

**KITSO AIDS Training Program**

**Lecture 14:**

**TB and HIV Co-Infection**

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**Introduction**

- The incidence of active TB in Botswana is presently 602 cases per 100,000 persons (2005), one of the highest in the world and a 3-fold increase over the years since 1989/1990.
- In Botswana, 80-90% of the population is infected with TB (latent or active TB).
- 80% of new TB cases in Botswana occur in HIV-infected patients, and TB infection is the most common OI in HIV-infected patients.

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**Immune Control of TB**

- T-cell immunity, especially CD4 cells, is crucial for immune control of TB infection. Any impairment of CD4 response markedly increases the risk for active TB infection.
- TB (both pulmonary and extra-pulmonary) is an AIDS-defining diagnosis.
  - Pulmonary TB in adults and children, plus lymph node TB in children, are WHO stage 3 conditions.
  - Extra-pulmonary TB (except for lymph node TB in children) is a WHO stage 4 condition
- Infants are born with immature T-cell function, and infants and children are therefore more likely to develop active disease, even in the absence of HIV infection.

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### Immune Control of TB (2)

- In an HIV-infected patient who is co-infected with latent TB, the risk of developing active TB is 10% **per year**, compared with a **lifetime** risk of 10% in an immunocompetent host.
- The greatest risk of active TB is during the first 2 years after initial infection.
- An HIV-positive patient with a CD4 count less than 100 cells/ $\mu$ L and with latent/dormant TB, has a 50% lifetime chance of having reactivation of TB infection.

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### Natural History of TB Infection

- TB initially infects the body by inhalation of infectious airborne droplets.
- Initially there is hematogenous dissemination and establishment of foci of TB infection throughout the body, especially areas of high oxygen tension (e.g., kidneys, upper lobes of lungs).

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### Natural History of TB Infection (2)

- Initial infection has two possible outcomes:
  - 1. Acute, primary TB disease, i.e., no latent period. (Common presentation in children, often with disseminated TB)
  - 2. Immune control of TB and establishment of latent/dormant TB, with tissue reaction and granuloma formation.
- Patients with latent TB infection are still at risk for eventual reactivation of the dormant TB, especially if immunity wanes (e.g., HIV, diabetes, cancer, old age, steroid therapy, cancer chemotherapy, renal failure, etc.).

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### Sites of TB Infection

- **Possible clinical presentations of active TB (either primary or reactivation):**
  - Pulmonary
  - Extra-pulmonary
  - Disseminated (“miliary”)
- **Common extra-pulmonary disease includes:**
  - Lymphadenitis
  - Pleural disease
  - Meningitis
  - Pericarditis
  - Peritonitis
  - Bone/spinal disease

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### Interactions of TB/HIV Co-Infection

#### HIV-infected patients have:

- Higher frequency of primary TB disease (up to 40%).
- Higher risk of reactivation of latent TB infection.
- Higher frequency of extra-pulmonary TB.

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### Interactions of HIV/TB Co-Infection (2)

- Similar responses to ATT as with HIV-negative patients
- Greater risk of relapse of TB infection after ATT, many of which are new exogenous TB infections and not just reactivation of latent/dormant TB
- With active TB infection, more rapid CD4 count decline and higher viral loads
- Increased mortality and morbidity from both infections

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### Diagnosis of Active TB Infection in the HIV-Infected Patient

- Mantoux is not useful in diagnosing TB in adults.
- If obtainable, AFB smears of sputum and other body fluids (pleural, CSF, etc.) must be done.
- However, with HIV co-infection, 15 - 40% of "smear-negative" cases may have culture positive TB, i.e., *actual active TB disease (as eventually diagnosed by culture), despite negative smears.*

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### Diagnosis of Active TB Infection in the HIV-Infected Patient (2)

- In the HIV-infected patient, the clinical presentation may be the familiar combination of cough, fever, and sputum production. However, HIV infection, especially with very low CD4 counts, often alters the symptoms of TB, which can be subtle and atypical, with dry cough, or no cough with fever only.
- The chest X-ray may be atypical and non-specific, even normal—e.g., a bronchopneumonia may be TB or bacterial.

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### Diagnosis of Active TB Infection in the HIV-Infected Patient (3)

- All patients with unexplained productive cough lasting 2-3 weeks should be evaluated for TB.
- The percentage of patients with positive sputum smears increases with increasing duration of cough (e.g., from 1-2 weeks to 3-4 weeks). Only one positive specimen is required for diagnosis.
- 3 sputum AFB smears should be done:
  - For out-patients: one spot specimen, one early morning specimen the next day, and one spot specimen the next day.
  - For in-patients: one early morning specimen on three consecutive days.

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**Diagnosis of Smear-Negative TB Disease in HIV-Infected Patients (4)**

- Consistent clinical symptoms
- Three negative AFB smears, *including at least one early morning specimen.*
- Chest X-ray consistent with TB
- For out-patients, lack of clinical response to 10-14 days of antibiotics. For ill in-patients, lack of response to 3-5 days of parenteral antibiotics and treatment for PCP.
  - Because TB is sensitive to quinolones and aminoglycosides, *these drugs should not be used in such empiric therapy, since, if TB is present, such monotherapy may cause resistance to these important MDR-TB drugs.*

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**Diagnosis of Active TB in HIV-Infected Patients (5)**

- Active TB cases in which TB culture with antimicrobial sensitivities should always be obtained:
  - HIV-infected children suspected of having active TB
  - Patients who have had treatment in the past
  - Patients who remain smear-positive at the end of the intensive phase and/or the end of the continuation phase of ATT
  - Active TB which develops while the patient is on IPT
  - TB diagnosis in the setting of repeatedly smear-negative microscopy
  - Contacts of MDR-TB or suspected MDR-TB
  - Laboratory and other healthcare workers
  - TB diagnosis from non-sputum sources such as urine, abscesses, CSF, and gastric, pericardial, and pleural fluids.

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**Pediatric HIV/TB Co-Infection**

- Up to 40% of all cases of TB in the developing world occur in children. In 2005, 10% of notified TB cases in Botswana were in children 0-14 years of age.
- TB is an important cause of acute and chronic pneumonia in HIV-infected African children, and TB is second to pyogenic pneumonia as a cause of death in children under 12 months of age.
- TB in children with HIV infection usually reflects primary infection, and often develops into severe and/or disseminated infection, which may cause death.
- Childhood TB represents a sentinel event within a community, suggesting recent transmission from an infectious adult.

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**Diagnosis of Active TB Infection in HIV-Infected Children**

- For young children (in whom AFB smears are more likely to be negative):
  - Induced sputum collection, when possible, or
  - Early morning gastric washing for AFB smears, or
  - Other histological or bacteriologic proof, or
  - **Two** or more of the following
    - History of adult TB contact
    - Suggestive symptoms of TB, including growth failure and unexplained fever, especially for more than 2 weeks
    - PPD reaction positive
    - Radiological findings compatible with TB
  - Response to ATT *must not* be used as diagnostic proof of active TB

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**Treatment of Active TB Disease in HIV-Infected Children: Botswana Guidelines**

- For “non-severe” TB: 2 RHZ/4RH (2 months of rifampicin [R], isoniazid [H], pyrazinamide [Z], followed by 4 months of rifampicin and isoniazid)
- For “severe” TB: add ethambutol to the 2 month intensive phase: 2RHZE/4RH.
  - As a rule, ethambutol should not be used in children < 14 years, except for severe disease, and only under specialist supervision.
  - Streptomycin should be used in place of ethambutol for TB meningitis, because of better CNS penetration.
  - All cases of severe TB should be managed under specialist supervision.

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**Treatment of Active TB Disease in HIV-Infected Children (2)**

- Directly observed therapy is necessary.
- Patients with suboptimal response should be discussed with a specialist. Treatment failure requires 8 months of ATT, starting with 5 drugs, with intensive adherence interventions.

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**TB Treatment: HIV-Infected Adults**

- New cases of pulmonary TB: the standard 6-month regimen of 2 months of HRZE followed by 4 months of HR.
- Sputum smears on patients on ATT should be done at 2 months and at 5-6 months of treatment.
  - Positive smears at or after 5 months indicate treatment failure. Obtain sputum culture with drug susceptibility tests and switch to the category II (retreatment or relapse) regimen: 2 months of SHREZ, then 1 month of HREZ, followed by 5 months of HRE.
  - For patients with extra-pulmonary TB, treatment response should be evaluated by clinical assessment.

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**TB Treatment in HIV-Infected Patients (2)**

- TB meningitis, TB pericarditis, disseminated TB, and spinal TB with neurological complications should be treated with at least 8 months of ATT (2HRZE/6HR).
- Adjunctive steroids should be given to all patients with TB meningitis and for TB pericarditis: prednisone 2 mg/kg/day, with a maximum dose of 60 mg/day for one month, with tapering over the next two months.

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**TB Treatment in HIV-Infected Patients (3)**

- Post-ATT chest X-ray often lags behind clinical improvement, and, as a rule, it should not be done.
- Conversion of positive smears to negative may lag behind the conversion of cultures, especially if the patient has extensive cavitary disease, which can contain a large number of organisms, many of which seen on smear have been killed, or are not viable.
- CTX prophylaxis (OD), regardless of CD4 count, should be given to all patients of all ages being treated for active TB.

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### TB Treatment in HIV-Infected Patients (4)

**Contact tracing:**

- Close contacts of patients with TB are at high risk for acquiring infection, especially children and HIV-positive patients.
  - Children are more likely to develop disseminated and serious forms of TB. Pediatric TB is a sentinel event signifying concomitant TB in an adult contact.
- Contact investigation can identify patients with previously undetected active TB or with latent TB infection.
  - Evaluation should include history (re: risks for active TB, history of TB/IPT, symptoms of active TB, etc.), physical examination, laboratory tests (CXR, sputum smears, but only if there are symptoms of active TB). TST should not be given to adults.
- In high incidence settings, contact tracing is a high-yield strategy for case finding.

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### Common Practitioner Errors:

- Underutilization of sputum AFB smears for diagnosis
- Over-reliance on chest X-ray for diagnosis and monitoring response
- Use of non-standard ATT regimens
- Incorrect doses and duration of ATT drugs
- Failure to monitor response to therapy
- Failure to monitor adherence and to provide necessary support. Private doctors are urged to refer patients to public facilities for free directly observed therapy.
- Failure to report to TB public health authority, for contact tracing. Reluctance to use CTX in HIV patients on ATT
- Failure to recognize drug interactions, especially with PIs, e.g., LPV/r
- Failure to routinely screen for TB at every clinic visit

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### Empiric Antibiotic Therapy While Ruling Out Pulmonary TB

Quinolones, e.g., ciprofloxacin, and aminoglycoside antibiotics, e.g., amikacin, should be avoided as empiric antibiotic therapy, except for infections documented to be resistant to conventional therapy and sensitive to quinolones, because of potential compromise of second-line ATT drugs if the patient has undetected active TB instead of other bacterial infections.

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### ATT and HAART

- Patients already on HAART, and who develop active TB, should continue HAART while ATT is initiated, but with close clinical and laboratory monitoring for hepatotoxicity.
- Patients with newly diagnosed TB and not on HAART should be treated for TB first, and HAART should be delayed, the length of delay depending upon the clinical and immunologic status of the patient.
- Early initiation of HAART in active TB infection will not enhance ATT, but will protect against other O.I.s. However, early HAART may risk hepatotoxicity and *worsen* TB symptoms, due to immune reconstitution inflammatory syndrome.

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### ATT and HAART (2)

*Decisions about when to initiate HAART after initiation of ATT must be individualized, taking both immunologic and clinical status into consideration. From revised TB guidelines:*

- CD4 count > 250 cells/ $\mu$ L: complete ATT first
- CD4 count < 100 cells/ $\mu$ L: start HAART 1-2 weeks after initiation of ATT, if the patient's condition is desperate.
- CD4 cell 100-200 cells/ $\mu$ L: start HAART within 2-4 weeks after initiation of ATT. If the patient's clinical condition is fair or good, HAART can be delayed until after 2 months of ATT.
- Patients with other serious manifestations of HIV disease may be started on HAART as soon as 2 weeks after ATT initiation, *but great care must be taken to monitor the patient for hepatitis and worsening of TB-related IRIS.*

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### ATT and HAART (3)

- All patients of all ages with active TB must be started on CTX prophylaxis, given OD. Once ATT ends, decisions about discontinuing CTX must be based on HIV-related immunologic and clinical criteria.
- For co-administration of ATT and HAART, AST/ALT should be monitored monthly for the first three months, more frequently as indicated.
- The first line regimens, which are EFV- and NVP-based, do *not* require dose modification with ATT, and the standard EFV dose of 600 mg should be used.

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### ATT/ARV-Induced Hepatitis

- The development of hepatotoxicity (AST/ALT > 5 X ULN) is a life-threatening complication of early initiation of HAART during the first 2 months of ATT.
- All medications with any potential to cause hepatotoxicity must be immediately discontinued, including HAART, ATT, and CTX.
- If elevated AST/ALT are < 10X the ULN, the HAART is NVP-based, and the patient appears non-toxic (no fever, jaundice, vomiting, severe rash), stop NVP and give a 3-5 day "tail" of the two NRTIs (but not ABC), to prevent the development of NNRTI resistance and thereby preserve EFV as a possible future treatment option after the hepatitis resolves.

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### ATT/ARV-Induced Hepatitis (2)

- Supportive measures should be undertaken: adequate rest and nutrition (with vitamins) and avoidance of alcohol, traditional medicines, and over-the-counter medications, e.g., paracetamol. If significant nausea and vomiting develop, then hospitalization is necessary for IV fluids and closer clinical monitoring.
- AST/ALT must be monitored at least weekly until a significant downward trajectory has been established.
- The patient must not be switched to "second line" ATT drugs as a temporizing measure, without first consulting an HIV Specialist for permission to do so.

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### ATT/ARV-Induced Hepatitis (3)

- Once AST/ALT have dropped below 2.5 times the ULN and clinical condition has improved, gradually re-introduce ATT first:

Table 6.6: Schedule for reintroduction of anti-TB drugs

Day	Drug and dose
1	INH 25 mg
2	INH 50 mg
3	INH 100 mg
4	INH 200 mg
5	INH 300 mg*
6	INH 300 mg + R 150 mg
7	INH 300 mg + R 300 mg
8	INH 300 mg + R 450 mg
9	INH 300 mg + R 600 mg*
10	INH 300 mg + R 600 mg + E 400 mg
11	INH 300 mg + R 600 mg + E 800 mg
12	INH 300 mg + R 600 mg + E 1200 mg*
13	INH 300 mg + R 600 mg + E 1200 mg + Z 500 mg
14	INH 300 mg + R 600 mg + E 1200 mg + Z 1000 mg
15	INH 300 mg + R 600 mg + E 1200 mg + Z 1500 mg
16	INH 300 mg + R 600 mg + E 1200 mg + Z 2000 mg*

\*All doses are weight-dependent and the highest dose might not be indicated for low-weight patients or children.

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### TB Immune Recovery Inflammatory Syndrome (IRIS)

- Initiation of HAART, either in the setting of active TB disease or in a patient with a past history of TB infection, may cause either a paradoxical worsening of TB symptoms or reactivation of TB, respectively, due to immune reconstitution inflammatory syndrome (IRIS), with marked T-cell responses to TB antigens. It may be difficult to distinguish IRIS from coincidental TB, including MDR-TB.
- Timing of HAART initiation in the setting of active TB disease affects the incidence of IRIS. TB usually occurs from 2 weeks to 3 months after HAART is started (median: 4 weeks).

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### TB IRIS (2)

- Most common with low baseline CD4 counts, rapidly decreasing viral load, and increasing CD4 count soon after initiation of HAART.
- High fever, adenopathy, and large effusions can be complications. Adenopathy is the most common symptom, and may cause obstructive symptoms (e.g., mediastinal node enlargement). Chest X-ray findings may worsen.
- Management: continue/initiate ATT; continue HAART; steroids for life-threatening reactions only (prednisolone 1mg/kg/day for 1-2 weeks, with rapid taper).

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### Isoniazid Preventive Therapy (IPT)

- IPT is effective, saves lives, and is indicated in all HIV-infected patients. It is not, however, indicated in children < 16 years of age, unless a child is a close (household) contact of a sputum-positive adult, in which case IPT is then indicated.
- One-third to one-half of all HIV-positive patients who do not have IPT will eventually develop active TB.
- IPT markedly reduces the subsequent risk for active TB by 36% over-all and by 62% in tuberculin skin test-positive adults. IPT can also reduce community transmission.
- The risk of active TB while on IPT is < 1%. INH resistance is rare when active TB does occur.

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### IPT (2)

- IPT should be given to all HIV-infected patients, regardless of CD4 count, who have not had ATT or IPT within the prior three years. Do not repeat IPT.
- Before starting IPT, active TB must be carefully ruled out, since clinical signs and symptoms of active TB may be atypical in HIV-infected patients:
  - Clinical symptoms alone
  - CXR (indicated *only* if there are TB symptoms)
  - Sputum AFBs (*only* if clinically indicated)
  - Use great care in ruling out TB with low CD4 counts.
- IPT may be safely used with both HAART and CTX prophylaxis. However, stepwise initiation of IPT and CTX with HAART is advisable, in order to lessen the risk of over-lapping drug toxicities.
- INH dosage should be 300mg OD, not 400mg OD, with 25mg pyridoxine

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### IPT Exclusion Criteria

- Symptoms of active TB (cough, fever, etc.).
- Terminal AIDS.
- Active hepatitis.
- TB diagnosed and treated in the last 3 years.
- Clinical suspicion of extra-pulmonary TB.
- Prior INH intolerance or allergy.
- Habitual treatment defaulter.
- Pregnancy (if patient has completed at least 3 months of IPT, it may be continued to conclusion)
- Children < 16 years of age, unless close (household) contact of a sputum-positive adult

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### Major Side-Effects of ATT Drugs

- Hepatitis (INH, RIF, PZA)
  - Can be worsened by concomitant HAART.
- Hyperuricemia, arthralgias, gouty arthritis (PZA)
- Autoimmune thrombocytopenia (RIF)
- Optic neuritis (ETM)
- Peripheral neuropathy (INH)
  - Can be worsened by HIV and/or concomitant HAART.
- Rash (RIF, as well as other ATT drugs)
- Ototoxicity (SM)
  - Contraindicated in pregnancy because of ototoxic risk to fetus

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### Drug-Resistant TB

- Drug resistance, especially multi-drug resistance, is largely man-made, and primarily occurs because of poor ATT management:
  - inadequate ATT regimens
  - adding only one drug to a failing regimen
  - failure to recognize existing drug resistance
  - poor adherence and failure to provide treatment support for adherence
  - poor quality drugs and drug shortages
  - over-use and misuse of aminoglycoside and quinolone antibiotics.

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### Drug-Resistant TB (2)

- Patient factors associated with drug resistance:
  - Prior ATT: the strongest factor
  - Poor adherence
  - Chronic TB (positive sputum after re-treatment)
  - Treatment failures (positive sputum after 5 months of ATT), especially if RIF was used throughout the ATT course
  - People, especially children and HIV-positive patients, who have had contact with an MDR-TB patient
  - Healthcare workers with contact with TB patients
  - HIV infection itself has *not* been shown to date to be a risk factor for MDR-TB.
  - Persistent fever in a patient receiving standard TB therapy suggests the possibility of MDR-TB and/or non-adherence.

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### Drug-Resistant TB (3)

- Acquired drug resistance is uncommon in patients who relapse after having completed an apparently successful course of treatment.
- However, TB strains from patients on ATT who are actually failing therapy are more likely to harbor drug resistance.
- TB resistance to at least INH and RIF is multi-drug (MDR) resistance.
- MDR-TB is most common in treatment failure, and is rare in newly diagnosed TB.
- Drug susceptibility testing for 2nd line ATT drugs is difficult and often unreliable.

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### XDR-TB

- Extensively drug resistant (XDR-) TB: an emerging public health problem in sub-Saharan Africa and world-wide.
  - XDR-TB is resistant to at least 1) INH and RIF, 2) any fluoroquinolone *and* 3) one of 3 injectable 2nd line agents (capreomycin, amikacin, and kanamycin).
  - A serious XDR-TB outbreak occurred in 51 coinfecting patients in rural Kwazulu-Natal, both nosocomial and community-acquired, with a 98% mortality rate.
  - In July 2007, BOTUSA began a previously planned drug resistance survey in Botswana (the last one was in 2002). Because of the XDR outbreak, a rapid assessment of resistance to 2<sup>nd</sup> line TB drugs was undertaken in February 2007, with results to be available later in the year.

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### Summary

- TB causes both acute and asymptomatic chronic infection, and is of epidemic proportions in Botswana.
- T-cell immunity, especially the CD4 cell, is crucial for immune control of TB infection. Any impairment of CD4 response markedly increases the risk for active TB infection/disease.
- TB is an HIV-related OI, and is an AIDS-defining diagnosis in an HIV-infected patient: pulmonary TB is a WHO stage 3 condition, and extra-pulmonary TB is a WHO stage 4 condition.

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### Summary (2)

- TB initially infects the body by inhalation of infectious airborne droplets.
- Initial infection has two possible outcomes:
  - 1. Acute, primary TB disease
  - 2. Immune control of TB and establishment of latent/dormant TB infection, which is asymptomatic.
- Patients with latent TB infection are still at risk for eventual acute reactivation of the dormant TB.

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### Summary (3)

- **Possible clinical presentations of active TB (either primary or reactivation):**
  - Pulmonary (WHO clinical stage 3)
  - Extra-pulmonary (WHO clinical stage 4)
  - Disseminated, “miliary” (WHO clinical stage 4)
- **Common extra-pulmonary disease includes:**
  - Lymphadenitis
  - Pleural disease
  - Meningitis
  - Pericarditis
  - Peritonitis
  - Bone/spinal disease

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### Summary (4)

- HIV-infected patients have:**
- Higher frequency of primary TB disease
  - Higher risk of reactivation of latent/dormant TB infection
  - Higher frequency of extra-pulmonary TB
  - Higher morbidity and mortality from TB and HIV infections
  - Similar responses to ATT compared to HIV-negative patients
  - Greater risk of relapse of TB infection after ATT, many of which are new exogenous TB infections

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### Summary (5)

- HIV-infected patients with active TB infection can have atypical chest X-ray findings, and are more likely to have negative AFB smears.
- If AFB smears are negative, but active TB is strongly suspected on clinical grounds, empiric therapy should be instituted while awaiting culture results.
  - If culture returns negative, but TB is still strongly suspected, the continuation of the full course of ATT is reasonable, if the patient has responded to initial use of anti-TB drugs.

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**Summary (6)**

- For an HIV-infected patient on ATT, try to defer HAART until the continuation phase of ATT.
- For a patient with pneumonia and negative AFB smears, the response to an empiric course of antibiotic therapy may be a useful indication of whether or not the AFB culture will eventually return negative.
- IPT for HIV-infected patients is safe and SAVES LIVES.
- MDR and XDR TB are major threats to the integrity of Botswana's HIV and TB programs.

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