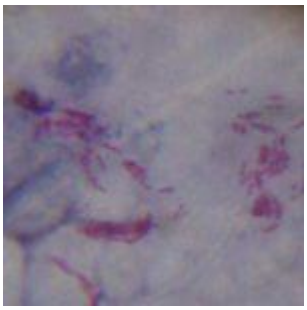
3 TB Vignettes



A 20 year old pregnant female presents for HIV care

A 20-year-old woman, in her first trimester of pregnancy, presents to the ante-natal clinic (ANC) for routine care. After counseling she volunteered for HIV testing and was found to be HIV positive. She is now enrolled in the pregnancy HIV clinic for antenatal care specific to her needs.

On History

This is her first pregnancy; it was unplanned and occurred due to unprotected sexual intercourse. She has never used oral contraceptives nor has she practiced safe sex. This is her third partner this year.

She complains that she has lost 4kg in the past two months. During this time she has also had a persistent cough.

On examination

- Thin, but no signs of wasting.
- No lymphadenopathy
- Crackles in the upper lobe of the left lung.

- No other significant findings

FBC:

5.40 WCC (4.00-10.00 x 109/L)
64% neutrophils; 33% lymphocytes.
Haemoglobin: 9.5 g/dl (12.1-16.3 g/dl)

CD4 count: 320 cells/mm^3 (1000-1800 cells/mm^3)
Sputum sample: AFB positive

Discussion

The essential or firstline TB drugs are:
Isoniazid, Rifampicin, Ethambutol, Pyrazinamide and Streptomycin.

There are three main properties of TB drugs:

- bactericidal activity
- sterilising activity
- ability to prevent resistance

The essential (firstline) TB drugs have these properties in different proportions. Isoniazid and rifampicin are the most powerful bactericidal drugs, active against all populations of TB bacilli. Rifampicin is the most potent sterilising drug available. Pyrazinamide and streptomycin are also bactericidal against certain populations of TB bacilli. Pyrazinamide is only active in an acid environment. Streptomycin is bactericidal against rapidly multiplying TB bacilli. Ethambutol is used in association with more powerful drugs to prevent the emergence of resistant bacilli.

TB treatment

Essential or firstline treatment for a newly diagnosed patient is isoniazid, rifampicin, pyrizinamide, and ethambutol for two months (initial phase), then isoniazid and rifampicin alone for a further four months (continuation phase). The first two months of treatment is given with DOTS (directly observed treatment, short-course) which helps to improve adherence.

Usually during the first two weeks tubercle bacilli are rapidly killed and infectious patients become non-infectious. During the continuation phase fewer drugs are needed but for a longer period. The sterilising effect of the drugs eliminates the remaining bacilli and prevents relapse.

At the end of the second month of treatment, most patients will have a negative sputum smear, however if a patient has a positive sputum smear at this time, this may indicate one of the following:

- most frequently, that the initial phase of therapy was poorly supervised and that patient adherence was poor;
- occasionally that there is a slow rate of progress with sputum smear conversion, e.g. if a patient had extensive cavitation and a heavy initial bacillary load;
- rarely, that the patient may have drug-resistant TB that does not respond to first-line treatment.

TB in pregnant women

Untreated tuberculosis (TB) represents a greater hazard to a pregnant woman and her foetus than the treatment does. The outcome of a pregnancy is not altered by TB drugs. Even though the drugs do cross the placenta they do not have harmful effects on the foetus. However, infants born to mothers with untreated TB are usually low birth weight babies and may be born with TB themselves. Therefore TB treatment of pregnant women should be initiated whenever the disease is present.

TB treatment in HIV positive pregnant women

In patients who have both TB and HIV, TB treatment takes priority over ARV therapy, and should never be compromised. If a patient is diagnosed with TB, they must be started immediately on treatment. Rather delay or replace the ARV therapy if there are drug interactions than delay the TB treatment. TB treatment with DOTS should be initiated immediately in a pregnant woman diagnosed with active TB, irrespective of whether she is on ARVs or not.

When TB infection is present before starting ARVs, consider the following:

- If CD4 count > 200 and patient is less then WHO stage IV disease – start TB treatment and asses the need for ARVs at completion of TB therapy using CD4 count and clinical criteria.
- If CD4 count < 200 and/or WHO stage IV disease present – delay ARVs until after 2 month of TB therapy
- If CD4 count < 50 – introduce ARVs as soon as patient is stabilised on TB therapy (typically 2 wks).
- If TB develops and patients are already on ARVs then continue ARVs throughout the TB treatment. The following changes should be made:

- 1st line ARV therapy change nevirapine to efavirenz
- 2nd line therapy lopinavir/ritonavir, increase the dosage of ritonavir to 400mg

Contraindicated treatments

Nevirapine and rifampicin should not be used together, because rifampicin is a potent inducer of liver enzymes and lowers the blood levels of nevirapine (Dose adjustments for co administration have not yet been established).
Nevirapine and rifampicin-based TB treatment should not be used together because of the potential hepatotoxicity. Efavirenz is contraindicated in pregnancy, especially during the first trimester, because of its potential for birth defects of the CNS. However, if there is no alternative drug available, efavirenz should only be used after the first trimester, and if it has to be used in the first trimester the mother must be counseled. Streptomycin is contraindicated in pregnancy because it is ototoxic to the foetus and can cause permanent deafness.

Plan for this patient:

Adherence counseling.
Begin ARVs after the first two months of TB treatment. Full

dose HAART to include stavudine, lamivudine, nevirapine. If the therapy is used for at least 12 weeks before delivery and throughout the breast feeding it will reduce HIV transmission rates to the baby down to 1-2%.
When ARVs are started TB symptoms may transiently worsen as part of Immune Reconstitution Inflammatory Syndrome (IRIS).

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Poor adherence in a TB patient

A 25-year-old man comes to clinic for his TB medicines. He is two weeks late for his scheduled appointment. Records show that he is on treatment for sputum-positive pulmonary tuberculosis.

On History
Patient complains of loss of weight, no energy and feeling depressed.
This is the third time that he has been on TB treatment.
He is currently prescribed isoniazid, pyrizinamide, rifampicin and ethambutol.

On Examination

- He is emaciated, weight 51 kg, height 1.76 cm (BMI 16.5)
- Persistent cough
- Crepitations in the entire right lung field.

Investigations
HIV rapid test – negative

Discussion
Re-treatment with first-line TB drugs
Previously treated TB patients include those patients treated

as new cases for more then one month who are smear or culture positive (failure, relapse, return after default). Re-treatment cases have a higher likelihood of drug resistance, which may have been acquired through inadequate prior chemotherapy. Adherent patients who fail initial treatment are at a high risk of multidrug resistant TB (MDR TB). Regarding the patient in this case, the treatment he is receiving should be changed to the re-treatment regimen.

Re-treatment regimen

The re-treatment regimen consists of using all 5 first-line TB drugs (rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin) in the initial phase and 3 drugs (rifampicin, isoniazid and ethambutol) in the continuation phase. This standardised regimen can cure patients excreting bacilli that are still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and streptomycin. Under proper case management conditions, MDR TB are those most at risk of failure in the re-treatment regimen.

Chronic and MDR-TB

Chronic TB is TB positive sputum at the end of a standard re-treatment regimen with essential TB drugs.
MDR TB (multidrug resistant) is when a patient has active TB with bacilli resistant to both rifampicin and isoniazid.
Reserve or second-line TB drugs are used for the treatment of chronic and MDR-TB cases.

Treatment of chronic and MDR-TB cases with reserve drugs is more expensive and more toxic than treatment with essential drugs. Many programmes will therefore choose hospitalization for the initial portion of therapy.
However, hospitalization entails increased risk of nosocomial transmission of MDR-TB to both staff and patients, especially those infected with HIV. Therefore after the drug regimen has been ascertained and the patient’s cooperation has been secured, the patient can be started on ambulatory treatment. Programmes with strong home-based care, well-trained visiting

health care workers and/or capable health care centres may choose to have ambulatory treatment from the outset. Ambulatory treatment reduces the risk of MDR-TB transmission in hospitals, which often lack adequate infection control capacity.

Reserve or second line TB drugs

Aminoglycosides:

- kanamycin and amikacin
- capreomycin (polypeptide)

Thioamides:

- ethionamide
- protionamide

Fluoroquinolones:

- ofloxacin
- ciprofloxacin

D-cycloserine (and terizidone)
P-aminosalicyclic acid (pas)

Reserve or second line TB treatment

A standardised treatment regimen should include at least 4 drugs which have never been used by the patient, including an injectable (capreomycin, amikacin or kanamycin) and a fluoroquinolone. Treatment should be given daily and directly observed. Bacteriological results (smear and if possible culture) should be monitored. Pyrazinamide and ethambutol can be included in the regimen because of the lower probability of resistance than to other essential drugs. However, in chronic cases that have received multiple treatments with ethambutol and pyrazinamide, these drugs may offer little advantage. An initial phase of at least 6 months should be followed by a continuation phase of 12-18 months using 3 of the most active and best-tolerated drugs.

Sputum smear examination is performed at the end of the initial phase of treatment, during the continuation phase of treatment and at the end of treatment.

Newly diagnosed TB patient

A 29 year old woman was diagnosed with pulmonary tuberculosis, based on positive smears. She was started on first-line TB treatment of isoniazid, rifampicin, pyrizinamide and ethambutol.

On History
The patient took the initial phase TB regimen by DOTS (directly observed treatment, short course) for the first 2 months and thereafter took the continuation phase for a further 4 months. At this time she had a routine HIV test done which showed her to be HIV positive. She was started on ARVs which she has been taking for the last 5 weeks.

On Examination
She is thin and appears unwell
Temperature is 38°C
Cervical lymphadenopathy, tender nodes
Lung fields are clear

Investigations
Rapid ELISA test – positive
AFB – negative

CD4 count – 140 cells/mm^3

Evaluation – Questions & answers

What is an important process to consider with a patient who has had a previous TB infection and is now on ARVs?

Immune Reconstitution Inflammatory Syndrome (IRIS), or Immune Reconstitution Disease (IRD), is defined as a paradoxical

clinical deterioration (despite decreasing viral load and rising CD4 count) after starting ARVs. It results from the interaction between an improving immune system and organisms that colonised the body during earlier stages of HIV infection. Clinical presentations vary depending on the causative organism and the organ system that is colonised. For example, IRIS caused by TB may present with high fever, lymphadenopathy, worsening of the original TB lesion and/or deteriorating CXR features.
WHO Stage IV disease and a low CD4 are risk factors for IRIS development. Patients starting ARVs in close proximity with diagnosis of an opportunistic infection are at a higher risk of developing IRIS. For example, patients who start HAART within two months of starting TB treatment are at risk of an IRIS reaction to dead or dying tubercle bacilli.

If a patient develops IRIS should treatment be interrupted?

Ideally, ARVs should be continued rather than risk the interruption of treatment. The IRIS event is occurring as a result of an infection other than HIV, and thus, the cause of the IRIS needs to be treated while ARVs are continued. However, if the case is life threatening, then an interruption of ARVs may be unavoidable and safer.

What will you prescribe immediately? (This question relates to A 20 year old pregnant female presents for HIV care)

Begin anti-TB treatment today. If you hesitate, the active tuberculosis will worsen as the pregnancy progresses.

Why will you not give ARVs right away? (This question relates to A 20 year old pregnant female presents for HIV care)

There is no need to begin ARVs right away because the patient is not markedly immunocompromised, and there is sufficient time for her to receive adequate ARV cover for the remainder of her pregnancy. Complicating her TB therapy with ARVs is an unnecessary risk to the health of the foetus.

What is the risk of poor compliance? (This question relates to Poor adherence in a TB patient)

This man, by evidence that he is late for his current round of TB treatment, was most probably non-compliant during the previous treatment rounds. It is possible that he has now

developed drug-resistant TB organisms that will not respond to conventional, first-line therapy. He should be tested for drug sensitivity, and based on results his treatment should be changed to include streptomycin (re treatment regimen) or started on reserve TB regimen.

Why should we test for HIV and TB? (This question relates to Poor adherence in a TB patient)

Every TB patient should be tested for HIV because in high prevalence areas, more than 50% will be HIV positive. Also many people infected with HIV in developing countries will develop TB as the first manifestation of AIDS. The two diseases represent a deadly combination, because they become more destructive together than either disease alone.

- TB is harder to diagnose in HIV-positive people.
- TB progresses faster in HIV-infected people.
- TB in HIV-positive people is associated with a high mortality rate if undiagnosed or left untreated.
- TB occurs earlier in the course of HIV infection than many other opportunistic infections.

What ARVs would you use? (This question relates to Newly diagnosed TB patient)

This patient needs to be on ARVs which are compatible with her TB therapy and which will be effective at treating her HIV. The NRTIs such as stavudine and lamivudine can be used, but it is difficult to choose a third ARV due to the interactions between rifampicin and the protease inhibitors or the NNRTIs. As long as she is not at risk of becoming pregnant, you can use efavirenz with a rifampicin based TB regimen rather than nevirapine. Nevirapine is contraindicated due to hepatotoxicity with rifampicin. If she is likely to fall pregnant she should be prescribed a non estrogen based contraceptive because efavirenz lowers the efficacy of estrogen.

Once she has completed her TB therapy her ARVs can be switched to a nevirapine based regimen.

Why would you be reluctant to use a regimen containing protease inhibitors (PIs)? (This question relates to Newly

diagnosed TB patient)

It is best to save the PIs for second-line drug therapy in the event there is first-line treatment failure.