    - Stops CD4 cell depletion during the initial phase of infection
    - Enhances immune reconstitution
- Decreases risk of transmission
  - Risk of infection increased 2.5-fold for every 10-fold elevation in viral load
Acute HIV Infection: Treatment

- **When to treat**
  - Immediately
  - Don’t wait for resistance testing results

- **What to treat with**
  - Tenofovir/Emtricitabine + boosted Darunavir
  - Tenofovir/Emtricitabine + Dolutegravir

- **How long to treat**
  - Forever!

Modify Rx when resistance test is back
Your 9:00 AM patient is in room 3 in the clinic. She is a 32 year old bank teller who went to Urgent Care for an ankle sprain. Routine screening revealed a positive HIV antibody test.
What should you do now?

1. Transfer care immediately to another provider
2. Feign an illness and go home on sick leave
3. Enroll patient in primary care in your clinic
4. Sign up to take part in Project ECHO HIV teleconference.
5. 3 and 4
What to do first

- Reassurance
- Reassurance
- Reassurance
History

- Current symptoms
- Risk factor screening
- Sexual history
- Substance Use
- Domestic violence
## Baseline Laboratory Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency Description</th>
<th>Use Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 Count</strong></td>
<td>At diagnosis &amp; q 3-6 months at first then every 6-12 month when viral load is undetectable and CD4&gt;200</td>
<td>Use one laboratory and methodology</td>
</tr>
<tr>
<td><strong>HIV Viral Load</strong></td>
<td>At diagnosis &amp; q 3-6 months at first then every 6 months after 2-3 years of virologic control</td>
<td>Use one laboratory and methodology</td>
</tr>
<tr>
<td>Genotypic antiretroviral resistance test</td>
<td>At diagnosis on all patients and with failure of virologic control</td>
<td>Test prior to starting antiretroviral therapy on all patients</td>
</tr>
<tr>
<td>Test</td>
<td>Frequency</td>
<td>Action/Recommendation</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>RPR</strong></td>
<td>At diagnosis and yearly</td>
<td>LP if evidence for neurosyphilis</td>
</tr>
<tr>
<td><strong>GC/Chlamydia</strong></td>
<td>At diagnosis and yearly</td>
<td>Order rectal &amp; pharyngeal test if MSM, in addition to urine</td>
</tr>
<tr>
<td><strong>Quantiferon assay or PPD</strong></td>
<td>At diagnosis and yearly</td>
<td>INH for 9 months if (+)</td>
</tr>
<tr>
<td><strong>HBsAg, HBsAb, HCV Ab, Hep A total Ab</strong></td>
<td>Once for all patients. Test MSM and IDUs annually for Hepatitis B and C</td>
<td>Vaccinate for Hep A and B if serology is negative</td>
</tr>
<tr>
<td><strong>Toxoplasma Ab</strong></td>
<td>Once</td>
<td>Prophylaxis if CD4&lt;100</td>
</tr>
<tr>
<td><strong>CMV Ab</strong></td>
<td>Once</td>
<td>Test only if low risk (non MSM, non IDU)</td>
</tr>
<tr>
<td><strong>Varicella Ab</strong></td>
<td>Once if no h/o Chickenpox or Shingles</td>
<td>Consider vaccination if negative and CD4&gt;200</td>
</tr>
</tbody>
</table>
## Baseline Laboratory Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>Once</td>
<td>Only if symptoms or PPD+</td>
</tr>
<tr>
<td>Cervical PAP Smear</td>
<td>Q 6 months x 2 then yearly</td>
<td></td>
</tr>
<tr>
<td>Anal PAP Smear</td>
<td>Annually in MSM or if there is a history of anal sex, abnormal cervical PAP, or history of genital warts</td>
<td>Recommended test. Refer positives for high resolution anoscopy/surgery clinic</td>
</tr>
<tr>
<td>Lipids</td>
<td>Baseline and annually</td>
<td>Avoid simva/lovastatin</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Baseline and annually if on Tenofovir</td>
<td></td>
</tr>
<tr>
<td>HGB A1c</td>
<td>Baseline and annually</td>
<td></td>
</tr>
<tr>
<td>G-6-PD Level</td>
<td>Once</td>
<td>If sulfa allergic</td>
</tr>
</tbody>
</table>
Antiretroviral Therapy Basics

- Treat all HIV positive patients regardless of CD4 count
Antiretroviral Basics

- TAF/FTC/Elvitegravir/cobicistat 1 po daily
  - Single pill
  - OK with antacids

- TAF/Emtricitabine 1 po daily plus Dolutegravir 50 mg po daily
  - Two pills
  - OK with antacids
  - Minimal drug interactions

- TAF/FTC 1 po daily plus Darunavir 800mg daily/ Cobicistat 150 mg daily
Antiretroviral Therapy Basics

- The goal:
  - Undetectable viral load at 4-6 months

- Consult ID if
  - Viral load fails to drop to undetectable at 4-6 month
  - Viral load rebounds to detectable level after previously undetectable
  - Pregnancy
  - Hepatitis B or C co-infection present
# Preventing Opportunistic Infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>CDC Count Cutoff</th>
<th>Drug Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis</td>
<td>≤ 200</td>
<td><strong>TMP/SMZ DS 1 po qd</strong>&lt;br&gt;<strong>Dapsone 100 mg po qd</strong>&lt;br&gt;<strong>Atovaquone 1500 mg po qd</strong></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>≤100 &amp; (+) serology</td>
<td><strong>TMP /SMZ DS 1 po qd</strong>&lt;br&gt;<strong>Pyrimethamine, Leukovorin Dapsone</strong></td>
</tr>
<tr>
<td><strong>Mycobacterium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avium complex</td>
<td>≤50</td>
<td><strong>Azithromycin 1200 mg po weekly</strong>&lt;br&gt;<strong>Clarithromycin 500mg po BID</strong></td>
</tr>
<tr>
<td>Disease</td>
<td>CD4 count requirement</td>
<td>Restart condition</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>&gt;200 for 3 months</td>
<td>&lt; 200</td>
</tr>
<tr>
<td>M. Avium</td>
<td>&gt;100 for 3 months</td>
<td>50-100</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>&gt;200 for 3 months</td>
<td>&lt; 100-200</td>
</tr>
</tbody>
</table>
Health Maintenance

• Eye Care:
  ◦ Annual eye clinic check-up to rule out HIV related eye disease.

• Dental Care:
  ◦ Annual dental clinic check-up to rule out HIV related oral disease.

• GYN Care:
  ◦ HIV positive women need 2 PAP smears six months apart after HIV diagnosis then annual screening if negative.
  ◦ Routine mammography is indicated starting at age 40.
Health Maintenance

**Bone Health**
- DEXA scans are indicated for post-menopausal women and for men age 50 or greater with HIV, especially those on Tenofovir.
- Vitamin D level testing is recommended once and periodically as indicated.

**TB screening:**
- A Quantiferon test (or PPD) should be done at diagnosis and annually.
- Nine months of INH are indicated for PPD tests greater than 5 mm induration (not 10 mm) or positive Quantiferon tests.
- INH-Rifapentine should be avoided due to drug interactions with aRT
- A symptom review and CXR are mandatory to prove there is no active tuberculosis.
- All HIV positive patients getting INH need pyridoxine 50 mg po daily to prevent neuropathy
Health Maintenance

- Vaccines:
  - Hepatitis B, influenza, TdAP and pneumococccus vaccines.
    - Consider double dose Hep B vaccine for failure to convert to HBsAb +
  - PCV-13 vaccines then Pneumovax and two months later
  - HPV vaccine for females and males 9-26
  - Meningococcal vaccine (Menactra® or Menveo®)
  - Consider Varicella vaccine if CD4 > 200 and nonimmune
Health Maintenance

• Mental Health:
  - All patients should be screened for depression, anxiety, suicidal ideation and substance abuse at every visit.
  - Refer to a mental health provider or substance abuse counselor.
  - Domestic violence screening is indicated at every visit.
Health Maintenance

- Spiritual Health:
  - All patients should be screened for spiritual health issues and referred to a medicine man or other spiritual health provider if desired by patient.
References

- Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America CID 2014:58 (1 January) • Aberg et al
- Feinberg J, Keeshin S, Management of Newly Diagnosed HIV Infection, Ann Intern Med; 167(1);ITC 1-15
- MacNeil JR, Rubin LG, Patton M, Ortega-Sanchez IP, Martin SW. Recommendations for Use of Meningococcal Conjugate Vaccines in HIV-Infected Persons — Advisory Committee on Immunization Practices, 2016 Source: MMWR. 2016;65(43);1189-94
A 37 year-old woman with a history of HIV infection returns after missing appointments for a year. She says she doesn’t feel well. Her sister who brought her in says “She isn’t quite right”. She has been forgetting things for about a month and is having trouble with cooking and driving a vehicle. On physical exam she looks chronically ill. She can’t recall the name of the US President. Her neck is slightly stiff. Her speech is slow but gait is normal. There are no focal motor abnormalities.
Which test is most likely to reveal the diagnosis?

1. Neuropsychiatric testing
2. MRI scan with gadolinium
3. CT then Lumbar puncture for cell counts, protein, glucose, cultures, cryptococcal Ag, VDRL, and TB PCR
4. Serum RPR
Differential diagnosis

- Neurosyphilis
- Cryptococcal meningitis
- Tuberculous meningitis
- Coccidioidal meningitis
- CNS toxoplasmosis
- HIV associated neurocognitive disorder
Diagnostic approach

- CT or MRI with gadolinium to rule out mass lesion
- Lumbar Puncture
  - Cell counts, protein and glucose
  - Routine, AFB, fungal Cx
  - VDRL
  - Cryptococcal Antigen (rapid: lateral flow assay)
  - Coccidioides CSF complement fixation Ab
  - MTb PCR
  - EBV, Toxoplasma, JC virus PCR if mass lesion present
Cryptococcal Meningitis: History and Epidemiology

- First isolated in 1894 from the tibia of a 31 year old woman with osteomyelitis
- First described case of meningoencephalitis was 1905
- Now infects 1 million new people per year, mostly in sub Saharan Africa, and kills 600,000 annually.
Cryptococcus neoformans: GLOBAL
- Ubiquitous in soil, decaying vegetation, pigeon droppings

Cryptococcus gattii: TROPICAL/SUBTROPICAL
- Eucalyptus trees

Most people are infected early in life
- Active disease represents reactivation due to immunodeficiency with loss of TH1 cellular immunity and a predominant TH2 cellular response
  - HIV Infection
  - Malignancy
  - DM
  - Steroid therapy
  - Transplant
  - CKD/Chronic liver disease
Clinical Presentation

- Headache (most common in US)
- Cough
- NV
- Focal neurologic defects (most common in Sub Saharan Africa)
- Seizures
- Altered mental status
Physical exam findings

- Meningismus
- Papilledema
- Molluscum like skin lesions
Cutaneous Cryptococcosis
Diagnosis

- CSF Analysis:
  - Opening pressure > 200: 66%
  - Low Glucose: 24%
  - Protein > 45: 55%
  - WBC > 20: 21%
  - India Ink positive: 74%

- Cryptococcal Antigen (CrAg)
- Lateral Flow Assay
- Culture
- Pathology: GMS or mucicarmine
Treatment of Cryptococcal meningitis

- **Induction** (14 days)
  - Amphotericin B 0.7-1 mg/kg IV daily plus Flucytosine 100 mg/d

- **Consolidation** (8 weeks)
  - Fluconazole 400-800 mg po daily

- **Maintenance**
  - Fluconazole 200 mg po daily until CD4 > 200 for 3-6 months

- In resource poor settings Fluconazole is substituted for Flucytosine
Treatment of Cryptococcal Meningitis

- Increased intracranial pressure > 250
  - Lumbar puncture REPEATED DAILY
  - CSF shunting performed if pressure does not fall
- Monitoring
  - Lumbar puncture performed after 2 weeks for culture to prove CSF sterilization
Immune Reconstitution Inflammatory Syndrome

- Paradoxical worsening of symptoms after starting HIV Antiretroviral therapy (ART)
- Difficult to distinguish from relapse of infection during maintenance phase
- Prevention ➔ Start ART 4-6 weeks after starting anti cryptococcal Rx
References


A 42 year-old man is referred to ID clinic with a positive PPD at 10 mm after being exposed to a case of active pulmonary TB. He has a history of reactive arthritis but is not on immunosuppressive therapy. Review of symptoms is completely negative and physical exam is unremarkable. A CXR is normal. He is offered Isoniazid therapy but declines.
Case Presentation

- Nine months later the patient presents with chronic cough and fever. On exam he is tachycardic and has diffuse rales. A rapid HIV test is positive. A CXR is obtained…
Which tests should be performed first?

1. Sputum viral culture for CMV
2. *Strongyloides stercoralis* serology
3. Bronchoscopy with bronchoalveolar lavage
4. Sputum AFB testing
HIV Pulmonary Infiltrate Differential

- Bacterial pneumonia
- Tuberculosis
- M. kansasii
- Pneumocystis
- Toxoplasmosis
- Cryptococcosis
- Coccidioidomycosis
- Blastomycosis
- Aspergillosis

- Strongyloidiasis
- CMV
- VZV
- Kaposi’s Sarcoma
- Lymphoma
- Lymphocytic Interstitial Pneumonitis
Initial evaluation of infiltrates

- Routine Gram stain and culture
- Blood cultures
- Sputum AFB smear and culture X 3
- Induced sputum for PCP immunofluorescence
HIV Pulmonary Infiltrate Therapy

- Typical pneumonia, high CD4 count
  - Third generation cephalosporin plus a macrolide

- Atypical pneumonia, low CD4 count
  - Trimethoprim/Sulfa plus a cephalosporin plus a macrolide
HIV: Further Infiltrate evaluation

- What to do next if routine tests are negative
  - Bronchoalveolar Lavage
  - Transbronchial lung biopsy
  - Transcutaneous lung biopsy
Case Presentation

- The patient is admitted and treated empirically for bacterial pneumonia with Ceftriaxone/Azithromycin and for *Pneumocystis jiroveci* with Trimethoprim/Sulfa. Sputa are induced for AFB and the smears are positive. The CD4 count comes back at 197.
The patient is started on INH, Rifampin, pyrazinamide and ethambutol. Tenofovir, Emtricitabine and Dolutegravir are started 2 weeks later. Cultures grow *Mycobacterium tuberculosis*. 
Case Presentation

- The patient has a rapid improvement in his fevers and cough. One month later in clinic he notes worsening cough and exam reveals low grade fever and bronchial breath sounds. A F/U CXR shows a new cavity in the right mid lung zone.
TB/HIV Clinical Presentation

- TB in early HIV behaves like HIV (-) disease
  - Cough
  - Hemoptysis
  - Fever
  - Night sweats
  - Weight loss
  - Upper lobe pulmonary disease with cavitation
TB/HIV Clinical Presentation

- TB in late HIV disease is different
  - Looks like primary TB
    - Lymphadenopathy present on exam and CXR
    - Miliary pattern
    - Cavitation is less frequent

- Extrapulmonary sites involved in 40-80%:
  - Lymph nodes, brain, meninges, pericardium, abdomen
TB/HIV Clinical Presentation

- Subclinical TB disease is common in HIV
- Smear negative disease is more common in HIV
- 22% of patients with HIV and TB have a normal CXR
Diagnosis of TB

- Sputum AFB x 3 in 24 hours including one early AM
- Culture
  - BACTEC and MGIT technology
- Nucleic Acid Amplification
  - CDC recommends sending one on every patient
  - Xpert MTB/RIF assay
Treatment of TB in HIV

- **Latent TB**
  - Diagnosis with PPD or IGRA (quantiFERON assay)
  - Rule out active TB first
  - Treat with INH for 9 months

- **Active TB**
  - Treat with four drugs
Active TB: Drug interactions

- Rifampin lowers the drug levels of CYP3A4 metabolized drugs including efavirenz, protease and integrase inhibitors, dilantin, opiates, steroids and other drugs.

- Rifabutin metabolism is inhibited by ritonavir
  - Dose cut 50% and give daily, not thrice weekly
Treatment of TB in HIV

- If already on **Efavirenz**
  - Use INH, PZA, EMB and **RIFAMPIN 600 mg po daily**
- If already on a **boosted Protease Inhibitor**
  - Use INH, PZA, EMB and **RIFABUTIN 150 mg po daily**
- If on an **integrase inhibitor**
  - Do not treat with boosted elvitegravir
  - Limited experience with Raltegravir and Dolutegravir and Rifampin
  - Raltegravir 800 mg po bid or Dolutegravir 50 po bid achieve good levels in non-HIV infected individuals on Rifampin in pharmacokinetics studies and Dolutegravir does not interact with Rifabutin 300 mg po daily
Immune Reconstitution Inflammatory Syndrome

- Re-awakening immune syndrome unmasks or causes paradoxical disease:
  - Cryptococcal meningitis
  - PML (JC virus)
  - PCP
  - CMV retinitis/gastroenteritis
  - Tb and MAC

- Risk Factors: low CD4, high viral load, HLA -B44
Immune Reconstitution Inflammatory Syndrome

- Two TB syndromes:
  - Subclinical TB is unmasked after anti HIV therapy is started
    - Fever, adenopathy, pulmonary, neurologic symptoms
  - Paradoxical worsening of pre-existing TB after starting ARVs
    - New cavitation
    - Hypercalcemia is a hallmark.
    - Can occur even in HIV negative patients with anti Tb therapy
Immune Reconstitution Inflammatory Syndrome

- **Prevention**
  - Start TB therapy right away
  - Delay start of HIV Therapy
    - CD4 count < 50 → Start antiretrovirals by ≤ 2 weeks
    - CD4 count ≥ 50 → Start antiretrovirals by 8-12 weeks

- **Treatment**
  - NSAIDS
  - Steroids
References