ATIC News

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

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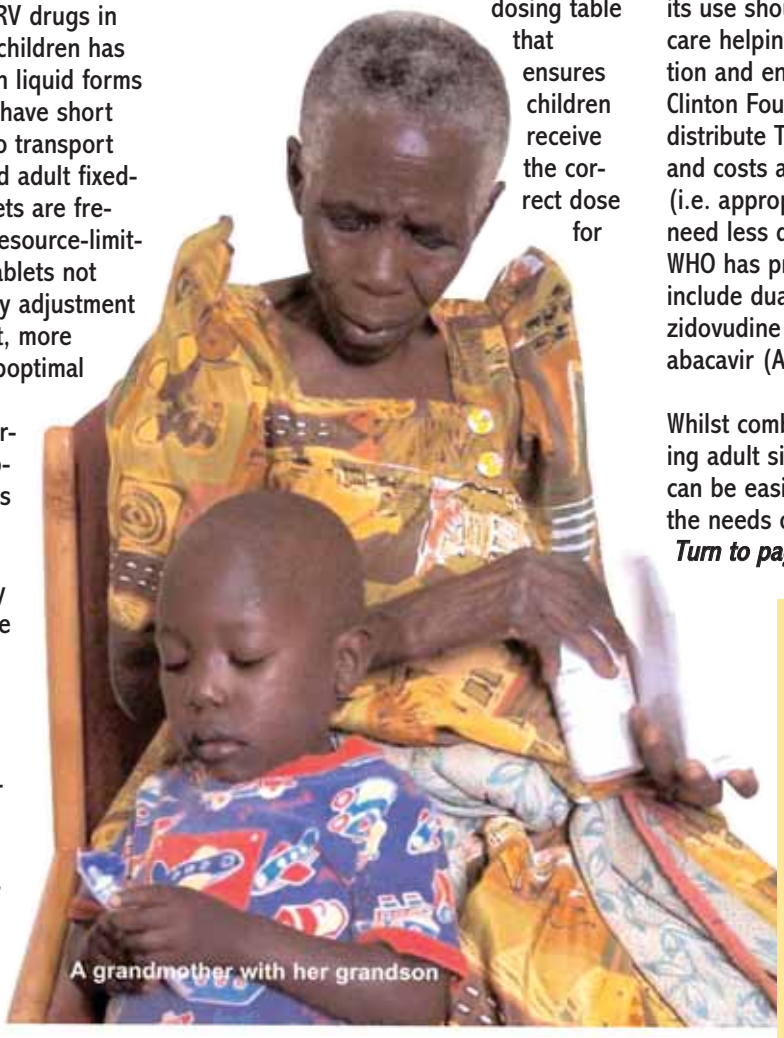
Development of New Paediatric Antiretroviral formulations

Increasing access to antiretrovirals in resource constrained settings

The simplification and standardisation of antiretroviral (ARV) therapy is an essential feature of HIV treatment "scale-up". Whilst there has been much progress in drug options for adults, the development of affordable ARV drugs in appropriate formulations for children has lagged behind. While ARVs in liquid forms are available they are costly, have short shelf-lives, and are difficult to transport and store. As a result divided adult fixed-dose combination (FDC) tablets are frequently given to children in resource-limited settings. Parts of adult tablets not only prevent reliable and easy adjustment of doses as a child grows but, more importantly, often contain suboptimal ratios of drugs for children, risking either toxicity or under-dosing and the rapid development of drug resistance. This is a particular concern given that children face a lifetime requirement for ARVs and key first line drugs like Nevirapine (NVP) and Lamivudine (3TC) are highly susceptible to the development of resistance.

This lack of child friendly formulations appropriate for resource-limited settings has been recognised by the WHO, national regulators and funding bodies who have prioritised their development. In 2007, tentative approval for a children's formulation of the adult FDC, Triomune, (Cipla Pharmaceuticals Ltd, see pictures inset) was given by the FDA, followed by WHO prequalification. Triomune Baby (stavudine 6mg: 3TC 30mg: NVP 50mg) and Triomune Junior (double these concentrations) are the first FDCs licensed for use in children under 12 years. Being scored and layered they can easily be snapped in half allowing use within a simple weight band dosing table that ensures children receive the correct dose for their weight.



A grandmother with her grandson

They have the added advantage of being crushable and dispersible in water. Currently, these are appropriate for children >6Kg but further work in Zambia through the CHAPAS trial (whose pharmacokinetic data contributed to FDA approval) will assess their use in even smaller infants. As Triomune Baby/Junior contains the same drugs as adult Triomune its use should aid a family approach to HIV care helping to prevent sharing of medication and encouraging adherence. The Clinton Foundation has already begun to distribute Triomune Baby/Junior in Uganda and costs are similar to adult Triomune (i.e. appropriately cheaper as children need less drugs). Other FDCs that the WHO has prioritised the development of include dual and triple combinations of zidovudine (ZDV), 3TC, NVP, efavirenz and abacavir (ABC).

Whilst combining drugs is ideal, even scoring adult single drug tablets so that they can be easily broken would help to meet the needs of many children over the age

Turn to page 2

Inside this Issue>>

From the Editor

Earlier this month, Uganda hosted the First Global Forum on Human Resources For Health which was attended by local, regional and international guests. The meeting was convened by the Global Health Workforce Alliance which is a partnership dedicated to identifying and implementing solutions to the health workforce challenges with which we are all familiar. It is currently estimated that Sub-Saharan Africa has 11% of the world's population, 24% of the global burden of diseases but has only 3% of the worlds health care workers. The meeting covered important topics such as migration, retention, compensation, capacity building, task-shifting, training and workplace violence. At the close of the meeting, a draft of a Global Action Plan called the Kampala Declaration and Agenda for Global Health was launched by the

Executive Director Dr. Francis Omaswa which represented the best thinking of those taking part in the meeting. The Plan called on governments, development partners, civil society, private sector and professional organizations to strengthen leadership and management capacity at all levels.

At ATIC, we too wish to contribute to this action plan by providing up to date continuing medical education for all cadres of health care workers and also by expanding our remit to include articles of direct relevance to support the busy health care provider such as career development, presentation skills, leadership and time management.
We hope that you will enjoy this edition of the ***ATIC Newsletter.***

New Paediatric Antiretroviral formulations

of around four years. For example, the ARROW trial, which has three sites in Uganda, is pioneering the use of scored ABC, 3TC and Combivir (3TC + ZDV) tablets. By allowing carers to break the tablets in real time, there is no danger of degradation of drug components (which might occur if drugs are broken in pharmacy and then dispensed) or further breaking of divided parts. Taken together with Cotrimoxazole1 (also available in scored tablets) the use of child friendly ARVs will help reduce hospital admissions of HIV-infected children and enable them to lead healthier lives.

Such prioritisation, development and registration of paediatric formulations is particularly important given the increasing proportion of infections in children now present in the HIV pandemic (in 2001 children accounted for 14.3% of new infections, in 2007 it was 16.8%). In addition, while ~20% of adults urgently needing ARVs receive them, only half as many HIV infected children (~10%) are receiving ARVs. The goal for the future is clear – Paediatric formulations which include a combination of drugs which are scored/layered and crushable for treatment of even the youngest children using a simple weight band table still need further development.

References

1) L'homme R et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. AIDS in press.

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3) Mulenga V et al. Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. AIDS 21: 77-84, 2007.

This article was put together by the following team;

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ALUVIA: The "Back Bone" Protease Inhibitor in second line HIV/AIDS Therapy in Africa.

By Picho Brenda
Pharmacist

Composition

Each film-coated tablet contains 200mg lopinavir and 50mg ritonavir.

Introduction

Aluvia is an ARV from the class of protease inhibitors. It is a fixed dose combination of Lopinavir and ritonavir. It is manufactured by Abbot Laboratories, a US manufacturer.

Pharmacodynamics

Aluvia film-coated tablet is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 and HIV-2 protease enzyme. As co-formulated in Aluvia, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Mechanism of action

Lopinavir prevents cleavage of the gag-pol polyprotein, resulting in the production of immature, non- infectious viruses.

Formulation and dosing

Lopinavir/ritonavir is available in tablet and oral liquid formulations. The capsule formulation (Kaletra) is being phased out. Two tablet formulations are available: 200mg Lopinavir + 50mg ritonavir and 100mg lopinavir + 25 mg ritonavir (the latter is for pediatric dosing). The liquid formulation contains 80mg lopinavir + 20mg ritonavir per ml. Lopinavir is approved for twice-daily dosing: it is also approved for once-daily dosing in treatment-naïve adults. For treatment-experienced patients, only the twice-daily option is recommended.

Adult Dosing

Tablets (200mg Lopinavir/50mg ritonavir); 400/100mg BID **or 800**/200mg QD
*QD dosing is recommended only for treatment-naïve adults. Lopinavir/ritonavir should not be administered once-daily in regimens that include efavirenz, nevirapine, amprenavir, fosamprenavir or nelfinavir.

Clinical use: Drug Interactions

The ritonavir component of Aluvia is a potent inhibitor of cytochrome P450 3A (CYP3A) and CYP2D6, as well as an inducer of other hepatic enzyme systems. Co-administration with Aluvia therefore causes clinically significant alterations in serum levels of several antiretrovirals and of a variety of drugs including certain cholesterol-lowering agents, rifabutin, antiarrhythmics, sedative-hypnotics, erectile dysfunction agents and oral contraceptives. Drugs that affect metabolism by CYP3A can lead to a decrease or increase in lopinavir levels. For example, some antiretrovirals, including efavirenz, nevirapine, fosamprenavir, and tipranavir, as well as other medications such as rifampin, decrease lopinavir levels significantly.

Side effects

The most common symptomatic side effects of lopinavir/ritonavir are diarrhea and nausea. Some other undesirable effects include headache, insomnia, nausea, vomiting, abdominal pain, abnormal stools, dyspepsia, and flatulence. Common laboratory abnormalities include elevated cholesterol and triglyceride levels: liver toxicity is also observed. Lipid abnormalities may be more common with Aluvia than with other PIs such as atazanavir.
As with other protease inhibitors, lopinavir/ritonavir may contribute to abnormalities of body fat distribution.

Contra-indications

Aluvia is contra-indicated in patients with known hypersensitivity to lopinavir, ritonavir or any of its excipients.
Aluvia should not be co-administered concurrently with medicines that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Pregnancy and Lactation

The safety of this medicine in pregnant women has not been established, as there are no adequate and well-controlled studies in pregnant women. Aluvia should be used during pregnancy only if the potential benefits clearly outweigh the potential risks.

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. In addition, because of the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Aluvia. It is not known whether lopinavir is secreted in human milk.

Storage conditions

Aluvia tablets do not require any special storage conditions, one of its major advantages over previous lopinavir/ritonavir formulations. However, it should be stored in conditions below 30 C, away from direct sunlight.

Switching between nevirapine and efavirenz after NNRTI-associated rash

Kristin Hurt ***(PharmD, BCPS)***

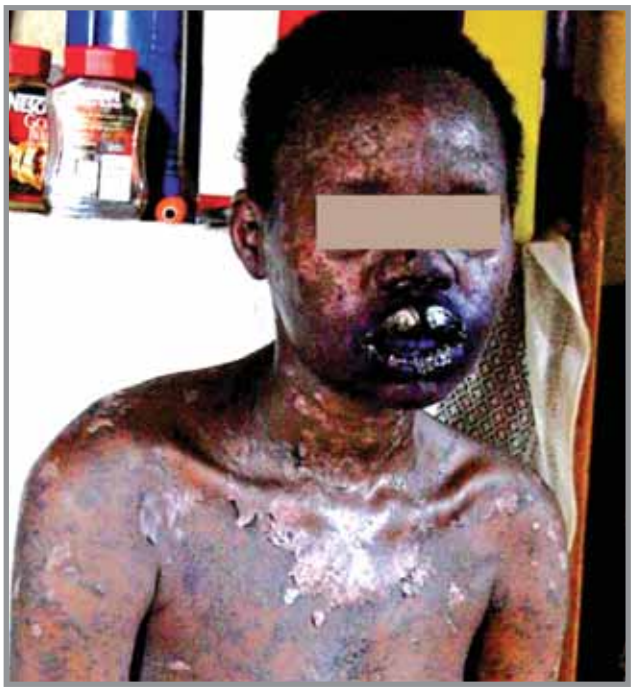
Cutaneous adverse events have been reported with all of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine (NVP) and efavirenz (EFV).

Due to limited options for second-line therapies in resource-limited settings, switching between these NNRTIs after occurrence of rash is often necessary. Although chemically distinct, there is concern for cross-reactivity between NVP and EFV, and with limited data available; the safety of this practice is questioned.

In clinical trials, the incidence of rash has been reported to occur in approximately 15% of patients taking NVP, although a frequency of 38% was reported in a subgroup analysis of Thai patients. [1,2] Occurring most often during the first six weeks of treatment, NVP-associated rash is generally mild to moderate, diffuse erythematous or maculopapular, with or without pruritis.

However, cases of severe rash (extensive erythema, rash with moist desquamation or rash with angioedema) were reported in 1.5% of patients, including life-threatening cases of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis in 0.3% - 1% of patients. 1 Additionally, DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, often with hepatitis, has been reported in patients taking NVP, including a recent report in an older child. [3,4,5]

Clinical trials with EFV report the overall frequency of rash to be 26%.[6] However, severe rash with blistering, moist desquamation or ulceration occurred in < 1% of patients, and SJS or erythema multiforme occurred in 0.1%. In the randomized 2NN trial comparing nevirapine to efavirenz, grade 3 or 4 rash occurred in 3.4% of patients in the NVP twice daily arm compared to 2% in the EFV arm. [7] Additionally, rash was the reason for discontinuation in 6.5% and 3.8% of patients, respectively. One patient in the NVP twice daily arm developed SJS and later died, despite initial improvement.



Given this high incidence of rash, as well as the potential for serious life-threatening cutaneous reactions, the safety of switching from one NNRTI to another after development of a rash is uncertain. Recently in Lancet Infectious Diseases, Dr. Ushma Mehta and Prof. Gary Maartens addressed this clinical concern in an article titled, "Is it safe to switch between efavirenz and nevirapine in the event of toxicity?" [8] In this review, the authors summarize the evidence to-date regarding the safety of switching from one NNRTI to another after development of cutaneous hypersensitivity or hepatotoxicity. The results regarding hepatotoxicity are beyond the scope of this summary article.

Nevirapine-associated rash: Is it safe to switch to efavirenz?

Mehta and Maartens reviewed available data, including two case reports, ten retrospective cohort studies and one subanalysis of a randomized, controlled trial. From these findings, there were 239 patients with NVP-associated rash subsequently challenged with EFV identified. Of these, 30 (12.6%; 95% CI: 2.7%-22.4%) patients developed a recurrent cutaneous reaction while on EFV, of which 13 resulted in discontinuation of the drug.

Over half of the patients included in the review by Mehta and Maartens were from a retrospective Thai cohort by Manosuthi and colleagues (122 patients) who received NVP initially, but required a switch due to rash. [9] Interestingly, 46 of the 122 patients (37.7%) had previously developed a severe rash on NVP, [8] (6.6%) of which included NVP-associated SJS. Of the 122 patients challenged with EFV, [10] (8.2%) had a recurrent cutaneous reaction, all resulting in discontinuation of EFV. Of note, one patient challenged with EFV developed SJS, and of the eight patients with initial NVP-associated SJS, 2 (25%) developed a skin rash on EFV.

Although the true incidence of cross-reactivity cannot be determined, this analysis suggests that initiation of EFV after development of a NVP-associated rash is likely safe. It can be noted that the rate of rash recurrence was no higher than the reported rate of rash in patients taking EFV without prior NVP exposure.

Efavirenz-associated rash: Is it safe to switch to nevirapine?

In the same analysis by Mehta and Maartens, there were only 16 reported cases of NVP administration in patients that previously developed an EFV-associated rash. Of these 16 cases, [8] (50%; 95% CI: 26.7%-73.3%) patients developed a recurrent reaction on NVP (the number resulting in discontinuation was not reported in the studies). Due to the high frequency of recurrent rash and the small number of reported cases, the

Turn to page 7

Career Management for Health Care Professionals

By Ceppie Merry (PhD, FRCPI)

Much attention was focused at the First Forum on Human Resources For Health on the brain drain of bright young professionals from the developing world to the developed world. This has been identified as a significant contributor to the difficulties poorer nations experience when trying to implement reforms to improve the lives of their citizens. Agencies and donors from the western world now go to extraordinary lengths to ensure that they are not seen to contribute in any way to the brain drain. However, at the meeting it was acknowledged that the situation in reality is far more complex than this. Health care worker migration is a reality and it is the right of any individual to seek overseas employment. While it is important to develop a code of practice on the international recruitment of personnel, the key issue is really to shape the health workforce market in favour of retention locally.

There is also movement of staff from less well paid local jobs within ministries, universities and government to better paying jobs offered by NGOs, research agencies and foreign multinational companies. Finally, little attention is focused on the far worse reality of professionals from resource poor countries who move to the developed world and fail to secure suitable employment as they have limited career management skills and poor understanding of cultural differences. In reality, thousands of doctors from the developing world leave their home country each year in search of training opportunities or better living conditions. Unfortunately many of these highly trained professionals experience significant difficulties securing employment and spend considerable time either unemployed or working in a non-professional capacity and sadly many of these young hopefuls end up working for some time as security guards, gas station attendants and valets in their new country. The reason for this is partly the fact that many Health Care prosfessionals have limited training in career management and this deficiency is more evident when they are faced with a new cultural setting. Despite feverish attention to educational progression, career management is seen as an unnecessary soft skill. Third level institutions rarely emphasise basic career literacy skills such as preparation of a CV, interview techniques, career planning, time management and effective presentation and communication skills. Another major and unrecognized contributor to the brain drain is the loss to the productive workforce of heath care professionals who enroll in serial overlapping courses in a misguided attempt to secure better employment which again can be traced to poor career management.

Many young doctors are busy trying to pass the membership/fellowship /PLAB and are not aware that there is an entire scientific discipline dedicated to career literacy and cultural sensitivity. This is not the case for their contemporaries in the world of business-multinational companies that invest considerable time and money in training their young executives in these disciplines in order to gain a competitive advantage. As the definition of the brain drain is much broader and more complex than initially thought, fortunately so too are the possible solutions. In the following series of articles we will provide practical advice for health care providers as optimal career management for health care professionals could reduce the brain drain and thereby contribute to the health of nations and the happiness of individual health care providers and their families.

(Part A; For the section below, please score accordingly, 5 strongly agree, 4 agree, 3 don't know, 2 disagree, 1 strongly disagree . A total score of anything greater than 10 suggests that you could benefit from career management skills).

Lets start by looking at your baseline attitude and competency in career literacy.

1. I think that career management is less important for doctors as compared to professionals in the business sector.
2. I usually update my CV the week before I apply for a new job.
3. I do not enjoy updating my CV.
4. I am nervous at interviews
5. I am nervous presenting in front of my peers.
6. I do not have a specific five year career plan.
7. I think it will be easier to get jobs once I get the membership/fellowship and have some research.
8. It is difficult to get research publication as a junior doctor.
9. Skills of time management do not apply to the working life of a young doctor
10. It is hard to succeed in medicine especially if you are from overseas.

(Part B; Answer True or False to the following and you get +1 for a correct answer and – 1 for a wrong answer)

1. Curriculum Vitae should be presented in:

a. Times New Roman size 10 font
b. Times New Roman size 12 font
c. Times New Roman size 14 font
d. Verdana size 12 font
e. Verdana size 14 font

2. With regard to the Curriculum Vitae:

a. It is worth having one excellent CV and submitting it for all jobs
b. The CV is much more important than the cover letter
c. Standard paper from the photocopier is adequate for printing a CV
d. There are no good books written on how to prepare a CV
e. Interviewers pay little attention to your CV

3. Predicatable interview questions that you should prepare for in detail include:

a. Tell us about yourself?
b. What are your strengths?
c. What is your career plan?
d. Why have you applied for this job?
e. Is there anything you want to ask us?

4. With regards to Career Management:

a. It is of limited relevance in the health care sector .
b. There is too much uncertainty in medicine to have a five year plan.
c. It is less important than exam results, publications and experience.
d. There are less job opportunities in the resource limited setting for doctors now than twenty years ago.
e. There are more job opportunities in the resource limited setting for doctors now than twenty years ago.

5. Presenting in public:

a. Has been shown to be the number one fear for most people.
b. It is best to start the presentation with introducing your self and the topic.
c. If possible it is good to include sophisticated computer skills such as animation.
d. Should always include a summary slide with global stastistics on the disease of relevance.
e. There are limited opportunities to practice presenting in public.

See Page 12 for Answers

RATIONAL USE OF ANTIBIOTICS

By Francis Kalemeera *(Bsc, BPharm, MPS)*
Dr. Pauline Byakika *(MMed)*

You may want to know why we have chosen "Rational Use of Antibiotics" as one of the topics in this ATIC News. The major reason is that antibiotics are one of the most commonly prescribed drugs today and that if not used rationally, there is increased toxicity for patients, antibiotic resistance may emerge, and subsequently there is an increase in health care costs.

How would you define 'rational use of antibiotics'?

The use of antibiotics is said to be rational when the right medicine, right dose, right frequency and period of administration, right disease, right instructions, and the right patient, inform the process: - from diagnosis to treatment. I would like to add: 'at the lowest possible cost'. To use antibiotic(s) rationally is possible when the health care worker answers these questions in assessing the patient:

i) Perception of need: is an antibiotic necessary?
ii) Choice of antibiotic: what is the most appropriate antibiotic?
iii) Choice of regimen: what dose, route, frequency and duration are needed?
iv) Monitoring efficacy: is the treatment effective?
v) Monitoring side effects: is the treatment safe?
vi) Affordability: Can the patient afford the drug?

These stages in decision making constitute the medicine (antibiotic) use process.

The Process

Need for an antibiotic:

The first step in the medication use process is diagnosis. When a bacterial infection is diagnosed, must antibiotic therapy be given? Not always. Even where a bacterial etiology is established, an antibiotic may not always be necessary. Many bacterial infections resolve spontaneously. Minor superficial skin infections may be more suitably treated with a local antiseptic. Collections of pus should be drained surgically and if drainage is adequate, antibiotics may sometimes be required. The localization of the infection is an important determinant of the need for an antibiotic. If the patient has sepsis, for example, antibacterial therapy is immediately required and often a combination of antibiotics effective against both Gram negative and Gram positive organisms may be warranted.

This is the most important step to really think about. Overuse of antibiotics is common, even in centers of excellence. Viral "flu" like infections, upper respiratory infections, and viral diarrheal illnesses are often treated with antibiotics unnecessarily. Often the patient expects it, and if not given a prescription feels like they are leaving uncared for. And just as often the health care practitioner feels the need to "do something" and so writes the prescription knowing it is unnecessary.

Choice/Regimen of antibiotic:

The choice of the antibiotic will determine the outcome of therapy. Many times antibiotics are prescribed based on the clinical condition of the patient. This is referred to as empirical therapy and may require broad spectrum antibiotic therapy, until the organism causing the infection is identified.

The choice or dose of drug must depend on significant patient factors, for example:

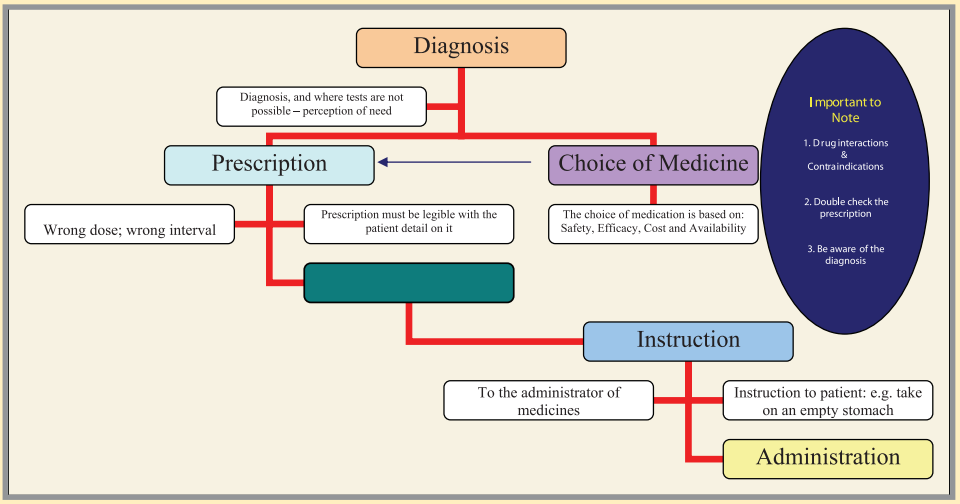
- Patients with renal failure or hepatic impairment may require dosage adjustment if the medicine is cleared by the kidney or metabolised by the liver, respectively. These patients may need reduced doses of an antibiotic or one with a preferable pharmacokinetic profile.
- The patient's age may help determine choice of agent. The very young and the very old tend to be more prone to the adverse effects of the antibiotics. Young children have a low capacity to metabolize hepatically cleared antibiotics while the old have reduced renal function.
- Medicine allergy; previously known drug allergy or reaction may limit the choice of an antibiotic and may dictate the use of another class of agent with a similar spectrum of activity.
- Antibiotic therapy will be successful when the therapeutic concentration of the drug is achieved at the site of the infection. This is subject to the pharmacokinetic parameters of the medicine. Knowledge of the pharmacokinetics of the medicine is therefore important.

The oral route of drug administration is the easiest and most friendly route however, the patient may not be able to swallow and their clinical condition might necessitate parenteral administration of the antibiotic. The duration of treatment is dependent on signs and symptoms but also on the specific bacterial infection.

Safety and efficacy of antibiotic:

Some antibiotics are very toxic and may

The Medicine Use Process



require switching. Identification of toxicity often requires appropriate laboratory tests, and clinical follow-up of the patient. The patient should also be reviewed for the efficacy of the antibiotic. Undesired effects of the medicine and absence of efficacy will necessitate a change of the regimen.

Medicine price:
The patient must be considered when a prescription is given. Some antibiotics are too expensive for the average patient in resource limited settings. When there are less expensive antibiotics that have comparable efficacy to the expensive ones, the cheaper ones should be prescribed.

Irrational medicine use:
Any factors that hinder or obliterate the medication use process contribute to irrational medicine use. Irrational medicine use is said to occur when:

- A wrong diagnosis is made
- A wrong medicine is chosen for the patient or disease
- The prescription is poorly transcribed: using brand or trade names instead of the non-proprietary name
- The wrong medicine is dispensed
- The wrong instructions are given to the patient or health care worker
- The medicine is not dosed appropriately

Factors contributing to irrational medicine use
There are a number of factors that contribute to irrational medicine use. The list is long, so we only point out some. These include:

- **Health care worker factors**
  - Inadequate knowledge of the disease, signs and symptoms: wrong diagnosis and wrong prescription
  - Inadequate knowledge of drugs: The correct drug may be chosen, but the wrong dose prescribed, lack of knowledge of drug interactions so interacting drugs are prescribed together
  - Lack of confidence: lack of confidence hampers the decision making process and would hinder flow of correction of errors to the prescriber from the dispenser
  - Poor attitude towards patient care and work environment: the results of this include poor instructions or wrong instructions to the medicine user; poor packaging and lack of labeling of the dispensed medicine
  - Inadequate medicine supply: may lead to inadequate doses due to sharing between patients with the consequence of resistance development (especially for ARVs)
- **Patient factors**
  - Patient triggered interactions: this includes the use of herbal products that may significantly interact with the prescribed medicine
  - History of prior problems taking medicines
  - Poor adherence to medicines: one may have gotten a severe reaction to a medicine some time ago, and the problem was not explained. The result is a fear of all medicines

The rational use of antibiotics is about appropriate patient care. Patients should not be pushed to spend their savings on infections that do not need an antibiotic and on expensive antibiotics when cheaper but effective antibiotics are available. Because of limited knowledge in the general population, proprietary names may help to promote rational and affordable drug use in resource limited settings but should not be used if increased costs result.

It is our goal to improve the rational use of antibiotics, and in subsequent ATIC News issues, you will find further information on the rational treatment of specific bacterial infections.

Reference:
V K E Lim etal. Rational Use of Antibiotics. Available on ***http://www.acadmed.org.my/cpg/rational_use_antibiotics.htm***

Switching between nevirapine and efavirenz

safety of switching to NVP following an EFV-associated rash could not be confirmed.

When applying these findings to clinical practice, the inherent limitations of this review (also noted by the authors) must be considered, including inability to establish a causal relationship as well as the potential for publication bias.

In summary, the findings suggested by Mehta and Maartens coincide with recommendations made by the WHO and US Department of Health and Human Services (DHHS) in that EFV, along with close monitoring, is a potential treatment option following non-severe (grade 1 or 2) NVP-associated cutaneous reactions.[10,11] Due to the life-threatening potential, neither the WHO nor US DHHS recommend the use of NVP or EFV following NNRTI-associated SJS. However, in situations where limited treatment options exist, the findings by Manosuthi and colleagues suggest that in some patients EFV may still be a treatment option following NVP-associated severe rash or SJS.

Unfortunately, the limited, but concerning data available regarding safety of NVP following EFV-associated rash makes this an unfavorable treatment option. In all situations, patients undergoing challenge with NVP or EFV following previous NNRTI-associated cutaneous reactions should be carefully monitored, especially during the first six weeks of treatment.

Please Contact ATIC for detailed list of references

Management in HIV infected children: Focus on Pruritic Papular Eruption (PPE)

By Victor Musiime MBchB, MMed
Paediatrician,
Joint Clinical Research Centre (JCRC)

Introduction

Skin diseases are a major manifestation of HIV infection. A prospective 3 year study of 1,161 HIV/AIDS patients showed that 69% (799/1161) developed skin diseases [1].

The skin diseases in HIV infected children include: viral infections such as herpes simplex, herpes zoster, chicken pox, molluscum contangiosum, verruca plana; fungal infections like tinae capitis, tinae corporis, candidiasis; bacterial infections like cellulitis, ecthyma, folliculitis, impetigo; arthropod infestations including insect bites, scabies; inflammatory conditions like seboerrhoeic dermatitis, psoriasis, eczema, pruritic papular eruption (PPE); malignancies like Kaposi's sarcoma, cutaneous B cell and T cell lymphomas; and other skin problems like adverse drug reactions (e.g. to Nevirapine), icthyosis, eosinophilic folliculitis. Among these, pruritic papular eruption (PPE) or prurigo nodularis is one of the commonest [2-4].

Pruritic Papular Eruption (PPE) of HIV

PPE in HIV Infected children is a chronic skin disorder characterized by symmetrically distributed pruritic papules on the trunk and extremities in the absence of other definable causes of pruritis ***(see Fig 1).*** It is more prevalent in the developing countries of the world.[5] Although, PPE is a WHO stage 2 illness in children, it has been found to be associated with more advanced HIV infection in adults [2, 6, 7].

Fig 1: Child with extensive PPE

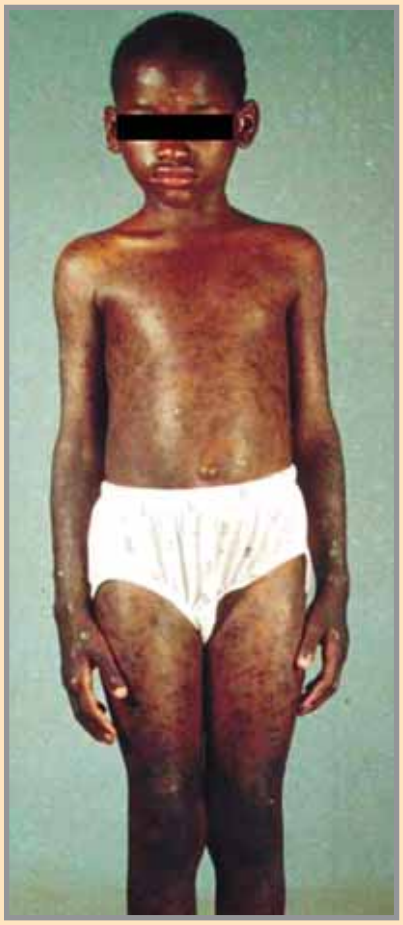


Photo courtesy of Israel Kalyesubula

Etiology of PPE

A study done in two HIV care clinics in Kampala (Mulago hospital and Reach out Mbuya Parish HIV/AIDS community Initiative), showed that 84.3% (86/102) had pathologic skin biopsy findings suggestive of arthropod bites suggesting that PPE may represent an unusual immune reaction to these bites[8].
This has also been suggested by other case series [7, 9]. The lesions of PPE can develop super-infection with bacteria or fungi as shown in ***Fig 2.***

Treatment of PPE in HIV infected children
Given its etiology anti-infectives other than HAART are not useful and the therapies for PPE include: antihistamines, oral prednisolone, topical corticosteroid preparations, ultraviolet B phototherapy and pentoxifylline [10, 11].

When there is suspected super – infection by bacteria or fungi, skin swabs and skin scrapings for culture and sensitivity are recommended to determine whether an antibiotic and or an antifungal agent need to be added to the therapy.

Fig 2: Child with extensive PPE

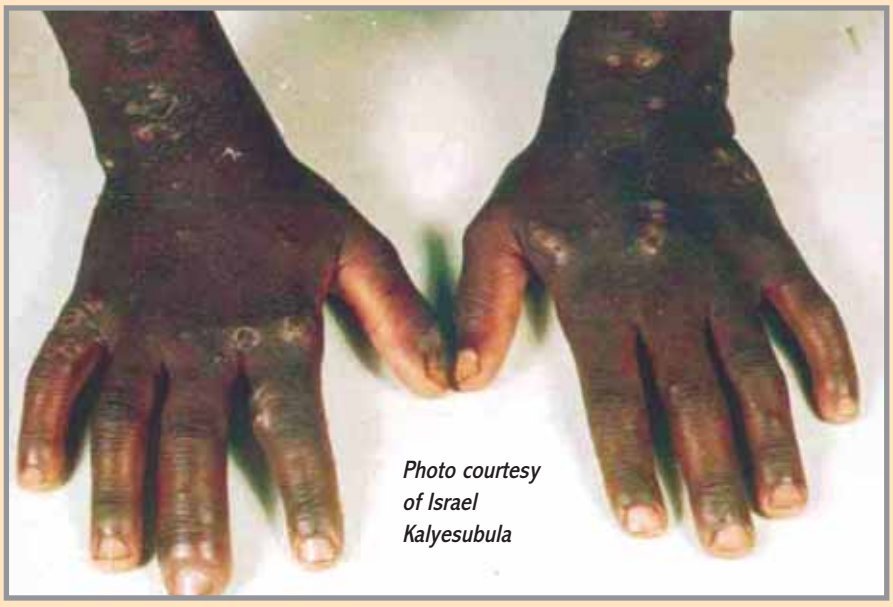


Photo courtesy of Israel Kalyesubula

Where bacterial super – infection is suspected and in the absence of culture and sensitivity services, drugs that cover Staphylococcus aureus and Streptococcus pyogenes are recommended, as they were the organisms most commonly associated with bacterial skin infections in a study done among children presenting to Mulago hospital [12].In that study oxacillin and vancomycin had the best susceptibility profiles.

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Ask ATIC

Francis Kalemeera
HIV Clinical Pharmacist

Let's say that you have a 7y.o. patient who weighs 23kg. The patient is HIV positive, and because the CD4 count and percentage are 157 cells/mm3 and 10% respectively; you want to start ART. However, in store you have Triomune-30® only.

- ***Should Triomune-30 be broken to suit the doses of stavudine, lamivudine, and nevirapine for this patient?***

Children who weigh 23 kg (or a rang of 20-24.9kg) should be given the following doses:

Medicine	Dose
Stavudine	20mg twice daily
Lamivudine	75mg twice daily
Nevirapine	300mg per day: 200 mg in the morning then 100mg in the evening

Can Triomune 30 provide these doses as required? Impossible: why?
Let's use d4T as the basis for breaking the tablet. To get 20 mg of d4T twice daily you need to break off 2/3 of the tablet; this 2/3 of the table will give you ? 100mg of 3TC; and ? 130mg of NVP. It is impractical to get 2/3 of this tablet, and yet if you try you will get a lower dose of nevirapine compared to what is recommended. 3TC is not really a problem though it is a higher dose.

So, regarding Triomune and the future for ART in children in Uganda, points to remember are summarised below:

Message-1: Triomune 30 ® is for adults (and bigger children) and should be swallowed whole. Breaking it has been shown to yield low concentrations of the drugs, especially nevirapine.

Message-2: Pediatric antiretroviral fixed dose combination (FDC) tablets, called Pedimune®, will soon be made available. NB: In the first article pediatric ART is mentioned.

Message-3: As we wait for the pediatric FDC tablets, stock preparations suspensions and syrups for children in your centre

Message-4: In case of difficulties in dosing, drug and regimen choice etc contact ATIC. Just beep this number **0414-307245 or 0414-304228**

Message-5: There is a training course for pharmacy health workers. In it we share information on ART in children.

Leprosy developing as part of the immune reconstitution syndrome in an HIV1- positive patient on HAART- a Ugandan experience

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[2]Kawuma Joseph Herman MBChB, DPH, Dip Derm
[1]St Francis Hospital,Buluba, [2]Germany Leprosy and TB Relief Association(GLRA), Uganda

Summary

Leprosy, presenting as part of the immune reconstitution syndrome (IRIS) in patients on highly active anti retroviral therapy (HAART) has been documented (1,2,3). The increasing availability of HAART in countries endemic for leprosy may lead to unmasking of latent leprosy in co-infected patients. We report an HIV positive patient who developed features of leprosy after initiating HAART and highlight the challenges that may face resource limited settings (RLS) in dealing with this co-infection.

Case report

In June 2006, a 30 year old male presented to a rural health centre where, a diagnosis of tuberculous lymphadenitis with HIV-1 infection was made. He was commenced on anti-TB treatment following the National TB/Leprosy Programme guidelines (4). He had "directly observed therapy" (DOT) for the initial two weeks and was discharged to continue treatment at home. He took the TB drugs irregularly and eventually stopped treatment during the 4th month for unknown reasons. After two weeks of anti-TB therapy, HAART (stavudine, lamivudine and efavirenz) had been started but the health centre did not have the facility to follow CD4 counts.

Six weeks after starting HAART, he noted multiple skin patches on his trunk. Three months later, he reported to the health centre where leprosy was suspected and was subsequently referred to our hospital. However, he could not afford to attend. In the 4th month of HAART, he noted progressive loss of feeling and weakness of the hands and feet while still taking his ARVs.

In June 2007, he was noted to have" severe peripheral neuropathy with hypopigmented skin lesions, a left claw hand and muscle wasting". A diagnosis of leprosy was "strongly suspected" and a second referral was made. His HAART was changed to lamivudine, zidovudine and nevirapine because stavudine-induced neuropathy may have also contributed to his neuropathy.

When seen at our hospital, he was found to have numerous, partly symmetrical, skin lesions on the face and extremities which were insensitive to light touch. The right great auricular, both ulna and radial cutaneous, common peroneal and posterior tibial nerves were enlarged but not tender (figures 1-3). He had bilateral facial weakness. Bilateral clawing of both hands and bilateral peroneal paresis with bilateral foot drops were noted. The general physical examination was otherwise normal. A diagnosis of multibacillary leprosy was made.

Skin smears were negative for AFB but histologic examination confirmed the diagnosis of leprosy but classified it as tuberculoid type. Repeat testing with the national algorithm confirmed his HIV-1 status. His CD4 count was 735 cells/ml. Renal and liver function tests were normal.

He was hospitalized and commenced on multi drug therapy (MDT) for leprosy and prednisolone and was given physiotherapy. He continued on his nevirapine based HAART regimen. By 6 weeks of treatment he had improved clinically and continued with supportive care.

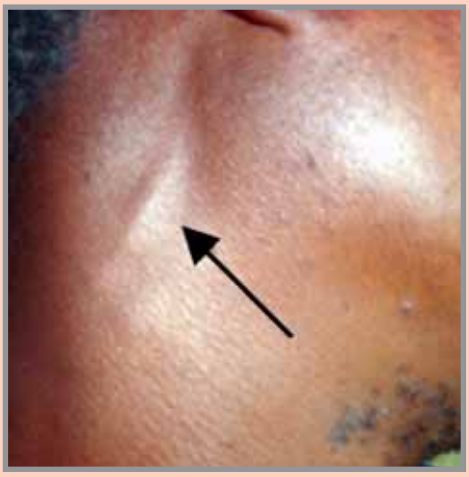

Figure 1.*enlarged great auricular nerve.*

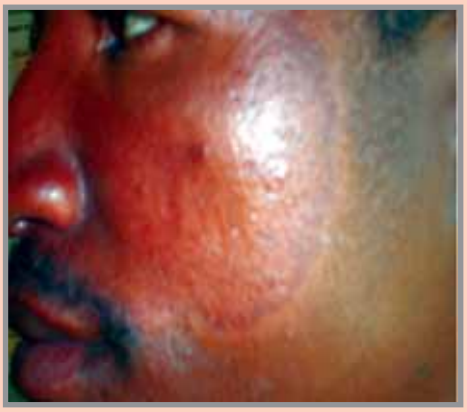

Figure 2. *reactional facial patch.*

Figure 3. *severe muscle with a claw hand.*

Discussion:

This case contributes to observations that have been made by other authors highlighting leprosy occurring as an immune reconstitution phenomenon (unmasking type) in HIV infected patients commencing HAART (1,2,3). No previous case has been reported from Uganda. This case also puts in perspective the challenges that face resource constrained countries when handling co-infection with M. leprae and HIV.

There is limited data on the relationship between HIV infection and leprosy in comparison with data on co-infection with M. tuberculosis (2,3,5,6). This has been attributed to the fact that HIV infected patients in areas where leprosy is also endemic rarely live long enough to develop opportunistic infections in the form of leprosy (1,2). If this hypothesis is sound, then we might expect an upsurge of leprosy cases with the scaling up of HAART treatment in many tropical countries.

Reports have highlighted a high prevalence of reversal reaction and rapid nerve damage in patients co-infected with HIV and leprosy resulting in early and severe deformities (2,3,5,6). Also because of poorly developed dermatological services in developing countries, most leprosy patients will have delayed diagnosis and treatment, predisposing them further to irreversible nerve damage.

Our patient developed leprosy related symptoms six weeks after starting HAART. This is similar to the patient reported by Lawn et al who developed leprosy symptoms 8 weeks of initiating HAART (3). He suffered a rapid silent neuritis resulting in irreversible deformities of the hands, eyes and feet .This observation has been documented by other authors (1,2,5,6). HIV infection may have played part in the rapid nerve damage though this is not conclusive. His CD4 level at the initiation of HAART and at the development of leprosy symptoms is not known. However, his CD4 count, after a year of HAART was 735/mm3.
We did not find enough evidence to support the initial diagnosis of tuberculous lymphadenitis. We think the markedly enlarged right auricular nerve was wrongly assumed to be matted lymph nodes.

The interaction of nevirapine and rifampicin has been documented in TB/HIV treatment programmes (4) but not in leprosy. The effect of a single dose of rifampicin 600mg per month for 6 or12 months (depending on the form of leprosy) on the bioavailability of nevirapine is not clearly known.

The best approach in such unclear circumstances would be to put the patient on a nevirapine free HAART regimen. This patient was continued on a nevirapine based regimen because of lack of options and he had already been exposed to five different basic antiretroviral drugs during the course of his treatment.

Dermatological disorders are very common and always challenging in the setting of HIV infection. There is need to ensure that primary health workers at different levels have the necessary basic skills to make appropriate decisions in the face of an unknown dermatological condition. Such decisions may be as simple as consulting a more knowledgeable colleague in a neighboring health unit (7,8,). Greater emphasis was put on this patient's dermatological problems but unfortunately only after he had developed irreversible nerve damage.

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Infectious Diseases Institute Training Calender 2008

		JAN	FEB	MAR	APR	MAY	JUN	JULY	August	sept	Oct	Nov	Dec	Jan	Feb	March	april	May	June
		2008	2008	2008	2008	2008	2008	2008	2008	2008	2008	2008	2008	2009	2009	2009	2009	2009	2009
A	Core Course	14.1. - 1.2. EXXON/DOD/Ot			7th -25th KCC/DOD	5th - 23rd				8th -26th		10th 28h		12th 30th				11th -29th	15th-3rd
AA	Nurses Core Course		18.2. - 29.2DOD/KCC nurses	3rd -14th DOD/ohers			9th - 20th		18th -30th		20th 31st					2nd -13th	13th -1st		
	Field work	28th-1st			28th-2nd	19th-23rd													
B-2	ART programmes and Epi Info																		
B-3	Research in HIV Care		4. - 8.2.		28th -2nd	26th - 30th				29th -3rd			1st -5th		2nd -6th			1st -5th	
B-5	Training of trainers		4.-8.2		28th -2nd	26th - 30th				29th -3rd			1st -5th		2nd -6th			1st -5th	
B4	Module for pharmacist and dispensers			3rd -7th KCC															
B-6	ART clinic management for nurses/CO																		
B1	Newly booked 1 week slots	7th - 11th UNHCR					2nd -6th Pharmaccess												
C	Multi-disciplinary training		11th -16th	26th -2nd			25-2nd		6th -13th		8th -15th		10th -17th		11th -18th	18th -25th	1st -8th		
	Palliative Care		25th -1st																
	CME weekends																		
D 3	Faculty of Medicine undergraduate		Medical Students																
M	JUMP Training Courses	7th-12th/21st -26th		10th-14th;17th-21st;26th-29th.	7th -12th/21st - 26		2nd -7th /16th - 21st												
BD	Lab Training Courses	Unit 1: 28th Jan - 8 th Feb		Unit II: 24th - 28th		Unit 1: 5th - 16 th	Onsite training 1	Unit II: 7th - 11th	Onsite training 2										
DT	Data Management Training	14th -18th																	

To apply for a course contact 0312-307208/0312-307212 or visit www.idi.ac.ug.

(Answers to Part B of Career Management Questions

1. a. - False
b. -False
c. -False
d. -False
e. -False

2. a. -False
b. -False
c. -False
d. -False
e. -False

3. a. - True
b. - True
c. - True
d. - True
e. - True

4. a. -False
b. -False
c. -False
d. -False
e. -True

5. a. -True
b. -False
c. -False
d. -False
e. - False

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