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FACULTY OF MEDICINE
MAKERERE UNIVERSITY

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INFECTIOUS DISEASES INSTITUTE

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

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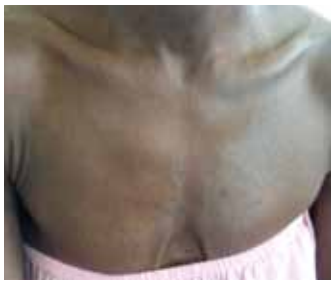

A 56 year old HIV infected woman with Chronic Headache, abnormal vision and vertigo.

Vennie Nabitaka [1], Brandon Auerbach [2], Aggrey Semeere [3]
Stephen Ssebulime [1], Stella Namirembe Magara [4]

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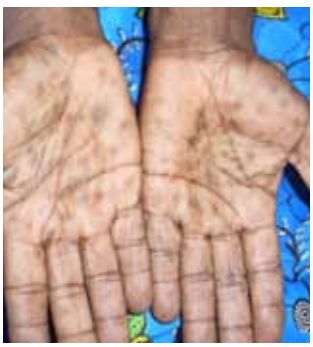
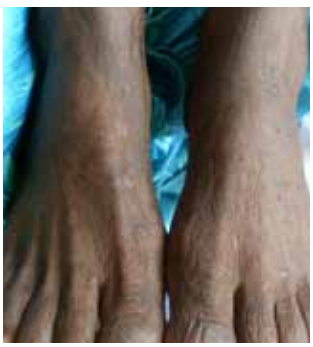
Abstract

A 56 year old ART-naïve HIV-infected woman presented to Kiboga with a 2month history of headache and vertigo, with associated mild confusion, memory loss, drooping of the right eye, dizziness and a staggering gait for 2 weeks. Clinically she had a generalized non-pruritic maculopapular rash on her palms and soles. She had a wide-based gait with shortened stride length, severe staggering (required assistance to walk) and a positive Romberg's sign. Both Serum and CSF RPR were positive. With a diagnosis of secondary syphilis with neurological symptoms, she was treated with intravenous Benzyl Penicillin and in 10 days the cutaneous and neurological symptoms had markedly improved and she progressively went on to be symptom free.

History of the Present Illness

A 56 year old HIV-infected woman who was ART-naïve presented to Kiboga hospital complaining of a headache and progressive vertigo for 2 months. The headache was moderate, frontal, was not throbbing and had no aggravating or relieving factors. The vertigo was initially mild and associated with a sensation of aural fullness, with no tinnitus but reduced hearing on the right side. She had no nausea or vomiting. She initially had staggering (unsteady) gait (ataxia) which worsened to a point that she needed help to walk over 2 months. Other associated symptoms include confusion, short term memory loss (she was forgetting days of the week and where she had placed things), with reduced vision in the right eye with floaters which she described as "small snakes in the eye". She neither had seizures, shooting pains nor lower limb sensory changes. She had full control of sphincters. She was treated with ibuprofen and promethazine for one week for suspected peripheral vertigo due to vestibular disease which never alleviated her symptoms. She had mild generalised tremors with no paraesthesias, peripheral neuropathy, dysarthria, or neck stiffness.





Review of other systems

She had a two month history of a generalized faint, diffuse skin rash that later worsened and became more evident on her palms and soles. She was also anorexic, had lost 8 kg over 6 months with no fever or night sweats.

Past medical and surgical history

She tested HIV positive, WHO Stage IV (HSV infection for > 1 mo and >10% wt loss, 1 year prior to presentation). Her CD4 count was 167 cells/mm^3 at presentation. She was on co-trimoxazole prophylaxis only and had no known drug allergies. She had no back deformity, pain or trauma.

Family & Social history

She had separated from her husband 3years prior as a third wife. She had had unprotected sex with a casual partner-20 years younger, 7months earlier. His HIV status was unknown. Both of her parents were alive and well and she occasionally used alcohol but not tobacco.

continues on Pg 2

Editorial

Dear reader,

ATIC is evolving into the Learning Innovations Center which will be used by the Infectious Diseases Institute (IDI) as a platform to reach out and build the capacity of health workers in Uganda and beyond, from right where they are, without compromising their work schedules. The ATIC newsletter is privileged to be one of the tools the Learning Innovation centre will use, and so you will see a few changes beginning with this edition.

We shall now have articles from health care workers in the field sharing with us their experiences. We encourage you our readers to write articles sharing with us your unique case studies, and experiences in the field. This month we kick start this with interesting cases from Kiboga and Mayuge districts. From Kiboga, we have a case that was presented through IDI's outreach programme KKP, and from Mayuge district, one of the ATIC callers shares his experience from a rural ART centre.

The new features in this newsletter will also include crucial updates. This month, we have two updates; one from the ARKS project at the Infectious Diseases Institute (IDI) which is running a Kaposi's sarcoma biopsy service for early detection of the disease, and the other about the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention held in July 2011, in Rome, Italy.

The Integrated Infectious Disease Capacity Building Evaluation (IDCAP) reminds us about the importance of keeping good quality medical records in the quality management of patients at our health centers.

As we strive to give you quality drug and treatment information for better patient management, we have included an article on Rifampicin's interaction with drugs other than antiretrovirals, as well as the informative 'Ask ATIC' section.

Please read on and enjoy the new ATIC newsletter.

Sheila Karamagi
ATIC Research and Communications

A 56 year old HIV infected woman | *continues on Pg 2*

Physical examination

She was drowsy, had difficulty answering questions and following simple instructions. Her skin had a diffuse generalized non-pruritic hyper pigmented maculopapular rash sparing mucus membranes but more marked on her palms and soles involving the creases as well. The lesions were non erythematous, scaly, circular and 8 mm in diameter. She had patchy alopecia, mild mucosal pallor with no lymphadenopathy. She had a healed Herpes Zoster scar at left T6 dermatome. Her BMI was 19.4.

Vital Signs: Temperature was 36.5 °C; BP 90/60mm/Hg, Pulse 119/min and Respiratory Rate 16 /min.

Nervous System:

She had bilateral ptosis and could not hear whispered words in her right ear. The pupils were equal and reactive to light. Fundoscopy and a split lamp exam were unavailable. Her muscle bulk was normal (in comparison to her borderline low BMI). Muscle power and tone were normal in all limbs. Reflexes were 2+ and symmetric. There were no resting tremors but mild tremors were present when she moved the hands.
Finger to nose testing revealed mild dysmetria (inaccuracy of targeting) at full extension of arm and finger. Heel to shin testing revealed moderate lower extremity in-coordination of her left leg.
She had a wide-based gait with shortened stride length, severe staggering (requiring assistance to walk), Romberg's sign was present (loosing balance when feet are put together and eyes are closed.)
Proprioception, temperature, pain, and light touch sensation were normal in her feet.
Cognitive assessment revealed predominately short term memory loss with reduced attention and concentration.
She had no physical deformity, lesion or area of tenderness in the back.
Cardiac, pulmonary and abdominal exam were unremarkable.

In view of the above history and exam findings, our differential diagnoses were:

1. Possible Syphilis infection with
a) Neurological manifestations as evidenced by

- Confusion (in-attention, poor concentration and Short term Memory loss)
- Positive Romberg's test –Ataxia suggests posterior column disease.
- Reduced coordination – Dysmetria and in-coordination.
- Hyporeflexia

- Hearing loss
- Nystagmus probably due to syphilis in the vestibular system.

b) Ocular manifestation; as possible uveitis

c) Skin Manifestation with the hyperpigmented generalized non-pruritic maculopapular rash.

2. Stage IV HIV with possible aseptic meningitis with possibly viral etiology affecting the cerebellum.

3. Toxo-encephalitis and opthalmitis

4. Spinal cord disease

Laboratory tests done were:

- Complete blood count: WBC: 5.5x103/μl (PMNs: 84%), PLT: 274 x103/μl and HB: 9.4 g/dl).
- Liver and Renal function tests were normal.
- Serum CRAG was negative
- Serum RPR was positive.
- CSF analysis: Clear and colorless. WBC count 270 x 106 cells/L (Lymphocyte predominant). There were no organisms on Gram and India ink stain. CSF RPR positive. CSF protein was not measured (unavailable strips).

Final diagnosis

In view of the neurological and cutaneous signs and symptoms in addition to the positive serum and CSF RPR, we concluded that the most likely diagnosis was Treponema Pallidum infection with WHO Stage IV HIV-infection. There were features of both secondary syphilis given the cuteanous manifestations as well as neurosyphilis given the myelopathy, ocular and neuropsychiatric manifestations.

Follow up:

She was admitted and received IV 2.4 m/u of Benzyl Penicillin (aqueous crystalline) which was given intravenously 6 hourly for 10 days (instead of 4 hourly for 14 days as planned due to understaffing). She was also prepared and initiated HAART with Tenofovir-300mg, Lamivudine-300mg and Nevirapine-200mg daily.(TDF/3TC/NVP). Within ten days, the headache, vertigo and ataxia had greatly improved. She still had a mild degree of memory loss, confusion and diminished hearing. A pelvic exam at this follow up visit revealed wet-appearing, mucous-covered papules in the intertriginous areas of the groin, consistent with condyloma lata .She was discharged on Doxycycline PO 100 mg BD x 2/12. This was done because she had had suboptimal therapy with penicillin.

Within six weeks following ART initiation and treatment for syphilis, she had gained 3kg. She still had photophobia and diminished hearing on the right side with no other neurological deficits.

At her ten week visit the photophobia had resolved, and her only complaint was diminished hearing on her right side. A repeat serum RPR was positive.
She is followed up in the HIV outpatient clinic and was encouraged to notify the partner.

Discussion

Syphilis is caused by the spirochete Treponema pallidum .The first, or primary, stage of syphilis presents as a chancre. Usually two to three weeks after sexual contact with a syphilis-infected partner, a painless papule which can grow to 2 cm in diameter, forms. Hematogenous dissemination of treponemes early in infection can result in the clinical manifestations of secondary syphilis. Non-specific symptoms of secondary syphilis include malaise, sore throat, headache, weight loss, low-grade fever, or muscle aches. More specific signs include rash, mucosal lesions, condylomata lata, alopecia, and generalized lymphadenopathy.

Late or tertiary syphilis may manifest as late benign or gummatous syphilis, cardiovascular syphilis, and neurosyphilis. In the general population, infection with Treponema pallidum causes early dissemination to the CSF (neuroinvasion), but neurological signs and symptoms do not manifest until tertiary syphilis. However in HIV-infected patients, neurological disease may present during all stages of syphilis, with secondary syphilis being the most common as in this patient.[1]

This patient presented with two months of headache, right-sided tinnitus, hearing loss, ataxia and confusion. She had patchy alopecia (alopecia areata) and a diffuse, non-pruritic maculopapula rash that was worse on her palms and soles and that did not spare the creases of her palms and soles. There are many causes of rashes in the palms and soles but syphilis in particular usually does not spare palmar/sole creases. Photophobia worse at night was probably a manifestation of syphilitic eye disease (uveitis, iritis, optic neuritis, neuroretinitis). Ataxia, hearing loss, and vestibular symptoms have been reported in HIV-infected patients with neurosyphillis.

A viral or bacterial middle/inner ear infection due to an organism other than Treponema pallidum could have resulted in inflammation causing this patient's tinnitus and vertigo. Central causes of vertigo, such as a cerebellar infarction, were unlikely because of the absence of dysarthria and tremor. The usefulness of a brain CT scan in this patient was considered although not done for financial reasons. HIV dementia is unlikely to explain two week history of confusion of abrupt onset.

Because of the inability to grow T. pallidum in culture, the diagnosis of syphilis depends upon the sexual exposure history, recognition of characteristic clinical features, and interpretation of diagnostic testing. Rapid Plasma Reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests are non-treponemal tests that detect antibodies to cardiolipin. False positives can be due to transient factors (acute bacterial, viral, malaria infections, pregnancy) and chronic factors (infections e.g. HIV, autoimmune disease, rheumatic disorders e.g. SLE, some malignancies like lymphoma, cirrhosis, drug abuse, and old age). Although there were factors like HIV infection that could render her positive RPR values false, the likelihood of neurosphyllis was high with the presence of all the clinical features described above. In neurosyphillis, CSF usually shows increased protein and nearly always > 5 WBCs/ml. RPR/VDRL in the CSF is highly specific though insensitive and may be negative in up to 50% of the cases. [2,3,4]

RPR/VDRL titers correlate with disease activity. Treatment response is monitored by dilution titers. In patients with high suspicion of syphilis but negative VDRL/RPR, the serum may need to be diluted first for the test to react. This is termed the "prozone phenomenon," and occurs because of the presence of a large amount of antibody. [3,4]

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The HIV-infected patient with syphilis should be treated with the same regimens as recommended for HIV-seronegative patients. The exact formulation varies with the stage of syphilis, but penicillin is the drug of choice. The recommended treatment for primary and secondary syphilis is long-acting benzathine penicillinG (2.4 million units IM) in a single dose. Neurosyphilis, HIV-infected patients with neurosyphilis or syphilitic ocular disease [15] should be treated with aqueous crystalline penicillin G (3 to 4 million units IV every four hours or as a continuous infusion for a total daily dose of 18 to 24 million units) for 10 to 14 days. Other than doxycycline, which penetrates the CNS well, there are few alternatives for the treatment of neurosyphilis[4]. Some cases of successful treatment of symptomatic neurosyphilis with parenteral ceftriaxone have been reported.[6-8].

It is recommended to avoid any sexual activity during treatment and to notify all sexual partners so that they can be tested and treated accordingly.

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Acknowledgements:

We appreciate the patient for her cooperation. We also would like to acknowledge the dedicated members of the Fogarty Kiboga study team: Justine Bukirwa (Fogarty laboratory technologist), Samuel Kabanda (Fogarty study nurse), Bbosa Robert (Fogarty study assistant and HIV counsellor), and the Fogarty study principle investigator Dr. Yuka Manabe. We thank the extremely hard working Kiboga ART clinic staff, led by the ART clinic in-charge Sister Mbabazi. Our gratitude also goes to Dr. Ivan Mambule for his support in the writing up this case report.

Does he need second line? Experiences from a rural ART centre, Uganda.

Buuka Godfrey Zziwa – Clinician ART clinic, Buluba Hospital, Mayuge District.

Summary

With the wide availability of first line HAART in Uganda close to 7 years now, treatment centres are already faced with the threat of patients failing to respond to their first line regimen and requiring a change to second line regimens. The decision about when to switch therapy and which second line regimen to switch to, should be made carefully. This decision requires some technical expertise and a careful consideration of the patients' history and lab findings and therefore remains a big challenge for rural health centers.

We share our experience from Buluba Hospital, a rural HIV treatment centre in Mayuge district through these **Case reports:** The following table summarizes the clinical profiles of three clients on HAART who were presented for discussion at one of the 'problem case meetings' in our ART clinic, the decision we made and lessons that we have learnt from them.

All the 3 clients had good self reported adherence to HAART and regularly kept their clinic appointments for ART. They had been clinically stable on ART. In all cases, decision to change to 2nd line was deferred by the attending clinician because they were 'clinical stable'.

	Clinical profile	CD4 cell count Profile	Clinical decision	Viral load (from JCRC).
Case 1	40 yr old female. Started ART on 20/09/06. Initial regimen D4T/3TC/NVP. Changed to AZT/3TC/NVP on 28/09/09 due to lipodystrophy. Still on this regimen. No h/o TB Her spouse is on 2nd line (Kaletra, AZT+3TC) for 7 months now.	No baseline CD4 cell counts were done at ART initiation due to lack of service at the time. WHO stage III Later CD4 cell counts : 6/08/07 = 156 27/06/09 = 51 11/06/10 = 49	Possible immunological failure. Do a Viral Load	< 40 copies per ml.

Case 2	42 yr old male. Had TB in June 2007 and found to be HIV-1 positive as well. Took TB drugs from June 2007 for 8 regular months. Started ART on 4/07/07 on D4T/3TC/EFV. Now on AZT/3TC/EFV.	Baseline CD4 cell count = 12 on 15/06/07 Later: 28/01/08 = 27 22/12/09 = 35 19/07/10 = 43	Poor immunological response. Do a Viral load	< 40 copies per ml.
Case 3	41 yr old female, started ART in 10/07 on AZT/3TC/EFV until now. No h/o TB.	Baseline CD4 cell count = 10 on 20/08/07. Later 24/01/09 = 159 15/07/10 = 10 17/09/10 = 18	Poor immunological response. Needs viral load	1,436 copies per ml.

Viral load done with COBAS TaqMan detection range 40-10,000,000 copies/ml.

Case 1: has been on HAART for over 4 years and with the generally expected average CD4 cell count rise of 50-100/ml per year [1], she should be having an average CD4 cell count of 350- 400cell/ml and above by now. Based on the available CD4 cell count profile, the appropriate decision would be to switch her to second regimen. However, the undetectable viral load implies that HAART is still effective in suppressing viral replication.

Case 2: has been on HAART for over 3 years but his CD4 cell count has not risen above100 cells/ml. His regimen should have been switched more than a year ago but the decision was not taken because he was clinically stable. His viral load report shows that his current regimen is still effective in suppressing viral replication.

For both cases, the final decision we made was to maintain them on their current regimen, re-emphasis HAART adherence, prevention of re-infection through proper condom use and continue with CD4 cell count monitoring. We also decided to monitor viral load for these patients but this is not guaranteed since none of the patients can meet the cost and for all the cases, the cost was paid by IRCU HIV Project (each viral load cost Sh.135,000).

Case 3: despite over 3 years of HAART, her CD4 cell count has not risen at all. Though we were expecting a markedly high viral load, the available viral load (1,436 copies/ml) may imply an attempt at suppression of viral replication. Our final decision was to defer switching but carry out an in depth assessment of the client. For all cases, CD4 cell count monitoring was irregularly done because of limited availability of testing services.

Discussion.

There has been a remarkable increase in the number of patients on HAART. According to the Uganda AIDS Commission (UAC), 54% of an estimated 373,836 individuals eligible for ART had received it by 2008 [5]. Indeed if all the eligible patients accessed HAART, it could make HAART one of the commonest administered chronic medications in Uganda. A sizeable number of clients have now been on HAART for some years and one of the predictable challenges will be failure to respond to the 1st line and a need to change to 2nd line therapy. Due to the limited experience with HAART among many clinicians, and the serious implications of making the switch early or late, making a decision to switch a client becomes a difficult one.

Treatment failure can be defined based on clinical, immunological or virological criteria[1]. In most treatment centers, virological monitoring is not available so most clinicians relay on clinical and immunological criteria.

Using immunological criteria, all the above 3 cases fulfill the definition of treatment failure.

However, use of viral load monitoring in the HIV positive clients has isolated a group of clients who present with suboptimal CD4 cell count reconstitution despite virological suppression [2]. Case 1 and 2 depict this observation. Risk factors for the suboptimal CD4 cell count reconstitution phenomenon include low CD4 cell count level, older age at initiation of HAART among others [2,3]. All 3 cases observed here were in their 40s and with very low CD4 cell count levels when ART was initiated.

The clinical implication of suboptimal CD4 cell reconstitution is still unclear. Studies on suboptimal CD4 cell reconstitution and its clinical implication have had mixed results. A study done in Uganda found no increased risk of opportunistic infections among such patients compared to those with good CD4 cell count response[2] while other studies have shown increased incidence of OIs / or death [4].

Some of the other unanswered questions we had concerning these patients were:

- Does any further CD4 cell count monitoring have any clinical benefit in these patients?
- If viral load monitoring is possible, how often should it be done?

From the above cases, it is clear that in order to maximize the benefits of 1st line therapy, patients with immunological failure should have a viral load done before switching to 2nd line therapy. This will prevent switching the clients unnecessarily.

Acknowledgment: We thank Dr Carol Nanziri and the team at IRCU for sponsoring the Viral load tests for the clients above.

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Supplement……

By. Dr. Damalie Nakanjako, Ssewankambo Research Fellow, IDI.

I write this in response to the question raised by Buuka Zziwa on suboptimal CD4 reconstitution in an HIV treatment program in rural Uganda.

Case 1 and Case 2 present typical patients with suboptimal CD4 reconstitution despite viral suppression (SO-CD4). The phenomenon of SO-CD4 has been described among 40% of individuals receiving antiretroviral therapy within the Infectious Diseases Research cohort[1]. However, it is difficult to identify the proportion of patients with this phenomenon within many HIV treatment centers in Uganda mainly because viral loads are not done routinely. Without viral loads, many of these patients may be switched to second-line ART regimen because of immunological failure. Given that the viral loads are undetectable then it makes clinical sense not to switch these individuals to second-line ART regimen. However, there are still unanswered questions about subsequent management of these individuals. As more patients in Africa remain on ART for longer durations, suboptimal responders are an emerging population that requires targeted interventions.

Identifying targeted interventions for this subpopulation requires further understanding of the mechanisms of suboptimal immune recovery. We have shown that patients with suboptimal immune recovery have significantly higher levels of T- cell immune activation and programmed cell death than optimal responders despite sustained viral suppression after four years of antiretroviral therapy[2]. These patients are being followed up in the infectious diseases cohort and we shall be able to describe their CD4 and viral load outcomes after developing suboptimal CD4 reconstitution. What is so far clear is that CD4 counts alone are not adequate to monitor HIV treatment for the suboptimal responders. This data will provide answers to the questions of how often the CD4 counts and viral load measurements should be done. We will also provide evidence on the role of immune modulators in modifying CD4 recovery among suboptimal responders[3]. There is a need for routine HIV treatment programs to identify these individuals and prioritize them for viral loads in order to avoid unnecessary switches to expensive second-line regimen.

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Importance of medical records in quality management of patients.

By Martin Mbonye, M&E Officer, Integrated Infectious Disease Capacity Building Evaluation(IDCAP)

Scenario

A health center incharge in a health centre IV in one of the new districts is having a regular quarterly staff meeting. One enthusiastic hardworking midwife raises pertinent issues-she is concerned that the health center is not matching its drug supply requisitions to the increasing numbers of patients and that over the previous week. Patients' attendants have been asked to privately buy ergometrine (a drug routinely given to mothers when giving birth to prevent bleeding) which had ran out of stock. The health center in charge is perplexed as he oversaw requisition and delivery of medicines-ergometrine doses two times the average health centre's quarterly births had been delivered. On checking the birth's records book, only five births had been recorded during the previous week, yet twenty expectant mothers had come through according to the admission register…,

Every health facility strives at providing quality health services. As human beings, everyone falls sick of one disease or another and requires quality medical care at one point life. Quality healthcare is defined as the extent to which health services provided to individuals and patient populations achieve desired health outcomes or to the extent to which health services reach expected standards of care. Quality health care is not only achieved through accreditation/inspection standards but also through

continuous review of medical records to assess treatment/procedure effectiveness and efficiency .

From the scenario above it is quite obvious that the health workers are working hard but their efforts are in vain as there is little evidence of their efforts due to poor documentation. As the common saying goes "if something was not documented then it never happened! "

Failure to maintain accurate, timely and complete records therefore, means the employees of a health facility are neglecting their institutional responsibility to the patients and the entire community the health facility serves. Medical records should be maintained and managed properly because they are very valuable to patients, physicians, the health facility as an institution, research teams, scholars, and the government. Not only did failure to document births in the scenario above affect the planning of medicine supplies in the facility but it also inconvenienced the mothers and put their lives at risk.

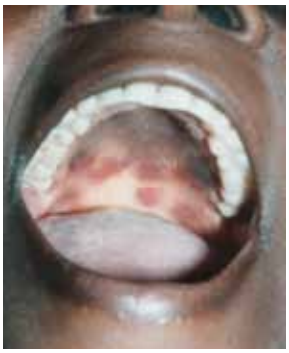
The practice of maintenance and care/management of medical/health records is usually referred to as Health Information Management (HIM). HIM is usually done by traditional (paper-based) and/or electronic means in the health facilities, health workers' offices/clinics, health facilities' departments, and other facilities that provide health care or maintain health records. A system is usually set up to manage this practice and in Uganda, this system is called the Health Management Information System (HMIS). HMIS involves collection, storage, use, and transmission of information to meet the legal, professional, ethical and administrative records-keeping requirements of health care delivery that also supports improvement in health information systems, development of health policy, and identification of current and future information needs .

In Uganda, HMIS reporting is done through a network of district health offices, which collect and summarise health information from health sub-districts and lower health facilities. Districts summary health reports are then submitted to the Ministry of Health where data is compiled to generate national figures on health and health management indicators. Through a feedback mechanism, the central health databank provides monthly summary analyses to all districts, showing their comparative performance in terms of performance and a selected list of health sector indicators.

At a health facility, a department usually called the Records Office, manned by a health information assistant or records officer is responsible for managing the HMIS. It is important to note that responsibility for patients' information should lie with everyone involved in patient management not only with the records department.

A good quality record is one that is complete and accurate, and recorded in a timely and concise manner. Therefore every health worker seeing a patient should strive to collect a quality record during management of a patient at any stage of health care i.e. triage, history taking, examination, diagnosis, treatment and even referral. The medical records are the principal documents by which the quality of healthcare rendered to the patient as well as the performance of any healthcare professional is measured. Examples of medical records in our health facilities settings include; the outpatient medical form five (MF5), the laboratory examination forms, inpatient treatment charts, referral cards, HIV care patient form, TB case identification forms, etc. In most circumstances, health workers record illegible data on these medical records during the process of providing care. This compromises the quality of care a patient receives e.g. when the dispensers are unable to read the handwriting on medical prescriptions making monitoring and evaluation of these records difficult.

A good HMIS coupled with a quality assurance programme including concurrent records review, reporting of incidence reports, utilization, review and other management measures in a timely manner will improve quality of care at any health facility.



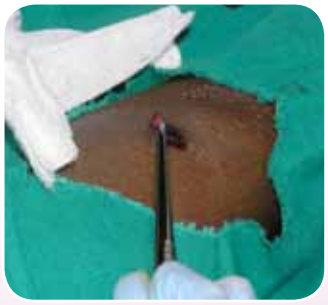
Kaposi's Sarcoma biopsy service for early detection

By Dr. Miriam Laker, ARKS Project Manager, IDI

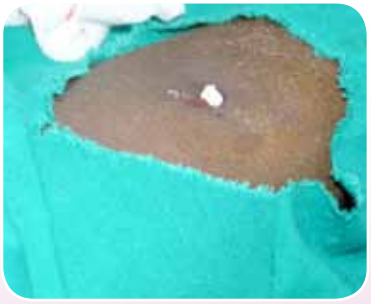
In Sub-Saharan Africa, the catastrophic intersection between the HIV epidemic and the endemic nature of Kaposi's sarcoma-associated herpes virus (KSHV) infection has resulted in Kaposi's Sarcoma (KS) becoming the most common reported malignancy amongst adults- and a growing threat in children- in many parts of the region. There are several theoretical interventions which could ameliorate the public health threat posed by KS. One is widespread use of antiretroviral therapy (ART) among all HIV-infected persons shortly after they become infected. Although not proven, this would likely prevent most cases of KS. Another is widespread availability of potent chemotherapy and a sophisticated medical support system to treat established KS. Neither of these interventions, however, is on the horizon in the foreseeable future and both are outside the realm of achievement by any single research group or consortium. Instead, because we have observed that the single largest obstacle to prevention of KS morbidity and mortality in Africa is late stage diagnosis, we believe that the fastest and most feasible route to the greatest public health impact on KS in Africa is by detection of the cancer in its earliest stages, at a time when ART alone is most effective.

Through KS studies that we have undertaken, that is, the Antiretroviral therapy for AIDS-related KS in Sub-Saharan Africa (ARKS) which is a clinical trial looking

Using the punch tool to obtain a biopsy core



Removing the core biopsy



Placing gel foam to achieve haemostasis

at different ART regimens to treat KS and the international epidemiologic database to evaluate AIDS (IeDEA) which seeks to study KS epidemiology at selected HIV clinics, we have found that there is virtually no understanding of KS among the general community and insufficient proficiency among health care providers. Moreover, at a national level, there is no cancer control plan for KS. The result is delay in presentation and in clinical recognition of KS. Furthermore the lack of punch biopsy equipment and expertise means biopsies for suspicious cutaneous KS lesions have to be done by specialized clinicians in the complex setting of a theater or at least a sterile environment with complex equipment requiring daily sterilization. This coupled with very limited pathology infrastructure in Uganda results in prolonged turnaround time for the histopathologic diagnosis.

To alleviate part of this problem, as an extension of the work we started as part of the ARKS study, we have established a biopsy service in the Infectious Diseases Institute Clinic where we provide skin punch biopsies for patients (HIV positive adults and children and they do not have to be registered in the IDI-clinic) with suspicious skin lesions and pathology reports to their care provider at no cost to the patients (we however do not cover transport expenses).
We believe that the availability of this service will motivate health care providers to examine and promote skin self examination among their patients with the purpose of finding KS early when treatment will still be likely to make relevant impact on the health and life of the patient.

Updates from the Antiretroviral Therapy for Kaposi's Sarcoma study(ARKS).

Over the last five years this study assessed for eligibility 1560 patients of whom 1323 did not meet eligibility criteria mainly because they had advanced Kaposi's sarcoma. It is likely that the majority of those who had advanced disease are already dead since in the absence of treatment, median survival with KS from the time the first lesion is detected is three to six months. It has also been reported that in spite of treatment, survival of HIV patients with KS remains very low with 8- 26% of patients dying in the first year of antiretroviral treatment in sub-Saharan Africa, most deaths occurring in the first few months. In Malawi 30% mortality at one year was observed, while our study observed 19% mortality at one year following initiation HAART and of this approximately 80% in the first six months. This goes to show that outcomes of KS in HV are still uncertain and it is possible that early detection and timely treatment initiation can to a certain extent alleviate this grim picture.

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.....So if your patient is taking Rifampicin, what other drugs other than Antiretrovirals should you be worried about?

By Monica Amuha, B.Pharm, MPS

For over 40 years rifampicin has been used in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by mycobacterium tuberculosis. For more than 25 years, discoveries of rifampicin interactions have been made and more are continuously being discovered. Rifampicin being a potent inducer of hepatic cytochrome P450 isoenzyme and the P-glycoprotein has significant drug interactions.
The interaction between rifampicin and antiretroviral drugs such as protease inhibitors and non nucleoside reverse transcriptase inhibitors is well documented and has been dealt with in the previous ATIC newsletter editions. In this issue we look at clinically significant drug interactions between rifampicin and drugs other than antiretrovirals. It is important to note however, that several other less well known but potentially harmful rifampicin-drug interactions do exist.

Oral contraceptives: it has long been known that when rifampicin is co-administered with oral contraceptives, there is decreased effectiveness of the contraceptives.

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News on Infectious Diseases

By Dr. Christine Kihembo, ATIC Team Leader.

This page is one of the new additions to the evolving ATIC newsletter featuring infectious disease updates from journals and conferences.

In this issue, we share with you the highlights of the July 2011 International Aids Society Conference on HIV Pathogenesis, Treatment and Prevention held in Rome, Italy.

Inline with the global strategic HIV/AIDS control effort of optimizing HIV prevention, diagnosis, treatment and care outcomes by revolutionalizing HIV prevention and eliminating new HIV infections in children among other core elements and with the conference theme focusing on HIV prevention, the pre-exposure prophylaxis(PreP) results of two African studies released at 13th July 2011 telephone news conference were right on time.

Pre exposure prevention studies

In the PreP study 4758 HIV sero-discordant heterosexual couples in different sites in Uganda and Kenya were followed up. Seronegative partners were randomized to either tenofovir, tenofovir/FTC (Truvada) or placebo and followed for 36 months with the primary end point being HIV seroconversion. The HIV negative partner would receive monthly HIV, pregnancy testing as well as safety monitoring whereas the positive partner would undergo 3 monthly follow up with CD4 count testing every 6months and standard HIV care according to national guideline.

The study found that tenofovir had a 62% efficacy in preventing HIV infection and Truvada an efficacy of 73% with no statistical difference between the efficacy of Truvada and tenofovir. There were no differences in efficacy between men and women

In the TDF2 study on the other hand, 1219 HIV-seronegative participants 18-39 years of age from Botswana were randomly assigned to receive either oral tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) or matching placebo once daily. Participants were followed up monthly for HIV testing and risk reduction counseling, sexually-transmitted infection management, and adverse event monitoring.

Truvada had an efficacy of 63%, but was 78% efficacious in patients who had last received study drugs less than a month ago and who therefore had pills available. The study however had no statistical power to demonstrate differences in efficacy between men and women.

The new data disqualifies the recent zero Truvada efficacy findings of the FEM-PrEP study that had brought up a theory that probably oral PrEP might not work for women because of low drug concentrations in the genital tract.

HIV treatment as prevention

In the area of HIV treatment as prevention, the HPTN 052 study showed a 96% reduction in the risk of HIV transmission to uninfected partners with early antiretroviral initiation – started at a CD4 count between 350 and 550 cells/mm3. In this study, 1763 HIV-infected individuals in sero discordant relationships, with CD4 counts between 350 and 550 cells/mm3 were randomised either to receive immediate antiretroviral treatment or to defer treatment until their CD4 cell count fell below 250 cells/mm3 on two separate tests. The study was conducted in Malawi, India, Zimbabwe, Botswana, South Africa, Kenya, Thailand, the US and Brazil.

Prevention of mother to child transmission.

On the other hand, pooled analysis of different individual clinical trials revealed that extended use of nevirapine or zidovudine and nevirapine in infants reduces the risks of HIV transmission through breast milk by over 70%.

The estimated cumulative risk of HIV infection among infants at risk of HIV infection, uninfected at birth was 5.8% (95% CI: 4.0 to 7.6), 3.7% (95% CI: 2.3 to 5.1), for the six week and 14 week nevirapine, 4.8% (95% CI: 3.2 to 6.4) for the 14 week dual AZT and Nevirapine-prophylaxis regimen and 1.8% (95% CI: 0.8 to 2.8), $p<0.001$ for the 28 week nevirapine regimen. This analysis further justifies WHO's rationale of revising the prevention of mother to child transmission guidelines in 2010.

Abstracts:

- *Baeten J Antiretroviral Pre-Exposure Prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP Study. Sixth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Rome, abstract MOAX0106, 2011.*
- *Thigpen M et al. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. Sixth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Rome, abstract WELBC01*
- *Grinsztejn B et al. Effects of early versus delayed initiation of antiretroviral therapy (ART) on HIV clinical outcomes: results from the HPTN 052 randomised clinical trial. Sixth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Rome, abstract MOAX0105, 2011.*
- *Hudgens M et al. Pooled individual data analysis of five randomized trials of infant nevirapine prophylaxis to prevent HIV-1 transmission through breast milk. The Sixth IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, 2011, abstract WELBC03.*

This is due to the induction of the oestrogen and progesterone metabolism. It is thus advisable that alternative forms of contraception such as barrier methods be considered when offering contraception alternatives to our female patients receiving rifampicin.

Oral anticoagulants: Not only does HIV predispose to Tuberculosis disease but it is also an established risk factor for hypercoagulable conditions such as deep venous thrombosis(DVT). Warfarin, an effective anticoagulant agent, has been used in the treatment and prevention of venous thromboembolism for years and remains the mainstay of anticoagulation therapy due to its efficacy and lack of acceptable alternative options. For a patient on Rifampicin requiring warfarin medication would need increased warfarin dosing in order to achieve warfarin's therapeutic effects. This is because Rifampicin induces the hepatic metabolism of warfarrin, reducing its anticoagulant properties. Rifampicin-warfarin interaction is highly clinically significant requiring 2-5 fold increase in the warfarrin dose during concurrent therapy. Patients receiving rifampicin and anticoagulants such as warfarin therefore, should have their prothrombin time performed daily or as frequently as necessary to establish and maintain the required anticoagulant dosage.

Ciprofloxacin and Clarithromycin: These are potent enzyme inhibitors and concurrent use with rifampicin or rifabutin causes a drug induced lupus-like syndrome manifested by malaise, muscle aches, arthritis and peripheral edema. Serum concentrations of rifampicin are elevated when used with ciprofloxacin and/or clarithromycin. There is need for careful monitoring for drug induced lupus syndrome when these drugs are used concurrently.

Antifungal agents: rifampicin reduces serum concentrations of fluconazole, itraconazole, and ketoconazole. An increase in fluconazole dosage may be considered when these drugs are used concomitantly. However concomitant use of rifampicin with itraconazole or ketoconazole is not recommended.

Dapsone: In a study by Gattin G et al it was found that rifampicin increased dapsone clearance by 69% to 122% in 7 HIV-positive patients receiving 100 mg of dapsone twice weekly for Pneumocystis carinii pneumonia prophylaxis. The investigators believed that the increased clearance of dapsone was largely because of a significant first-pass effect. The metabolite of dapsone, monoacetyldapsone was also undetectable in plasma.

Antacids: Concomitant administration of rifampicin with an antacid may reduce the absorption of rifampicin and thus the manufacturers of rifampicin recommend that the daily dose of rifampicin is given at least 1 hour before ingestion of an antacid.

Cardiovascular drug: Simvastatin a drug used in lowering blood cholesterol, is significantly affected by the enzyme induction effect of rifampicin. A crossover study to examine the effects of rifampicin on the pharmacokinetics of simvastatin revealed that rifampicin reduced the AUC of simvastatin and its metabolite by over 80%. Thus concomitant use of rifampicin and simvastatin may significantly reduce the cholesterol lowering effect of simvastatin.
A study by Greiner et al found that rifampicin decreasing the oral bioavailability of digoxin by 30.1%. Patients should be closely monitored for arrhythmia control and signs and symptoms of heart failure during concurrent rifampicin administration.

Verapamil: Due to induction of the intestinal P-glycoprotein, rifampicin reduces the oral bioavailability of oral verapamil by over 90% diminishing the therapeutic effects of this drug. In patients where verapamil is deemed essential, it is advisable to consider an alternative to rifampicin.

Enalapril: concurrent use of rifampicin and enalapril has resulted into decreased concentrations of the metabolite enalaprilat. Dosage adjustments are required if indicated by the patient's condition.

Quinine: In a study by Pukrittayamee et al, of combined rifampicin and quinine in the management of uncomplicated malaria, it was found that the serum quinine dose decreased progressively throughout the treatment period with a malaria recrudscence five times higher in this group. Therefore in patients already on rifampicin, an alternative antimalarial agent other than quinine should be considered.

Isoniazid and Pyrazinamide: Because of increased risk of hepatotoxicity, patients receiving these drugs concurrently with rifampicin should be closely monitored for signs and symptoms of hepatotoxicity.

The table below shows rifampicin drug interactions of clinical importance;

Rifampicin Drug Interactions of Major Clinical Significance	
Type of Drug	Comments
Oral anticoagulants	Monitor international normalized ratio; increased anticoagulant dose will definitely be needed
Oral contraceptives	Use alternative form(s) of birth control; counsel patient and document in medical record
Digoxin	Monitor arrhythmia control, signs and symptoms of heart failure, and serum digitoxin concentrations

Glucocorticoids	Increase dose of glucocorticoid 2- to 3-fold
Itraconazole	Prefer to avoid use with rifampin; if must use, increase dose and monitor response
Ketoconazole	Avoid concomitant use if possible; if must use, increase dose and monitor response; space ketoconazole and rifampin doses by 12 h
Methadone hydrochloride	Increase methadone dose with concomitant rifampin therapy; monitor and control withdrawal symptoms
Midazolam or triazolam	Prefer to avoid use with rifampin; use another agent if possible
Phenytoin	Monitor serum phenytoin concentrations and seizure activity; increase dosage if needed
Quinidine	Monitor serum quinidine concentrations and arrhythmia control; increase dosage if needed
Theophylline	Monitor serum theophylline concentrations; increase dosage if needed
Verapamil	Use an alternative agent to verapamil because large oral verapamil doses may not be adequate; monitor patient for clinical response

Rifampicin being a potent enzyme inducer of the cytochrome P450, it is recommended that the possibility of a drug interaction should be explored before initiating patients on a rifampicin based regimen while taking other drugs.

Do not hesitate to contact ATIC for more information on suspected drug - drug interactions.

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- *G Gattin, et al., Population pharmacokinetics of dapsone administered biweekly to human immunodeficiency virus-infected patients, Antimicrob Agents Chemotherap. 1996 December; 40(12): 2743–2748.*
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ask ATIC

Dr. Christine Kihembo, ATIC Team leader

Q

Qn. We have an HIV positive adult patient in WHO clinical Stage IV with an intra abdominal abscess in the para-aortic area.

Microscopy of the ultrasound guided aspirate revealed AAFBs (++).
Should we manage this patient with anti-TB medications only or is surgical drainage necessary?

A

Surgical incision and drainage is not indicated unless there are complications.

Tuberculosis is the leading cause of mortality and morbidity, accounting for 30% of deaths among people living with HIV/AIDS. With the vicious cycle of viral and mycobacterial proliferation, HIV/TB co-infected people are more prone to atypical TB presentations such as extra-pulmonary presentations with the abdomen being one of the common sites affected. Mortality is higher among HIV infected than non infected TB patients particularly when TB is not treated early and adequately, in advanced HIV/AIDS disease and in cases of multi-drug resistant TB(MDR). Therefore proper TB management is paramount.

With the goals of treatment being curing the patient, preventing complications and mortality from TB, reducing transmission and preventing development of MDR, WHO recommends use of a 6 month rifampicin based standard daily antiTB regimen for abdominal TB management in HIV infected individuals. Adjuvant corticosteroid use is recommended to minimize fibrosis and cicatrization in TB meningitis and TB pericarditis but not indicated in abdominal TB.

In Uganda however, an eight month fixed dose combination regimen is still being used for most TB cases icluding abdominal TB. This includes a two months intensive phase of Isoniazid(I) and Rifampicin(R), Ethambutol(E), and Pyrazinamide(P) with a continuation phase of Ethambutol and Isoniazid for 6months i.e. 2HREZ/6EH. Streptomycin(S) for 2 months can be added if the patient is being retreated(relapse, treatment failure or defaulter) and the regimen is then 2SHREZ/HREZ/5HER.
Concomitant administration of daily pyridoxine 25mg is recommended to reduce Isoniazid associated neurotoxicity. This patient should also start co-trimaxazole prophylaxis or remain on it if already initiated.

Though surgery may be required for diagnosis, it plays a limited role as the first line management of extra-pulmonary TB, only being reserved for management of complications. In abdominal TB specifically, surgery is indicated in patients with acute and sub-acute intestinal obstruction who have not responded to conservative management and in patients with abdominal abscesses associated with gut perforation. Even then particular care is taken; for instance, conservative gut resection is done to avoid postoperative fistula formation which otherwise is associated with increased postoperative mortality and morbidity. It is worth noting that much as aspiration or incision and drainage of large fluctuant lymph nodes that are about to spontaneously drain has been shown to be beneficial in case reports, there is no clinical trial evidence to this effect. Therefore given the risk of gut perforation with resultant peritonitis in advanced immunosupression in this case, the risk of surgical drainage outweighs its benefit.

Additionally, according to WHO recommendation, this patient should be initiated on antiretroviral therapy (ART) as soon as possible as this has been shown to reduce the TB case fatality rate. In Uganda, ART is started 2 - 8weeks following anti TB treatment initiation as along as the TB drugs are well tolerated. Standard first line Efavirenz based ART regimen are recommended to minimize drug interactions with anti TB agents. Given the advanced stage of the disease, this patient is prone to paradoxical reactions with apparent worsening of symptoms-immune reconstitution (IRIS). If the patient gets IRIS, treatment should be continued. Predinisolone can be administered for 2 weeks and tapered over the following two weeks, in addition to other indicated symptomatic supportive treatment.

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