Management of HIV and TB Co-infection in South Africa

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Case Report

- 39 yr old female
- Referred to clinic on 14/06/2006 for consideration to commence antiretroviral therapy
- Diagnosed with pulmonary tuberculosis (smear +ve) at local clinic (10/03/2006)
- Good adherence to antituberculosis therapy
- Currently on maintenance phase: Rifinah 2 daily (isoniazid/rifampicin)
BACKGROUND HISTORY

- Diagnosed: HIV: Jan 2001 (at local clinic)
- No previous admissions to hospital
- No other past medical history
- Two children aged 17 and 13 yr - both well
- Husband died in 2001 (AIDS related illness)
GENERAL EXAMINATION

- No symptoms on history/enquiry
- Mild temporal muscle wasting.
- No significant lymphadenopathy.
- Oral thrush.
- No melanonychia
- PR 80 /min   BP 110/70   RR 14/min
- Apyrexial
Systemic Examination

- Cardiovascular System
  Normal

- Respiratory System
  Normal

- Abdomen
  Normal

- Central Nervous System
  Normal
39 year old female with HIV infection, on maintenance phase of tuberculosis treatment with oral candidiasis

World Health Organisation stage 3 HIV infection
INVESTIGATIONS

- FBC  Hb 11.1 g/dl  MCV 81 MCH 29
  - platelets 171    WCC 4.2
- UE   137/4.1/121/23.1/3.9/71/6.7
- LFT  84/29/11/79/39/29
- Calcium (corrected) 2.29
- Chest radiograph was normal
- CD4 count = 79 cells/µl
- Viral load = 67 000 c/ ml
Final Assessment

- 39 year old female on maintenance phase of tuberculosis treatment
- CD4 count = 79 cells/µl (AIDS)
- Medically suitable for antiretroviral roll-out programme
- Requires social/adherence counselling and ARV education
MANAGEMENT

- Assessed by multi-disciplinary team and found suitable for antiretroviral therapy
- Started *regimen 1a*: stavudine 40 mg bd, lamivudine 150 mg bd, efavirenz 600mg daily on 14/07/2006 whilst on maintenance phase of tuberculosis treatment
Management of HIV and TB Co-infection in South Africa
> 70% of 40 million HIV-1 infected people worldwide live in sub-Saharan Africa

high proportion are infected with tuberculosis

Tuberculosis: leading cause of morbidity and mortality in this sub-group

Highly active anti-retroviral treatment (HAART): reduced the incidence of HIV-1-associated-tuberculosis by more than 80% in some studies *

IMPACT OF HIV ON MTB

- HIV negative: 10% infected with TB bacilli develop active TB during lifetime.

- HIV positive: 50% develop TB.

- TB occurs at any time in the course of HIV, usually early.
IMPACT OF HIV ON TB

- Progression to Disease: TB accelerates HIV disease
- Infectious Pool: MDR TB
- TB associated with decreased survival in HIV:
  - Immune activation,
  - Expression of cytokines,
  - Increased viral replication
  (viral load 5-160 fold increase with active TB)*

*J Immunol 1996;157:1271
IMPACT OF MTB ON HIV

- Acceleration to AIDS

- Increases vertical transmission of HIV and increased congenital transmission of TB
How Does HIV Affect The Clinical Presentation Of TB?

- Unchanged (TBM, TB osteitis)
- Certain peculiar TB syndromes:
  - Pulmonary Syndrome
  - Lymphadenopathy Syndrome
  - Serositis Syndrome
  - Constitutional Syndrome
- Increased incidence of extra-pulmonary TB
DRUG METABOLISM INTERACTIONS
(PHARMACOKINETIC)
RIFAMPICIN

- Significant pharmokinetic drug interactions: standard tuberculosis treatment + ARVs

- Rifampicin (rifamycin): potent inducer of cytochrome P450 enzyme system, iso-enzyme CYP3A4
Rifampicin: ↑ metabolism + ↓ plasma levels of hepatically metabolised drugs:
- NNRTIs
- PIs

Decreased plasma levels may result in antiretroviral treatment failure.

HIV-infected patients treated with rifamycin- sparing regimens need prolonged streptomycin-based treatment: 9-12 months to prevent relapse.
RIFABUTIN

- CDC: rifabutin instead of rifampicin for patients taking PIs or NNRTIs
- Rifabutin: weaker enzyme inducer than rifampicin but unavailable in state sector
- Antiretroviral regimen - modified to make it compatible with standard, rifampicin-based tuberculosis treatment
Interactions with NNRTIs

- NNRTI levels reduced when given with rifampicin
- Area under curve of efavirenz is reduced by 22% and nevirapine by 37-58% *
- Trough levels of efavirenz and nevirapine remain therapeutic but are reduced
- CDC recommends: increasing efavirenz dose to 800mg daily

Interactions with NNRTIs

- Population pharmacokinetic study of efavirenz: hepatic clearance was 28% higher in white non-Hispanics than in African-Americans and Hispanics *

- Major ethnic differences exist in allelic variations of iso-enzyme CYP2B6 which is mainly responsible for metabolizing efavirenz

* Antimicrobial Agents Chemotherapy 2003; 47:130-137
Interactions with NNRTIs

- SA guidelines do not recommend increasing efavirenz dose when co-administered with rifampicin, due to increased risk of toxicity.
- No published data on efavirenz metabolism in the South African population.
- Nevirapine clearance also varies between ethnic groups.*
  Standard doses of nevirapine are effective when co-administered with rifampicin.

* Br J Clin Pharmacology 2004: 54; 378-385
Role of PIs

- Most PI levels significantly ↓ when co-administered with rifampicin and should not be used, except ritonavir.

- **Ritonavir ≥ 400mg bd** to overcomes the enzyme induction

- Ritonavir: GI intolerance
  - improved by gradual dose escalation over one week
Interactions with NRTIs

- 3 NRTIs regimens were previously recommended due to no significant interactions with rifampicin.
- Recent studies: these regimens are inferior to conventional NNRTI/PI regimens*
- 3 NRTIs are no longer recommended

SA Recommendations for Co-administering PI + NNRTIs + Rifampicin
<table>
<thead>
<tr>
<th><strong>Single PIs</strong></th>
<th><strong>Dose when combined with rifampicin</strong></th>
<th><strong>comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ritonavir</td>
<td>600mg 12hrly</td>
<td>poorly tolerated in adults: GI side effects. Not used as single agent</td>
</tr>
<tr>
<td>Amprenavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Rifampicin should not be used together with these single PIs</td>
<td>Change the regimen to make it compatible with rifampicin (do not use a drug that the patient has previously failed)</td>
</tr>
<tr>
<td><strong>Boosted PI Combinations</strong></td>
<td><strong>Dose when combined with rifampicin</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Saquinavir/ritonavir</td>
<td>Saquinavir 400mg plus ritonavir 400mg 12hrly</td>
<td>Limited clinical experience</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Kaletra 400mg/100mg plus Ritonavir 300mg 12hrly</td>
<td>Limited clinical experience</td>
</tr>
</tbody>
</table>
**NNRTIs** | **Dose when combined with rifampicin** | **Comments**
--- | --- | ---
Efavirenz | 600mg daily | CDC guidelines recommend 800mg but efavirenz metabolism is slower in Afro-Americans and increased CNS side effects may occur.
Nevirapine | 200mg twice daily | Possible increased risk of hepatotoxicity, particularly during the 1st two months of nevirapine-containing antiretroviral therapy.
Pharmacodynamic Interactions

- Additive risk of side-effects and drug toxicity when antiretrovirals combined with TB Rx
- Pyridoxine: give to all HIV-infected patients to reduce the risk of INH-induced peripheral neuropathy
- Alcohol excess: increased risk of hepatotoxicity and peripheral neuropathy, counsel regarding alcohol discontinuation
Common Causes of Shared Side-effects of Antituberculous and Antiretroviral therapy
<table>
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<tr>
<th><strong>Side-effect</strong></th>
<th><strong>Antiretroviral drug</strong></th>
<th><strong>Anti-tuberculosis drug</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Didanosine, Zidovudine, Ritonavir</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Nevaripine, Efavirenz</td>
<td>Rifampicin, Isoniazid, Pyrazinamide</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Stavudine, Didanosine</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Rash</td>
<td>Nevaripine, Efavirenz</td>
<td>Rifampicin, Isoniazid, Pyrazinamide, Ethambutol</td>
</tr>
</tbody>
</table>
Management of HIV-infected Patients diagnosed with active tuberculosis when taking antiretroviral therapy: SA National Guidelines
Currently on HAART and develop TB

- continue HAART throughout standard tuberculosis treatment,

- with changes where necessary, to the patient’s antiretroviral treatment regimen.
The recommended regimen for antiretroviral-naïve patients in the public sector: Regimen 1

1. Stavudine (d4T) 40 mg every 12hrs (or 30mg every 12hrs if <60mg), plus

2. Lamivudine (3TC) 150mg 12hrly, plus

3. Either efavirenz (EFV) 600mg nocte (or 400mg if < 40kg) or nevirapine (NVP) 200mg daily for 2 weeks, followed by 200mg every 12 hrs.

- Efavirenz is teratogenic, hence women of childbearing potential who want to fall pregnant are treated with nevirapine
Develop tuberculosis while taking NNRTI

- If on efavirenz continue antiretroviral therapy unchanged whilst on anti-tuberculosis treatment.
- If stable (preferably > 2 months) on nevirapine, when tuberculosis develops, the regimen can be continued.
- Nevirapine can also be changed to efavirenz, as the interaction between efavirenz and rifampicin is less marked.
Patients treated concomitantly with nevirapine and rifampicin should be carefully monitored for hepatotoxicity.

- Transaminase levels should be checked every month.
REGIMEN 2

- Fail regimen 1: commence on PI based second-line anti-retroviral therapy as follows:

  1. Didanosine (ddI) 400mg once a day (250mg daily if < 60kg), plus
  2. Zidovudine (AZT) 300mg 12 hourly plus,
  3. Lopinavir/ritonavir (LPV/r) 400/100mg every 12 hours
If tuberculosis is diagnosed in a patient taking the second-line treatment regimen, ritonavir 300mg twice daily should be added to the regimen.

When rifampicin is stopped, it takes two weeks before the cytochrome P450 iso-enzyme induction is reversed.

Thus, the added ritonavir should only be stopped 2 weeks after completion of tuberculosis treatment.
Management of HIV-infected patients diagnosed with active tuberculosis and not yet taking ARV therapy
Estimated that > 50% of new adult cases of tuberculosis in South Africa are co-infected with HIV.

Majority patients are not on ARV therapy, and many do not fulfil clinical criteria for ARV therapy initiation.

Clinical criteria for initiation of ARV therapy are as follows:
<table>
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<tr>
<th>Situation</th>
<th>Recommendations</th>
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| Pulmonary TB and CD4 count < 50/mm³ or extrapulmonary TB                  | Start TB therapy. Start ARVs as soon as TB therapy is tolerated:  
  • regimen 1a                                                           |
| Pulmonary TB and CD4 50-200/mm³ or total lymphocyte count 1000-1200/mm³ | Start TB therapy. Start ARV regimen after 2 months of TB therapy: |
| Pulmonary TB and CD4 >200/mm³ or total lymphocyte count >1000-1200/mm³   | Treat TB. Monitor CD4 counts if available. Start ART according to ART Guidelines |
World Health Organization (WHO) stage 4 disease (AIDS) or CD4 < 200 cells/µl.

Extrapulmonary TB, although a stage 4 defining illness, is not a criterion for initiating ARV therapy unless CD4 count < 200 cells/µl.

If no history of stage 4 illness and CD4 count > 200 cells/µl, antiretroviral therapy is not indicated.

Need for antiretrovirals should be reassessed on completion of tuberculosis treatment.
If ARVs indicated, 2 months of anti-tuberculosis therapy completed before starting ARVs, due to the risks of additive side-effects and drug toxicity.

If CD4 < 50 cells/µl or other serious HIV-related illness exists, ARVs started from 2 weeks. In this setting, first ensure that the patient is tolerating tuberculosis treatment and responding to it.
- Often difficult to establish patient readiness for antiretrovirals within 2 weeks.

- Patients should be started on 1st-line agents consisting of stavudine, lamivudine and efavirenz.

- Initiation of nevirapine during tuberculosis should be avoided because of limited experience and danger of shared hepatotoxicity.
All HIV-infected patients with multi-drug resistant tuberculosis should be considered for antiretroviral therapy, even if CD4 >200 cells/ul, since prognosis is poor.

Poor adherence and substance abuse must be excluded before starting antiretroviral therapy.
MULTI-DRUG RESISTANT TUBERCULOSIS

- Intensive adherence support is needed in treating these patients.

- Shared side-effects and potential drug interactions between antiretrovirals and drugs used to treat multi-drug resistant tuberculosis.
Patients taking both antiretrovirals and anti-tuberculosis treatment are required to take large numbers of tablets daily. Develop side-effects: GI intolerance - make treatment adherence difficult.

Intensive adherence support is needed.
ADHERENCE

- Side-effects that impact on adherence e.g. nausea, should be actively managed.

- If side-effects or pill burden cannot be tolerated, antiretroviral treatment interruption for the duration of tuberculosis treatment may be considered.
IMMUNE RECONSTITUTION

- Advanced HIV disease (CD4 <50 cells/ul): immune reconstitution syndrome during the first few months of antiretroviral therapy.

- Improving immune function may cause paradoxical deterioration of an opportunistic infection being treated or unmask a previously occult one.
Immune reconstitution syndrome

Clinical presentation:

- fevers
- lymphadenopathy
- worsening pulmonary lesions
- expanding lesions of the central nervous system
Management of Immune Reconstitution Syndrome

- Role of corticosteroids unclear: consider for severe reactions

Reactions are self-limiting although they may require a brief course of corticosteroids to reduce inflammation of CNS or severe respiratory symptoms
IMMUNE RECONSTITUTION

- Not indicative of treatment failure or a drug side-effect.

- ART should not be interrupted or changed if immune reconstitution syndrome occurs.
AREAS FOR FUTURE RESEARCH

- Current knowledge of antiretroviral interactions with anti-tuberculosis therapy is based on small studies and case reports.

- Evidence exists of genetic variability in metabolism of nevirapine and efavirenz, the clinical significance of which is unclear.
AREAS FOR FUTURE RESEARCH

- Need for pharmaco-epidemiological studies to assess frequency and severity of shared side-effects.

- Optimal timing of initiating antiretroviral therapy in patients with tuberculosis can only be addressed in a randomized controlled trial.
Thank you