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Tuberculosis and HIV: Treatment Considerations

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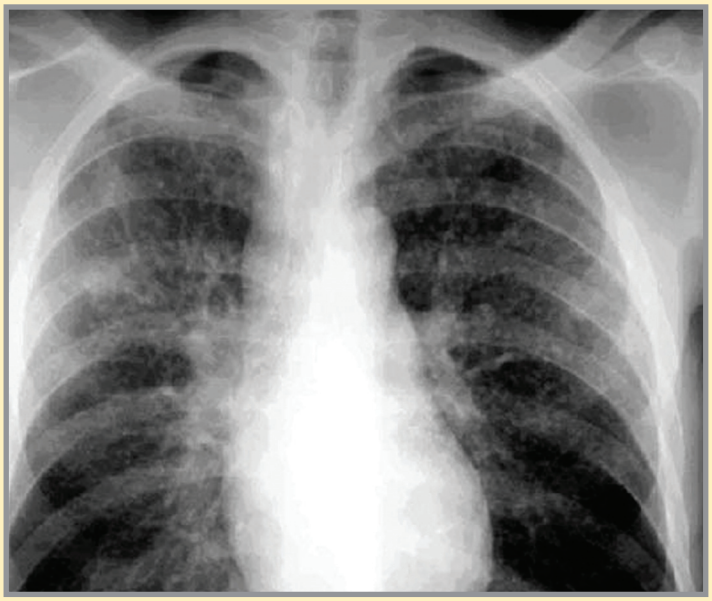
Worldwide, over 2 million people die of tuberculosis each year. Although the majority of immunocompetent people contain primary infection with TB, advanced immunosuppression due to HIV results in increased risk for active disease in primary infection and reactivation of latent infection. As a result, TB is the most common opportunistic infection among people infected with HIV. The key challenges to managing co-infected patients include adherence, polypharmacy, overlapping toxicity, drug-drug interactions, and timing of initiation of antiretroviral therapy given the risk of immune reconstitution inflammatory syndrome (IRIS). We will review these issues with recommendations based on currently available drugs. Where published supporting data exist, areas for advocacy are highlighted at the end for changing current practice in Uganda.

TB treatment recommendations

For patients initiating treatment for newly diagnosed tuberculosis, a 2 month (8 week) intensive phase of treatment with 4 drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) is recommended. A 6 month continuation phase of treatment with two drugs, isoniazid and ethambutol, is recommended to complete the 8 month total treatment duration. For patients with TB relapse (tuberculosis recurrence within 5 years of the initial treatment course) or default (received at least 4 weeks of treatment with the first diagnosis but did not complete therapy), streptomycin is added as a 5th drug in the 8 week intensive phase of treatment with an additional month of intensive phase therapy with the original 4 drugs. Continuation phase with three drugs (isoniazid, Rifampicin and ethambutol) will be administered for 5 months for a total of 8 months of therapy. Current guidelines suggest that these patients should also get sputum culture and drug sensitivity testing to rule out drug resistant tuberculosis infection.



A TB X-ray

Drug-drug interactions in HIV TB co-infection

If patients are already on HIV treatment at the time of TB diagnosis, the interactions between rifampin and both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) must be considered. Introduction of rifamycins to anti-tuberculous chemotherapy resulted in shortening of the duration of treatment. Because of its expense, rifampin is prescribed only for the first 2 months (intensive phase) of therapy in many resource-limited settings. The rifamycin class induces (upregulates) the synthesis of drug metabolizing enzymes, the cytochrome P450 enzyme system (CYP3A and the CYP2C8/9 enzymes). Rifampin is the most potent inducer; rifabutin is much less active as an inducer. Therefore, the addition of rifampin leads to upregulation of enzyme synthesis with a subsequent decrease in the half-life of co-administered drugs metabolized by the cytochrome P450 system. The interaction is particularly important with NNRTIs since these are the cornerstones of antiretroviral therapy in resource-limited settings where low-cost, fixed-dose generic regimens allow for the widespread treatment of HIV.

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From the Editor

We are glad to provide you with information that makes your tasks in patient care easier. In this ATIC News is a review on pharmacological management of TB, which is one of the commonest opportunistic infection in HIV-infected patients in resource limited countries.

One of the challenges of HIV therapy is the development of the immune reconstitution inflammatory syndrome (IRIS) soon after initiation of antiretroviral therapy. Researchers in the medical field from a number of countries convened a special meeting in Kampala to define IRIS. One of these researchers has contributed an article on IRIS for this ATIC News.

There are other challenges of TB – HIV co-infection that may significantly affect the outcome of HIV and/or TB therapy. In this issue of ATIC News you will find an article that will remind you of these challenges. Research still goes on with the goal of finding solutions, which would be answers for the treatment of TB that does not respond to conventional therapy.

We hope that you take pleasure in this edition of ATIC News, remembering that we are standing with you in the promotion of rational use of medicines.

Tuberculosis and the Immune Reconstitution Inflammatory Syndrome: case definitions

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The use of highly active anti-retroviral therapy (HAART) decreases mortality and improves the quality of life of persons living with HIV infection(1). Nevertheless, 10-25% of patients living in developing countries experience a worsening of their clinical status during the first 3 months of HAART despite immunological improvement(2;3). This paradoxical reaction is known as immune reconstitution inflammatory syndrome (IRIS) or immune reconstitution diseases (IRD). More than 20 different pathogens have been associated with IRIS(2;4) resulting from the restoration of pathogen-specific immune responses against alive or dead organisms(5). Mycobacterium tuberculosis (TB) is by far the most common pathogen involved in IRIS in countries with limited resources(6). IRIS has also been described with autoimmune disease, some cancers and some non-infectious granulomatous diseases such as sarcoidosis and Crohn's disease(5).

In November 2006, around 100 researchers (microbiologists, immunologists, clinicians, epidemiologists, clinical researchers, and public health specialists) from 16 countries met in Kampala to develop consensus case definitions for TB-associated IRIS that are appropriate for low-resource settings with limited laboratory capacity.

Tuberculosis-associated IRIS generally develops during the first 3 months following initiation of HAART and can present as one of two main syndromes:

(1) a paradoxical reaction after the start of HAART in patients receiving TB treatment (here termed **paradoxical** TB-IRIS), or

(2) a new presentation of TB that is "unmasked" in the weeks following initiation of HAART with an exaggerated inflammatory clinical presentation (here termed **unmasking** TB-IRIS).

DEFINITIONS:

1 Case definition for 'paradoxical TB-IRIS'

There are three components (A, B and C) to this case definition.

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A) Antecedent requirements Both of the following requirements must be met:

1) Diagnosis of TB: The TB diagnosis was made before starting HAART and this should fulfill World Health Organization (WHO) criteria for diagnosis of smear positive pulmonary TB (PTB), smear negative PTB or extra-pulmonary TB.

2) Initial response to TB treatment: The patient's condition should have stabilized or improved on appropriate TB treatment prior to HAART initiation e.g. cessation of night sweats, fever, cough, weight loss. (Note: this does not apply to patients starting HAART within 2 weeks of starting TB treatment as insufficient time may have elapsed for a clinical response to be observed).

B) Clinical Criteria

The onset of TB-IRIS manifestations should be within three months of HAART initiation, re-initiation, or regimen change due to treatment failure.
Of the following, at least 1 major criterion or 2 minor clinical criteria are required:

Major criteria

1) New or enlarging lymph nodes, cold abscesses or other focal tissue involvement (e.g. tuberculous arthritis)

2) New or worsening radiological features of TB (using chest radiography, abdominal ultrasonography, computerized tomography or magnetic resonance imaging).
3) New or worsening central nervous system TB (meningitis or focal neurological deficit e.g. due to tuberculoma)

4) New or worsening serositis (pleural effusion, ascites or pericardial effusion)

Minor criteria

1) New or worsening constitutional symptoms such as fever, night sweats or weight loss.

2) New or worsening respiratory symptoms such as cough, dyspnoea or stridor.

3) New or worsening abdominal pain accompanied by peritonitis or hepatomegaly or splenomegaly or abdominal adenopathy.

C) Alternative explanations for clinical deterioration must be excluded if possible*:

1) Failure of TB treatment due to TB drug resistance.

2) Poor adherence to TB treatment.

3) Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear negative PTB and extra-pulmonary TB where the initial TB diagnosis has not been microbiologically confirmed.

4) Drug toxicity or reaction.

* It may be difficult or impossible in resource poor settings to confirm TB drug resistance and to exclude certain other infections or neoplasia. Cases where alternative diagnoses cannot be fully excluded because of limited diagnostic capacity should be regarded as 'probable paradoxical TB-IRIS'. In these probable cases, should resolution of clinical or radiological findings of the suspected IRIS episode occur without a change in TB treatment or HAART, the episode could then be reclassified as 'paradoxical TB-IRIS' cases.

2 Case definition for 'unmasking TB-IRIS'

1) Patient is not receiving treatment for TB when HAART is initiated and then presents with active TB within 3 months of starting HAART
AND

2) Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include TB lymphadenitis or TB abscesses with prominent acute inflammatory features, presentation with pulmonary TB that is complicated by respiratory failure due to acute respiratory distress syndrome [ARDS] and those who present with a marked systemic inflammatory syndrome related to TB.

Recognizing IRIS is important, as it is a temporary state which usually resolves without additional treatment. However, in rare cases, particularly in patients with central nervous system infections, IRIS can lead to death. For the moment there are no evidenced based guidelines for the management of IRIS. A randomized trial is currently underway in South Africa to determine the effect of corticosteroids on IRIS. Corticosteroids may decrease the symptoms but may be associated with side effects particularly after prolonged use. In addition, their effect on mortality of TB-IRIS is unknown. Hopefully, this and other studies will answer this important question.

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Tuberculosis and HIV: Treatment Considerations

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The effect of rifampin on nevirapine concentrations is greater than that with efavirenz. The well-characterized and comparatively modest effect of rifampin on efavirenz, makes this drug the preferred NNRTI when anti-tuberculous regimens containing rifampin are to be used in adults. However., use of efavirenz in the first trimester of pregnancy is contraindicated due to teratogenicity in primate models. In children, some reports of suboptimal levels of efavirenz with and without rifampin raises general concerns about the use of this NNRTI in children.

Rifampin also upregulates the synthesis of glucuronosyl transferase which mediates the metabolism of zidovudine, another important NRTI widely used in HIV treatment. Although there is a 50% decrease in zidovudine (AZT) levels with concomitant rifampin use, increasing the dose of AZT is not recommended.

For patients with NNRTI-resistant HIV who transition to second line therapy with a protease inhibitor (PI), rifampin cannot be used because of increased and rapid metabolism of all protease inhibitors, Co-administration of rifampin and protease inhibitors results in the reduction of serum PI concentrations by over 75%, risking virologic failure. Proposed alternatives for second line ARV regimens in the setting of co-administration of rifampin include triple nucleoside regimens such as AZT, lamivudine, abacavir or nucleoside/nucleotide regimens (AZT, lamivudine, tenofovir +/- abacavir)., However, these regimens are known to be less potent and consideration should be given to a switch to a PI containing regimen once the need for rifampin is over (ie during continuation phase of TB treatment).

Toxicity of TB/HIV regimens

Overlapping toxicities of HIV regimens and TB treatment is another important consideration. Nevirapine is known to be hepatotoxic especially in patients with higher CD4 T cell counts (>400 cells for men, >250 cells for women). Studies in which the dose of nevirapine was increased from 200 mg twice daily to 300 mg twice daily resulted in increased incidence of hypersensitivity to nevirapine in those taking the higher dose. Since pharmacokinetic data also demonstrate adequate trough levels of nevirapine on those treated with rifampin, these data support the use of standard dose nevirapine with rifampin in patients unable to tolerate efavirenz or in women who are either at risk for becoming pregnant or in the first trimester of pregnancy. However, in a recent publication on ART coadmimistered with rifampicin, it was shown that, the time of TB infection, with regard to ART administration was associated with virologic outcomes. Virologic failure was associated with administering NVP based ART [not EFV based ART] to patients already on rifampicin based antituberculosis therapy. For patients who got TB while on NVP based ART, the results where comparable to the EFV based regimen: virologic success (Boulle et al., 2008). Further studies on the interaction between rifampin and generic formulations used in resource-limited settings will be important in supporting the rational use of nevirapine-based regimens in co-infected patients. For the PI interaction, increasing the dose of co-formulated lopinavir-ritonavir by 50% or 100% has been suggested to overcome the inducing effect of rifampin. However, studies in healthy volunteers have shown an increased risk of hepatotoxicity with this approach. Further studies on the pharmacokinetics and toxicity of increased doses of PIs with rifampin will be needed before such regimens can be endorsed in co-infected patients. Preliminary pharmacokinetic data suggested that increased doses of co-formulated lopinavir/ritonavir in the presence of rifampin leads to adequate concentrations of the PIs. However recent pharmacokinetic data has shown that the concentration of PIs given with rifampin in children remain subtherapeutic even after doubling the PI dose.

Timing of antiretroviral therapy in patients initiating treatment for tuberculosis and eligible for HIV treatment

For patients who have been diagnosed with tuberculosis, anti-TB therapy should be started immediately. According to the 2006 WHO recommendations, patients with extrapulmonary tuberculosis and those with CD4 T cell counts <200 cells/?I should be started on HAART as soon as anti-TB medications are well tolerated (2 weeks to 2 months). Recent data suggests that the risk for IRIS, which is 7-35% overall, decreases with increasing time between the initiation of anti-TB therapy and ARVs. However, the increased risk of IRIS must be balanced against the risk for development of other opportunistic infections and increased mortality for those with the most advanced immunosuppression. For patients with CD4 T cell counts between 200-350 cells/ul, therapy should be initiated after the intensive phase of therapy, which includes rifampin, has concluded and interactions with rifampin can be avoided. For patients with CD4 T cell counts >350 cells/ul, ARVs are not currently recommended in resource-limited settings.

Areas for advocacy consideration

In non-resource-limited settings, rifampin is used in both the intensive phase (4 drug therapy) and the continuation phase in combination with isoniazid. This regimen is clearly superior in HIV-infected patients. Because of increased cost to national programs as in Uganda, rifampin is often used only in the intensive phase. Advocacy to decrease the price of rifampin to make it available in the continuation phase for resource-limited settings is urgently needed. Next in priority is the addition of rifabutin to the national TB program which would allow for the continuation of PIs in those patients who develop TB while already on second line ARV therapy with PIs. Finally, adequate dosing of rifampin at an adult dose of 600mg per day should replace the dose found in the blister pack combination therapy used during intensive phase. Currently, pills containing only 225mg rather than 300 mg are offered resulting in doses under 10mg/kg for most adults if the recommended 2 pills/day are used.

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Tenofovir-induced Nephrotoxicity: Emphasis on Prevention

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I. Introduction:

Current management of HIV infection dictates the use of highly active antiretroviral therapy (HAART). Some components of HAART may lead to the development of various toxicities including drug-related nephrotoxicity and acute renal failure. Amongst the nucleos(t)ide reverse-transcriptase inhibitors (NRTIs), Truvada, which is a fixed dose combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), is a common first choice for an NRTI "backbone" in combination with other antiretroviral medications in the management of HIV. Truvada is being used more often in Uganda as well, as efforts continue to phase out stavudine (d4T) use due to its unfavorable metabolic toxicity profile. The use of Truvada is also being studied for PEP (post exposure prophylaxis) and is the treatment of choice for HIV patients co-infected with hepatitis B, which responds to both tenofovir and emtricitabine (or lamivudine). However, several case reports and retrospective clinical studies have raised concerns about the potential nephrotoxicity of TDF, especially in patients who may have preexisting chronic renal insufficiency [1, 2, 4]. The aim of this article is to summarize our current knowledge about TDF, its relation to kidney disease and how this toxicity may be prevented.

II. Tenofovir Pharmacokinetics and Toxicity Profile:

Tenofovir is packaged together with FTC as a single pill called Truvada although the single agent is also available for use. Several clinical trials studying the efficacy of tenofovir indicated that the drug itself was not associated with renal failure [3, 8-9]. However these studies were limited as they excluded patients with pre-existing renal failure in their study design. Since then, several case reports and observational studies have shown that renal proximal tubular toxicity is a concern with TDF [1, 2, 4, and 10].

TDF is primarily excreted by the kidneys and elimination of drug metabolites is accomplished by both glomerular filtration and active tubular secretion, in a concentration dependent manner. It is hypothesized that the proximal tubular accumulation and toxicity of TDF occurs by direct transport with the human organic anion transporter 1 (hOAT1) of the proximal renal tubular cells [1, 2, 10]. Once accumulated intracellularly, the nucleotides are secreted into the urine through another protein (MRP2) on the apical side of the proximal tubular cell [2]. Clinical studies have indicated that a dysfunction in the MRP2 protein can cause accumulation of tenofovir within the cells leading to proximal tubular toxicity.

III. Significant Adverse Effects and Drug Interactions with Tenofovir:

Suggested risk factors for tenofovir-associated renal toxicity in HIV patients include pre-existing renal insufficiency or poorly controlled HIV disease who have a longer overall antiviral treatment duration. Reported complications of tenofovir, alone or in combination with other antiretrovirals, include renal failure, acute tubular necrosis, Fanconi syndrome (hypophosphatemia, hypouricemia, glycosuria without hyperglycaemia, and proteinuria), and severe hypokalemia [2, 4, 10]. Most of these adverse reactions can be reversed with discontinuation of the drug. Patients who are taking TDF in combination with protease inhibitors such as ritonavir may be more susceptible to renal toxicity as indicated in ***Box 1*** [1, 2, 4, 10]. ***Box 2*** outlines other antimicrobials that are eliminated by the kidney, and when not dosed appropriately may cause adverse renal dysfunction.

There is also a significant drug interaction between tenofovir and didanosine (DDI). Therefore, when co-administered with TDF, it is important to make an appropriate reduction in dose of DDI in patients weighing 60 kilograms or more [1]. Because of the poor virologic outcomes when TDF and DDI combination is given with NNRTIs this combination should be avoided.

Box 1

Proposed HAART medications that that may increase the likelihood of Tenofovir induced Nephrotoxicity [1, 2, 4, and 10].
-Lopinavir / Ritonavir -Ritonavir -Atazanavir -Amprenavir

Box 2

Antimicrobial and antiviral medications commonly administered for patients with HIV infection that require renal dosage adjustments [1]
-Acyclovir -Amphotericin (Avoid in renal insufficiency) -Fluconazole -Anti Tuberculous agents (Isoniazid, Rifampin, Ethambutol and Pyrazinamide) -Trimethoprim-sulfamethoxazole (Septrin) - Ciprofloxacin - Clarithromycin - IV Pentamidine (Avoid coadministration)

IV. Tenofovir Dosing:

The usual dosage of TDF for HIV patients without significant renal insufficiency is 300mg daily. However, it is important to remember that many patients with HIV may present with muscle wasting while receiving HAART, which is associated with low serum creatinine levels. In such patients,

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serum creatinine measurement alone is an insensitive measurement of glomerular filtration rate, and patients could have significant renal insufficiency with normal serum creatinine levels. Therefore, clinicians should make appropriate adjustments in the dosage based on the patient's creatinine (CrCl) clearance as calculated by the Cockcroft-Gault equation as outlined in box 3 [7].

The Cockcroft-Gault Equation for Estimating Creatinine Clearance (CrCl) [7]

$$CrCl = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \ [\times 0.85 \text{ if patient female}]}{72 \times \text{serum creatinine (mg/dl)}}$$

Combination therapy with Truvada (which includes 300mg TDF and 200mg of FTC) requires dose adjustments for creatinine clearance of 30-49 mL/min as indicated in Table 2. However, the Truvada combination pill is not recommended for patients with CrCl below 30mL/min. Clinicians may opt to prescribe TDF, as a separate drug with dose adjustment for renal impairment, in combination with other appropriately dose-adjusted ARVs as a component of HAART.

Table 1: Tenofovir Dose Adjustments Based on Creatinine Clearance [1]

Creatinine Clearance	Tenofovir Dosage
CLcr >= 50 mL/min	No Adjustment Necessary
CLcr 30-49 mL/min	300mg per 48h
CLcr 10-29 mL/min	300mg per72h
Receiving Hemodialysis	300mg every 7 days

Table 2: Truvada Dose Adjustments Based on Creatinine Clearance [1]

Creatinine Clearance	Tenofovir Dosage
CLcr >= 50 mL/min	No Adjustment Necessary
CLcr 30-49 mL/min	One tablet per 48hrs
CLcr <30 mL/min	Not recommended
Receiving Hemodialysis	Not recommended

V. Prevention of Tenofovir Nephrotoxicity

Multiple drug interactions between TDF and other HIV-related medications may lead to renal tubular toxicity and acute renal failure. However, data so far, including that from the DART (Development of Antiretroviral Therapy) Trial indicate a very low incidence of tenofovir-induced renal toxicity (ranging from 0.5% – 1.6%) in patients who have normal baseline renal function, [8,9,12] . Although no formal guidelines for preventing tenofovir-induced renal damage exist, the literature recommends that routine renal laboratory monitoring including serum electrolytes, creatinine, blood urea nitrogen, calcium, phosphorus and a urinalysis be performed at least twice yearly for patients without renal insufficiency who are receiving tenofovir therapy [1]. Closer monitoring for tenofovir-induced proximal tubular renal disease is recommended in patients with a history of preexisting renal dysfunction, those with a longer duration of TDF therapy (5-64 weeks) or in those with patients with low body weight [1, 2]. The concurrent use of TDF with ritonavir, commonly given as lopinavir-ritonavir (Kaletra or Alluvia), mandates an even closer evaluation of renal function (twice monthly for the first two months of therapy) [2]. It is also important to carry out urine examination for proteinuria which may be an indication of kidney disease. An increase of 50% in the serum creatinine should suggest tenofovir-induced renal insufficiency in any TDF recipient. This is critically important as most cases of tenofovir-induced renal toxicity can be reversed with discontinuation of the medication, with an estimated recovery period of 5 weeks. Complex patients with HIV and renal disease can be referred for further evaluation to the Nephrology outpatient clinic at Mulago Hospital which meets each Tuesday.

VI. Conclusion:

Over 30% of HIV patients will suffer from some form of renal disease during the course of their infection, varying from acute renal failure to end stage renal disease [11].

Health care professionals must be aware of the toxicity profiles of TDF and make appropriate dosage adjustments for TDF to prevent renal toxicity.

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Treatment of hepatitis B virus infection in patients co-infected with HIV in Uganda

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Chronic hepatitis B virus (HBV) infection is among the leading causes of death in the world. As many as one third of the world's 6 billion people have acquired hepatitis B of whom 400 million have chronic hepatitis B, defined as persistence of hepatitis B surface antigen (HBsAg) for more than 6 months from time of exposure. The pandemic of human immune deficiency virus (HIV) infects close to 40 million people and therefore the two infections commonly occur together

Unfortunately both hepatitis B and HIV are more prevalent in sub-Saharan Africa than in the developed world. In Uganda, the chronic hepatitis B infection rate is close to 10%, although it varies from region to region, with rates of up to 25% reported in the North and North Eastern parts of the country. The average HIV prevalence rate has been estimated at 7% in the country.

Hepatitis B and HIV share primary modes of transmission, both being transmitted by exposure to body fluids through childbirth (perinatal transmission), sexual transmission, and exposure to blood and blood products. However, Hepatitis B is 100 times more infectious than HIV infection following needle stick injuries, probably based on the number of viral particles in the blood of carriers, which is generally lower in chronic HIV infection.

Worldwide, 4 million people are estimated to have HIV/HBV co-infection. However, the prevalence of co-infection varies from country to country and from cohort to cohort. According to studies conducted at the Infectious Diseases Institute in Kampala, Uganda up to 10% of HIV infected patients seen at this large, multidisciplinary HIV clinic are co-infected with hepatitis B virus.
Although, unlike hepatitis C virus, the hepatitis B virus does not seem to significantly influence HIV disease progression, HIV infection does affect hepatitis B virus characteristics and liver disease outcome in various ways:

- HBV replication is accelerated, thus leading to higher HBV viral loads
- Increased rates of chronic infection after primary acquisition of hepatitis B are seen
- Higher rates of antiretroviral drug related hepatotoxicity are noted
- Higher rates of active hepatitis B flares and more rapid progression of liver disease to cirrhosis and HCC are seen
- Lower rates of hepatitis B e antigen sero-conversion take place
- Lower rates of HBV vaccine serocon version rates are noted
- Higher rates of lamivudine resistance in HBV have been found in co-infection

All these factors put co-infected patients in a special category requiring important treatment decisions for both their hepatitis B and their HIV infections.

Drug treatment for Hepatitis B and HIV

A number of drugs have been approved by the Food and Drug Administration (FDA) of the United States for the treatment of hepatitis B mono-infected patients. Some of these drugs are also effective against HIV while others are not. Unfortunately in resource poor countries such as Uganda, many of these drugs are unavailable. Table 1 below lists the drugs in use for treating HBV and their activity against HIV infection. Currently, the reverse transcriptase inhibitors, lamivudine, emtricitabine and tenofovir are the drugs that are effective against both HBV and HIV and thus may be useful in treating co-infected patients.

Table 1. Drugs effective against HBV and HIV

Drugs	Active against HBV	Active against HIV
Lamivudine	Yes	Yes
Adefovir (at 10 mg daily)	Yes	No
Entecavir	Yes	No
Emtricitabine	Yes	Yes
Telbivudine	Yes	No
Tenofovir	Yes	Yes

Considering all these drugs, only lamivudine and tenofovir (and in some cases, tenofovir and emtricitabine in the combination tablet, Truvada) are currently available in Uganda.
In HBV mono-infected patients resistance to lamivudine occurs at a rate of 20% per year and this resistance rate is much higher in HIV co-infected patients. This makes lamivudine inferior to tenofovir in the management of HBV even in HBV mono-infected patients. In fact in most developed countries lamivudine is no longer recommended as monotherapy for treatment of HBV mono infected patients. It is important to note that when lamivudine resistance occurs, fatal liver disease flares may develop.

Tenofovir has very good activity against HBV and a good resistance profile. Therefore, in many HIV clinics, the treatment for co-infected patients now includes tenofovir as part of highly active antiretroviral therapy (HAART). Since the recommended treatment for hepatitis B is to use at least two drugs which are effective against the virus, the use of either tenofovir + lamivudine or Truvada (tenofovir + emtricitabine) has become popular as the nucleos(t)ide backbone of HIV therapy.

In conclusion, HBV is common among HIV infected patients in Uganda and can lead to cirrhosis and HCC even in patients with well-controlled HIV infection. It is time we begin to test all Ugandan patients for HBV infection (presence of HBsAg) before initiating HAART. If co-infection is documented then HAART should employ Truvada as its nucleos(t)ide backbone.

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Fluoroquinolone use in the treatment of Tuberculosis.

By Violet Okaba Kayom,
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Tuberculosis (TB) continues to be one of the most important global health problems. Now, even more challenging is the emergence of multidrug-resistant tuberculosis (MDR-TB : resistance to isoniazid and rifampicin) and extensively drug resistant tuberculosis (XDR-TB : MDR-TB with additional resistance to the fluoroquinolones and injectable antituberculous medication). Therefore there is an urgent need for new TB drugs to improve, shorten and / or simplify treatment of drug susceptible tuberculosis, to improve treatment of patients with MDR-TB, to provide effective therapy for patients intolerant to the current first line drugs and to provide effective treatment for patients with latent tuberculosis infection [1].

Fluoroquinolone antibiotics have been shown to have bactericidal activity *in vitro* against *Mycobacterium tuberculosis* (Garcia – Rodriques 1993, Davies 1987, Yew 1994), and this has been confirmed in animal models. They are rapidly absorbed and have high availability with oral administration. They are highly concentrated in respiratory tract tissues, secretions and inside macrophages and in addition, they are generally well tolerated over the extended time periods necessary for treatment of TB. [2].

A study by Chaisson et al found that adding moxifloxacin to a standard combination of other antituberculosis antibiotics increased by 17% the number of patients who cleared active infection from their lungs (raising cure rates from 68% to 85%), after just 2 months of therapy, compared to patients taking the standard combination with ethambutol. It has also been thought that substituting moxifloxacin for one of the key ingredients in DOTS could shorten the treatment period by nearly 2 months [3]. Studies to date indicate that the early bactericidal activity of moxifloxacin is not significantly different from that of isoniazid [4, 5]. Another study indicated that culture conversion among patients randomized to receive levofloxacin was more rapid compared to those on ethambutol [6].

However, some other studies have produced different results. A study by Moadebi et al found that in patients with susceptible *M. tuberculosis* strains, substitution of therapy with a fluoroquinolone did not improve cure rates or radiological improvement at 8 weeks or failure at 12 months. Substitution of older fluoroquinolones into a regimen, especially ciprofloxacin, resulted in a *higher* rate of relapse and a longer time to sputum-culture conversions [7].

Ziganshina et al found no statistically significant difference in trials substituting ciprofloxacin, ofloxacin or moxifloxacin for first-line drugs in relation to cure, treatment failure, clinical or radiological improvement. Substituting ciprofloxacin into first-line regimens in drug sensitive TB led to a higher incidence of relapse and longer time to sputum culture conversion [8].

In summary, older fluoroquinolones like ciprofloxacin have limited activity in tuberculosis treatment, but newer fluoroquinoloes may have potent sterilizing activity. The most potent of the currently available fluoroquinolones in descending order of *in vitro* activity against *Mycobacterium tuberculosis* are; moxifloxacin, gatifloxacin, levofloxacin, ofloxacin and ciprofloxacin [9]. Fluoroquinolones, at the moment, should not be used in the treatment of TB susceptible to first-line regimens. They may have an important role as substitute agents for those who are intolerant to one or more of the first-line drugs.

The most significant role of fluoroquinolones currently is in the treatment of MDR-TB. Despite the limited number of randomized clinical trials on use of fluoroquinolones in MDR-TB treatment, they have been found to work effectively in a large case series [9].

What about Fluoroquinolone resistance?

Broad spectrum antibiotics such as fluoroquinolones are widely used for treatment of bacterial infections like urinary tract infections, community acquired pneumonias, and pelvic inflammatory disease. Considering that the number of cases of MDR-TB in Uganda is on the rise, there is a pressing need to look closely into the issue of possible *Mycobacterium tuberculosis* resistance to fluoroquinolones to avoid losing these important second-line drugs.

Mycobacterial resistance to fluoroquinolones develops as a result of gyrA gene mutations and there is extensive cross-resistance among the 6 fluoroquinolones (moxifloxacin, ofloxacin, levofloxacin, sparfloxacin, gatifloxacin and sitafloxacin) [10]. Thus patients with prior exposure to any of the quinolones are likely to develop resistance to other fluoroquinolones.

A study by Ginsburg, et al showed that the incidence of *M. tuberculosis* fluoroquinolone resistance in patients with newly diagnosed TB was high particularly among patients with prior fluoroquinolone exposure [11].

It is extremely important to rule out pulmonary TB in a patient presenting with features of community acquired pneumonia before initiation of a fluoroquinolone therapy. Studies have shown that initial empiric therapy with a fluoroquinolone is associated with a delay in

the initiation of appropriate antituberculous treatment and poor prognosis in endemic areas [12, 13]. This also puts the patient at risk of developing mycobacterial fluoroquinolone resistance if it turns out to be MDR-TB.

Conclusion

Fluoroquinolones are highly efficacious, broad spectrum antibiotics. Older fluoroquinolones have limited activity in treatment of TB but newer agents have potent sterilizing activity. They have an important role in the treatment of MDR-TB and for patients intolerant to the first-line TB agents. The activity of the newer fluoroquinolones has not been fully evaluated in randomized controlled trials. There are a number of such trials now being carried out and there will be a need for even more studies of these important anti-tuberculous agents. Fluoroquinolones should be avoided for the treatment of community acquired pneumonias unless a diagnosis of pulmonary TB has been ruled out. The inappropriate use of fluoroquinolones, often in sub-therapeutic doses, is likely to enhance quinolone resistant microorganisms, including *M. tuberculosos.* **There is therefore a need to educate healthcare workers about fluoroquinolone cross-resistance so we can save this important group of drugs for future use in the treatment of MDR-TB.**

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Ask ATIC

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HIV Clinical Pharmacist

In some HIV patients after initiation of ARV's there is a slow recovery of the CD4 cell count. However measurements of the viral load show that the virus has been suppressed and is undetectable. Therefore my question is that in HIV positive patients in whom for some reasons CD4 does not go up fast but viral loads are undetectable, should we continue Septrin prophylaxis until the CD4 comes to 200 or discontinue when the viral load is undetectable. I know this phenomenon only happens in only a few patients.
Sister Musana
Masaka

This phenomenon has been described as the disconnect syndrome where persistent low CD4 (+) cell counts are observed in patients treated for human immunodeficiency virus (HIV)-1 infection despite their having prolonged undetectable plasma viral loads. The mechanisms responsible for the low-level regeneration of CD4 (+) cells involve, at least, deficiency in the regeneration of central CD4 (+) cells and excessive apoptosis.

Considering the question of whether patients such as these should be continued on Septrin despite an undetectable viral load, our answer would be yes. Septrin prophylaxis should not be discontinued in these patients. Studies in well-resourced settings have demonstrated the safety of discontinuing co-trimoxazole as prophylaxis against PCP and toxoplasmosis among people with immune recovery (CD4 >200 cells per mm3) in response to antiretroviral therapy. Data in resource-limited settings have demonstrated similar findings. However the general recommendation is to continue co-trimoxazole prophylaxis among adults living with HIV indefinitely. Therefore regardless of CD4 counts higher than 200, based on benefits such as reduced incidence of malaria episodes; and reduced incidence of gastrointestinal diseases, please continue the patient on Septrin.

Can I Take My ARVs without Food?

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Over the past year, prices of staple foods have risen in many parts of the world, including developing countries like Uganda. This article highlights some of the issues surrounding antiretroviral treatment and food and summarizes the dosing of antiretroviral drugs in relation to meals.

Case presentation

NR is a 42 year old widow who was diagnosed with HIV in 2005. Because she had a low CD4 count (150 cells/uL), she was started on antiretroviral therapy (zidovudine, lamivudine plus efavirenz). Unfortunately, after the loss of her husband she had been unable to cope financially and had difficulty providing food for herself and her fifteen year old daughter. She reported missing doses of her ARVs and had missed clinics because she did not have money for transport. On a clinic visit in 2006, her doctor informed her that her regimen was failing and switched her to a "second line" regimen of zidovudine and didanosine tablets plus lopinavir/ritonavir (Kaletra®) capsules. She was informed by the counselor to take the didanosine before meals while zidovudine and lopinavir/ritonavir were to be taken after meals. She took her didanosine as advised every day but because her meals were irregular, she took her zidovudine and Kaletra® intermittently. One year later, she developed purple nodules on her shins consistent with Kaposi's sarcoma and her CD4 count had dropped to 20 cells/u.

The management of HIV requires lifelong adherence to a combination of antiretroviral drugs. Food can affect HIV treatment in several ways. Firstly, food may affect adherence as illustrated in this case. Beliefs that antiretrovirals are 'strong medicines' which must be taken with food in order to prevent side effects are very common. Health workers reinforce this belief while counseling on the need to take food along with other commonly used drugs e.g. the antimalarial drug, Coartem®. Unfortunately, as a consequence of poor adherence drug resistance may occur. When resistance develops, HIV may progress to AIDS leading to the occurrence of opportunistic infections and malignancies, siuch as Kaposi's sarcoma in this case. Patients failing therapy because of poor adherence often require treatment with even more complicated drug combinations which will be difficult to adhere to.

Secondly, antiretroviral drugs may need to be taken either with food or without food, depending on the absorption kinetics of individual ARVs, to ensure enough of the drug is absorbed from the gut to the blood-

Table 1 - Food advice for commonly used antiretroviral drugs

Drug	Food Advice
Zidovudine (ZDV)	**No meal restrictions**
Lamivudine (3TC)	**No meal restrictions**
Emtricitabine	**No meal restrictions**
Stavudine (d4T) – *being phased out as a first- line drug in Uganda*	**No meal restrictions**
Didanosine (ddI-EC)	**Take on an empty stomach (1 h before, or 2 h after food)**
Tenofovir (TDF)	**No meal restrictions**
Efavirenz (EFV)	**Take at bedtime without food**
Nevirapine (NVP)	**No meal restrictions**
Lopinavir/ritonavir (Aluvia® tablets)	**No meal restrictions**
Triomune® (D4T/3TC/NVP) – *being phased out as a first- line drug in Uganda*	**No meal restrictions**
Atripla® (TDF/FTC/EFV)	**Take at bedtime without food**

stream. Protease inhibitors (PIs) often require the patient to take a meal before drug intake. In the absence of food, the amount of PI getting to the bloodstream can be unpredictable. In order to increase drug levels in blood and reduce the effect of food on absorption, PIs are often combined with low-dose ritonavir which prevents the metabolism of other PIs by inhibiting the cytochrome P450 system of the liver. Kaletra® (lopinavir combined with low-dose ritonavir) capsules have been used the treatment of patients failing treatment with first-line drugs in many African countries. However, these capsules required refrigeration and had to be taken with food in order to ensure adequate blood concentrations. Recently, a new tablet formulation of lopinavir/ritonavir called Aluvia® has replaced Kaletra® capsules and is now widely available. In healthy volunteers taking these new tablets, the amount of drug getting to the bloodstream was found to be adequate even when drugs were taken without a meal [1]. It is therefore important that health workers advise patients to continue taking their drugs as prescribed, even if they miss a meal.

For most nucleoside reverse transcriptase inhibitors, patients can take their medicines with or without food. The main exception to this is didanosine which is best absorbed on an empty stomach. The non-nucleoside reverse transciptase inhibitor, efavirenz, is also recommended to be taken on an empty stomach because food enhances drug absorption and therefore the known side effects of the drug such as dizziness and vivid dreams are more likely to occur with higher (but unnecessary) concentrations of the drug in the blood when taken with food (fatty meal) [2]. Nevirapine on the other hand, can be taken with or without food. Table 1 summarizes food advice for commonly used antiretrovirals.

It is important to note that most of the information on food effects was obtained from pharmacokinetic studies carried out in HIV negative people eating a western-style diet. Studies to assess the impact of local diets on antiretroviral drugs are required. However, based on information that is currently available, health workers should provide drug dosing and adherence information to support patients receiving HIV treatment based on studies of food effects from these pre-licensing and post-licensing studies.

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Maize is commonly used and fortified with

"Burnout": A real threat to staff

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Any one who works in a health- care institution knows about "burnout". Staggering work loads and endless hassles are the "name of the game". Many frustrations large and small, can affect staff morale and mental health. If ignored, burn out can take a severe toll.

Burnout is used to describe a syndrome that goes beyond physical fatigue from overwork. Stress and emotional exhaustion are part of it, but the hallmark of burnout is a developing sense of detachment that goes on in response to the overload. Burnout is also defined as a loss of enthusiasm for doing the job at hand.

Job burnout is a consequence of the perceived disparity between the demands of the job and the resources available (both material and emotional) that an employee has before him or her. When the demands in the workplace are unusually high, it becomes increasingly impossible to cope with the stress associated with poor working conditions.
Job burnout is both an occupational hazard and a phenomenon induced by distress. It is characterized by some degree of physical and emotional exhaustion, socially dysfunctional behavior-particularly detachment and insulation from fellow workmates, psychological impairment-especially strong, negative feeling towards self and organizational inefficiency from decreased output and morale.

While having too much to do can cause stress, it does not necessarily cause burnout. More often burnout happens when people feel out of control of the situation at hand. When employees are working in a chaotic environment where it's not clear who is in control, they can burnout. Other critical factors that contribute to burnout are lack of recognition and reward, lack of community and support in the workplace, or a perceived absence of fairness. The biggest contributing factor in burnout, however, is a mismatch in values between the institution and self. When there are value problems or conflicts, you see greater numbers of employees with burnout.

In healthcare institutions like IDI, burnout occurs when the rewards of patient care are dwarfed by workload and absence of job satisfaction. This phenomenon is what is referred to as "second round" burnout. The first round occurred in the beginning of the HIV/AIDS epidemic when for the first decade of the pandemic, people were drawn to HIV care to try and make a difference. Initially there was high excitement and energy for being involved.; there was a cause. But after some time, this enthusiasm and energy declined due to the sheer volume of patients, the lack of funding, and the fact that the majority of patients providers had cared for and become close to, ultimately died.

Burnout is a condition deeply feared by many successful people and is a real threat to many health care workers in challenging and stressful jobs; it can quickly cause the end of otherwise promising careers in the healthcare profession.

Improvements in staff morale and a reduced likelihood of staff burnout are associated with receiving personal recognition, career promotion and skill development opportunities, sufficient funding and personnel, a fair distribution of work, and effective training and orientation of new staff.

IDI Health care wokers excersising

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