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FACULTY OF MEDICINE
MAKERERE UNIVERSITY

ATIC newsletter

VOLUME : 8 | ISSUE : 2 | JUNE 2011

INFECTIOUS DISEASES INSTITUTE

Quarterly Newsletter of the AIDS Treatment Information Centre, Infectious Diseases Institute, Makerere University, Kampala

Case Report: Skin Reaction to Tenofovir

By Dr. Gyaviira Makanga (Mmed Int.Med) & Dr. Stella Zawedde - Muyanja (MBChB)

A 30 year old female presented to a local HIV Care Centre in Kampala, Uganda for Routine Counselling and Testing for HIV after her husband had tested HIV positive from another centre. She had no major complaints apart from a history of heavy menses, no prior major opportunistic infections and physical exam was unremarkable.

She underwent routine pre and post-test counselling and was found HIV positive on two rapid HIV tests i.e. determine and statpak respectively. She was initiated on cotrimoxazole prophylaxis and ferrous sulphate 200mg three times a day. Her baseline labs were as below;

Test	Result
CD4 cell count	323 cells/μl
Hb	9.2g/dl
Serum Creatinine	1.0mg/dl
AST	29U/l
ALT	27U/l
Urinalysis	Unremarkable

NB: The above are the basic initial laboratory tests done by the clinic, viral load, Hepatitis B and C tests are not routinely done due to cost.

Based on her CD4 cell count (<350), she underwent three pre-anti retroviral therapy (ART) counselling sessions with the counselling team as per the Centre/Current ART guidelines and was initiated on ART 2 months from time of first presentation.

She was started on tenofovir/emtricitabine (TRUVADA®) plus nevirapine 200mg OD for 14 days, with no major adverse effects. Her nevirapine dose was then escalated to 200mg BD, which she tolerated well for the next 2 months with a rise in CD4 to 487 cells/μl after 3 months on ART. The Nevirapine dosing was then escalated to 400mg OD. (once daily dosing of nevirapine has been found to have ARV efficacy similar to twice daily nevirapine and is recommended for treatment simplification)

Three days after the new dose, she reported back to the clinic with a generalised itchy maculo-papular rash involving the oral mucosa as small blisters. All her medications were stopped including cotrimoxazole. She reported no herbal remedies used prior to the rash. No repeat laboratory tests were done. She improved within 2 weeks and was re-started on TRUVADA®/efavirenz. One day after medication, developed another generalised erythematous itchy maculo-papular rash but no mucosal involvement. The ART was stopped, with clearance of the rash within 4 days.

One week later, was re-initiated on TRUVADA® and ALUVIA®. One day after this new medication, developed another generalised itchy macula-papular rash with mucosal involvement, she stopped her medication and reported back to the clinic.

Further consultation with colleagues at the AIDS Treatment Information Centre (ATIC) located at the Infectious Diseases Institute, Makerere University; Kampala suggested the offending drug could be tenofovir. A TRUVADA® switch was therefore suggested.

One week later, she was counselled and re-initiated on AZT/3TC (COMBIVIR®) plus ALUVIA® and cotrimoxazole was restarted. She did well on this new regimen with no further complication. She has continued to do well to-date with no further skin or mucosal adverse reactions.

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INSIDE THIS ISSUE :

Editorial

Dear reader,

A typical day in the life of a healthcare worker will often find them dealing with a rather wide range of health related issues, some similar and others unique to particular patients.

This edition of the ATIC Newsletter reflects the life of a health worker that has to read up on different issues as they deal with different patients.

When most of us think of skin reactions to ARVs, Nevirapine and Efavirenz are the drugs that come to mind. In this article, we share with you a unusual case from Nsambya Home Care HIV Clinic about a patient who got a skin reaction to Tenofovir.

We also share with you another interesting Case Report from the Infectious Diseases Institute on Skin Tuberculosis.

Over the past months, a number of you have called ATIC with queries on how to manage patients with suspected Ethambutol toxicity and so we present you an article on Ethambutol associated Optic Neuritis in patients treated for Tuberculosis. We trust this will give you more information on the issue.

Our special collaboration with the London School of Hygiene and Tropical Medicine continues in this edition with more articles on the Neglected Tropical Diseases. This time, we bring you an article on the Buruli Ulcer, and another on Filarial diseases.

Please read on and learn from the different experiences and information we have specially packaged for you.

Sheila Karamagi – ATIC Research and Communications

Discussion :

Although hypersensitivity skin reactions in HIV infected people are more commonly attributed to cotrimoxazole and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), they can also be caused by Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs/ NtRTI), although with much less frequency. 15-27% of patients receiving EFV and 17% of patients receiving NVP develop a rash compared to 9% of patients receiving CBV+3TC.

The possibility of an NRTI or NtRTI causing a maculopapaular rash should be suspected if a rash does not resolve with discontinuation of cotrimoxazole and the NNRTI component of an ART regimen.

Skin and subcutaneous reactions i.e. urticaria, vesiculobullous rash, pustular rash, maculopapular rash, pruritus and skin discoloration are seen in one to ten out of 100 people taking Truvada. It is therefore plausible that the patient improved after discontinuation of Tenofovir.

Although the culprit drug was later found to be Tenofovir, we should stress that NVP should be used with caution in women with CD4 cell counts above 250 due to increased risk of hepatotoxicity and that when a maculopapular rash occurs on NVP, patients should also be assessed for hepatotoxicity as the two adverse drug reactions tend to occur together.

Case is from a patient attending Nsambya Home Care HIV clinic

* The programme this patient was enrolled in uses the WHO 2010 cut off point of 350 to initiate patients on ART*

References

- *Once daily dosing of NVP versus twice daily dosing of NVP. Journal of Antimicrobial Chemotherapy 2008 61(1) 13-16*
- *www.medicines.ie : Truvada : Summary of Product Characteristics*
- *Medical Management of HIV Infection: Drug information: Nevirapine and Efavirenz*

Skin Tuberculosis: A Case Report

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Abstract.

We report a case of primary cutaneous tuberculosis (lupus vulgaris) from the Infectious Diseases Institute, Mulago Hospital Complex, Kampala, Uganda.

A 28 year old, HIV positive woman presented with a four month history of large leg ulcers, fever and night sweats.

A wedge biopsy of the ulcer revealed stratified epithelium with foci of acathosis, ulceration of the epithelium and stroma with numerous Langerhans giant cells, necrosis and epitheloid cells with ill-defined granulomas.
The patient was started on anti-tuberculous drugs and has had excellent clinical response.

Case History

A 28 year old woman who first presented to the Infectious Diseases Institute (IDI) clinic in August 2010 with a four month history of spontaneous, progressively enlarging ulcers on the anterior aspect of the left leg. At that visit, she was tested and found to be HIV positive with a CD4+ cell count of 295 cells/µl.

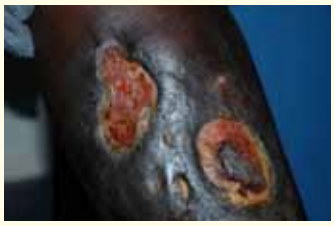
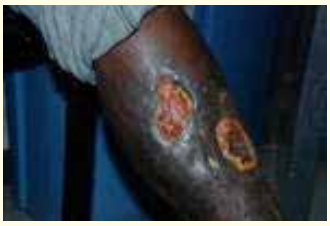
She also had an intermittently productive cough, persistent evening fevers, drenching night sweats and poor appetite. She also reported a 2-week history of voice hoarseness during that period.
She reported no history of weight loss, no history of trauma preceding the ulcers. She had no prior history of TB disease or treatment and had no known contact with a TB patient.

She had used various oral antibiotics but with no improvement in the leg ulcers.

On physical exam, she was in good general condition, no wasting, temperature was 37.4C. She had oral candidiasis, no lymphadenopathy, no figure clubbing.

Examination of the lower extremities revealed two large irregular ulcers on the inferior aspect of her left leg measuring 5cm x 4cm with undermined edges. The ulcer base had a light greenish discharge (see figures 1& 2).

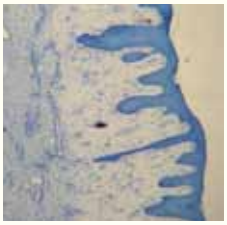
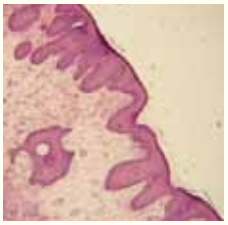
Fig 1 Fig 2

The physical exam was otherwise normal including the respiratory system. Laboratory testing revealed a normal complete blood count, normal renal & liver function tests, normal chest radiograph and sputum was negative for acid fast bacilli.

Purulent material gathered from the ulceration was cultured and identified as pseudomonas aeuruginosa that was sensitive to gentamicin and piperacillin tazobactam and resistant to ciprofloxacin and cefepime.

A skin biopsy was performed which showed stratified epithelium with foci of acanthosis, ulceration of the epithelium and stroma with numerous Langerhan giant cells, necrosis and epitheloid cells with ill defined granulomas consistent with lupus vulgaris (see figures below) .


As a result of this biopsy and the culture, the patient was diagnosed with primary skin TB with pseudomonal super infection and treated with a 4–drug oral anti–TB therapy (ethambutol, rifampicin, pyrazinamide and isoniazid) and also intravenous gentamicin 160mg daily for 5 days. Two weeks later, she was started on zidovudine, lamuvudine and efavirenz (CBV/EFV) combination anti-retroviral therapy. Over the next 16 weeks, there was marked improvement of the symptoms and ulcer regression (see figures 6 and 7).

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Fig 6

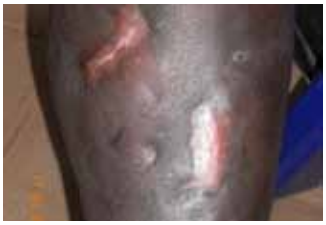

Fig 7

Discussion

Tuberculosis (TB) is an airborne, communicable disease that occurs after inhalation of infectious droplets expelled from patients with laryngeal or pulmonary TB during coughing, sneezing or speaking. The most common site of the primary lesion is within alveolar macrophages in sub-pleural regions of the lung. Although mycobacteria are spread by blood throughout the body during initial infection, primary extra-pulmonary disease is rare except in severely immunocompromised hosts.

Cutaneous tuberculosis is invasion of the skin by mycobacterium tuberculosis and it is an uncommon form of extra-pulmonary TB. It is more common in crowded parts of India and china. In Uganda and in particular at the Infectious Disease Clinic where 400 HIV patients are seen daily with 30 of these in TB Clinic, no such case has been reported before.

This may be due to limitations in diagnostic capacity but also as a result of the very low index of suspicion among clinicians. Even in areas with high TB prevalence, it occurs in less than 0.1% of TB patients[1,2]. It has four common presentations that is; verrucosa cutis, lupus vulgaris, scrofuloderma and tuberculoid.

Verrucosa cutis occurs after direct inoculation of TB in the skin of a previously infected person. It presents a purplish or brownish red warty growth on the knees, feet and buttocks.

Lupus vulgaris is a persistent, chronic skin ulceration. Lesions appear in normal skin as a result of direct extension of underlying tuberculous foci, of lymphatic or hematogenous spread, after primary inoculation , BCG vaccination or in scars of old scrofuloderma[3].

Definitive diagnosis is made histologically. The pathologic hallmark is an epitheliod granuloma with central caseation necrosis[4].

In this case the patient had chronic ulcers that were treated with many courses of antibiotics without improvement. This scenario of chronic, non–healing ulcers in an HIV (+) patient led the attending physician to suspect and investigate for cutaneous TB. The suggestive biopsy results and the excellent clinical response to anti–tuberculous medications further secured the diagnosis.

Non–healing ulcers in a setting of endemic, high burden TB should warrant further biopsy-driven investigation for skin tuberculosis especially in the immunocompromised.

Acknowledgements

The authors would like to gratefully acknowledge the patient and the staff of the IDI clinic. Funding for John Mark Bwanika and Yuka C. Manabe has been provided from the National Institute of Health, DMID under the Tuberculosis Clinical Diagnostics Research Consortium.

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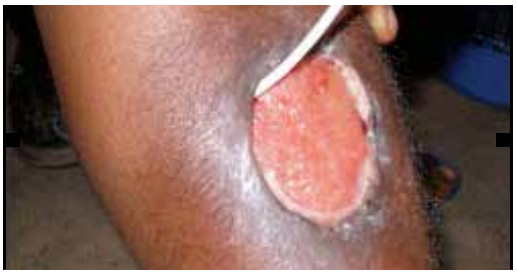
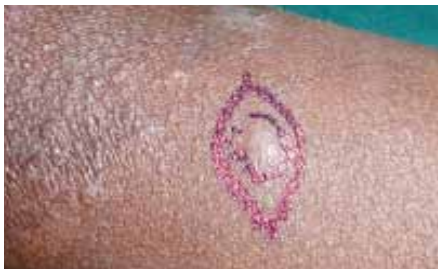
Buruli ulcer | *By Dr. Natalie Prevatt*



Buruli ulcer is a necrotizing disease of skin and soft tissue. It is caused by an environmental mycobacterium named Mycobacterium ulcerans.

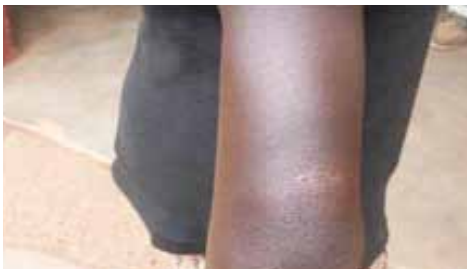
M ulcerans produces a toxin called mycolactone that has cytotoxic properties, which cause tissue necrosis (death of body tissue). Mycolactone is also immunosuppressive, and patients do not therefore present with fever or lymphadenopathy.

Over weeks/months a nodule or papule breaks down into a necrotic ulcer



Nodule (Buruli commonly begins as a 1-2cm nodule)

Papule



Plaque (occasionally it starts as a skin plaque)

Epidemiology

Buruli ulcer was first described in Buruli, Uganda (now Nakasongola district) but has been reported in numerous African countries, in Asia and Australia. Children under 15 years are most at risk in Africa. Infection rates are equal for males and females.

M. ulcerans live in slow moving or stagnant water, the exact transmission method is unconfirmed but is assumed to be through contamination of pre-existing minor wounds.

Human to human transmission is very rare. The true prevalence of Buruli ulcer is not known because there is underreporting and *the variable presentation means that health workers often mistake it for other things.*

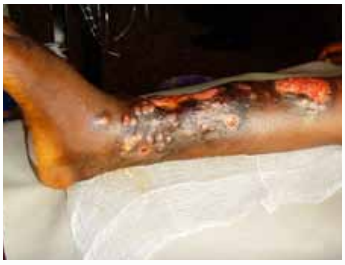
Is Buruli ulcer dangerous?

There is a low mortality rate, but because infection extends deep into fascia, muscle and bone it often leads to permanently restricted function and considerable morbidity. The scars left behind also have a social and emotional impact on the patients' life.

How does buruli ulcer present?

Lesions are normally on the limbs, especially the legs.

Buruli begins as a small firm nodule which is mobile in the subcutaneous fascia, or sometimes as a painless papule (in the dermis), or an elevated dry plaque. This is occasionally pruritic. In a period ranging from days to weeks it begins to ulcerate.



Many patients present after ulceration has occurred. The ulcer is large, but remains painless. It usually has scalloped borders and necrotic slough in the base. A Buruli ulcer has an undermined edge and thus the lesion appears smaller than it really is. It may destroy vessels, nerves and bone. From here M. ulcerans can spread via lymph or blood to another site and satellite ulcers may develop

Lesions eventually heal with disfiguring scars and contractures.

**less frequently an oedematous form may be seen which starts as a painful non–pitting oedmatous area.*

What are the differentials?

Early infection may look like an insect bite or pimple, psoriasis, or leprosy.

The nodule can be mistaken for a cyst, lipoma, or onchocercoma. Later it may appear similar to cutaneous leishmaniasis and TB, or the ulcer may appear like a venous ulcer or tropical ulcer, or as a deep fungal infection.

Buruli ulcer patients are not sick or febrile but the ulcer may become secondarily infected leading to sepsis or tetanus.

Is Buruli Ulcer more common in HIV?

Although Buruli is a mycobacterial infection there is little evidence to suggest higher rates in HIV positive patients.

How do you confirm the diagnosis?

A direct smear of exudate from the necrotic base of the ulcer (or under the edge) should be sent for ZN stain. This may show acid-fast bacilli. ZN stain only has 40% sensitivity and so if negative it should also be sent for culture.

Culture is performed between 30-33 C (lower than for M.tb) and takes 6-8 weeks on Lowenstein-Jensen medium. Culture has around 40% sensitivity.

PCR of biopsy specimens has very high sensitivity >90% and provides results in 48 hours. PCR diagnosis is being rolled out in some African reference laboratories but is not available in the field.

Biopsies taken at operation can also confirm the diagnosis where culture does not rule out other causes.

Do you need to confirm the diagnosis?

Diagnostic confirmation is a long process with low sensitivity. Treatment must be started early and so diagnosis is most often made based on epidemiological and clinical acumen.

Management

Medical (all stage treatment)

In 2004 WHO reported the effectiveness of specific antibiotics - the recommended treatment is now *directly observed rifampicin and streptomycin with or without surgery.*

Medication	Recommended dose	Side effects
Rifampicin	Adults: 10mg/kg/day up to 600mg/day PO Children: 10-20mg/kg/day up to 600mg/day PO	Gastro intestinal symptoms, flu like symptoms, headache, altered liver functionbodily secretions e.g. urine turn orange/red colour
Streptomycin	Adults: 15mg/kg up to 1g OD Children: 15mg/kg up to 1g OD	Nephrotoxicity, neurotoxicity, diarrhoea
Other drugs:	Ciprofloxacin or clarithromycin can be used as alternative to IM streptomycin– studies show no significant difference in regimes	

Adapted from WHO guidance [1]

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There is no vertical Buruli ulcer programme in Uganda. Thus treatment should be given in local health centres, district and referral hospitals, without delay. WHO suggests that in endemic countries such as Uganda treatment should follow a protocol, which is seen here divided into 3 categories:

Category	Form of disease	Treatment	Primary aim
1	Small early lesion (nodules/papules/ plaques/ulcers <5cm diameter)	Start antibiotics at least 24 hours before surgery and continue for 4 weeks Schedule immediate excision and suture wound If cannot excise then treat with same antibiotics for 8 weeks	cure
2	Large ulcerative lesions (>5cm), oedematous/plaque forms (ulcerative/ non ulcerative) lesions on the face/head/neck	Give 4 weeks antibiotics before surgery (then surgery if still required) followed by another 4 weeks antibiotics (total 8 weeks)	Reduce extent of surgery required
3	Mixed/ disseminated disease including osteomyelitis/osteitis	Start antibiotics at least 1 week before surgery and continue for 8 weeks	Reduce extent of infection before surgical excision

Amended from WHO table [1]

Although this recommendation was based on observational studies, a recent RCT in Ghana [2] showed this treatment to be very effective for patients with small early lesions: 96% of patients treated with eight weeks of rifampicin and streptomycin had healed lesions at one year.

Surgical (late stage treatment)

Nodules/ papules and small ulcers are excised and closed.

Large ulcers are excised and closed with skin grafts. The addition of rifampicin and streptomycin to surgery has reduced recurrence rates ten fold [2].

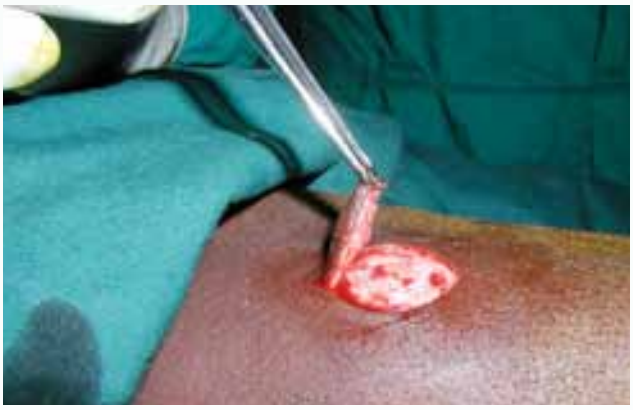
After treatment

Ultrasound can be used to assess extension of ulcers under the skin and thus response to treatment.

Prevention

There is some evidence that BCG vaccination is protective but only for a short time. The Global Buruli Ulcer Initiative[3] aims to improve the situation by increasing awareness among health professionals and encouraging early clinic attendance for patients with suggestive early lesions.

Major advances are only likely to be made when a rapid diagnostic test becomes available for early disease.



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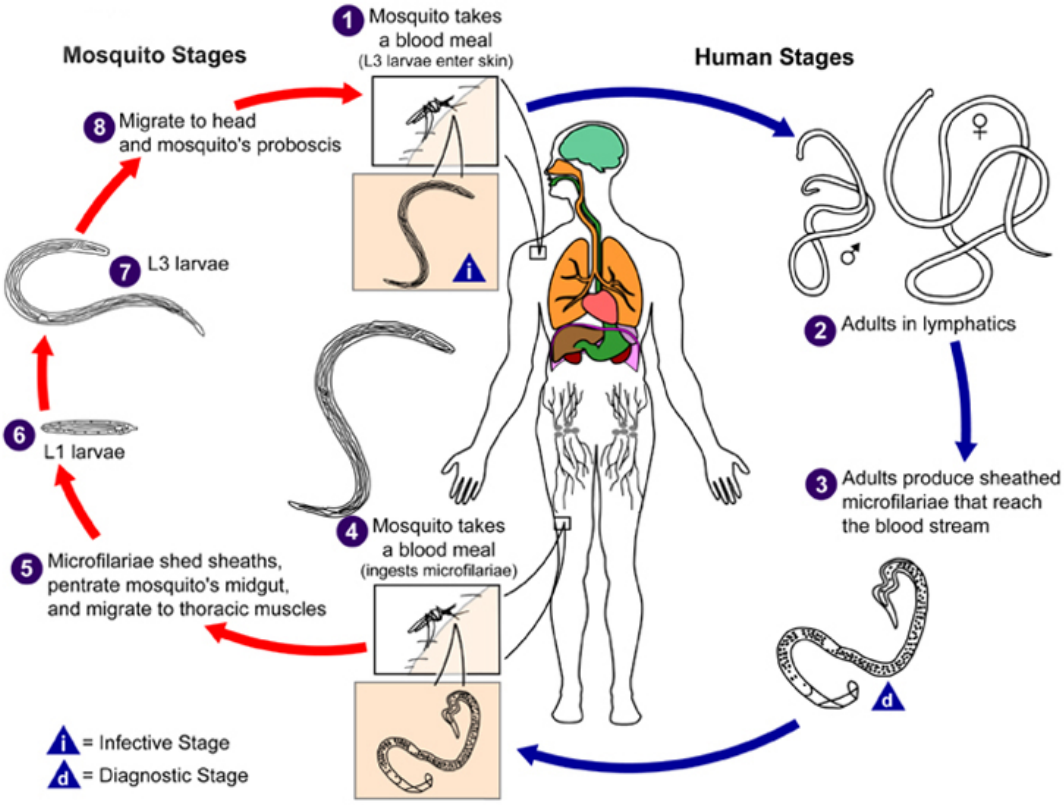
Filarial Diseases

Dr Jenny Goldblatt



Three diseases caused by filariae can affect people in Uganda; these are lymphatic filariasis, onchocerciasis, and loa loa (figure 1). They are all spread by insect vectors. Whilst not fatal they do cause chronic conditions which impact on patients' quality of life and their economic and social functioning. It is important to discuss the filarial diseases at the same time because the treatments used to kill one type of filariae can cause serious and sometimes fatal reactions in patients infected with another.

Life of filariae inside humans

Filarial larvae gain entry to humans through the bites of infected insects. They migrate into the body to mature into adults over a number of weeks. Adults produce millions of microfilariae which can be found in many types of bodily fluid including blood and CSF. The vector ingests the microfilariae when biting, thus continuing the life cycle.

Diseases

The complications of filarial infections often result from ineffective immune defense leading on to chronic carriage and inflammation.

Lymphatic Filariasis (Wuchereria bancrofti)

Epidemiology:
An estimated 120 million people worldwide are at risk of Lymphatic Filariasis (LF), 13 million of who live in Uganda. It is estimated that the disease disfigures a third of people infected.

Vector: Mosquito species (Aedes, Anopheline, Culex, Mansionia or Ochlerotatus)

Major features: Lymphoedema of the limbs, ***genitals*** or breasts, progressing to elephantiasis. Complications include bacterial super-infection and "filarial fevers" (acute exacerbations) characterised by headache, malaise, pain and fever.

Disease course: Infection is usually acquired in childhood. Lymphoedema can develop several decades later and is caused by damage to the lymphatics from recurrent attacks of lymphangitis due to dying adult worms. Superimposed bacterial infections contribute to the severity of lymphedema from inflammation and fibrosis and subsequent progression to elephantiasis.

Differential diagnosis

Oedema: Thrombophlebitis, venous thrombosis, cellulitis, bacterial lymphangitis, proximal lymphatic occlusion, heart failure, cirrhosis, nephrotic syndrome.

Scrotal Swelling: epidydimo-orchitis, abscess formation, hernia, varicocoele, congential hydrocoele, epididymal cyst, testicular carcinoma

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Diagnostic tests:

Filariasis is diagnosed by identifying microfilaria on giemsa stained blood film smears. Blood should be drawn at night (when the vector is expected to bite), diagnosis can also be made with a card-based antigen detection kit.

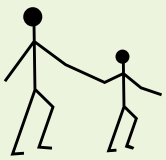
Management:

The mainstay of management is preventing complications: Advice the patient to keep the affected area clean by washing with clean water and soap, drying carefully and avoiding injury to the skin. Affected limbs should be elevated where possible and patients should exercise to aid lymphatic drainage.

If filarial fever occurs patients should take antipyretics and antibiotic treatment if bacterial skin infection is present. Patients should be advised against cutting the skin. The WHO produces educational material for healthcare workers and patients on this topic. ***If you have any more concerns about filariasis, you can contact ATIC on 0800200055***

There are limited trials that examine optimal drug treatment as part of filariasis management. Current recommendations are based on limited trials and expert opinion. Adult worms are killed with the use of ***Diethylcarbamazine*** DEC for 21 days, though this does not reverse existing changes (see table 1). DEC must be used with caution if co-infection with onchocerca volvulus is possible (see Onchocerciasis).

Table 1: Doses of medications commonly used in filarial disease

<table>
<tr><th>DISEASES</th><th>PURPOSE</th><th>DRUG</th><th colspan="2">DOSE</th></tr>
<tr><td rowspan="8">Lymphatic filariasis (LF)
  </td><td rowspan="8">Control (appropriate to Uganda)</td><td>Treatment</td><td colspan="2">Diethylcarbamazine (DEC)</td><td>1mg/kg first day, building up over 3 days to 6mg/kg/day (in 3 doses) for 21 days</td></tr>
<tr><td>Albendazole +
Ivermectin</td><td colspan="2">400mg taken once</td></tr>
<tr><td rowspan="6">150 mcg / kg taken once</td><td>Weight</td><td>Number of tablets</td></tr>
<tr><td><15 kg</td><td>0</td></tr>
<tr><td>15-25 kg</td><td>½</td></tr>
<tr><td>26-44 kg</td><td>1 ½</td></tr>
<tr><td>45-64 kg</td><td>2</td></tr>
<tr><td>> 64 kg</td><td>2 ½</td></tr>
<tr><td rowspan="2">Onchocerciasis
  </td><td>Treatment and control</td><td>Ivermectin</td><td colspan="2">As for LF. Repeated every 6-18 months for several years.</td></tr>
<tr><td>Treatment of adult worms</td><td>Doxycycline (with Ivermectin)</td><td colspan="2">200mg OD for 6 weeks (doxycycline not in children <12 or pregnant women)</td></tr>
<tr><td>Loa Loa
  </td><td>Treatment</td><td>DEC</td><td colspan="2">1mg/kg first day, building up over 3 days to 6 mg/kg/day (in 3 doses) for 21 days</td></tr>
</table>

Prevention - Mass Drug Administration (MDA)

In the past, there has been annual mass treatment to prevent LF across Uganda, using Ivermectin and Albendazole. This programme is no longer active. It is recommended that population based treatment programmes are repeated annually for 5-6 years.

Onchocerciasis (river blindness)

Epidemiology:

Nearly 3 million people live in regions of Uganda in which onchocerciasis is endemic. These are largely those areas along the Western borders of the country *This includes areas like Arua, Yumbe, Moyo , Adjumani, Hoima, Kasese and Kisoro*

Vector:

Onchocerciasis is spread by blackflies (Simulium sp), which live near fast flowing water. Bites are very painful.

Features:

Patients complain of intensely pruritic skin. This itch is due to death of microfilariae as they migrate through tissue. As patients

continuously scratch, the skin of the thighs and buttocks becomes lichenified and depigmented and loses its elasticity. This dermatitis progresses to atrophy where the typical hanging groin can be seen.

There are several manifestations in the eye including sclerosing keratitis, cataract formation and optic atrophy, all of which can cause blindness. Eye disease usually starts as an itchy red eye due to inflammation triggered by parasite migration.
The Onchocera volvulus adults may lie in subcutaneous nodules. These are often seen near bony prominences which the worms have been unable to pass by.

Differential diagnosis

Skin manifestations: atopic dermatitis, contact dermatitis, chronic eczema, malnutrition, loa loa, superficial mycoses, streptocerciasis, vitiligo, lipoma.

Ocular manifestations: glaucoma, trachoma, cataract

Diagnostic tests:

Skin snips are taken from near a nodule or a high yield area such as the thigh. The skin is lifted with point of a needle and a 1mm scalpel snip is collected and sent to laboratory in saline to look for microfilarae and typical histological changes. Serology does not distinguish between past and current infections.

Management:

The mainstay of treatment is Ivermectin (see table 1). This can improve both ocular and dermatological manifestations. Ivermectin ***prevents production of microfilaria*** (but has no action against adult worms, which can live in humans for around 12 years, and so treatment must be repeated every 6-18 months for a number of years.

Doxycycline has some activity against adult worms and can be given at a dose of 200mg daily for 6 weeks in addition to Ivermectin but not in children under 12 years.

Treatment carries a risk of allergic / inflammatory reactions which can lead to facial oedema, anterior uveitis, keratitis, tachycardia and postural hypotension as well as myalgia, lymphadenopathy, synovitis and headache. Although this is markedly more common with DEC, particularly in the malnourished, 1-5% of those treated with Ivermectin alone may also be affected.

The use of low dose dexamethasone (3mg/kg) may reduce the severity of this reaction without reducing anti-microfilarial activity. Ivermectin is not safe for pregnant women, lactating mothers, children younger than five years and people with heart, liver and kidney diseases.

Surgical removal of skin nodules can be performed.

Prevention

Community directed MDA programmes
Some community directed programmes using Ivermectin have been established in parts of Uganda where there is a higher risk of Onchocerciasis.

Loa Loa

Importance:

People infected with Loa Loa can have serious adverse reactions such as encephalopathy and retinal haemorrhage if treated with Ivermectin. Loa Loa is know to be prevalent in Central and West Africa, including regions bordering Uganda, and has previously been reported in Uganda, so it is important to be vigilant for evidence of this disease in areas in which Ivermectin may be given.

Vector: Mango Fly (Chrysops sp).

Features:

Infected individuals are often asymptomatic. Localised, sudden onset and short-lived inflammation may occur as a result of migration of adult worms through the subcutaneous tissues. This Calabar swelling, often at the wrist, is reported by the patient as a swelling which appeared and disappeared leaving no trace. Worms may visibly migrate under the sclera of the eye, which is distressing for the patient.

Differential Diagnosis of Calabar swelling:

Reactive arthritis, onchocerciasis, idiopathic angioedema

Diagnostic tests:

Visualisation of microfilariae in blood taken at noon when the vector is most likely to bite. Serology has been used for population screening.

Treatment:

DEC can be used against adult worms (see table 1). Encephalitis has been reported in patients with high microfilarial loads due to death of migrating worms.

Adults migrating across the eye can be removed surgically if it is not possible to do this with the corner of a piece of paper.

Interaction with HIV

There is no clear evidence of significant interaction between HIV and filarial infections, though there is experimental evidence to suggest that lymphocytes from those infected with filariae may be more susceptible to HIV infection.

Adults larvae produce millions of microfilariae which can be found in many types of bodily fluid including blood and CSF.

Ethambutol Associated Optic Neuritis : One Of The Side Effects To Look Out For In Patients Treated For Tuberculosis

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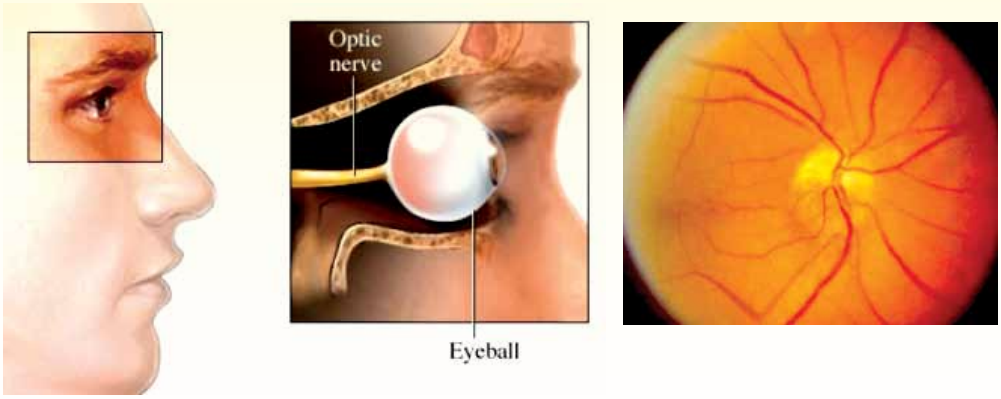

Ethambutol is a synthetic antituberculosis agent used in combination with other antituberculosis agents in the treatment of clinical Tuberculosis (TB). Tuberculosis caused by Mycobacteruim tuberculosis, is a major cause of morbidity and mortality in Uganda. Uganda was ranked 18th out of the 22 tuberculosis high-burden countries in the world during 2009. The incidence of TB is 330/100,000 population for all TB cases and 136/100,000 population for sputum smear-positive pulmonary TB. The Annual Risk of TB Infection (ARI) for Uganda is estimated at 3 percent.

The interaction between TB and HIV is increasing the burden of both diseases. HIV is one of the major risk factors for the development of active TB among individuals infected with Mycobacterium tuberculosis. At present, an estimated 60% of TB patients in Uganda are also infected with HIV. TB accounts for 30 percent of all deaths among HIV positive patients.

The recommended first line anti-tuberculosis agents used in management of TB include; rifampicin(R), Isoniazid (H), Pyrazinamide(P) and Ethambutol(E).

The current WHO 2010 TB guidelines no longer recommend an 8 month regimen of 2RHZE and 6EH as the first line treatment for tuberculosis in adults. They instead recommend a 6 months regimen containing 2RHZE and 4RH . This is because the use of rifampicin for only 2 months in the intensive phase was associated with a high rate of relapses and deaths.

However, in Uganda we are yet to adopt this recommendation and are still using an 8 months regimen of 2RHZE/6EH. With this regimen, there is a longer duration of exposure to ethambutol thus increasing the risk of ethambutol associated side effects.

Ethambutol has several side effects that include optic neuritis, headache, malaise, dizziness, mental confusion, fever, abdominal pain, anorexia, nausea and vomiting and more rarely peripheral neuritis, rash, pruritus, urticaria, hepatitis and thrombocytopenia. The most important of these is optic neuritis.

Patients who develop optic neuritis may complain of bilateral progressive painless blurring of vision or decreased color perception. Some individuals may be asymptomatic with abnormalities detected only by vision tests.

Examination by an ophthalmologist may reveal pupils that are bilaterally sluggish to light, decrease in visual acuity with minimal or no light perception, constriction of visual fields, areas of diminished vision within the visual field(scotomas), and loss of red-green color discrimination which may be the earliest sign of toxicity.

Characteristics of ocular toxicity of ethambutol

The extent of ocular toxicity appears to be dose and duration related. However, such toxicity has also been reported rarely only after a few days of therapy with the drug.

Dose-related

The reported incidence of ethambutol-related optic neuritis varies between 18% in patients receiving more than 35 mg/kg per day, 5% to 6% with 25 mg/kg per day, and less than 1% with 15 mg/kg per day (the recommended dose) of ethambutol for more than 2 months. 50% of ethambutol is excreted in urine, therefore patients with poor renal function are at higher risk of ocular toxicities..

Duration-related

The manifestation of ocular toxicity is usually delayed, and generally does not develop until at least 6 weeks after treatment. The mean interval between onset of therapy and toxic effects has been reported to be 3 to 5 months. However, manifestations of toxicity as late as 12 months after therapy initiation have also been reported.

Other factors that predispose subjects to toxicity include diabetes and optic neuritis related to tobacco and alcohol consumption.

Management

Patients in whom ethambutol is relatively contraindicated should be identified before initiation of TB treatment. These include patients who are unlikely to notice or describe visual symptoms, such as patients with dementia, mental retardation and children. In some of these patients e.g. children below 12 years, ethambutol should be avoided, (recommended first line regimen for children below 12 yrs is 2 months of RHZ and 4 months of RH) and in others pharmacovigilance should be encouraged.

The dose of ethambutol must always be carefully calculated on a weight basis and the dose or the dosing interval should be adjusted based on creatinine clearance in patients with impaired renal function. If creatinine clearance is between 10-50ml/minute: administer 15mg/kg of ethamutol every 24-36 hours, if creatinine clearance is <10ml/minute administer 15mg/kg of ethamutol every 2 days.

Patients treated with ethambutol should be educated on the presenting sign and symptoms of ocular toxicity i.e. blurred vision and/or decreased colour perception. They should promptly seek medical advice if their sight or perception of color deteriorates. In this case, ethambutol should be stopped and replaced with streptomycin during the intensive phase and rifampicin and isoniazid should be given for the continuation phase for 4 months.

Where possible patients commencing treatment with ethambutol should have a baseline eye examination including best corrected visual acuity, color vision and visual field. These parameters should then be monitored periodically (every 1 to 3 months) .

Outcome

When ocular toxicity is detected early and ethambutol is discontinued promptly, the visual effects are generally reversible over a period of weeks or months. Rarely, depending on the degree of impairment, recovery may be delayed for up to 1 year or more, or the effect may be irreversible. Care should be taken to be certain that variations in vision are not caused by underlying pathologic conditions such as cataracts, diabetic retinopathy or CMV retinitis in HIV positive individuals.

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ask ATIC

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As a Quality Improvement advisor at health centers in Eastern Uganda, I have observed some challenges in provision of antiretroviral therapy (ART) at the facilities I supervise.

Due to challenges in logistics management, some health centers experience occasional stock outs of antiretrovial drugs (ARVs) ranging from single drug formulations to fixed dose combinations.

This often leads to rationing of the available ARVs for clients as providers wait to receive more stocks. Sometimes, this rationing leads to treatment interruptions for varying durations among HIV/AIDS clients on antiretroviral therapy.

Are there risks of resistance associated with such unplanned interruptions in antiretroviral therapy ?

If so, after what duration of interruption do you anticipate emergence of resistance and recommend change in treatment regimen ?

A

Yes there are.

Treatment Interruptions whether planned or unplanned are not recommended during Antiretroviral Therapy. Evidence that treatment interruptions are not a good treatment option comes from previous clinical trials that explored different treatment interruption schedules

One of these clinical trials was a randomized trial nested within a bigger trial (the DART Trial) . This trial compared fixed length Structured Treatment Interruption and Continuous Treatment in adults on first line Antiretroviral Therapy (ART).

Patients who had been on ART for more than 48 weeks and were clinically stable with CD4 cell counts above 300cells/ul were randomized to continue taking ART continuously or to undergo Structured Treatment Interruptions with repeated 12 week periods on or off therapy

This trial was stopped early because patients in the structured treatment interruption arm had a greater risk of disease progression and more HIV related complications than patients in the continuous treatment arm.

Trials of treatment interruption done in other countries produced similar results with more deaths, drug related complications and HIV related events in patients who underwent the treatment interruption.

The speed at which resistant mutations emerge after treatment interruption depends on the type of ART regimen and the mode of discontinuation.

Patients whose treatment gets interrupted while on Non-Nuleoside Reverse Transcriptase Inhibitor (NNRTI) based regimens develop resistance (to the NNRTI component) very quickly. This is because the NNRTIs (efavirenz and nevirapine), have very long half lives and stay in the bloodstream longer than the Nuleoside Reverse Transcriptase Inhibitors (NRTIs). Patients are in effect exposed to monotherapy with NNRTIs which leads to resistance. The situation is worse if the ART regimen is stopped without a twoweek lead out dose of the NRTIs. This is unfortunately what happens in most cases of unplanned treatmentinterruption.

A study done in Kampala , which followed up HIV-positive, antiretroviral-naive individuals initiating ART on stavudine, lamivudine and nevirapine for 24 weeks, found that treatment interruptions were significantly associated with drug resistance. At the end of this study, none of 33 participants who did not interrupt treatment for over 48 h had drug resistance, whereas eight of 62 (13%) participants who did interrupt therapy experienced drug resistance.

It is therefore important for all personnel involved in ART care to realize that they should do their best to ensure continuous supply of ART so that their patients can continue their treatment without interruption. A few measures that healthcare workers can put in place to achieve this are ;

- Submitting drug order forms to the district focal person and to National Medical Stores (NMS) in a timely manner to facilitate drug processing and delivery.
- Accurate quantifying their drug needs so that all patients on their programme are catered for

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