ATIC News

Vol 4 Issue 4 Dec 2008

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

Beep ATIC Hotlines +256 312 307245/307228 /+256 414 307245/307228 for FREE advice on Patient Management

Making Pharmaceutical Supply Management Training Effective

By Paul Kutyabami BPharm, MPS, Department of Pharmacy, Makerere University

Background

Accessibility to health facilities, the presence of qualified staff and the availability of pharmaceutical products are important components of an effective health care system. Whereas the government of Uganda has made tremendous achievements by constructing new and improving on the existing health facilities, there are still major difficulties in recruiting enough qualified staff and ensuring constant supply of quality pharmaceutical products. The establishment of the National Drug Authority and the National Medical Stores with the respective enabling legislations was one of the government efforts to ensure availability and accessibility of quality pharmaceutical products in the country. However reports of stock outs, expiry of medicines and other logistical problems are still common issues in the Ugandan media and this has been supported by a number of studies. Indeed because most of the leading causes of morbidity and mortality are due to diseases that could be treated, prevented or alleviated using pharmaceutical products, morbidity and mortality figures of Uganda are still high.

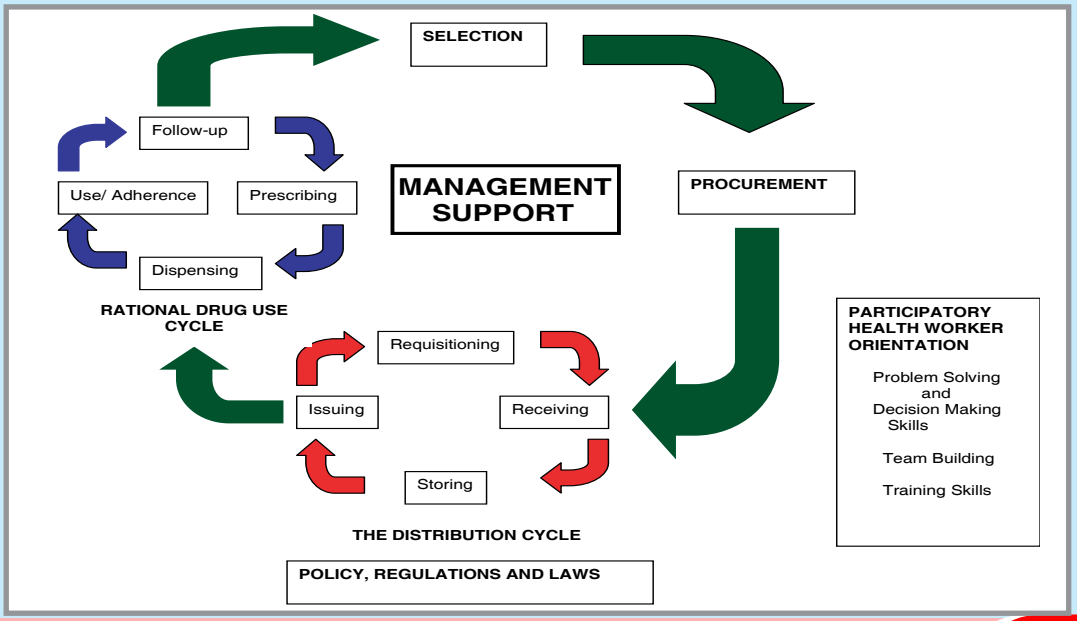
It is recognized that well trained human resource is very valuable in any health services system with evidence showing a direct and positive causal link between the health workforce and health outcomes. Inadequate human resources provide major impediments to many global health initiatives and developing a strong workforce is vital in ensuring successful implementation of health related initiatives

Pharmaceutical Supply Management

The Division of Pharmacy at the Ministry of Health Uganda has intervened in increasing accessibility and availability of pharmaceutical products. With the assistance of development partners this has been done by conducting trainings workshops for health workers on Pharmaceutical supply management. Perhaps this is one of the major interventions that can address the stock outs of medicines, expiries and other logistical problems. However there are concerns about the approach to trainings being employed. Under the present approach, trainings are organized in a project format whose life span is limited. The objectives of the projects focus on short term outputs rather than long term outcomes, such as number of health workers trained rather than reduction in stock outs. The mode of training focuses on transferring of facts to the trainees rather than making them better problem solvers and life long learners. The present approach

continues on page 2

The Pharmaceutical Supply Management Cycle Figure 1



Inside this Issue>>

USAID FROM THE AMERICAN PEOPLE

MSH SPS Strengthening Pharmaceutical Systems

From the Editor

Dear readers we are glad to present yet another exciting issue of the ATIC News. This will be the last issue of the year 2008. On the 1st of December we celebrated the World AIDS day. It was a chance to remind ourselves that HIV/AIDS is still a problem in our country that we must all join hands to fight. The scourge of HIV/AIDS still resounds across much of Sub-saharan Africa. We must use concerted efforts to ensure that those that are HIV negative remain HIV negative and those that are HIV positive are able to have fulfilling and fruitful lives. One of the biggest contributors to a fulfilling and fruitful life for patients with HIV/AIDS and other diseases is the availability at their health centre's of the right drugs at the right time to manage their care.

One of the biggest challenges faced by the health care system is the lack of a steady supply of drugs to manage various conditions. Many centre's struggle with stock outs for months on end. While these stock outs may be related to problems in the internal system of the centre, many times extraneous factors play a key role in drug stock outs. In this issue we focus on pharmaceutical management and the role it has to play in the efficient running of a health centre.

We hope that you will find this issue enlightening and enjoyable. We here at ATIC wish you a wonderful festive season and we look forward to supplying you with other exciting issues of ATIC News in the New Year.

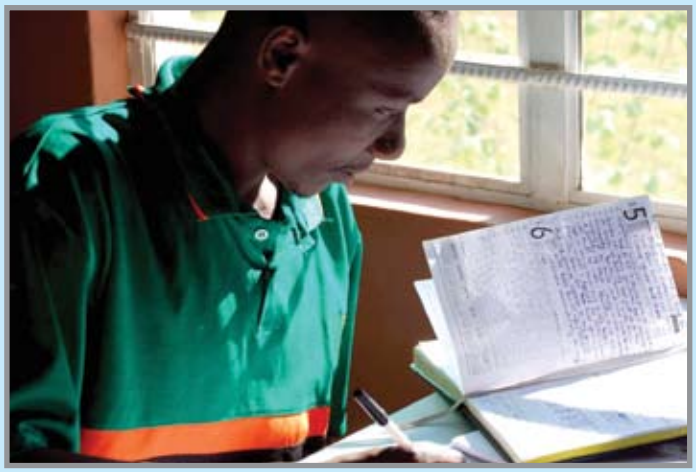
Making Pharmaceutical Supply Management Training Effective

continues from page 1

does not address barriers trainees meet as they try to implement knowledge acquired at their respective health units. These together with the high attrition of health workers at health facilities make this approach ineffective.

Approach to Pharmaceutical Supply Management Training

Traditional methods of training lead to retarded information recall, leading the trainees to rapidly forget the information. Pragmatic approaches to training that address barriers to implementing new pharmaceutical supply management systems at facilities need to be adopted. Management Sciences for Health (MSH) has implemented the Monitoring, Training Planning (MTP) approach with tremendous results. Another study being done by Anyama and colleagues from the Department of Pharmacy, Makerere University has tested the Participatory Health Worker Orientation (PaHO) approach whose results are also encouraging. The two training approaches provide facts on pharmaceutical supply management but go further to provide training and problem solving skills to the trainee. This makes the trainee not only a problem solver but a trainer of others when they return to their units thus making these approaches effective in addressing stock outs, expiries and other logistics problems at health centers. PaHO should be integrated into training at every point of the pharmaceutical supply management cycle i.e. selection, procurement, distribution and use. This will go a long way into ensuring adequate drug management at health centres.



Innovative training techniques must be adopted to increase knowledge retention

References

- **Management Science for Health, Managing Drug Supply, 2nd Edition, 1997,** Kumarian Press
- Anyama N, Kutyabami P, Odoi R et, al; **How the use of first-line Antimalarial Medicines can be improved at peripheral health units: Translating policy into practice** (Research in progress)

TURNING THE SPOT LIGHT ON A WIDELY USED ANTIBIOTIC- CIPROFLOXACIN

Ciprofloxacin is widely used incorrectly in the management of many conditions including coryza. This incorrect use is mainly attributed to its ready availability and low cost. **Robinah,** a Pharmacist summarizes the drug profile of Ciprofloxacin. This will guide health care workers to prescribe it rationally as they manage different conditions in their patients.

Robinah.N.Lukwago BPharm, MPH, MPS
Infectious Diseases Institute

Mechanism of action

Ciprofloxacin like other quinolones acts principally by inhibiting bacterial (but not human) DNA gyrase, so preventing the super coiling of DNA, a process that is necessary for compacting chromosomes into the bacterial cell. It is bactericidal. In general ciprofloxacin is particularly active against Gram-negative organisms including Escherichia coli, Salmonella sp., Shigella sp., Neisseria sp., Pseudomonas aeruginosa, Heamophilus influenza and Legionella pneumophila. Ciprofloxacin has moderate activity against Gram-positive organisms such as Streptococcus pneumoniae and Enterococcus faeclis. It should not be used for pneumococcal pneumonia. It is active against chlamydia and mycoplasma; however most anaerobic organisms are not susceptible.

Indications

- Uncomplicated and complicated urinary tract infections (UTI)
- Complicated intra-abdominal infections (in combination with metronidazole)
- Infectious diarrhoea
- Endocervical and urethral infections caused by N. gonorrhoea
- Empiric therapy for neutropenic fever; typhoid fever
- Nosocomial pneumonia
- Prostatitis
- Acute sinusitis
- Skin and soft tissue infections; bone and joint infections
- The ophthalmic solution can be used to treat bacterial conjunctivitis and corneal ulcers
- The otic suspension can be used to treat acute otitis externa

Available formulations

- **Oral tablets:** 250mg, 500mg and 750mg
- **Oral extended release tablets:** 500mg, 100mg
- **IV vials:** 200mg, 400mg
- **Opthalmic suspension:** Ciprofloxacin 0.3%/Dexamethasone 0.1%

Dosage and administration

The dosage depends on the condition being treated. Dosages for some of the most common conditions are outlined below:

- Uncomplicated UTI: 250mg orally twice daily or 500mg orally once daily x 3 days.
- Complicated UTI: 500mg orally twice daily x 7-10 days.
- Nosocomial pneumonia (P. aeruginosa): 400 mg IV q8h, then 750mg orally twice daily x 10-14 days.
- Salmonellosis: 500-750mg orally twice daily or 400mg IV twice daily x 7-14 days for mild disease (note: treat for 4-6 wks in HIV-infected patients with CD4 <200 and/or bacteremia).
- Traveler's diarrhea: 500mg orally twice daily x 3 days.

Renal disease

The dose of ciprofloxacin should be halved when the glomerular filtration rate is less than 20ml/min.

Caution

- Quinolones should be used with caution in patients with history of epilepsy or conditions that predispose to seizures. This is because some studies have suggested that quinolones may lower the seizure threshold.
- Quinolones cause arthropathy in the weight-bearing joints of immature animals. They are generally not recommended in children and growing adolescents. For the same reason it is also advised that they should be avoided in pregnancy as safer alternatives are available.

Adverse drug reactions

It is generally well tolerated.

Occasional- Candida vaginitis, rash and pruritus, GI intolerance: nausea, dyspepsia, abdominal pain and diarrhoea, CNS: headache, malaise, insomnia, restlessness and dizziness.

Rare- Photosensitivity, allergic reactions, QTc prolongation, peripheral neuropathy, interstitial nephritis, restlessness, depression, confusion and disturbances in vision. Tendon damage (including rupture) has been reported rarely in patients receiving quinolones and can occur within 48 hours of starting treatment. The risk of tendon rupture is increased by the concomitant use of corticosteroids and elderly patients are more prone to tendinitis. If tendinitis is suspected, the quinolone should be discontinued immediately.

The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur.

Drug Interactions

Some quinolones are potent enzyme inhibitors and impair the metabolic inactivation of other drugs including warfarin, theophylline and sulphonylureas, increasing their effect.

Magnesium (Mg) and Aluminium (Al) containing antacids impair the absorption of quinolones from the gut probably through forming a chelate complex. Note that Al-Mg contained in buffered didanosine would have the same effect; ferrous sulphate and sucralfate also reduce quinolone absorption. Administer ciprofloxacin 2 hrs before cations.

Others;

- Milk or dairy products: decreased GI absorption of ciprofloxacin by 36-47%. Administer ciprofloxacin 2 hrs before dairy products.
- Non steroidal anti-inflammatory drugs: may increase risk of seizure. Avoid co-administration in patients with epilepsy and seizure history.

Antiretroviral therapy;

ciprofloxacin can be administered with antiretroviral drugs. However concomitant use of oral ciprofloxacin and didanosine administered as either chewable/dispersable buffered tablets admixed with an antacid may decrease absorption of ciprofloxacin.

Use in pregnancy

There are no adequate and controlled studies using ciprofloxacin in pregnant women. Since fluoroquinolones cause arthropathy in immature animals, ciprofloxacin should be avoided in pregnant women.

References

For a detailed list of the references used for this article, please contact queries@atic.idi.co.ug.

PRESS RELEASE: Primary prophylaxis of invasive cryptococcal disease using fluconazole prophylaxis in HIV infected Ugandans.

Background

Cryptococcal disease is the most common infection of the brain and spinal cord (Central Nervous System) in patients with advanced HIV infection in Africa. It is caused by a fungus that is present in the soil, and affects those people who have a damaged immune system (immunosuppression). It commonly presents with severe headache and is fatal unless treated. The treatment is quite intensive and costly, and unfortunately not always successful. Survivors are often left with disabilities. Treatment with antiretroviral therapy (ART) has led to a decrease in cryptococcal disease, but ART coverage remains low, with only 30% of individuals who need ART in Africa receiving it. Due to this, so many HIV infected people are still dying from cryptococcal disease. To address the above challenges, a number of measures have been taken; including research to find alternative prevention approaches.

In this respect, the Medical Research Council (MRC) Uganda Research Unit on AIDS, The AIDS Support Organisation (TASO) and the Ministry of Health of Uganda are pleased to announce the results of a large collaborative trial which was designed to assess whether the routine use of the anti-fungal drug called fluconazole is effective and safe as a primary prevention for cryptococcal disease in HIV infected individuals in Uganda.

This trial was conducted by the MRC, the Uganda Virus Research Institute (UVRI) and Liverpool School of Tropical Medicine, UK (LSTM) and TASO; in collaboration with Kalangala District Health services, Masaka Regional Referral Hospital, Kitovu Mobile Home Care and Uganda Cares Masaka. The study clinics were sited at TASO Masaka and Kalangala health centres.

One thousand five hundred and nineteen (1519) Ugandan adults infected with the HIV virus were enrolled into the trial between November 2004 and January 2008. All the enrolled participants consented and fulfilled strict inclusion and exclusion criteria. All participants enrolled had severe immunosuppression with a CD4 cell count of less than 200 cells/μL. Half of the individuals enrolled into the trial were given a 200mg fluconazole capsule three times a week and half an identical looking capsule containing no fluconazole (placebo). Participants took one capsule three times a week. Neither the participants nor the trial team knew whether the drug given was active or placebo. All the participants were referred for ART to local providers, and were reviewed every 8 weeks by the trial team and encouraged to attend if unwell. Enrolled participants were seen after 4 weeks and then every 8 weeks for routine follow up. Liver function tests (LFTs) done every 8 weeks and CD4 counts measured every 16 weeks. Participants continued the trial drug until the end of the trial or until their CD4 count reached 200 cell/ul. The trial drug was also stopped if LFTs exceeded five times upper limit of normal, if women became pregnant or if participants wished to leave the trial or moved from the study area.

Prophylactic treatment for patients with HIV is life saving

Results

One patient developed cryptococcal disease in the fluconazole group and 18 patients developed cryptococcal disease in the placebo group. Therefore, the individuals receiving fluconazole were much less likely to develop cryptococcal disease than those receiving placebo. Fluconazole was effective at preventing cryptococcal infection of the brain and other cryptococcal diseases both before and after starting antiretroviral therapy. Fluconazole was also found to reduce the occurrence of candida (another fungal infection) affecting the oesphagus (gullet), oropharyngeal (mouth and throat) and vagina, when compared to placebo. There was no difference in deaths from any cause between the fluconazole and placebo groups, probably because the medical care provided under these research project conditions were excellent. The drug was very well tolerated, and the researchers did not observe any drug safety problems among the participants that took fluconazole.

In conclusion, fluconazole therapy is safe and very effective at preventing cryptococcal disease (mainly a brain disease caused by a fungus) and should be considered in patients with advanced HIV infection, both before starting antiretroviral drugs and in the early months of antiretroviral therapy until the immune system recovers.

It is worth noting that fluconazole, a drug used to treat dangerous fungal infections would provide complementary protection for HIV/AIDS patients, in addition to cotrimoxazole that many patients take already as a prophylaxis against dangerous bacterial infections.

About the drug

Fluconazole is a safe drug that can be and has been used to prevent and treat a variety of fungal infections. It is a relatively cheap drug with minimal side effects. It is hoped that the price of the drug will reduce over time, making it possible to use it as a prophylactic drug in HIV care programs in Uganda. This drug is being distributed free for secondary prophylaxis against cryptococcal meningitis in Uganda. It is however not yet national policy that fluconazole should be given for primary prophylaxis.

A brief on Fluconazole

Indications

- Treatment of oropharyngeal and esophageal candidiasis
- Disseminated candidiasis (including peritonitis, pneumonia, and Urinary Tract Infections)
- Chronic mucocutaneous candidiasis
- Vulvovaginal candidiasis
- Disseminated cryptococcosis

- Treatment and suppression of cryp tococcal meningitis

Usual adult dosing

- Cryptococcal meningitis, induction phase: 400-800 mg PO once-daily x 10-12 wks +/- flucytosine 100 mg/kg/d x 6 wks
- Cryptococcal meningitis, consolidation phase: 400 mg PO once-daily x 8 wks;
- Cryptococcal meningitis, maintenance phase: 200 mg PO once-daily (until CD4>100-200 x > 6 mos)
- Vaginal candidiasis: 150 mg PO stat. Multiple recurrences: fluconazole 150 mg PO once a week (topical azoles preferred)
- Esophageal candidiasis: 200 mg PO once-daily x 14-21 days (or IV up to 800 mg/d). Use chronic maintenance therapy (same dose) for recurrent esophagitis
- Oropharyngeal candidiasis (thrush): 100-200 mg PO once-daily x 7-14 days (topical therapy with clotrimazole preferred to avoid azole resistance)
- Histoplamosis: 800 mg daily (itraco nazole preferred).

Adverse drug reactions

Generally well tolerated

Occasional

- GI intolerance with bloating, nausea, vomiting, pain, anorexia
- Reversible alopecia (with >400 mg/ day)
- Transaminase elevation

Rare

- Hepatitis (fatal hepatotoxicity in patients with serious underlying medical conditions; monitor LFTs)
- Dizziness
- Headache
- Hypokalemia

Drug interactions with NNRTI's and PI's

There are no clinically significant drug-drug interactions with PI's and Efavirenz. There is an increase in Nevirapine plasma concentrations when its administered with Fluconazole. Patients should be monitored closely for adverse effects of Nevirapine.

The role of health care workers in improving patient adherence to medication

By Douglas Keene Pharm.D, M.H.S and Dr. Andy Stergachis Ph.D., R.Ph.

The treatment of HIV disease is chronic and managed long-term with antiretroviral therapy and other medications. Adverse events such as stock-outs contribute to reduced options for regimen changes and treatment interruptions that have implications for medication adherence, drug resistance, as well as potential for spread of HIV. Moreover, since persons with HIV/AIDS are often on long-term, multidrug therapy, it is crucial that they remain adherent to their drug regimens and take responsibility for their health. Barriers to treatment can include forgetting to take medication, travel time, stigma, high cost of obtaining medication, food availability, lack of information, and side effects. For the health care provider, strategies for improving the appropriate use of antiretroviral therapy include;

- Being well-informed about HIV/AIDS and antiretroviral treatment.
- Communicating, at the educational level of the patient, the importance of taking medications as prescribed, including explaining the connection between adherence and resistance.
- Conveying confidence in effectiveness of antiretroviral treatment.
- Whenever possible, tailoring medication regimens to fit into the patient's activities of daily living.
- Detecting and documenting if a patient is taking their medication in the manner prescribed and, if not, then taking action (i.e. patient education, regimen simplification) to improve adherence.
- Providing medication leaflets upon dispensing of medications, including the use of pictograms to illustrate information about medicines and how they should be used. Additionally, pharmacy waiting areas present opportunities for providing positive medication-related messages through posters and reading material.

Mr. Douglas Keene is the Director, Strengthening Pharmaceutical Systems Program and Rational Pharmaceutical Management Plus Program, Washington. Dr. Andy Stergachis is a professor of Epidemiology and Global Health and Adjunct Professor of Pharmacy at the Northwest Center for Public Health Practice School of Public Health & Community Medicine University of Washington

ALUMNI, ALUMNI, ALUMNI

Are you an Alumnus of the Infectious Diseases Training program? If so, then this applies to you!!

THE FIRST IDI ALUMNI ASSOCIATION

The Alumni Association of the Infectious Disease Institute is an extention of our Ugandan based organization that nurtures lifelong relationships with and among current and future IDI Alumni. The Association offers programs of relevance and service to Alumni and creates support for the Institute. Underlying all that we do is the belief in the value of training and education to the well being of a society, and a commitment to research and quality care for the people we serve. We are making changes to our website and will have important information included in the next ATIC newsletter.

Upcoming programs/services will include:

- Alumni Events
- Fellowship Opportunities
- Job Opportunities
- Training Courses
- CME Classes

And that's just the beginning!!

Make sure you update your current information so you too, can take advantage of these amazing programs and services only offered to Alumni.

Please be sure to update your contact information through email by contacting alumni@idi.co.ug or beeping the ATIC hotlines 0414307245 or 0414307228.

A FRAMEWORK FOR STRENGTHENING PHARMACEUTICAL SYSTEMS IN RESOURCE-LIMITED SETTINGS

Andy Stergachis, Ph.D, R.Ph, and Douglas Keene, Pharm.D., M.H.S.

Introduction

There is little question that people's lives have improved because of increased availability of medicines; many patients are now surviving medical conditions that were previously considered fatal diseases. Assuring that access to medicines improves health outcomes, particularly in resource limited settings, is complex and can be challenging to achieve. It involves more than just making medicines available. It also requires assuring geographic accessibility, affordability, cultural acceptability, and the presence of a trained and accessible health care workforce. Medicines must also be effective, safe, of good quality and prescribed and dispensed appropriately for patients to benefit from their use. This article describes a framework for improving pharmaceutical systems in resource-limited settings.

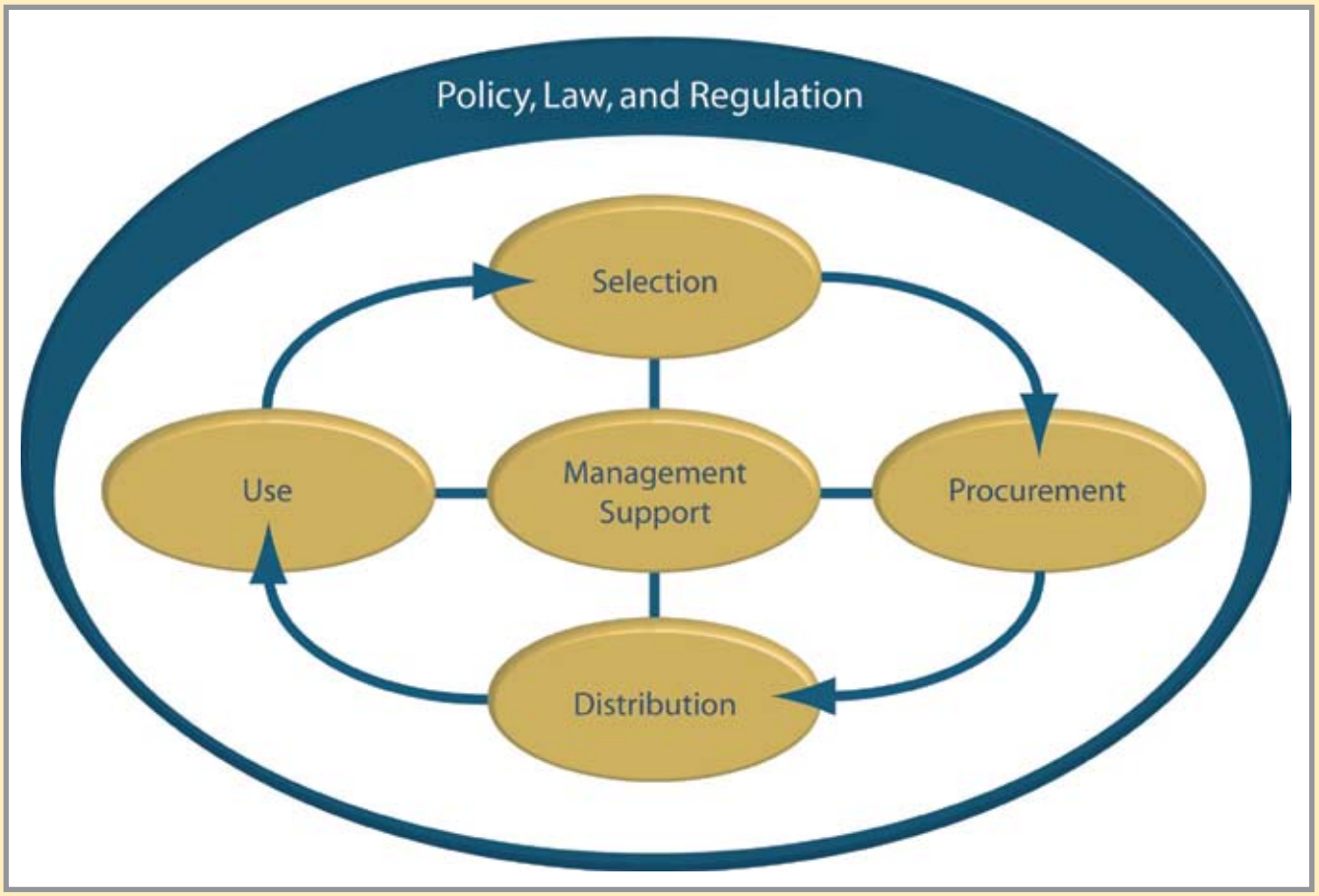
Initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; the U.S. government's programs, particularly the President's Emergency Plan for AIDS Relief (PEPFAR) and the President's Malaria Initiative (PMI), and others have dramatically increased investments for the procurement and distribution of medicines for HIV/AIDS, tuberculosis , and malaria in addition to other health commodities. For example, about one million people in developing countries gained access to antiretroviral drugs in 2007. These initiatives, while providing much needed support for countries to acquire life-saving medicines, create additional pressure on supply systems that must now accommodate and account for a substantially increased volume and range of health commodities. Most countries in resource-limited settings struggle in terms of their capacity to provide care and medicine to all people who need treatment. Now more than ever, development partners recognize that reliable access to quality medicines and vaccines and a functioning pharmaceutical system are essential to achieving public health goals.

The Pharmaceutical Management Framework

Because medicines are so important and resources so limited, public health managers at all levels seek ways to improve the supply and use of medicines while

continues to page 7

The Pharmaceutical Management Framework Figure 2



continues from page 6

minimizing costs. As depicted in Figure 2, the pharmaceutical management framework represents the flow of activities that must be coordinated to ensure that appropriate, high-quality medicines are available when patients need them. The framework emphasizes the relationships between selection, procurement, distribution, and use activities, all of which are supported by a strong management support system.

Each component of the framework depends on the success of the previous component and contributes to the viability of the next. But what role does each component play in getting medicines to the people who need them?

Policy, Law, and Regulation

A country's policies, laws, and regulations define the general goals and parameters for effective pharmaceutical management overall, therefore encircling the other elements in the framework. Medicine policy includes such elements as allocating budgets, prioritizing research and development, promoting education initiatives, and defining the role of the public and private sectors. By establishing pharmaceutical laws and regulations, countries can set pharmaceutical quality standards and price limits, require registration of pharmaceutical products, and establish guidelines. Good governance in the form of transparency and accountability prevents waste of scarce resources and increases people's trust in the government and the health care system.

Selection

Establishing and using a list of carefully selected essential medicines is perhaps the single most cost-effective action that any health care system can take to promote a regular supply of pharmaceuticals. Essential medicines are those best suited to treat the most prevalent illnesses afflicting a population. If these medicines are made available, prescribers can be sure of a sufficient supply to treat the most common illnesses. Selecting the most useful medicines also helps prevent the wasting of scarce resources on unnecessary, unsafe, or ineffective medicines. Evidence-based selection of the most appropriate medicines requires that health managers and policy makers have access to current information on common illnesses, budgetary limits, and pharmaceutical advances, as well as input from doctors and pharmacists.

Procurement

The availability and costs of medicines are firmly tied to the effectiveness of the procurement process. Strong procurement processes ensure that selected medicines are purchased at reasonable prices, of high quality, and in the right quantity. Procurement strategies vary widely, but most models include the following critical activities: pharmaceutical needs quantification, bid management, supplier selection, and medicine quality assurance. Good procurement practices, supported by adequate information systems, can help ensure that the selected medicines are made available for distribution.

Distribution

A primary goal of pharmaceutical distribution systems is to deliver procured medicines and supplies to the clinics, hospitals, and centers that use them. Effective distribution includes clearing the pharmaceutical products through customs, transporting them safely and delivering them in a timely manner, record keeping, maintaining adequate stock levels, and managing available stock. Storage managers monitor expiration dates, inventory levels, and storage conditions such as light, temperature, and sanitation. When distribution systems function well and are supported by good procurement practices, patients are more likely to receive the medicines they need, on time, and in good condition.

Use

To ensure the most effective, rational use of medicines, patients must receive the correct dosage of medicines that best treat their illness. In addition, patients must receive a supply of medicine sufficient to treat their illness for the required period of time, at a low cost to themselves and/or to the health system. For example, if treatment for a respiratory infection requires 10 days of an antibiotic, taken three times daily, the patient should be prescribed, receive, and take 30 units of antibiotics. Labels with proper information and warnings help the patient use the medicines correctly and consistently. The prescriber, the dispenser, and the patient must each understand their role in treating the illness. The rational use of medicines is also supported through the development and use of national and institution-specific treatment guidelines, drug utilization reviews, drug information services, and drug and therapeutic committees.

Management Support

Management support reinforces each component of pharmaceutical management and unifies the framework. The entire pharmaceutical management system depends on effective integration and management of finances and budgets, maintenance of accurate, useful, and up-to-date information systems, identification and motivation of capable staff, and the institution of monitoring and evaluation systems. The expertise and organizational structure provided through management support is critical at each stage of the pharmaceutical management framework.

Summary

Using a model like the pharmaceutical management framework to analyze the strengths and weaknesses of a pharmaceutical system, organizations and countries can identify specific barriers and their root cause and then design and target appropriate corrective interventions. Ensuring that pharmaceutical supply systems are effective is an ongoing process and countries in resource limited settings will require the collective involvement of the public sector, the private sector including the NGO community, the pharmaceutical industry, academic institutions and professional associations, foundations and donors.

Mr. Douglas Keene is the Director, Strengthening Pharmaceutical Systems Program and Rational Pharmaceutical Management Plus Program, Washington.
Dr. Andy Stergachis is a professor of Epidemiology and Global Health and Adjunct Professor of Pharmacy at the Northwest Center for Public Health Practice School of Public Health & Community Medicine University of Washington

DRUG - DRUG INTERACTIONS BETWEEN LOPINAVIR/RITONAVIR AND RIFAMPICIN IN HIV INFECTED CHILDREN WITH TUBERCULOSIS.

By Dr. Violet Okaba MBChB, Pharmacokinetics team, Infectious Diseases Institute

Great success has been achieved with the roll-out of antiretroviral therapy across Sub-Saharan Africa. However, with many children commencing life-long therapy, cases of resistance to the first line drugs is on the increase and a significant number of children have moved on to the second line therapy. Despite the significant success, the treatment of HIV infection and co-infections still poses a great challenge. Tuberculosis is one of the commonest opportunistic infections in children and the combination of antiretroviral therapy with antituberculous agents is very complex.

Lopinavir/ritonavir (LPV/r), a formulation of two protease inhibitors is an important second line antiretroviral drug. Lopinavir is a highly potent and selective inhibitor of protease, an essential enzyme for the production of mature infective HIV. However its in-vivo activity is greatly attenuated by a high first-pass hepatic metabolism.
Both Lopinavir and Ritonavir are substrates for the hepatic cytochrome P450 (CYP) 3A4 isoenzyme. However ritonavir also potently inhibits this enzyme and acts as a pharmacokinetic enhancer of lopinavir.

LPV/r is the only protease inhibitor approved for use in children as young as 6 months of age. The formulation is made in a ratio of 3:1 (LPV/r). In children less than 15kg, it's given as 12mg/kg (lopinavir) twice daily and in those who are 15kg or more it's 10mg/kg (lopinavir) twice daily.

Rifampicin is a strong inducer of Cytochrome P450 (CYP) particularly the CYP3A isoenzyme. When co-administered with LPV/r it results in sub-therapeutic levels of lopinavir. A study by Bertz el al in which healthy adult subjects were give rifampicin at 600mg once daily with LPV/r at 400/100mg twice daily showed reduction in lopinavir concentrations by 75%. This clearly indicates that low dose ritonavir does not prevent rifampicin-mediated decreases in lopinavir concentrations. (1)

Porte et al studied the pharmacokinetics of adjusted-dose LPV/r combined with rifampicin in healthy adult volunteers. In one arm the subjects received LPV/r at 800/200mg BID in a dose titration while subjects in the other arm received LPV/r at 400/400mg BID. Rifampicin was given 600mg once daily to all subjects. Lopinavir exposure was substantially higher in both study arms compared to the data on LPV/r at 400/100mg BID, (2). The WHO recommendation is to give 400/400mg BID in treating adults under close clinical and laboratory monitoring to detect hepatotoxicity.

A few of these pharmacokinetic studies have been done in children. Ren et al evaluated the effect of additional ritonavir on plasma lopinavir concentrations in HIV infected children receiving rifampicin-based treatment of TB. The children were given LPV/r in a ratio of 1:1, e.g. for a child given LPV/r 200/50 (4:1), the ritonavir was increased by 150mg to make LPV/r 200/200. 87% of the children had lopinavir Cmin greater than the recommended minimum therapeutic concentration. The effect of rifampicin based antitubercular treatment on lopinavir concentrations was attenuated by adding ritonavir to rifampicin in children. (3)
A cohort study found similar virological and immunological outcomes of antiretroviral therapy among children treated with super-boosted lopinavir and rifampicin-based tuberculosis treatment compared to children treated with standard dose LPV/r. (4)

There are some emerging unpublished pharmacokinetic data on use of Double dose LPV/r in HIV infected children on rifampicin based antituberculous treatment. A study in South Africa in which double dose LPV/r was administered to HIV infected children on Rifampicin has been terminated because the blood levels of lopinavir was unacceptably low.

CONCLUSION

LPV/r is an important second-line therapy that has significant drug to drug interactions with rifampicin. Use of standard dose LPV/r is contra-indicated in children on rifampicin based antituberculous treatment. Though double dose LPV/r can be used in adults on rifampicin based antituberculous treatment, it is contra-indicated in children. In the mean time LPV/r in the ratio of 1:1 is the recommended combination to be used in children on rifampicin based TB treatment.

To increase the dose of RTV to make 1:1 dosing in children, use RTV syrup available in 400mg/5ml. The syrup is administered using a syringe because often doses less than 5ml are used.

References

For a detailed list of the references used for this article, please contact queries@atic.idi.co.ug.

Ask ATIC

Francis Kalemera
HIV Clinical Pharmacist

Question

AK is a 23 year old female patient who has been on Triomune for 8 months. She was switched from Triomune to an AZT[1] based regimen based on current MoH guidelines to switch patients from Triomune to an AZT based regimen. After 3 weeks on AZT, she developed anemia. She was then switched to Truvada and Nevirapine. Now, however, we have run out of Truvada. Should we put this patient on Triomune again?

BR
Masindi, Uganda

Answer

This is a good and relevant question. The answer is "YES, you can put this patient on Triomune until you get your supply of Truvada/Nevirapine".
Does this apply to all patients who were once on Triomune? NO it does not. Why?

Scenarios differ. For example:

- **Scenario One:**
  If a patient was switched from Triomune to other combinations because of an ADR[2] to d4T[3] e.g. peripheral neuropathy, lactic acidosis, and pancreatitis, you cannot put this patient on Triomune again. It is advisable to build partnerships with other health centres so as to get the required medication to sustain continuous ART[4] for the patient.
- **Scenario Two:**
  If a patient was switched from Triomune to the other combinations because of the MoH[5] directive on d4T usage, then you may switch this patient back to Triomune until you get your Truvada supply.

This query represents many of the logistics challenges that health care workers working across sub-Saharan Africa are facing. It is important that efforts to increase access to antiretroviral therapy be increased. This will ensure that patients down to the grass roots can have an uninterrupted supply of their antiretroviral drugs promoting adherence to their therapy. This in the long run will reduce development of drug resistance caused by interruptions in drug supply.

1 AZT, Zidovudine (Azidothymidine)
2 ADR, Adverse Drug Reaction
3 d4T, Stavudine
4 ART, Antiretroviral Therapy
5 MoH, Ministry of Health

Celebration of partnership

Recognizing the importance of pharmaceutical management systems to the successful treatment of AIDS and other infectious diseases, the Infectious Disease Institute (IDI), Department of Pharmacy, the Department of Pharmacology and Therapeutics at Makerere University, Kampala, Uganda, have formed an alliance with the Management Sciences for Health's (MSH) Strengthening Pharmaceutical Systems (SPS) program. SPS is a five-year USAID-funded program with a mandate to build capacity within developing countries to effectively manage pharmaceutical systems and ultimately save lives by improving access to quality-assured medicines. In collaboration with MSH/SPS, the three parties listed above will collaborate in building capacity for individuals and organizations throughout East Africa by focusing on strengthening pharmaceutical management aspects of existing programs that are aimed at achieving high quality care and prevention for HIV/AIDS, malaria and improving laboratory management through training and information dissemination. The University of Washington (UW) also partnered with MSH in support of the SPS program to support the development and implementation of programs and systems related to pharmaceutical care services, drug safety/pharmacovigilance, and pharmaco-economics.

Acting Deputy Principal College of Health Sciences, Makerere University Prof. John Kakitahi at the launch of the partnership on 18/11/2008 at IDI.

CORRECTION: In Vol 4, Issue 2, on the discussion of lipo-atrophy, we apologize for accidentally mislabeling the photographs. The second one, where the patient appears healthy, was taken 6 months on initial ART and does reflect her well being. The first picture showing severe facial lipo-atrophy, is labeled correctly as three years on ART.

Innovative approaches to improving access to medicines using the Private sector - The Tanzanian ADDO Model

By Aziz Maija
Senior Program Associate,
Strengthening Pharmaceutical Systems Project (SPS) Centre for Pharmaceutical Management (CPM)

Most people in developing countries get their medicines from retail drug sellers. Care-seeking patterns differ according to culture, geography, wealth, and health condition, and in these countries, people often buy medicines from the most convenient source, which is usually the local retail drug outlet referred to in Ghana, as the chemical seller shop; in Uganda, the drug shop; in Tanzania, duka la dawa baridi (DLDB).

Such shops typically constitute the largest group of recognized (although often unaccredited and unregulated) outlets for non-prescription drugs in the country. Assessments carried out by the Government of Tanzania in collaboration with MSH in 2001 under the Strategies for Enhancing Access to Medicines (SEAM) program revealed that Tanzania had more DLDB than all other health facilities public and private combined (4,627 versus 4,288). Ghana had nearly 1,000 pharmacies located almost exclusively in urban areas, while there were close to 8,000 registered chemical sellers and possibly 2,000 more that were unregistered. This is a common scenario in many developing countries, and it illustrates the potentially broad impact of improving the quality of products and services in retail drug outlets in order to ensure access to essential medicines.

A problem with having retail drug sellers deliver health care is that they are largely untrained, and therefore, customers are not counseled on or sold the proper medicines, dosages, or quantities to effectively treat common ailments, including malaria. The SEAM assessment in Tanzania found that few dispensers at DLDB dispensed malaria treatment according to guidelines, and other studies have found similar results (Abuya et al, 2007). An increase in the number of drug sellers who dispense common medicines rationally would have the potential to affect many people in many countries and could help curtail the spread of antimicrobial resistance. This is a critical issue with introducing any new anti-infective medicine, such as artemisinin-based combination therapies (ACTs).

The Tanzanian Ministry of Health and Social Welfare (MOHSW) through the Tanzania Food and Drugs Authority (TFDA) in collaboration with MSH, and with funding from the Bill & Melinda Gates Foundation, conceptualized and introduced the Accredited Drug Dispensing Outlets (ADDO) program in the country. The aim was to improve access and quality of medicines to people living in rural and peri-urban areas. The program was initially piloted in Ruvuma region starting in 2003. The objective was to use a combination of training, marketing, commercial incentives, supervision, inspection, and support strategies to transform DLDB into regulated, profitable ADDOs, providing a range of quality drugs and professional services, including referrals, to underserved populations

The pilot program achieved the following results:

- Improved quality of medicines - the proportion of unregistered medicines found in drug shops was reduced by a factor of 13, from 26% to 2%.
- Improved quality of dispensing practice - few ADDO dispensers sold/recommended an antibiotic for upper respiratory tract infections and the percentage of referrals for malaria symptoms increased.
- Increased availability of essential medicines - by an average of 30%.
- Demonstrated potential of financial sustainability - on an average, ADDOs made a profit of TSH 80,000 per month.
- Improved inspection and regulatory capacity - TFDA granted certain inspection activities to local government authorities. Special regulatory committees and inspection teams were formed at district and ward levels with inspections carried out quarterly and results reported to TFDA for further enforcement action if necessary.

Based on the achievements of the ADDO pilot in Ruvuma region, the government of Tanzania decided to roll out the program to the whole country by the year 2010. Out of 21 regions in the mainland, 4 regions have been completed and a Global Fund Round 7 grant was awarded to the National Malaria Control Program for roll-out to 8 additional regions.

The ADDO shops in Tanzania have also been used as a platform for Public health interventions such as;

- Distribution of subsidized artemisinin-based combination therapy (ACTs) and Insecticide-treated nets (ITNs) through the private sector
- Expanded child health services based on IMCI with a focus on appropriately managing children for malaria, diarrhoea, and acute respiratory infections
- HIV/AIDS prevention and palliative care with a focus on distribution of condoms and home-based carekits, dissemination of Information Education and Communication (IEC) and Behaviour Change Communication (BCC) materials, and training of ADDO dispensers

Oshara Duka la dawa Baridi before conversion to ADDO

Oshara Duka la dawa Muhimu after conversion

ADDO billboard at the bus stop in Songea fostered public awareness

in palliative care. Building on the success from Tanzania, the Bill & Melinda Gates Foundation provided Management Sciences for Health (MSH) a three-year grant to continue its efforts in East Africa to involve private drug sellers in enhancing access to essential medicines through the East African Drug Seller Initiative (EADSI).

EADSI's goal is to create a sustainable model to replicate and scale-up private-sector drug seller initiatives that will help to meet the health-related goals of the countries and ultimately operate independent of donor support. To meet its goal, EADSI's three main objectives are to;

1) Develop a regional strategy to support the implementation of sustainable private-sector drug seller initiatives
2) Strengthen the ADDO model in use in Tanzania to facilitate scaling up and sustainability
3) Develop a plan to replicate the ADDO model to scale in a second East African country and demonstrate the adapted model in one district

Uganda was selected for implementation of the third objective with Kibale as the implementation district.

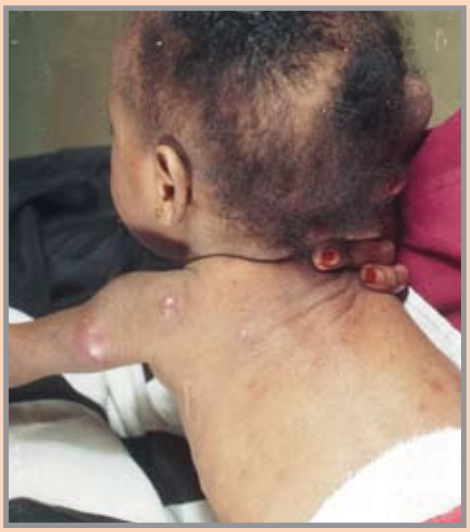
In conclusion, low availability of essential medicines in the public sector coupled with readily available but poorly regulated private sector drug sellers pose major challenges in ensuring access to quality essential medicines and dispensing services in developing counties. Public-Private Partnerships that use Innovative approaches like the ADDO model in Tanzania are an important step in addressing this challenge.

UPDATE ON NEW GUIDELINES FOR PAEDIATRIC ANTIRETROVIRAL THERAPY

By Dr.Sabrina Bakeera-Kitaka (Paediatrics Infectious Diseases' Specialist/Sewankambo Research Scholar Infectious Diseases Institute)

Introduction

The burden of Paediatric HIV continues to remain at epidemic levels in sub Saharan Africa. By March 2008, it was estimated that in Uganda, there were over 110,000 HIV infected children below the age of 15 years. The majority of these acquired the infection from mother to child transmission.



Rationale for the new guidelines

Treatment of HIV in infants is complex, since the dosage of antiretroviral therapy (ART) is usually determined by the body surface area, and the weight of the child and the dose must be adjusted as the child grows. Infant formulations of syrups carry their own disadvantages including poor adherence, spillage and sometimes requiring refrigeration for storage. In addition, the infant is always dependent on an adult to administer the therapy, which is taken for life. There is also a high risk of death and disease progression in infancy

with over 30% of babies born with perinatally acquired HIV dying before their 1st birthday.

Early infant diagnosis and recommendation for starting all newly diagnosed infants has been placed high on the agenda for various Paediatric advocacy fora, including the African Network for Care of Children Infected/Affected by HIV/AIDS (ANECCA) regional meeting of June 2008. Moreover, CD4 counts and viral load are poor predictors of disease progression or death in infants.

The new Paediatric guidelines from the WHO (June 2008), are based on results from the **Children with HIV Early Antiretroviral Therapy (CHER)** Trial which was conducted in South Africa. It hypothesized that early ART until the 1st or 2nd birthday will have long-term benefits by delaying disease progression and delaying the need for long-term continuous ART.

Patients in this trial were randomized into three arms: CHER trial investigators randomized 6- to 12-week-old HIV-infected infants to one of three strategies: (1) treatment with lopinavir/ritonavir plus AZT/3TC delayed until the CD4% fell below 20% (or below 25% after August 2006), (2) immediate treatment with the same regimen and planned interruption at 1 year of age, or (3) immediate treatment with planned interruption at 2 years. All children received cotrimoxazole prophylaxis and Pneumococcal vaccine. Children with a CD4% already below 25% were not randomized because they all began ART according to World Health Organization guidelines.

Results from the CHER Trial demonstrated that starting ART before 12 weeks of age irrespective of the CD4 count or viral load reduces early mortality by 75%.
Following these results, the new recommendation is to initiate early infant diagnosis, and to start all infants on ART below 12 months of age, irrespective of their clinical, immunological or virological staging. These children are then followed up for life on ART.

Recommendation for what ART to start with;

- For infants who have received single dose Nevirapine (NVP) for PMTCT, a Protease inhibitor(PI) based triple regimen should be initiated when starting on combined antiretroviral therapy
- (c ART) i.e. 1 Boosted PI + 2 NRTIs
- Where PIs are not available or feasible or affordable, NVP should still be used in the 1st line regimen i.e. 1NNRTI + 2 NRTIs
- For infants with no prior exposure to NVP, then the usual standard 1st line regimen (NVP + CBV or NVP + D4T + 3TC) should be used to initiate c ART.

OLD IMMONOLOGICAL CRITERIA

	<12 months	1-3 years	3-5 years	>5 years
Stage IV	Start all irrespective of CD4			
Stage III	Start ALL	Start all. CD4 guided in those with TB,LIP, Thrombocytopenia OHL		
Stage II & I	CD4 guided			
CD4%	<25%	<20%	<15%	<15%
CD4% count	<1500	<750	<350	<200
TLC	<4000	<3000	<2500	<2000

NEW IMMUNOLOGICAL CRITERIA

Criteria to start ART				
Age	Infants <12 months	12 months through 35 months	36months through 59 months	5 years and over
%CD4	All	<20	<20	<15
Absolute CD4*		<750	<350	As in adults<250

*Absolute CD4 count is naturally less constant and more age dependent than CD4%; It is not therefore appropriate to define a single threshold

Anticipated challenges

With over 25,000 new infections occurring in Uganda annually through PMTCT, the major challenge will be to ensure early infant diagnosis especially in the rural areas. Currently there are very few referral laboratories which are capable of processing DNA-PCR for early diagnosis. Further more, there is a big shortage of Paediatric staff to handle the large number of babies to be initiated on cART. In addition, if LPV/r (Kaletra) is to be used in syrup form, it will need refrigeration, and this creates another major challenge.

Adherence challenges with liquid formulations and fatigue with lifelong treatment in seemingly well infants in the face of non disclosure has serious implications for early treatment failure, and the unsaid challenge of future drug options for low resource countries.

Conclusion

In spite of the impending challenges, governments need to work towards abiding by the new ART guidelines and improving on the health and lives of our children. "Every child counts."

References:

Kekitiinwa. A, Oral presentation, 2nd National Paediatrics HIV Conference, August 2008, Kampala, Uganda.

Gibb.D et al, CHER Trial WHO guidelines on care and treatment of Paediatric HIV, June 2008

Violari. A, Cotton. M et al, Early antiretroviral therapy reduces mortality in HIV-infected infants: evidence from the CHER trial. New England Journal of Medicine 359(21): 2233-2244. November 20, 2008.

AIDS Treatment Information Centre (ATIC),
Infectious Diseases Institute, Makerere University Kampala, Tel: +256 312 307245 / +256 414 307228, Email: queries@atic.idi.co.ug, Website: http://www.idi.ac.ug

NOTE: *This newsletter is made possible by the generous support of the American people through the U.S. Agency for International Development (USAID), under the terms of cooperative agreement number GHN-A-00-07-00002-00. The contents are the responsibility of Infectious Diseases Institute and do not necessarily reflect the views of USAID or the United States Government.*