Tuberculosis and anti-retroviral therapy

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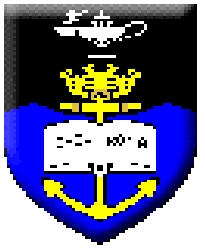

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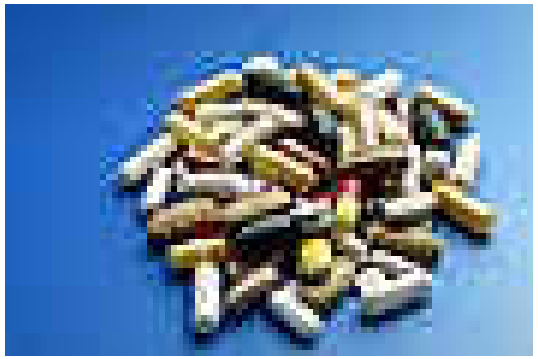
Importance of drug interactions

- HIV positive patients are often on a number of drugs.
  - Drugs for prophylaxis.
  - Anti-retrovirals.
  - Drugs to treat ART side effects.
  - Drugs to treat concomitant illnesses.
  - Over the counter and herbal medications.



- Drug interactions may result in increased toxicity.
- Drug interactions may result in decreased levels of antiretroviral medication.

Are drug interactions clinically important?

- 2 large retrospective chart reviews of in- patients on protease containing regimen - 50% on at least one drug that could potentially cause a drug interaction.

- 50% of these drug interactions were potentially serious or life threatening

Potential problems when administering ART and tuberculosis treatment

- Rifampicin is a potent Cytochrome P450 inducer
- enhanced metabolism of concomitantly administered drugs
- may lead to sub-therapeutic levels of many protease inhibitors and NNRTI's
- Rifampicin levels are not significantly affected by anti-retroviral therapy.

Options

- delay anti-retroviral therapy until TB therapy is complete
- interrupt antiretroviral therapy for the duration of tuberculosis therapy
- modify anti-retroviral regimen taking drug interactions into account

When initiating therapy...

- Additive side-effects and toxicities

- It is suggested that there should be some delay between starting tuberculosis treatment and initiating anti-retroviral therapy

- for patients already on ART regimen with problematic drug interactions, non-rifampicin containing regimen may be considered

How well do non-rifampicin containing regimens work?

- British MRC studies:
- 86-94 % sputum conversion at 3 months
- relapse rates @ 30 months: 18-24%
- relapse rates 5-6% if treatment continued for more than 9 months
- A non-rifampicin containing regimen may be considered provided that:
  - duration at least 9mnths
  - streptomycin containing regimen

Recommended adjustments for anti-retrovirals with rifampicin

Drug/drug class	Adjustment with rifampicin
NRTIs	No change in dose
Nevirapine	Insufficient data
Efavirenz	No change in dose *
Indinavir	Contraindicated
Saquinavir	Contraindicated
Nelfinavir	Contraindicated
Ritonavir	No change in dose
Ritonavir + Saquinavir	No change in dose

* Some authorities recommend increasing the dose of efavirenz to 800 mg

CDC recommendations for rifampicin and ART

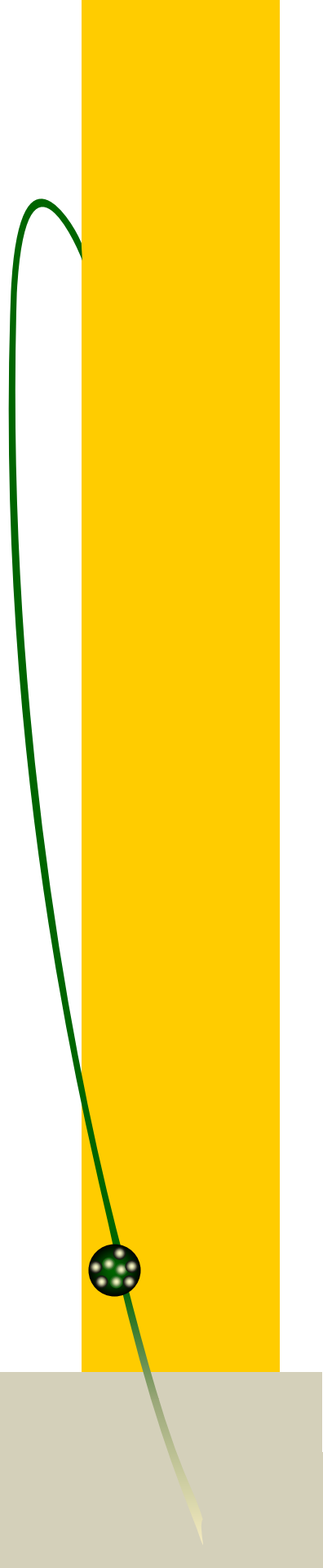
- Can use rifampicin in the following situations:
- in a patient whose antiretroviral regimen includes the NNRTI efavirenz and two NRTIs;
- in a patient whose antiretroviral regimen includes the protease inhibitor ritonavir and 2NRTIs
- in a patient whose antiretroviral regimen includes the combination of the two protease inhibitors ritonavir and saquinavir (400mg bd of both drugs)

CDC recommendations for rifabutin

- The dose of rifabutin should be reduced (150 mg two or three times per week) when it is administered to patients taking ritonavir (with or without saquinavir)
- the dose of rifabutin should be increased(either 450 mg or 600 mg daily or 600 mg two or three times per week) when rifabutin is used concurrently with efavirenz
- Rifabutin is not available on the national TB programme in South Africa

Conclusion

- Drug interactions must be considered when prescribing ART- education of prescribers
- Our choice of anti-retroviral therapy regimen should take into account potential interactions with rifampicin
- Any South African guideline for ART must include clear guidelines for anti-retroviral management of HIV infected patients with TB.



Metabolic interactions: the Cytochrome P450 enzyme system

- **A metabolic system which evolved to enable organisms to deal with lipid soluble substances.**
- **Cytochrome P450 oxidizes, reduces or hydrolyses substances.**
- **Conjugation enzymes then form a water soluble compound, which can be excreted.**

Cytochrome P450 enzyme system

- At least 11 families of cytochrome P450 enzymes.
- 1, 2 and 3 are most important in humans.
- Further subdivided into subfamilies, and individual proteins within a subfamily
  - 1A2, 2C19, 2C9, 2D6, 2E1, 3A4,5,6
  - genetic variation
- Drugs may be substrates, inhibitors or inducers of cytochrome P450.
- Some drugs, eg ritonavir, nelfinavir and efavirenz, may do all or a combination of the above, depending on the specific drug combination.

- 32 year old woman - WHO 4 - cryptosporidium with severe diarrhoea and weight loss. At death's door. Started on Combivir and efavirenz - diarrhoea resolved - 5kg weight gain. Then fevers with anaemia - bone marrow biopsy - granuloma with AFBs - disseminated TB. Struggling

Case 5

- 32 year old woman with advanced HIV infection CD4 count <20. Works as a counselor at a TB hospital. Presents with high fever and chest X Ray suggestive of miliary TB, after having been screened for a study
- Started on retreatment regimen- responded well
- 2 months later she was randomised to take Nevirapine/D4T/3TC
- How should her TB be managed further?

Case

- 24 year old man
- HIV positive since 1997
  - Never sought medical care
  - Antiretroviral naive
- PTB 1999 – fully treated x 6 months
- Acutely ill
  - Temp 39 / p 110 / oral thrush + odynophagia
  - Severe wasting
  - Collar stud abscess left supra-clavicular region
- CD4 17 / VL > 750 000 copies/ml

Case 4

- Start TB meds +/- ART?
- Which ART regimen to start with?