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FACULTY OF MEDICINE
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CROI 2010 CONFERENCE COVERAGE

HIV AND TUBERCULOSIS CO-INFECTION

Dr Mohammed Lamorde, Clinical Pharmacology Research Fellow, Infectious Diseases Institute

In Africa, tuberculosis (TB) is a major cause of death among HIV-infected patients. New strategies are urgently needed for TB prevention, diagnosis and treatment in order to improve patient outcomes. At the 17th Conference of Retroviruses and Opportunistic Infections (CROI) in San Francisco in February 2010, several interesting studies were presented on these issues. This article summarizes some of the important. Findings presented at the meeting

INSIDE stories

PREVENTION

Antiretroviral therapy for prevention of TB?

Starting antiretroviral therapy at higher CD4 counts has resulted in marked reductions in opportunistic infections in western countries. In Uganda, the impact of antiretroviral therapy commencement at higher CD4 counts on TB incidence was investigated in a retrospective, longitudinal study comparing the incidence rates of TB in patients starting antiretroviral therapy in 2005 (when antiretroviral treatment was generally initiated at CD4 <50/ul) with rates in 2007 (when treatment was commonly initiated at CD4 < 250 ul).[i] In 2005, patients generally presented with very advanced disease and CD counts at initiation were generally lower than 50/ul. In contrast in 2007, patients generally had higher CD4 counts at initiation (but below 250/ul).

This study found a 43% reduction in the risk of developing TB in 2007 compared to 2005 and a 39% reduction in the risk of death for the same periods. These findings suggest that commencing antiretroviral therapy at higher CD4 counts protects from the development of TB and from death. While these data are observational in nature, they are consistent with findings in other settings. This study highlights the need to strengthen efforts to initiate antiretroviral therapy before severe deterioration of the immune system occurs.

Drugs for TB prevention in HIV-infected patients:

Ilsoniazid (INH) prophylaxis is effective for prevention of TB among HIV-infected persons. However, the ideal duration of preventive therapy for TB for HIV-infected persons in TB-endemic countries is not known. In a landmark randomized controlled trial in India, researchers compared the efficacy of a 6-month regimen containing INH and ethambutol (EH) with a 36-month regimen containing INH alone for TB prophylaxis among 683 HIV infected patients.[ii] In that study, incident TB was similar in both arms (EH arm - 2.4 per 100 patient-years [95%CI 1.4 to 3.5] and INH arm - 1.6 per 100 patient-years [95% CI 0.7 to 2.4]). Mortality and proportions of patients on antiretroviral therapy were also similar in both arms. Adverse events requiring treatment termination were rare.

This study demonstrated that the shorter course regimen was as effective as longer INH prophylaxis courses. This is an important finding for TB control programs in resource-constrained settings where shorter treatment courses may result in significant cost-savings. However, the study also raises concerns about the risk of acquisition of drug resistance to first-line antiTB agents when breakthrough infections occur. Of 44 patients who developed TB in the study, eight had INH resistance and two had multidrug resistant TB. Therefore, the researchers recommend that facilities for drug sensitivity testing should be made available when antiTB agents are used for TB prevention.

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Please note: The clinical research findings in this article represent new medical information. These findings may or may not correspond with the current treatment policy in your area. For further information on these abstracts and how they may affect your practice please call ATIC on +256-414-307228/245 or send an email to queries@atic.idi.co.ug.

EDITORIAL

Welcome to another edition of the ATIC newsletter.

One of the issues we ll deal with in this edition is how to manage patients who get adverse drug reactions
Drugs are potent chemicals that often have effects in the body beyond the desired action. These effects may range from mild and expected side effects to dramatic and life threatening anaphylaxis. Drug reactions are more common in people living with HIV than in the general population, and they increase with increasing immunodeficiency.

We are glad to bring you an article of how to carry out desensitisation on patients who have reacted to cotrimoxazole. This drug is given to people living with HIV in order to reduce opportunistic infections that may affect them because of the low immunity. The most common side effects of co-trimoxazole are fever, skin rash and itching. These symptoms may not appear for as many as 10 days after starting the medication. The common ADRs include hematological and cutaneous (skin) manifestations.

The treatment of cutaneous drug eruptions essentially rests on accurate history, a thorough physical examination, discontinuation of the offending drug, and supportive care.

A thorough knowledge of presentation, identification and management of adverse drug reactions is important since they are a significant cause of morbidity and mortality.

Allen Mukhwana
Editor

CROI 2010 CONFERENCE COVERAGE

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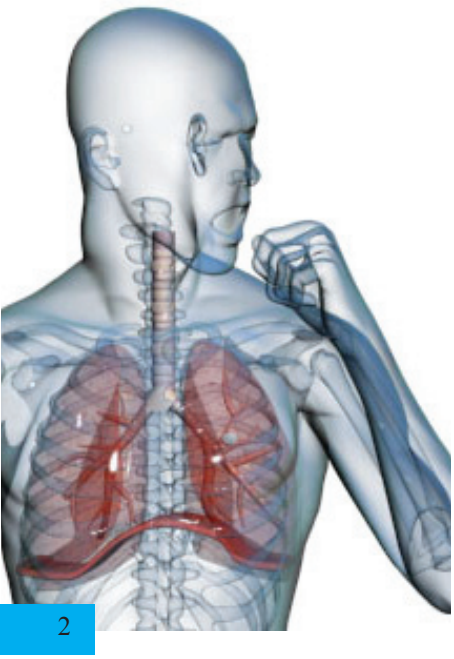

DIAGNOSTICS

Improving diagnostic tools but relevance to Africa still uncertain

In many resource-limited settings, diagnosis for TB depends on sputum examinations, chest radiographs and Mmantoux tests. However, with these tests, TB diagnosis is sometimes missed in co-infected patients. Therefore, new tests with greater sensitivity are required. A recently introduced ELISA blood test for TB (QuantiFERON-TB Gold®) quantifies interferon gamma released from lymphocytes of patients with TB. Unfortunately, this test is less sensitive when lymphocytes are depleted (eg in HIV patients with low CD4 counts) and this limits its role for TB diagnosis in co-infected patients. At the CROI meeting,it was reported that when the ELISA test was combined with a second blood test measuring a chemokine known as IP-10, the sensitivity of testing increased from 82% to 88% (95%CI 80 to 97%) among co-infected patients. However these new tests may be more expensive than existing tests for TB and high costs can delay uptake of novel diagnostics in developing countries.

TB & HIV CO-TREATMENT

Early initiation of antiretrovirals beneficial in co-infected patients with high CD 4 counts

In Uganda, it is recommended that antiretroviral therapy be deferred until TB treatment is completed in HIV and TB co-infected patients with CD4 counts >350/ul. A Ugandan study investigated the benefit of commencement of antiretroviral therapy in co-infected patients with CD4 counts above this threshold. Patients were randomized to an intervention arm receiving antiretroviral therapy for six months plus antiTB treatment (n=109), and a control group receiving antiTB treatment alone (n=114).[iv] At

12 months no patient in the intervention arm achieved an outcome (CD4 count decline <250, AIDS diagnosis or death) versus 5% of participants in the control arm (p = 0.03). These findings suggest that antiretroviral therapy may improve clinical outcomes among co-infected patients with high CD4 counts. In recently released guidlines, the World Health Organization (see article on WHO 2009 Rapid Advice in this issue) now recommends that co-infected patients should be started on antiretroviral therapy as soon as possible, regardless of CD4 counts.

Drug interaction between nevirapine and rifampicin

Rifampicin induces metabolism of nevirapine leading to lower nevirapine levels in blood. Nevirapine levels in blood were compared when initiated with a lead-in or without a lead-in in co-infected patients who had already been receiving rifampicin-based TB treatment[v]. Nevirapine concentrations were sub-optimal during the first two weeks in the lead-in arm while initiation without a lead-in resulted in satisfactory drug levels. However, by the third week, average concentrations were sub-therapeutic in both study arms. Although initiation of nevirapine based antiretroviral therapy without a lead-in is preferred, more research is needed to determine the appropriate maintenance dose during rifampicin co-administration in Ugandan patients. Until additional pharmacodynamic and clinical outcomes data become available, clinicians should follow their local treatment guidelines (e.g. prescribe efavirenz or other recommended alternatives) for co-infected patients receiving concurrent rifampicin treatment.

CONCLUSION

The management of TB among HIV-infected patients remains a challenge in developing countries. Concerted efforts are needed to translate research results into policy, and ultimately into clinical practice in order to reduce the burden of disease.

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[iv] M Walusimibi, E Charlebois, R Lin et al. Randomized trial of 6-month Punctuated Course of ART in Ugandan HIV+ Adults with Pulmonary TB and CD4 >350. Abstract # 105.

[v] M Lamorde, P Byakika-Kibwika , VO Kayom, et al. Nevirapine plasma concentrations during initiation with 200 mg versus 400 mg daily in HIV/TB co-infected adults on rifampicin. Abstract # 602.

Drug Interaction Alert – Rifabutin interaction with lopinavir/ritonavir

For HIV/TB co-infected patients on second-line treatment with lopinavir/ritonavir (LPV/r), rifabutin is recommended instead of rifampicin because rifampicin dramatically reduces LPV/r levels in blood.

Current guidelines recommend using 150 mg of rifabutin thrice weekly during co-treatment with LPV/r.

However, two recent studies indicate that the recommended dose results in low rifabutin levels in blood. This may place patients at greater risk of failing their tuberculosis treatment.

In the next edition of the ATIC newsletter, we will provide details of this interaction and discuss the implications of this finding on the clinical management of co-infected patients on second line treatment.

COULD AN NRTI-ONLY REGIMEN BE AN ALTERNATIVE FIRST LINE REGIMEN FOR THE TREATEMENT OF HIV IN SUBSAHARAN AFRICA?

By Stella Zawedde-Muyanja
Medical Officer- ATIC

Since highly active antiretroviral therapy (HAART) became the standard for HIV care all over the world, WHO recommendations for 1st line regimens have involved a combination of drugs from at least 2 classes of ARVs, mostly from the nucleoside reverse transcriptase inhibitors (NRTIs) and the non nucleoside reverse transcriptase Inhibitors (NNRTIs).

Although the first generation NNRTIs (nevirapine and efavirenz) show good antiviral efficacy when used as part of the 1st line, they have a few limitations including:

- Significant drug-drug interactions e.g. nevirapine and rifampicin,
- Adverse drug reactions e.g. nevirapine and hepatotoxicity
- Contraindications for special populations e.g. efavirenz during the 1st trimester of pregnancy, or in patients with a history of central nervous system disorders and
- Cross-resistance between nevirapine and efavirenz

As a result, alternative regimens that have less drug-drug interactions, less severe side effects and spare more classes of drugs for future use, remain attractive to clinicians in HIV clinical care.
To this effect, a number of NRTI-only regimens have been explored in clinical trials. Earlier trials that were conducted in developed countries yielded mixed results.

In the USA, a study by Roy M Gulick et al showed that an NRTI-only regimen consisting of ABC, 3TC and TDF was inferior to a regimen consisting of TDF, 3TC and EFV. A higher percentage of patients experienced virologic failure in the NRTI-only group (23% vs. 11%.). These patients also had a shorter time to virologic failure.

However, in another study where AZT was part of the NRTI-only regimen, the results were different. In this study by Masquelier B et al, an NRTI-only regimen containing AZT/3TC/TDF demonstrated good antiviral efficacy in antiretroviral naïve patients.
Another study by Khanlou H et al showed that an NRTI-only regimen containing ABC/AZT/3TC plus TDF created an efficient treatment option especially in moderately pretreated individuals. In that study, the common resistance pattern observed were Thymidine Analogue Mutations (TAMs) while AZT protected against the selection for the K65R mutation.

In the DART trial which was a randomized non-inferiority trial that compared 2 monitoring strategies for the delivery of antiretroviral therapy in Africa, about 75%of the patients were on an NRTI-only regimen consisting of TDF+3TC+AZT, another 9% were on an NRTI regimen consisting of AZT+3TC+ABC and the rest were on an NRTI/NNRTI regimen.
By the end of 5 years of follow up, only 20% of all the patients had been switched to a second line regimen.
Substudies done as part of this trial showed

- a trend towards a lower rate of adverse drug reactions in the NRTI-only arm compared to an NNRTI plus 2NRTI arm
- Good early virological response with more than 70% of the patients on CBV+TDF achieving viral loads below 400 copies by week 24.

CONCLUSIONS

In low resource settings, treatment options are limited. Therefore, the use of NRTI-only regimens as alternative first line regimen for treating HIV and AIDS needs to be explored further.
Because of their efficacy, toxicity and drug interaction profiles; these regimens may be useful first-line alternatives for special populations e.g. pregnant women and people with TB /HIV co-infection.

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Paula Munderi and the DART Trial Team

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Lancet 2010:375:123-131

WHO 2009 RAPID ADVICE

Dr. Ceppie Merry, HIV Physician and pharmacologist
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One of the ways that the World Health Organization (WHO) tries to help the roll out of antiretroviral drugs (ARVs) in low and middle income countries is through the WHO HIV Treatment Guidelines for Adults and Adolescents. These guidelines were first introduced in 2002 which is when many resource poor countries accessed free ARVs. The WHO reviews all available data and evaluates the quality of the data and then makes recommendations based on the best available evidence at that time. The guidelines have been revised since then and updated with the latest information with the most recent revision in late 2009.The guidelines are written primarily for policy makers and take a public health approach. Individual countries can then review the guidelines and make changes to tailor the guidelines for the local context. This saves time for policy makers in individual countries as they have a very useful starting point as they develop their national guidelines.

The key changes in the most recent 2009 WHO guidelines are listed below but these are just suggestions and may not be incorporated into national guidelines in your country.

When To Start ARV Therapy

All HIV infected adults, adolescents and pregnant women with a CD4 count of less than or equal to 350 cells/mm3 should start on ARV regardless of their clinical status. Patients with WHO stage 3 or 4 disease should start of ARV regardless of the CD4 cell count.

What To Use In First Line ARV Therapy

First line therapy should include two NTRI + one NNRTI. One of the NRTI should be AZT or tenofovir where possible rather than d4T because of the long term toxicity of d4T.

What To Use In Second Line ARV Therapy

Second line therapy should include a ritonavir boosted PI plus two NRTIs. The recommended PIs are ritnoavir boosted atazanavir or rinonavir boosted lopinavir. One of the NRTI should be AZT or tenofovir whichever was not used in the first line regimen.

What To Do For Third Line Therapy

National programs should develop policies for third line therapy and ideally should include new drugs such as integrase inhibitors or second generation PIs or NNRTIs. In the meantime patients who are tolerating but failing a second line regimen with no new ARV options should stay on the second line ARVs.

How To Monitor Patients

All patients should have access to CD4 cell count testing. Viral load testing should be used to confirm treatment failure. Symptom directed or targeted use of lab tests should be used to monitor drug toxicity.

What To Do With HIV/TB Co-Infection

Patients with HIV/TB coinfection should be started on ARV as soon as possible after starting TB treatment regardless of the CD4 count.

What To Do With HBV/HIV Co-Infection

Patients with HIV/Hepatitis B coinfection who need treatment for the HBV should start ARV as soon as possible regardless of the CD4 count and first and second line therapy should include an ARV such as 3TC or FTC which has activity against HBV.

As clinicians it is important for us to be aware of these new guidelines and to begin to consider the logistics of incorporating these new guidelines into our local practice if they were adopted as national policy. Realistically incorporation of any of these guidelines into national policies will be influenced by factors other than just the quality of the supporting data such as drug availability and projected funding support which is a challenge in the current economic and political environment.

For more information please see http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf.

Update on the management of IRIS

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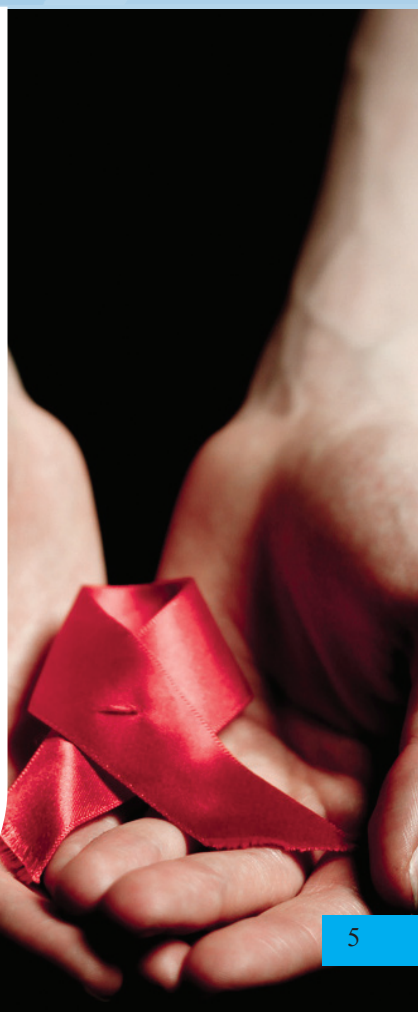
Immune Restoration Inflammatory Syndrome (IRIS) is a relatively common complication in HIV-infected patients when starting highly active antiretroviral therapy (HAART). During immune reconstitution the response against infective or non-infective antigens can lead to an inflammatory reaction in tissues which manifests as IRIS (1).

The most common forms of IRIS are presented in association with tuberculosis (TB), Cryptococcosis, progressive multifocal leukoencephalopathy, Karposi's sarcoma, mycobacterial avium complex, cytomegalovirus, various dermatologic conditions and hepatitis B and C infection (1).

There are two types of IRIS: the paradoxical type and the unmasking type. Paradoxical-IRIS is defined as the clinical deterioration of an infection, which had been under successful treatment before the initiation of HAART. Unmasking-IRIS is described as the appearance of undiagnosed infections early after HAART initiation (2).

Low CD4+ T-cell count, disseminated opportunistic infection (OI) while starting HAART and a short interval between the start of the OI treatment and the initiation of HAART are commonly accepted risk factor for IRIS (3;4).

There is no specific laboratory test to diagnose or predict IRIS. Currently the diagnosis of IRIS is mainly clinical. Other causes of clinical deterioration such as antimicrobial drug resistance of the underlying OI, poor adherence to treatment, other concomitant infections or malignancies, and drug toxicity have to be excluded.



Therapy:
Most cases of IRIS are self-limiting. When IRIS symptoms are mild it is sufficient to initiate or optimise treatment for the underlying infection. Common symptoms like pain and fever may respond to simple analgesia and antipyretic drugs.

Depending on the clinical manifestation of IRIS, therapeutic procedures will be necessary. Suppuration of lymph nodes and cold abscesses, often seen in TB-IRIS and crypto-IRIS, might need repeated aspirations (1).

In case of neurological involvement and a spinal tap opening pressure more than 25 cm H2O, daily lumbar punctures should be performed. Up to 20 to 30 ml of cerebrospinal fluid can be removed to reduce the opening pressure to less than 20 cm H2O. This should be continued until the opening pressure has been normal for several days (1).

The interruption of HAART therapy should only be considered when IRIS is life threatening e.g. in patients who present with neurological manifestations of IRIS and decreased consciousness. In patients with sever hepatitis HAART should also be stopped, since it is hard to distinguish viral hepatitis IRIS from drug-induced liver injury. (1)

In a recent double-blind placebo-controlled randomised clinical trial done in South-Africa, corticosteroids have shown to reduce the duration of hospitalisation and numbers of procedures in non life-threatening TB-IRIS (5). Patients fitting the case definition of TB-IRIS (6) received either placebo or prednisone at 1.5 mg/kg/day (2 weeks) then 0.75 mg/kg/day (2 weeks). No excess of adverse events were seen in the prednisone arm during the 12 weeks follow-up.
The American Thoracic Society guidelines suggest that severe TB-IRIS should be treated with prednisolone or methylprednisolone at a starting dose of 1 to 2 mg/kg/day, which can be gradually reduced after 1 to 2 weeks. Lesho (7) suggests the use of prednisolone 10 to 40 mg/day for moderate, and 1 to 2 mg/kg/day for severe IRIS associated with mycobacteria, fungi and certain viruses. Most patients will respond to a few weeks of treatment. However, some will experience a symptom relapse when reducing dosage or discontinuing corticosteroid treatment.
For other types of severe IRIS, clinical trials have not been done so far, but the use of corticosteroids should definitely be considered. However, risk and benefits of corticosteroid therapy should be evaluated as patients become more susceptible to infections and to reactivation of latent infections. In case of viral hepatitis-associated IRIS corticosteroids should not be given (1).

The benefits of other anti-inflammatory and immunomodulatory treatment options such as NSAID's, pentoxifylline, leukotriene antagonist (montelukast), thalidomide, tumor necrosis factor-α inhibitors, and hydroxychloroquine are currently only affirmed by limited anecdotal reports (1).

Take home message:
Two main types of presentation: paradoxical IRIS and unmasking IRIS.
Risk factors: low CD4+ T-cell count, disseminated and extrapulmonary TB while starting HAART, and a short interval between the start of TB treatment and the initiation of HAART.

Diagnosis: no specific laboratory test; clinical diagnosis and exclusion of other causes of clinical deterioration (antimicrobial drug resistance of the underlying opportunistic infection, poor adherence to treatment, alterative infections or malignancy, and drug toxicity).

Management:
Mild symptoms: continuance of HAART and symptomatic treatment: pain relief, abscess drainage, lumbar punctures if high intracranial pressure
Severe symptoms: corticosteroid therapy, interruption of HAART to be considered
Severe viral hepatitis: stop HAART, no corticosteroids

Other therapy: Insufficient data to recommend NSAID's, pentoxifylline, leukotriene antagonist (montelukast), thalidomide, tumor necrosis factor - inhibitors, and hydroxychloroquine.

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MANAGEMENT OF HIV AND SYPHILLIS CO-INFECTION

Jane O'Halloran, MRCPI , University College Dublin

Syphilis, sometimes referred to as the 'great imitator' because of its diverse range of clinical presentations, has been described with certainty as far back as the 15th centaury. The disease is caused by the spirochete Treponema pallidum which is predominantly sexually transmitted however alternative modes of transmission do exist. For example infection at the time of delivery in children born to mothers with lesions in the birth canal, as well as congenital syphilis which results from in utero transmission. Syphilis in pregnancy has been extensively described in a previous ATIC article ***(Vol 5 issue 3 page 4, June 2009)***. Approximately 3% of Ugandan adults age 15- 49 are thought to be infected with syphilis with higher incidence in the older population, while 6% of the same age group are HIV sero positive.

Primary syphilis involves the development of a chancre or ulceration that is usually painless. These are most commonly located in the genital region however can be extra genital. Chancres usually occur approximately three weeks after exposure and frequently go unnoticed. Secondary syphilis may develop several weeks after the resolution of the primary lesion and manifests as the characteristic rash involving the palms of the hand and soles of the feet along with fever, headache, lymphadenopathy and general malaise.

The final stage in the diseases process was previously termed tertiary syphilis and is now referred to as latent syphilis. This can be subdivided into early latent- up to one year post infection- and late latent syphilis. Patients with late syphilis can go on to develop central nervous and cardiovascular system involvement as well as gummatous syphilis if not treated.

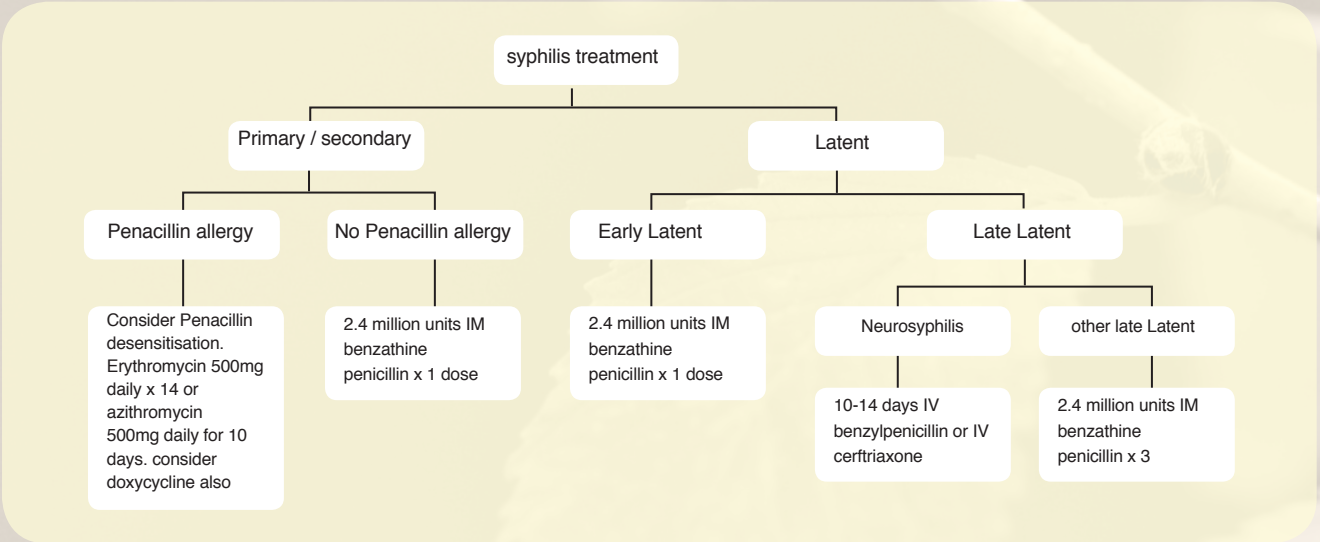
Co-infection with syphilis can impact on HIV infection in several ways. Like other diseases that cause genital ulceration the presence of chancres and condylomata latas, seen in secondary syphilis, can increase the rate of HIV transmission.

By and large the clinical manifestations of syphilis in HIV sero positive patient are similar. Some differences have been noted in the past including patients presenting with multiple chancres which occurs more frequently in HIV infected patients along with an overlap between the presence of a chancre and the symptoms and signs of secondary syphilis. Rapid progression to late syphilis has also been observed as well as increased rates of neurosyphilis which does not exclusively occur in the late latent stage in either sero negative or sero positive patients.

Syphilis has been shown to have a deleterious effect on the immune system of HIV sero positive patients with studies demonstrating a decreased CD4 count in such patients with subsequent improvement once syphilis has been treated. For this reason testing for syphilis in asymptomatic HIV infected patients may be even more beneficial.

The optimal diagnostic test for syphilis, irrespective of the patients sero status, is direct visualization of the spirochete on dark ground microscopy, however this is not usually possible as patients must have a chancre or condylomata lata at the time of presentation and it also requires significant laboratory expertise. In general both the non treponemal (Venereal Disease Reference Laboratory , the Rapid Plasma Reagin RPR) and the treponemal (Treponema pallidum particle agglutination assay TPPA, Treponema pallidum enzyme immunoassay) tests can be interpreted accurately in HIV sero positive patients. It is strongly recommended that patients with co-infection who have late latent syphilis have a lumbar puncture regardless of neurological symptoms however this may be difficult to achieve particularly in the out patient setting where the majority of these patients are managed.

Little data exists surrounding the treatment of HIV sero positive patients outside of the use of penicillins which should remain first choice where possible. Below is a treatment algorithm in keeping with local guidelines.



For further queries on the management of syphilis in HIV sero positive or sero negative patients contact the ATIC team.

DESENSITIZATION AFTER CO-TRIMOXAZOLE ADVERSE DRUG REACTIONS

Barbara Namirembe, BPharm, MPS,
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Co-trimoxazole also known as Septrin or Sulfamethoxazole-Trimethoprim is a broad spectrum antimicrobial agent that targets a variety of aerobic Gram-positive and Gram-negative organisms and protozoa.

The drug is widely available in both syrup and solid formulations at low cost in most places, including resource-limited settings.

Co-trimoxazole plays a role in:

The prevention of bacterial infections (Pneumococcus, non-typhoidal Salmonella (NTS)), diarrheal disease (Isospora, Cyclospora).

- Primary or secondary prophylaxis for prevention of Pneumocystis jiroveci pneumonia (PCP) (formerly Pneumocystis carinii pneumonia) and toxoplasmosis
- Effective in preventing malaria

The Uganda Ministry of Health Guidelines for cotrimoxazole use 2009:

Current guidelines recommend that:

- All HIV positive adults irrespective of their CD4 count start Co-trimoxazole prophylaxis.
- In exposed infants and children, Co-trimoxazole should be started at 4-6 weeks after birth or at the first encounter with the Health Care System and continued till HIV infection is ruled out.
- In children who are breast-fed by an HIV infected mother,Co-trimoxazole should be continued till HIV infection can be excluded at least 12 weeks after complete cessation of breastfeeding.
- Co-trimoxazole should be avoided in the first trimester of pregnancy but should be continued there after.
- Breastfeeding HIV infected women should be on Co-trimoxazole prophylaxis.
- Sulphadoxine/pyrimethamine–based intermittent presumptive therapy for malaria, is not necessary in pregnant women already on Co-trimoxazole prophylaxis.
- The doses for Co-trimoxazole prophylaxis in the different age groups are shown in Table 1

Adverse reactions (ADRs) to co-trimoxazole

Common ADRs include blood and skin related manifestations.

These ADRs occur with different severity among individuals on Co-trimoxazole prophylaxis ranging from mild (grade1) to very severe (grade 4).

The classical sulfonamide hypersensitivity reaction manifests within 7 to 14 days after initiation of therapy. Common potential adverse reactions include:

- Skin-rash:which can manifest as a mild moderate or severe rash
- Liver toxicity characterized by jaundice
- Neutropenia: A situation where the number of neutrophils in the blood is too low. Neutrophils are very important in defending the body against bacterial infections, and therefore, a patient with too few neutrophils is more susceptible to bacterial infections
- Anemia: Commonly defined as Hb<13.5g/dl for men and Hb>12.0g/dl for women. These definitions may vary slightly depending on the source and the laboratory reference

Table 1: Doses, as given once a day

Age	Syrup: 5 mls containing 200 mg/40 mg	Single strength Tablet: 400mg/80mg	Double strength Tablet: 800mg/160 mg
6 months	2.5 mls	¼ tab	-
6 months - 5years	5 mls	½	-
6–14 years	10 mls	1	½ tab
14 years and Above	-	2	1

Below is the toxicity grading scale for ADR skin manifestations in adults and adolescents as adapted from: WHO Expert Consultation On Co-trimoxazole Prophylaxis In Hiv Infection (May 2005)

Toxicity Grade	Clinical presentation	Recommendation
Grade 1	Erythema: abnormal redness of the skin	Continue co-trimoxazole with repeated observation and follow-up. Treatment: antihistamines
Grade 2	Diffuse maculopapular rash: sand-papery rash and peeling off of dry skin it usually occurs within the first 1-3 days after administration of the drug, usually not accompanied by fever, and resolve spontaneously on withdrawal of the drug.	Continue co-trimoxazole with repeated observation and follow-up. Treatment: antihistamines
Grade 3	Vesiculation: Blistering rash	Discontinue Co-trimoxazole until symptoms completely resolve (usually two weeks). Treatment: desensitization
Grade 4	Exfoliative dermatitis: scaling and shedding of the skin usually accompanied by redness Erythema multiform: Begins as blisters and progresses to ulcers. Stevens-Johnson syndrome: A more advanced form of erythema multiform that can be severe and fatal these reactions typically occur 7 to 14 days after initiation of a primary course of therapy.	Co-trimoxazole should be permanently discontinued

Co-trimoxazole Desensitization

Desensitization is a way of overcoming hypersensitivity to a drug in a patient by gradual re-exposure to the drug. The hypersensitivity is usually due to sulphonamide component in the Co-trimoxazole which is lacking in dapsone. The procedure depends on constant presence of drug in the serum and so must not be interrupted; desensitization is immediately followed by full therapeutic doses.

This desensitization protocol was adapted from:
WHO Expert Consultation On Co-trimoxazole Prophylaxis In HIV Infection (Geneva, 10-12 May 2005)

Day 1: 2 mL equivalent to 80 mg SMX + 16 mg TMP
Day 2: 4 mL equivalent 160 mg SMX + 32 mg TMP
Day 3: 6 mL equivalent 240 mg SMX + 48 mg TMP
Day 4: 8 mL equivalent 320 mg SMX + 64 mg TMP
Day 5: 1 single-strength tab (400 mg SMX + 80 mg TMP)
Day 6: Two single-strength tablets or one double-strength tablet (800 mg SMZ + 160 mg TMP)

PS:

- Patients start an antihistamine regimen of choice, for instance: chlopheniramine, cetrizine one day prior to starting the regimen and continue daily until completing the dose escalation
- After the first day, the dose of Co-trimoxazole is subsequently advanced a step each day.
- If a grade 3 reaction reoccurs, the desensitization regimen is terminated.
- If a patient experiences a grade 1 or 2 reaction, the patient may remain on the same step for an additional day. If the reaction subsides, the patient may advance to the next step; if the reaction worsens, the patient should not advance and the desensitization regimen is terminated.

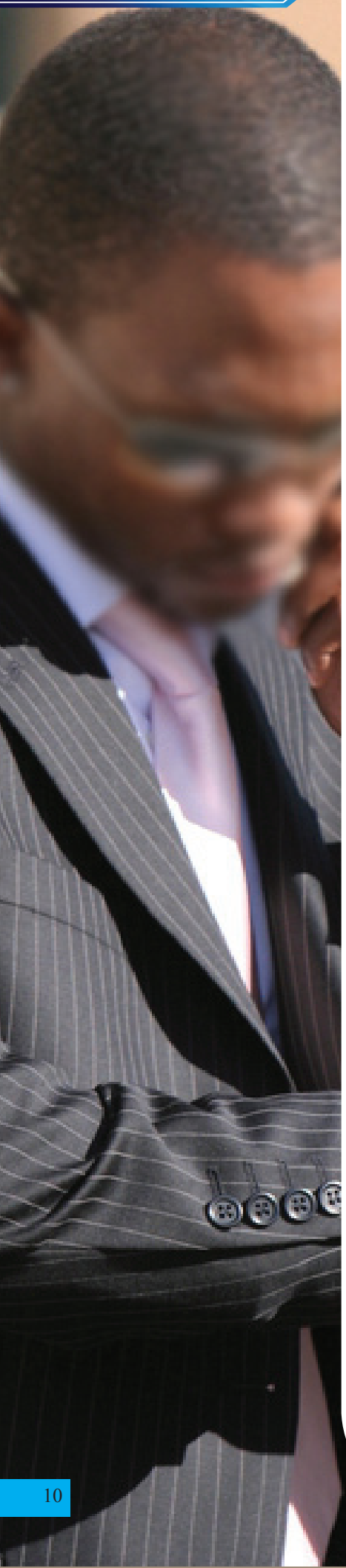
Patients could reach the full prophylactic dose of Co-trimoxazole in 5-9 days depending on how long each escalation takes

Alternatives to Co-trimoxazole

There is no single drug currently known to provide a similar range of protection against morbidity or mortality at such an affordable cost as Co-trimoxazole.
If desensitization is not successful, the only alternative currently recommended by MoH Uganda is dapsone
Dapsone: should be given at a dose of 100 mg per day for adults and 2mg/kg in children as an alternative prophylactic agent against Pneumocystis Jiroveci pneumonia.
When given with pyrimethamine, it also offers protection against toxoplasmosis.
However, it has two major short comings:

- Less effective in the prevention of PCP
- Lacks the broad antibacterial activity of Co-trimoxazole

No other alternative recommendation can be made in resource-limited settings like ours
It is therefore desirable to attempt desensitization to co-trimoxazole, if feasible in the clinical setting, among individuals with a previous non-severe reaction, before substituting with dapsone



HOW TO MANAGE
WORK RELATED STRESS

By Ismail Simwogerere
Career Guidance & Counseling Coordinator
Infectious Disease Institute

Work stress is the harmful physical and emotional responses that occur when the requirements of a job do not match the capabilities, resources or needs of the worker. Everyone can be stressed at work, not just if you are not fully able or trained to do a job, but also if the nature of the job is such that it does not meet your emotional or psychological needs.

Stress can be caused among other factors by; Heavy workload, Having little control or, influence in decisions, Tension or conflict with other employees, Poor supervision or, management, Lack of belief in the objectives of the organisation, Job insecurity or lack of opportunity to develop, Lack of interest or fulfillment in the nature of the work, and Unpleasant or dangerous work environments. Using knowledge of industrial psychology please allow me draw your attention to tips of stress management below;

1. **Get along with people.** Low-stress employees invariably have smooth working relationships with practically everyone. To achieve this, find things you have in common with others and act friendly with absolutely everybody from the Chief Executive down to those who clean the office.
2. **Always be diplomatic and tactful.** Avoid acting angrily or impatiently even when you re frustrated. Expressing anger in the workplace usually results in direct or indirect retaliation, which surely increases stress.
3. **Learn what is expected of you.** Find out your boss s expectations of you and the expectations of your boss s boss. These people will make or break your career and greatly affect your stress levels. By meeting their expectations you simultaneously can get ahead plus decrease a possible cause of stress.
4. **Be a team player with your boss and co-workers.** Team players are appreciative and receive much less grief than employees who act rebelliously or act like loners.
5. **Give three compliments a day at work.** People love receiving compliments and will try to make your life easier since you made them feel good with a compliment. They ll remember the compliment when you ask for a favor.
6. **Set goals for yourself, personal and work-related.** High-stress people rarely do things to accomplish their goals. Low-stress people, on the other hand, spend more than half their time doing things that help them achieve their short-term or long-term goals. Typically people spend less than five percent of their time doing activities that will achieve their goals, and feel more frustrated when they don t accomplish their goals.
7. **Prepare a daily to-do list.** Every day before leaving work, write a list of what you need to do the next work day, That little bit of organization can help prevent you from being overwhelmed by tasks that need to be done.
8. **Keep a neat desk or work space.** We re not talking obsessive neatness here. However it is important to clear a work station from mess and to remember to have work space on your table with proper storage of pending work.
9. **Exercise at least a little every day.** Even a 10-minute walk will help. People bottle up emotional tension or stress in their muscles. By exercising a little, you can release emotional and physical stress and be more clearheaded when deciding how to tackle a stressful situation.
10. **Consider changing jobs.** If the above nine tips don t help you, then it may be time to find a new job. Like the saying; “If you can’t stand the heat, get out of the kitchen.”

Work stress can increase your risk for heart disease, psychological disorders and other health problems. Early warning sign of potential health risks can include headaches, disturbed sleep and difficulty in concentrating. If you are experiencing any of these signs to a significant degree you should consider consulting your doctor.

ASK ATIC:

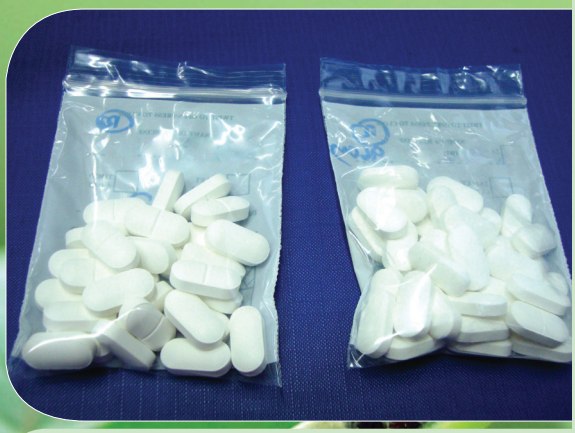
Dr. Stella Zawedde-Muyanja
Medical Officer- ATIC

Question 1	Answer
I have a client who is eligible for ART at CD4 cell count 231, However, He is jaundiced. His liver US Scan shows fatty fibrosis. His Liver Function Tests show elevated LFTs ALT : 81U/L (N : up to 40): Total Bilirubin is 31.8umol/l (N <17umol/l) Direct Bilirubin: 16.8umol/l (N: 0-17umol/l His RFTs are normal. His HepBsAg is negative 1) What ARV regimen should I start him on?	When managing this patient, it would be advisable to start him on TDF +3TC + EFV. Because this patient already has fatty fibrosis in the liver, we should stay clear of drugs that are likely to cause hepatic steatosis e. g d4T, ddI and AZT. TDF and 3TC would therefore make the best NRTI backbone for this patient. TDF and 3TC are both primarily excreted unchanged by the kidney and are therefore suitable in a patient with liver disease. The NNRTI of choice would be EFV. EFV is metabolized by the liver but can be used in moderate liver disease i.e. ALT elevated between 2-5 times the normal.
We should always keep in mind as we deal with patients like this that the main aim of therapy in patients with HIV and Liver dysfunction is to control the HIV infection while preventing progression of liver disease to cirrhosis or cancer	

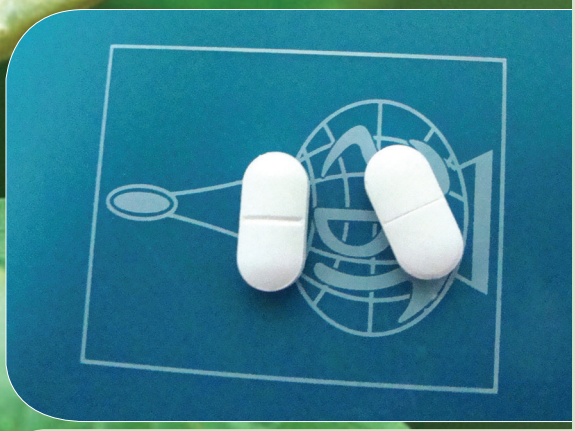
Question 2	Answer
1. What is the most appropriate first line regimen for an HIV infected patient with decompensated Liver Cirrhosis (ascites) and mildly deranged liver enzymes? 2. How should this patient be monitored	To properly manage this patient, it would be best to find out the primary cause of his liver cirrhosis. If it is secondary to infection e.g. Hep B infection which is common in HIV positive patients, then the best combination would be Truvada + EFV or TDF+3TC+EFV. This is because both these combinations contain at least 2 drugs that are active against both HepB and HIV .i.e Tenofovir + Emtricitabine and Tenofovir + Lamivudine If cirrhosis is secondary to another cause e.g. Alcoholism: It would be prudent to first try to solve the alcoholism with help of a psychiatrist. When the patient is stable and able to adhere to his ART, we should then start him on TDF +3TC+ EFV. Tenofovir and 3TC are excreted largely unchanged by the kidney and so are safe in liver disease. EFV is metabolized by the liver but can still be used in mild to moderate liver disease. Zidovudine not a good choice, it is metabolized and excreted by the liver. It can be used in mild hepatic disease but is best avoided in moderate and severe hepatic disease because the dose cannot be adjusted. Monitoring of patients with liver dysfunction should be done at baseline and every 6 months thereafter. The following tests should be done; CBC, Aminotransferases, Bilirubin. Se Albumin and Prothrombin Time may also be monitored if resources allow. Therapy should be modified according to results

HEALTH WORKER ALERT!

Standard one month dispensing of Duovir-N and co-trimoxazole tablets



Two week dispensing of Duovir-N and co-trimoxazole tablets in sachets side by side



Duovir-N and co-trimoxazole tablet side by side

In recent months, due to challenges with drug logistics, some clinics have been unable to provide a full months supply of antiretroviral drugs (ARVs) of refills to their HIV-infected clients. In some clinics, health workers have dispensed two weeks supply instead of a one month supply of ARVs.

Usually, ARVs are dispensed in their original containers; however, the 2 week s doses are usually taken out of their containers and dispensed in sachets. These are the same sachets that many other drugs (including co-trimoxazole) are dispensed.

ATIC has received reports of clients mixing up Duovir-N with co-trimoxazole in some clinics. The white zidovudine, lamivudine plus nevirapine tablet (Duovir-N) is identical to the 960mg cotrimoxazole tablet making it easy for clients to confuse the tablets. It is important to prevent this from happening because Duovir-N should be taken twice daily while co-trimoxazole should be taken once daily. If patients take Duovir-N once daily, it may be inadequate to suppress HIV and patients will be at increased risk of developing resistance to their ARVs.

This is therefore to ask all health workers to help patients avoid this medication error.

Practical steps that can be taken include:

- All pharmacy health workers should intensify patient counseling at the dispensing window and caution them to avoid mixing up the drugs.
- Sachets should be marked clearly with the name of the drug and the number of times a day the drug should be taken NOT just the number of times a day the drug should be taken.
- When drugs are dispensed in sachets, counselors and health workers should check with the patients at each subsequent visit to make sure that they are taking their drugs correctly.