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Interaction between Malaria and HIV

By By Dr Pauline Byakika-Kibwika (M.B.Ch.B, MSc. CEB, MMed)

Malaria and HIV infection contribute to significant morbidity and mortality. Worldwide, approximately 2,200 million people are exposed to malaria annually. Of these, about 300-500 million develop clinical malaria, with over 90% occurring in sub-Saharan Africa. Malaria kills between 1.5 – 2.7 million people annually in sub-Saharan Africa[1].

Currently 40 million people worldwide are living with HIV/AIDS. 70% of these are in sub-Saharan Africa, where about 29 million people are infected (UNAIDS 2002).

Given the extensive overlap in the geographical distribution of the two diseases in sub-Saharan Africa, even a small interaction between the two could have profound public health consequences.

This interaction is plausible when the immunological mechanisms involved in both diseases are considered. Humoral and cell mediated immunity are critical to development of an effective immune response to malaria. CD4 T lymphocytes modulate the production of antimalarial antibodies and production of cytokines, like tumour necrosis factor alpha (TNFα), which are directed against merozoites and cellular immune-recruitment to control or modulate clinical infection. The antibodies produced block parasites from invading red blood cells (RBCs), block malaria toxins as well as adherence of red blood cells to endothelium. Activated CD4 and CD8 cells coordinate the cell mediated immune response and facilitate antibody dependent cytotoxicity of infected RBCs, which results in death of intra-erythrocytic parasites.

HIV, on the other hand, infects CD4 lymphocytes, causing depletion of the CD4+ T lymphocytes through mechanisms like cytolysis, syncytial formation, and apoptosis. The loss of CD4+ cells results in diminished T helper 1 (Th1) and T helper 2 (Th2) responses. Th2 depletion prevents B cell activation with resultant humoral immunodeficiency while Th1 deficiency causes impaired cellular immune response due to diminished interferon gamma and TNFα production, which impairs the killing of intracellular pathogens. There are several ways that malaria and HIV could potentially interact, with effects on incidence, prevalence, transmission, clinical manifestations, treatment outcomes, drug interactions and toxicity.

Trainees examine malaria parasites in a lab

Effect of HIV on malaria incidence, parasitemia, clinical presentation and treatment outcome

HIV and non-pregnant adults: Early in the HIV pandemic, several studies reported no convincing association between HIV and malaria[2]. A systematic review published in 1998 supported this conclusion. However, the authors pointed out several limitations of these earlier studies such as inadequate sample size, short follow-up periods and inability to stratify patients by level of immunity. In contrast, more recent evidence has shown a clear association between HIV infection and an increased risk of malaria, with HIV-infected patients having over twice the incidence of clinical malaria compared to HIV-uninfected individuals[3,4]. Additionally, a "dose-response" relationship, of decreasing CD4 counts associated with increasing rates of clinical malaria and higher parasitemia has been demonstrated.

HIV and malaria in pregnancy: The association is stronger and more consistent among pregnant women of all parities. HIV-1 infected pregnant women have a higher prevalence of peripheral and placental malaria and higher parasite densities with more adverse birth outcomes than non HIV-infected women. A recent review on HIV-malaria co-infection in pregnancy showed that the gravidity-related pattern of malaria in pregnancy is

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Inside

From the Editor

Malaria remains one of the worst enemies for populations in the tropical resource limited settings. Clinical malaria is diagnosed in 300-500 million people worldwide per year but 90% of these are in sub-Saharan Africa.

The interaction between HIV infection and malaria is pertinent. The body's defense system against malaria involves CD4 T-lymphocytes, which instigate the production of antibodies and cytokines. On the other hand the human immunodeficiency virus utilises the CD4 T-lymphocytes for replication. This results in a drop of the CD4 T-lymphocyte count and thus reduced immunity.

In this issue of *ATIC News*, our lead article exposes the impact of the interaction between malaria and HIV/AIDS, and thus the need for appropriate anti-malarial and antiretroviral therapy. We also point out some important drug interactions between the new first line anti-malarial drug combination Coartem and other commonly used drugs. However, information on the interaction between anti-retroviral drugs and Coartem are not yet published, but are in the pipeline for studies.

We encourage our fellow health-care workers to contact ATIC in case of difficult AIDS and Malaria cases.

Thank you and enjoy this quarter of 2007

Drug interaction - updates from CROI

Several hundred abstracts and posters were presented t the 14th Conference on Retroviruses and Opportunistic Infections (CROI) in Los Angeles, California, USA. ***Marta Boffito, MD PhD,*** *captured key studies on drug-drug interactions involving ARVs.*

Identification of Drug Interactions Involving ART in New York City HIV Specialty Clinics

Overall 1 in 5 patients receiving ART had a potential drug interaction. 20% of these interactions could have been associated with reduced antiretroviral drug plasma concentrations, which may compromise virologic response. Therefore, identifying potential drug interactions promptly is fundamental and may prevent drug resistance from developing, especially if multiple providers may be prescribing therapy.

Pharmacokinetic Interaction between Efavirenz and Diltiazem or Itraconazole after Multiple-dose Administration in Adult Healthy Subjects

In this study efavirenz was shown to significantly decrease the exposures of diltiazem (DTZ), itraconazole (ITR) and its active metabolite (hydroxy ITR [HITR]). Therefore, when combined with efavirenz, DTZ dose adjustment should be guided by clinical response. In terms of the interactions with ITR, currently there are no data using higher doses of ITR in combination with efavirenz, thus, no dose recommendation can be made and use of alternate treatment may be necessary for optimal antifungal therapy. Finally the study medications were generally safe and well-tolerated when administered alone or in combination.

Pharmacokinetics and 12 Weeks Efficacy of Nevirapine, 400 mg vs 600 mg per day in HIV-infected Patients with Active TB Receiving Rifampicin: A Multicenter Study

Thirty HIV-infected Thai adults with CD4 count < 200 cells/mm^3 and active tuberculosis were randomised to receiving a rifampicin 2-6 weeks and a nevirapine 400 (arm 1) or 600 mg (arm 2) per day plus zidovudine and lamivudine. A nevirapine lead-in 2 weeks period was performed, as per standard of care, in both groups at 200 and 400 mg/day, respectively. Plasma nevirapine concentrations were measured at week 2, 4 and 12. In patients treated concomitantly with nevirapine and rifampicin, as many as 80% in the 400 mg arm had suboptimal nevirapine concentrations at 2 weeks after the lead in period, whereas nevirapine 600 mg/day was associated with a high rate of nevirapine hypersensitivity. Therefore, nevirapine 400 mg/day may be sufficient for Asian HIV-infected patients receiving rifampicin, but a 200mg nevirapine lead-in period should be avoided. In addition, zidovudine should also be avoided during the first 3 months of advanced HIV/TB. Rifampicin-ZDV co-administration results in a significant reduction of the ZDV concentration in plasma. This may result in a partial or total loss in the ZDV efficacy (www.hiv-druginteractions.org). While, short-term efficacy is comparable in this study, a long-term efficacy study is under way.

Drug Interaction between Antimalarial Drugs and Efavirenz

An artemisinin-based combination therapy including artesunate (AS) plus amodiaquine (AQ) is now approved for first-line treatment of malaria in 15 African countries. The present study was aimed at investigating the pharmacokinetics of AQ and its active metabolite desethylamodiaquine (DEAQ) in the

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Co-artem, the frontline weapon

By Francis Kalemeera (BSc, B Pharm, MPS)

Coartem is an antimalarial drug combination containing artemether and lumefantrine [AL]. One tablet contains 20mg and 120mg of artemether and lumefantrine respectively. Artemether is a sesquiterpene lactone derived from artemisinin, a natural substance from Artemisia annua. Lumefantrine is a synthetic racemic fluorine mixture.

Table 1: Coartem Dosage and Administration

	Day 1	Day 2	Day 3
Adults and children ≥ 35kg	4 tabs stat then 4 tabs after 8hr	4 tabs b.d	4 tabs b.d
Children: 25 to <35kg	3 tabs stat then 3 tabs after 8hr	3 tabs b.d	3 tabs b.d
Children: 15 to <25kg	2 tabs stat then 2 tabs after 8hr	2 tabs b.d	2 tabs b.d
Children: 5 to <15kg	1 tab stat then 1 tab after 8hr	1 tab b.d	1 tab b.d

**b.d: twice daily*

Indications

Coartem (AL) is used for the treatment of uncomplicated malaria and has been found to be safe and effective against *Plasmodium falciparum* and mixed infections including *P. falciparum*. Coartem is effective against drug sensitive and drug resistant *P. falciparum* and it is thus recommended in areas where the parasites may be resistant to other antimalarials, including sulphadoxine-pyrimethamine and chloroquine, the commonly used drugs in resource limited settings[1,2].

Mechanism of action

Artemether and lumefantrine both act in the food vacuole of the malarial parasite. It is thought that there, they inhibit the conversion of haem (toxic product from haemoglobin breakdown) to haemozoin, malaria pigment. While lumefantrine is thought to interfere with the polymerization process, artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron.

Pharmacokinetics

Artemether's absorption is fairly rapid, reaching peak plasma concentrations after two hours. Lumefantrine is a highly lipophilic compound whose absorption starts after a lag time of two hours and peak plasma concentrations are seen after 6-8 hours. Coartem should be taken with food as food enhances the absorption of both artemether and lumefantrine.

Artemether and lumefantrine are both highly bound to serum proteins in vitro (95.4% and 99.7% respectively). Artemether is rapidly metabolised to its biologically active metabolite, dihydroartemisinin through the enzyme CYP3A4. Artemether also has the capacity to induce CYP2C19 and CYP3A4. Lumefantrine is metabolised mainly by CYP3A4. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic concentrations.

Warnings and precautions

- For severe manifestations of malaria including cerebral malaria, pulmonary oedema and renal failure, other effective drugs such as quinine are recommended.
- If a patient deteriorates while on Coartem, alternate therapy should be started without delay. In such a case, however, the patient should be closely monitored (with an ECG) since lumefantrine and quinine may lead to cardiotoxicity.
- If a patient has been treated with halofantrine, Coartem should not be administered earlier than one month after the last dose of halofantrine.
- If Coartem is given to patients after mefloquine, close monitoring of food intake is important. Mefloquine induces a reduction in bile production. Patients are thus advised to eat at dosing times, which compensates for the associated decrease in bioavailability.
- Caution is advised when Coartem is given with some drugs that are inducers, substrates or inhibitors of the Cytochrome P450 isoenzyme 3A4

Pregnancy and lactation

Coartem is contraindicated in pregnant mothers during the first trimester of pregnancy. Women of child bearing potential should be advised to practice contraception while on Coartem. Coartem should not be given to breastfeeding women until after 28 days. However Coartem may be used in the above mentioned women if the benefit to mother outweighs risk to the fetus.

Side effects

Very common: Headache, dizziness, abdominal pain, anorexia
Common: Sleep disorder, palpitation, cough, diarrhoea, vomiting, nausea, pruritus, rash, arthralgia, myalgia, asthenia, fatigue
Uncommon: Somnolence, involuntary muscle contractions, paraesthesia, hypoesthesia, abnormal gait, ataxia
Very rare: Hypersensitivity

Contraindications

The side-effects, pharmacokinetics and pharmacodynamics of Coartem have significant impact on the decisions made for the use of Coartem. It is contraindicated in patients hypersensitive to the ingredients, first trimester of pregnancy and electrolyte imbalance. Due to the inhibition on CYP2D6 it is contraindicated in patients on drugs metabolised by this isoenzyme, amitriptyline, clomipramine, etc. Coartem is contraindicated in patients taking drugs that are known to prolong the QTc interval such as Antiarrhythmics of classes IA and III, neuropleptics, antidepressant agents, certain antibiotics including some afents of the following classes: macrolides, Fluoroquinolones, imidazole, and triazole antifungal agents.

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Ask ATIC

Robinah N. Lukwago

Q: *Should we continue to use* sulfadoxine-pyrimethamine *for Intermittent Preventive therapy (IPT) for malaria in pregnancy given that there is resistance to Fansidar?*

F.G, Kisoro, Uganda

A: The alarming increase of sulfadoxine-pyrimethamine (SP) resistance in Africa has raised concerns about its use as IPT for malaria. Pharmacokinetic modeling suggests that the suppressive prophylactic effect of SP, assuming similar pharmacokinetic profiles as in non-pregnant adults, may last approximately 2–3 months in areas with sensitive parasites. The period of effective post-treatment prophylaxis then progressively shortens with increasing drug resistance, compromising the efficacy of the two-dose regimen given at 3-month intervals. SP resistance is linked to mutations in the dihydrofolate reductase (dhfr) and dihydropteroate synthetase (dhps) genes. Parasites with four mutations in the dhfr gene, including the 164L mutation, are fully resistant. Such parasites have already been observed in Malawi, Uganda, and western Kenya though their rate of spread cannot be predicted. It might be slowed if SP use in the general population is not widespread and is limited to IPT. Semi-immune pregnant women respond better to failing antimalarials than symptomatic young children. Meta-analysis of two trials in primigravidae and secundigravidae has shown that the protective efficacy of two-dose IPTp-SP against placental malaria remains high (52%, 95% CI 32–67), even in areas where the treatment failure rate by day 14 in symptomatic children is between 20% and 40%. This is the basis for the continued use of SP for IPT. However there is no data on IPTp with SP efficacy in areas with high SP resistance (more than 40% treatment failure by day 14 in children). This reveals a priority area for research in Uganda that will help inform the policy making process on whether we should continue to use fansidar for IPT in Uganda.

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Updates from CROI

From Page 2

presence of efavirenz in healthy volunteers. The study was terminated after the first 2 subjects developed asymptomatic but significant elevations in liver transaminases following completion of the study. Addition of efavirenz to AQ resulted in total exposure increases of 114 and 302% for AQ and total exposure decreases of 23.7 and 8.5% for DEAQ for the first 2 subjects, respectively. Efavirenz exposure was at or above historical results for healthy volunteers. Other infectious or metabolic aetiologies were excluded as causes of transaminase elevations. Liver function monitoring is needed in individuals requiring AQ/AS treatment for malaria in the setting of chronic efavirenz therapy.

Plasma Concentrations of Efavirenz and Lopinavir in Children with and without Rifampicin-based Anti-TB Treatment

The study evaluated the plasma concentrations of efavirenz or lopinavir in children taking efavirenz or lopinavir/ritonavir plus 2 nucleoside reverse transcriptase inhibitors with and without rifampicin-based tuberculosis treatment. Standard recommended doses of all investigated agents were used and extra ritonavir was given during tuberculosis treatment to children receiving lopinavir/ritonavir.Rifampicin did not significantly reduce efavirenz concentrations. However, it was noted that 50% of children had an efavirenz minimum concentration below the minimum recommended concentration. This raises concern that a substantial proportion of children may be at risk of the rapid emergence of efavirenz-resistant mutations and treatment failure, suggesting that efavirenz doses should be revaluated, especially because therapeutic drug monitoring is seldom available in developing countries. Lopinavir minimum concentration was similar between the 2 groups. In all the 28 children studied, lopinavir minimum concentration was above the minimum therapeutic level of 1 mg/L. This study confirmed that additional ritonavir can be used to delay lopinavir elimination, thus overcoming the reduction of lopinavir concentrations caused by rifampicin. However, concern remains in terms of toxicity when higher ritonavir doses are administered.

Abacavir Plasma Pharmacokinetics in the Absence and the Presence of Atazanavir/Ritonavir or Lopinavir/Ritonavir) and Vice Versa in HIV+ Patients

The aim of this study was to investigate abacavir plasma pharmacokinetics in the absence and presence of atazanavir/ritonavir or lopinavir/ritonavir and vice versa in HIV-infected patients. No changes in atazanavir, lopinavir, and ritonavir exposures were observed following addition of abacavir to the regimens containing these protease inhibitors. However, mild (17%) and moderate (32%) decreases in abacavir plasma exposure were observed following addition of atazanavir/ritonavir or lopinavir/ritonavir, respectively. The mechanism of interaction, the impact on intracellular triphosphates and the clinical implications remain unclear and should be investigated further.

Effect of Rifampin on Pharmacokinetics and Safety of Twice-daily Atazanavir: ACTG Protocol A5213

In order to test the hypothesis that adequate plasma concentrations of atazanavir can be maintained if given at higher than approved doses (300 mg and 400 mg twice daily, un-boosted) with concomitant rifampicin, steady state pharmacokinetics and safety of atazanavir and rifampicin were determined in healthy volunteers. However, although safe and generally well tolerated, atazanavir 300 mg or 400 mg every 12 hours did not maintain adequate plasma exposure to effectively treat HIV infection when co-administered with rifampicin 600 mg every 24 hours. Therefore, co-administration of atazanavir and rifampicin must be avoided and further study is needed to investigate the role of ritonavir in limiting the inducing effect of rifampicin on atazanavir exposure.

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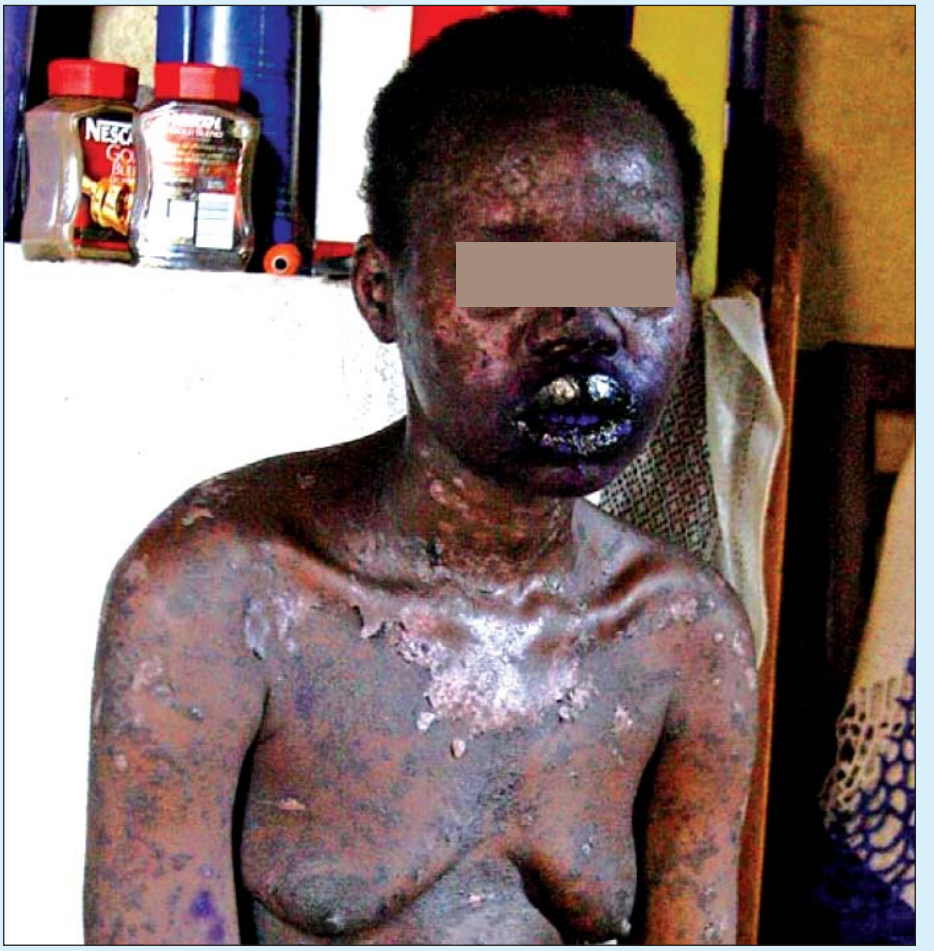
Can Septrin be given with antimalarials?

By Robinah.N.Lukwago (B. Pharm)

Approximately one million pregnancies per year are thought to be complicated by co-infection with malaria and HIV in sub-Saharan Africa[1]. Maternal malaria infection has been associated with maternal anaemia, infant low birth weight and maternal and infant mortality. Maternal HIV infection has also been associated with maternal anaemia and low birth weight and with increased risk of maternal malaria[2]. HIV-associated risk of maternal malaria affects women of all gravidities, thus attenuating or even eliminating the decrease in malaria parasitaemia normally seen in HIV-negative multigravidae[3]. The prevalence of maternal anaemia and incidence of low birth weight are both higher in pregnancies affected by HIV/malaria co-infection than in pregnancies affected by malaria or HIV alone. In the presence of co-infection, anaemia prevalence and low birth weight incidence may both exceed 35% in some subgroups[4]. Maternal malaria/HIV co-infection may also increase the incidence of mother-to-child transmission of HIV, perhaps because malaria infection is known to increase HIV viral load, although published evidence has been inconsistent[4, 5].

WHO now recommends insecticide-treated bednet use and intermittent preventive treatment for all pregnant women living in areas of stable *Plasmodium falciparum* transmission in Africa, along with antenatal HIV testing and antiretroviral therapy if indicated[6, 7]. Sulfadoxine-pyrimethamine (Fansidar) is generally regarded as the preferred antimalarial medication for intermittent preventive treatment, although its effectiveness is now threatened by rising levels of drug resistance[8,9]. Daily prophylaxis with Co-trimoxazole (Septrin) has been recommended for all HIV-infected pregnant women in sub-Saharan Africa[10]. Thus, opportunistic infection prophylaxis with Septrin and malaria prevention with fansidar involve two similar sulfa drugs for HIV-infected pregnant women, which may pose problems in view of the potential risk of increased adverse drug reactions (ADR's).

Many HIV-infected people are intolerant of Septrin because of its sulfonamide component[11, 12]. The risk of adverse reactions to Septrin in HIV-infected people has been estimated at 26·3 per 100 person-years, increasing substantially with advancing immunosuppression. The likelihood of adverse reactions also appears to vary by sex and race, and may be higher in women[11]. Studies have shown that concurrent administration of fansidar and septrin has been associated with a substantially increased incidence of severe adverse reactions in HIV-infected patients, and is therefore not recommended[4].



A patient suffering from a severe adverse drug reaction

Because Fansidar is not as effective against bacterial pathogens[13, 14] Septrin might be used to prevent both bacterial infections and malaria. Septrin has been used effectively to treat malaria in children, and daily use of Septrin by non-pregnant HIV-infected adults has been associated with reductions of over 70% in the incidence of febrile malaria parasitaemic syndromes[15, 16, 17]. However, no published data yet describe the effectiveness of daily Septrin for the prevention of malaria and its consequences (specifically maternal anaemia, placental parasitaemia, and low birth weight) during pregnancy. Nevertheless, WHO now recommends daily Septrin as an alternative to intermittent preventive treatment with Fansidar for immunocompromised HIV-infected women[1].

Septrin has been used effectively to treat malaria in children, and daily use of Septrin by non-pregnant HIV-infected adults has been associated with reductions of over 70% in the incidence of febrile malaria parasitaemic syndromes.

Operational constraints resulting from late diagnosis may limit the use of daily Septrin for malaria prophylaxis. Women who are not diagnosed with HIV until after the first antenatal visit may not present for HIV care until late pregnancy, especially where HIV care is not offered at the antenatal clinic itself. In many settings, prescription

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Management of patients with fev

By Umaru Ssekabira (**M.B.Ch.B, MSc CEB**)

Introduction

Presumptive treatment of patients with fever as malaria is widely advocated in Africa. In resource limited settings like Uganda, febrile episodes are commonly treated with an antimalarial, often in the absence of a blood smear or even when the smear is negative.

Over-treatment of malaria was acceptable and even promoted in the era of inexpensive and safe chloroquine monotherapy. In the new era of artemisinin-based combination therapy (ACT), presumptive treatment becomes economically and clinically less acceptable. All clinicians need to appreciate the potential benefits of withholding antimalarial treatment from patients with a negative blood smear for malaria parasites which include:

- Clinicians are more likely to focus on the true cause of fever.
- The true cause of fever may be managed in a timely manner instead of being delayed by unnecessary antimalarial treatment.
- It reduces the number of unnecessary antimalarials given which is more cost-effective.
- Targeting antimalarial treatment to those patients who have malaria may limit the development and spread of drug resistance.
- It reduces the risk of adverse events due to unnecessary antimalarials.

The reasons why health workers treat patients with a negative blood smear with antimalarials include:

- Belief that a febrile patient may still have malaria even when the blood smear is negative
- The need to adhere to the MOH treatment guidelines which recommend treatment of fever with an antimalarial even when the blood smear is negative.
- Inability to make any other definitive diagnosis.

In a study done at Mulago Hospital, out of 1,602 patients whose blood smears for malaria parasites were negative at the first visit, only 12 (0.8%) patient's progressed to uncomplicated malaria within seven days. This suggested that the majority of patients whose blood smears were negative did not have malaria.

Interpretation of a negative blood smear in a patient with fever

The purpose of doing a blood smear is ideally to confirm diagnosis and guide treatment decisions. A negative blood smear in a patient with fever may mean the following:

- The patient has been exposed to a partially effective antimalarial or inadequate doses of an effective drug
- The patient may have malaria but parasites not seen because of low parasite count or technical error
- The patient may not have malaria but another disease that presents as malaria

Possible causes of fever in a patient with a negative malaria smear

For children

- Respiratory tract infections: common cold, pneumonia, tuberculosis and sinusitis
- Otitis media
- Viral infections: measles, mumps, rubella, chicken pox and HIV
- Urinary tract infections
- Gastroenteritis
- Meningitis
- Septicemia

For adults:

- Bacterial infections: meningitis, tuberculosis, typhoid and sepsis
- Parasitic infections: toxoplasmosis, filariasis and amoebiasis
- Viral: HIV, infectious mononucleosis, yellow fever
- Tumors: lymphomas
- Drug reactions

Management of a patient with fever but a negative smear

Assuming that the test has been done with a well maintained microscope and stains, the clinician should re-assess the history, clinical examination findings and the laboratory results. If the health facility and the laboratory can do more investigations the clinician should investigate for other causes of the fever basing on the history and clinical findings.

Further investigations in febrile illness with negative blood slide

Below is an outline of investigations that may be carried out in a patient who presents with fever but a negative smear:

- Blood films (Repeat a malaria smear, comment on the morphology white blood cell and red blood

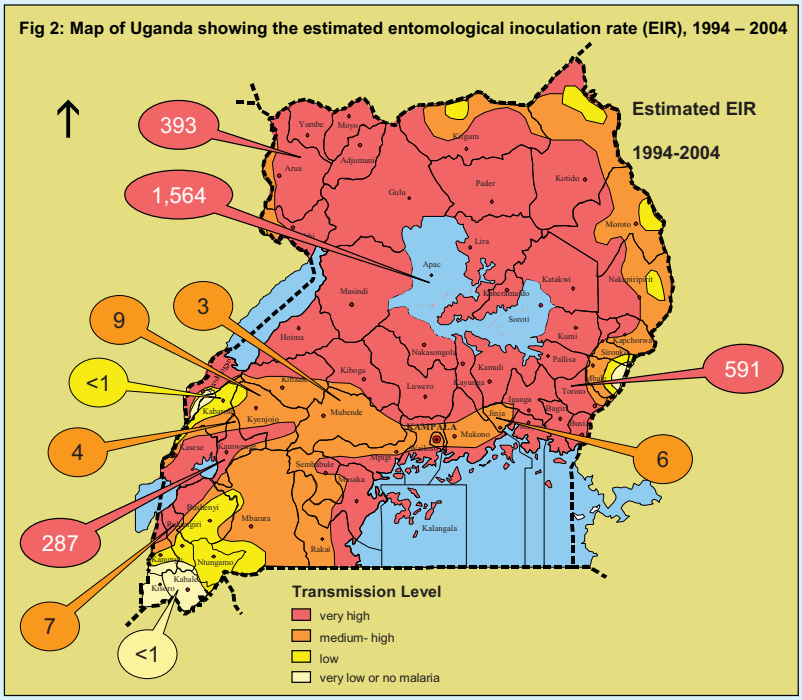

Fig 2: Map of Uganda showing the estimated entomological inoculation rate (EIR), 1994 – 2004

ver but no malaria parasites seen

cell distribution)
- White blood cell count
- Urinalysis
- Stool analysis
- Chest x-ray
- Sputum microscopy
- Blood culture & sensitivity
- Serology
- HIV, Hepatitis
- Biopsy

Blood film examination can be an important tool in excluding important causes of fever like leukemia and sickle cell anaemia. Bacterial infections are commonly associated with increased neutrophils while viral infections are associated with increased lymphocytes. Some cancers, for example leukemia and lymphoma, are also associated with markedly raised white cell count. There are also situations that are associated with abnormally low white cell counts. Examples include viral infections like HIV and conditions that depress the bone marrow.

When all the above is finalised, the clinician should manage the patient according to the algorithm in Figure 1.

To determine the probability that a patient has malaria, consider the following factors:
- Age: Children less than five years are at highest risk.
- Immune status: Pregnant women and HIV-positive patients are at higher risk.
- Transmission intensity: risk is directly proportional to the entomological inoculation rate (EIR), which is a measure of the frequency of infection and is defined as the number of infective bites by anopheles mosquito per year.

Situations where antimalarials can be given

If a patient has previously taken antimalarials, he/she should be asked about what drug was taken, at what dosage, and whether or not they vomited drugs given orally.

If inappropriate drugs or dosages were given, then give the recommended antimalarial drug in the correct doses. The current malaria treatment policy recommends use of artemether/lumefantrine as the first line drug for uncomplicated malaria amongst patients who are five months and above and are not pregnant.

If a patient received an appropriate drug but did not complete treatment, he/she should be encouraged to complete the treatment.

If the reassessment does not lead to identification of the actual cause of the fever, it's advisable that the patient be given an anti-pyretic and be followed up in two days or advised to return earlier than that if the condition worsens. If there is an identified cause of fever then the clinician should give treatment appropriate for that illness (refer to the national standard treatment guideline for Ministry of health 2005).

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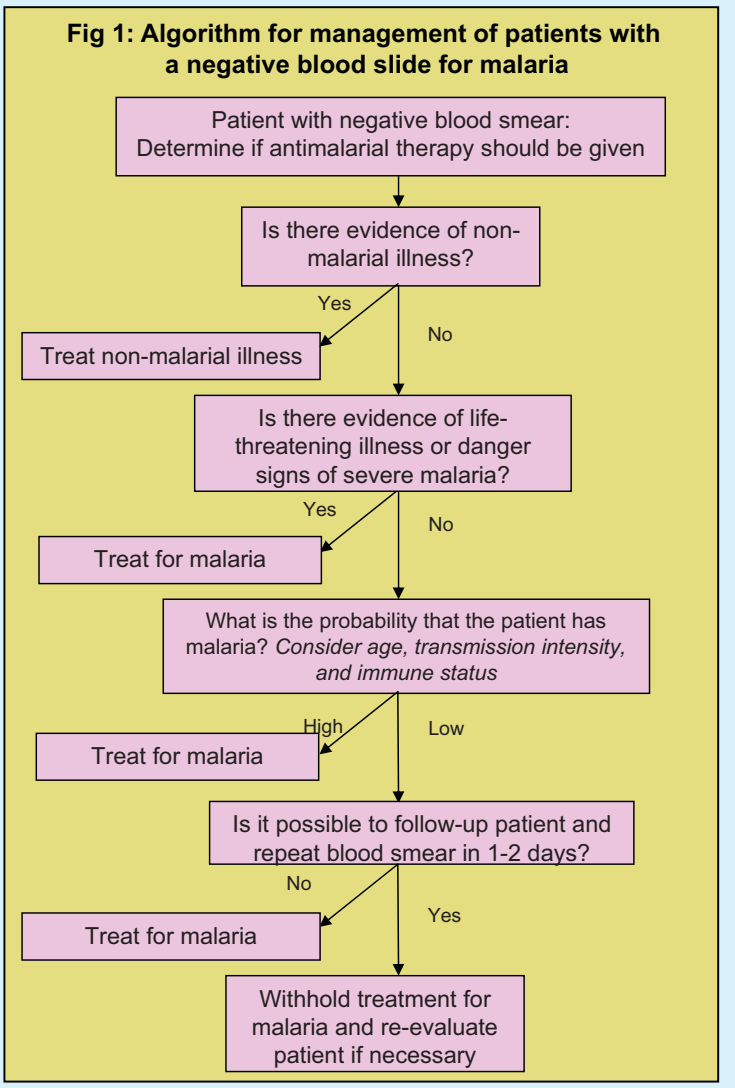
Fig 1: Algorithm for management of patients with a negative blood slide for malaria



Septrin vs antiretrovirals

of Septrin may also be contingent on clinical and/or laboratory staging, which may introduce further delays in initiation of Septrin prophylaxis. If Septrin is not begun until the third trimester, malaria-related maternal anaemia and fetal growth retardation may already have developed.

Therefore given that both malaria and HIV/AIDS are leading infectious diseases in our resource limited setting, it is important that studies are conducted to generate evidence on the efficacy of Septrin prophylaxis on reducing rates of placental malaria and anemia in HIV-infected pregnant women.

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Circumcision Checks HIV

Review by Mohammed Lamorde (MBBS)

On December 12, 2006 the Data and Safety Monitoring Board halted the circumcision study in Rakai, Southwestern Uganda, due to efficacy. Interim results of the randomised controlled trial in Rakai revealed 51% fewer HIV infections in a group of circumcised men compared to an uncircumcised control group over a period of two years. With these results male circumcision becomes the first new, proven HIV prevention method in over a decade.

The Rakai circumcision study was initiated following observational studies suggesting lower rates of HIV transmission in areas with high rates of male circumcision. The foreskin is vulnerable to tears and ulcers (e.g. secondary to sexually transmitted infections) and this can create an entry point for HIV. Following circumcision the new skin is keratinized, reducing its vulnerability to HIV.

The Rakai trial enrolled 4,996 men aged 15 - 49 and randomized them into two groups. The intervention arm (n=2464) was offered circumcision within two weeks of enrolment. For the control arm (n=2522) circumcision was to be offered after a delay of two years. Informed consent was obtained .

Adult male circumcision was found to be safe when performed by trained healthcare workers under aseptic conditions. The benefit of circumcision was not obvious in the first six months but became progressively more protective after that time. There were also 50% fewer episodes of genital ulceration among circumcised study participants. The trial results are supported by findings in studies in Kenya and South Africa which also found similar rates of protection in circumcised participants.

The study was done by the Rakai Health Sciences Programme, a partnership involving the Uganda Virus Research Institute, Makerere University Institute of Public Health, Columbia University and Johns Hopkins University.

The investigators caution that circumcision offers only partial protection and must be used as a part of a comprehensive HIV prevention strategy including education, limiting sexual partners and condom use.

The writer is a PK Medical Doctor, Infectious Diseases Institute

Teamwork is key in malaria care

By Jimmy Andama

The Integrated Management of Malaria course at IDI provides an excellent opportunity to build teams and improve the quality of services in health care settings. All staff of Omugo Health Centre IV in Arua District and members of the District Health Management Team (DHT) were trained as a team on management of patients with malaria. The training was attended jointly by clinicians, lab personnel, records staff and members of the DHT. This training was unique because earlier malaria management training only targeted specific categories of health workers independently. The records staff had never been thought about as an important and relevant category of staff in the management of patients.

The course is offered by Joint Uganda Malaria Training Programme (JUMP), Uganda Malaria Surveillance Programme, Makerere University-University of California San Francisco collaboration and Ministry of Health.

As part of the training we were facilitated to develop a health facility work plan aimed at improving the quality of care that we offer to patients suspected to have malaria. We have implemented this plan and it has contributed to the overall improvement in our health care delivery systems. These include:

- Since the training took place, there has been a general improvement in management of fever, particularly malaria, through the use a more team-based approach. There is increased utilisation of the laboratory. This indicates that clinicians try to confirm malaria before deciding the treatment to prescribe. The number of malaria blood slide smears that are positive has decreased, indicating that there is improvement in malaria management especially the preventive aspects which we started emphasising after the training.
- Irrational use of the antimalarial containing artemether and lumefantrine (Coartem) has greatly reduced and thus the total number of doses of coartem dispensed to patients has reduced. Before the training, most fever patients were being given antimalarials despite a negative blood slide.
- Distribution of insecticide-treated mosquito nets to pregnant mothers at antenatal care (ANC) has reduced the number of malaria cases in pregnancy and most mothers tested for malaria, test negative.
- A health education programme on malaria prevention and control was started within the health unit and the community including schools.
- Data on malaria cases is being collected in time, kept securely, analysed and fed back given to every staff. This data is being utilised to plan for ordering of supplies.
- As a result of prompt and proper management of patients at the outpatient department, there have been fewer patients admitted with severe malaria.
- There has been increased team work in the management of patients at the centre, resulting in the better patient management. The staff have formed a task force that is supposed to hold a meeting every month to review issues pertaining to malaria. This task force makes a presentation about their work in every general staff meeting.

The author (R) in class with other trainees

Challenges

- The new approach has increased the work load in the laboratory, since we prefer that every fever be investigated.
- The national drug supply system has remained poor, leading to stockouts of vital drugs.
- Because of the improved services, staff are overwhelmed by the influx of patients from outside our usual catchment area.

Conclusion

This course has turned our performance around in a very dramatic way. It has helped to re-align us in the true medical professional path, and I would like to suggest that it be rolled out country wide so that every Ugandan Health worker is reached thus contributing to the effort to significantly reduce the burden of malaria in this country.

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A group photo of trainees attending a course at IDI on integrated management of malaria

Interaction between Malaria and HIV

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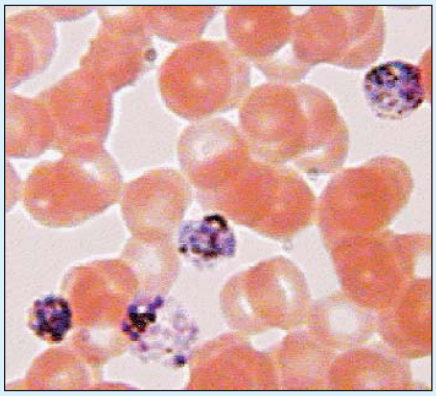
altered by HIV so that the burden is shifted from primigravidae to all pregnant mothers[5].

HIV and severity of malaria: Whether HIV infected individuals are at risk for severe malaria is still inconclusive. Few studies have examined the effect of HIV on the severity of malaria and these have shown that HIV-infected adults in regions of unstable malaria transmission are at increased risk for severe and complicated malaria and death[6].

HIV and malaria diagnosis and treatment outcome: Diagnosis of malaria in many resource-limited settings is based on presence of fever. Drugs are commonly prescribed without laboratory confirmation. Given that HIV infected individuals may present with fevers due to other opportunistic infections, absence of laboratory confirmation of malaria may cause over-estimation of the malaria burden and inappropriate administration of antimalarial drugs. A study done in Tanzania found that 95% of all patients presenting with fever were treated with quinine and yet only 46% of them had a positive blood smear for malaria[7]. This misdiagnosis puts patients at risk of death from other causes of fever that may not be treated as well as risk of adverse effects of drugs that they do not require.

Regarding treatment outcome, some studies have suggested that HIV-infected individuals may have inferior responses to antimalarial therapy because of impaired host immunity. This could result from increased susceptibility to new malaria infections, or because of recrudescence of infection. Early studies did not show association between HIV infection and antimalarial treatment response[8]. However, more recent studies suggest that HIV infected patients may be at higher risk of treatment failure. A study done in Ethiopia showed delayed clearance of parasitemia in HIV infected adults treated with artemisinin for uncomplicated malaria[9]. A Ugandan study showed increased risk of re-infection rather than recrudescence among HIV infected patients after antimalarial treatment[10] while another study in Zambia showed that HIV infected patients with malaria and CD4 count <300/ul have higher risk of a recrudescent infection[11]. Conversely another study in Uganda found that the HIV positive patients who took routine cotrimoxazole prophylaxis had reduced risk of treatment failure when they were treated with sulphadoxine-pyrimethamine (SP)[12].



Deadly allies: Malaria parasites (L) and the Human Immunodefficiency Virus (R)

HIV and malaria transmission and prevention: Given that HIV infection increases the risk of malaria with increased parasitemia and treatment failure, we can hypothesise that even malaria transmission increases with increased disease burden on health care facilities. However, no studies have been conducted to support this association. Health care providers need to be more rigorous in preventing malaria in the HIV infected population. Routine cotrimoxazole prophylaxis has been shown to reduce the incidence of malaria[13]. Other malaria control measures include insecticide treated bed nets (ITNs), indoor residual spraying and intermittent preventive treatment (IPT) with SP in pregnancy. A study in Uganda reported a reduction in febrile parasitemia of 76% with cotrimoxazole prophylaxis, 92% with cotrimoxazole and antiretroviral treatment (ART) and 95% when ITNs were added to cotrimoxazole and ART[14]. Another study demonstrated that the risk of malaria among HIV-infected children receiving cotrimoxazole alone was decreased by 35% while the risk of malaria acquisition in individuals receiving CTX and ITNs was decreased by 97%15. Use of IPT with SP in pregnancy has been shown to be effective in reducing the burden of malaria in pregnancy[16]. Pregnant mothers require two doses of SP in the second and third trimester; however, a clinical trial in western Kenya showed that HIV-infected mothers require at least three doses to achieve a reduction of placental parasitemia similar to that seen in HIV-negative women receiving two doses of SP[16]. A recent study in Malawi confirmed that monthly SP (median three doses) was more effective at reducing rates of placental parasitemia than two-dose regimens, in women with and without HIV. However, IPT with SP may not be administered to HIV positive pregnant mothers on routine cotrimoxazole prophylaxis.

Reports from Malawi and Uganda showed a rise in viral load at the time of malaria infection and this reduced with effective antimalarial treatment. However, the effect that this may have on HIV disease progression is not known.

Effect of malaria on HIV: The immune response to malaria may increase the pool of lymphocytes available for HIV infection. Malaria antigens and pigments released during the burst of RBCs, stimulate cytokines like TNF alpha and G-CSF, which activate HIV replication, thus increasing viral load. Malarial episodes transiently increase viral load, and thus could theoretically have an impact on HIV disease progression and transmission. Reports from Malawi and Uganda showed a rise in viral load at the time of malaria infection and this reduced with effective antimalarial treatment. In areas where malaria infection is endemic, recurrent infection occurs. However, the effect that this may have on HIV disease progression is not known. Repeated

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malaria infections may accelerate HIV disease progression, thus the need for rigorous malaria prevention and treatment in HIV positive individuals. High viral loads have been shown to be associated with increased potential for HIV transmission.

Antiretroviral drugs, by boosting immunity, reduce risk for opportunistic infections including malaria. Some ARVS have been shown to possess antimalarial properties in vitro[17]. With increasing rates of antimalarial drug resistance, the World Health Organisation recommends the use of artemisinin-based combination therapy (ACT). However, there is no data on ACT interaction with antiretroviral drugs. The potential for interaction between ARVS and antimalarials should not be overlooked because these drugs follow similar processes when administered and are metabolised by the same cytochrome family of enzymes[18]. This interaction could result in increased or reduced plasma levels of either drug, with increased risk of toxicity or development of resistance respectively.

In summary, Malaria and HIV interact, leading to effects on the incidence, prevalence, clinical manifestations, treatment outcomes, drug interactions and toxicity. There are still gaps in knowledge on this interaction calling for research.

The potential for interaction between ARVS and antimalarials should not be overlooked because these drugs follow similar processes when administered and are metabolised by the same cytochrome family of enzymes

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Updates from CROI

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Drug-drug Interaction between Lopinavir/Ritonavir and Rosuvastatin

Hyperlipidemia is a common complication in HIV-infected persons on antiretroviral therapy but few HMG CoA reductase inhibitors (also known as statins) are used in this population because of the potential for drug interactions. Rosuvastatin is not a substrate for cytochome P450 3A4. Thus, drug interactions between rosuvastatin and protease inhibitors seemed unlikely.
Nevertheless, van der Lee et al [CROI 2006] showed a 1.5-2 fold increase in rosuvastatin (10 mg once daily) trough concentrations in HIV-infected subjects on lopinavir/ritonavir and advised to monitor possible adverse events when rosuvastatin is co-administered with protease inhibitors. The healthy volunteer study presented this year, however, showed that in the presence of lopinavir/ritonavir rosuvastatin (20 mg once daily) area under the curve (indicating total plasma exposure) and maximum concentrations were unexpectedly increased 2.1- and 4.7-fold and concluded that the co-administration should be avoided and studies to elucidate the mechanism for this interaction are needed.

The Effect of Atazanavir and Atazanavir/Ritonavir on UGT1A4 Using Lamotrigine as a Phenotypic Probe

There are two major categories of metabolism reactions called Phase I and Phase II; and drug interactions may involve drugs metabolised through both phases. Glucuronidation is the most important Phase II reaction and antiretrovirals may be eliminated following glucuronidation and may impact the activity of the reaction. For example, recently, it has been shown that lopinavir/ritonavir induces glucuronidation using lamotrigine as phenotypic probe for UGT1A4 (reduction in lamotrigine exposure of 55%). Atazanavir is known to inhibit glucuronidation through UGT1A1, leading to asymptomatic hyperbilirubinemia. The objective of this study was to evaluate the effect of atazanavir and atazanavir/ritonavir on UGT1A4 using lamotrigine as phenotypic probe. While atazanavir alone did not significantly influence glucuronidation of single-dose lamotrigine, atazanavir/ritonavir resulted in moderately decreased exposure (32% decrease) to lamotrigine.

Effect of Famotidine 20- and 40-mg Dosing Regimens on the Bioavailability of Atazanavir with Ritonavir in Combination with Tenofovir in Healthy Subjects

Atazanavir absorption is pH dependent. Previously, a reduction of 18 to 28% in atazanavir plasma exposure was observed when the H2-receptor antagonist, famotidine 40 mg every 12 hours was administered with atazanavir/ritonavir 300/100 mg in healthy volunteers. Tenofovir also decreases atazanavir exposures when coadministered with atazanavir/ritonavir by approximately 25 to 30%. The effect of lower doses of famotidine and tenofovir when simultaneously co-administered with atazanavir/ritonavir has not been studied. The objective of this study was to evaluate dosing strategies for famotidine to maintain atazanavir exposure when coadministered with tenofovir, in the presence of ritonavir. When famotidine 20 mg twice daily was administered with atazanavir/ritonavir and tenofovir, an estimated 20% decrease in atazanavir minimum concentrations was observed. When famotidine 40 mg was administered once daily, 12 hours apart from atazanavir/ritonavir, atazanavir minimum concentration was 23% lower relative to the control treatment. Famotidine 40 mg administered twice daily temporally separated from atazanavir/ritonavir and tenofovir (10 hours before and 2 hours after) resulted in decreases in atazanavir maximum concentrations, area under the curve and minimum concentrations of 26%, 21% and 28%, respectively.

Effects of Minocycline and Valproic Acid Co-administration on Atazanavir Plasma Concentrations

There is interest in studying the effects of both valproic acid and minocycline as adjunctive therapy for the treatment of HIV-associated cognitive impairment. The purpose of this study was to determine whether minocycline alone or in combination with valproic acid influenced atazanavir plasma concentrations in patients receiving atazanavir plus ritonavir. Minocycline coadministration resulted in decreased atazanavir exposure (area under the curve 33% decrease, minimum concentration 50% decrease), and there was no evidence that the addition of valproic acid mediated this affect

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In the news

Iopinavir/ritonavir tablets

Lopinavir/ritonavir capsules (Kaletra) should be stored in the refrigerator to maintain their stability. However this has been a challenge for many patients in the developing world who have limited access to refrigeration facilities. The development of a new dosage formulation of Lopinavir/ritonavir that does not have to be stored in the fridge has therefore been received with enthusiasm in many parts of the developing world. The new formulation is called Aluvia. It is the same high-quality, non-refrigerated product as Kaletra capsules manufactured by Abbot. Lopinavir/ritonavir is a recommended second-line treatment for HIV infection in the developing world by the World Health Organisation. Protease inhibitors, such as lopinavir/ritonavir, are important treatment options in the fight against HIV when first-line regimens fail. Abbott is developing a pediatric version of the lopinavir/ritonavir tablet to provide greater dosing flexibility for physicians to treat children living with HIV.
Source: www.abbott.com

Pharmacologists to meet

A four day networking meeting for clinical pharmacologists working in the field of HIV/AIDS, tuberculosis and malaria is being organised by the Infectious Diseases Institute and the Department of Pharmacology, Makerere University. The meeting will focus on the development of Clinical Pharmacology in Africa and is supported by the European-Developing Countries Clinical Trials Partnership (EDCTP). Participants will come from from Uganda, South Africa, Nigeria, Ireland, United Kingdom and USA.