Academic Alliance for AIDS Care and Prevention in Africa

ATIC News

March 2005

A quarterly newsletter of The AIDS Treatment Information Centre

Vol. 2, Issue 1

Tackling viral resistance and treatment failure in Africa

Medical Research Council

Currently in Uganda we have only two chances at a regimen. The first is NNRTI-based with 3TC, and either AZT or D4T

By Charles Steinberg

ONE of the biggest challenges in the use of ARVs in a resource-limited setting like ours is the correct diagnosis of viral resistance and treatment failure. In most studies, ARV therapy succeeds in 70%-80% of patients over a one year follow-up. How will we know who is in the unfortunate 20%-30%?

First, there are patients in whom we can expect the risk of failure to be increased. These would include the ones who have been on ARVs before, especially those treated incorrectly (or before we knew better), those who received sub-optimum doses and others who received Prevention of Mother-to-Child Transmission (PMTCT) treatment, a form of brief monotherapy. There were patients who took their ARVs unknowingly with other medications that cause unfavourable drug interactions, such as rifampicin or whose source of drugs was unreliable such as intermittent sponsorship and of course, those in whom we are concerned about adherence.

"Virologic" failure is inability to reach or maintain an undetectable viral load on ARVs, and is the least helpful concept where viral load testing is unavailable or unaffordable. "Immunologic" failure is when the CD4 cell count drops on treatment, or fails to increase as expected. This is something we can evaluate where CD4 testing is available. But remember, CD4 cell counts are notoriously variable, and a variation of up to 20% can be expected just on patient and laboratory variability. So a CD4 count of 180 going to 150, three months later may not be significant. Only with significant drops (180 to 80) and perhaps several over time (180 to 80 to 60), will we be confident in diagnosing immunologic failure.

"Clinical" failure is what we will most likely diagnose, when we see deterioration of the clinical condition. Of particular concern would be the return of a problem that had cleared up on initial ARV therapy. This may be a recurrence of rashes such as Papular Puritic Eruptions (P.P.E), oral thrush, chronic vaginal candidiasis, herpes zoster, unexplained weight loss or fevers, or the appearance of a new opportunistic infection. In patients with severe immune-suppression who begin treatment, this will take careful clinical judgment. Is this new opportunistic infection a sign of failing therapy or just therapy that hasn't had time to work yet?

In my previous North American practice, the "best practice" was to try to diagnose ARV failure as early as possible, with frequent expensive viral load monitoring, and change regimens as soon as possible, guided by even more expensive genotypic and phenotypic resistance testing, to prevent further emergence or resistance.

Turn to page 2

This project is funded by The Bill and Melinda Gates Foundation and Roche Pharmaceuticals

From The Editor

P. O. Box 40008, Kampala, Uganda.Tel (queries): 256-31-307245/ 307228.Tel (admin.): 256-41-542352/ 542283; website:www.atic-africa.org

ATIC is located on 1st floor Makerere University Institute of Public Health, Mulago Hospital. ATIC acknowledges the support of Pfizer, Makerere University, Mulago National Referral Hospital and all its partners.

ATIC now official ARV site

The AIDS Treatment Information Centre (ATIC) has taken on yet more responsibility regarding the use of antiretrovirals (ARVs). It has been nominated by The Ministry of Health to become the official national referral centre for switching from one HIV drug to another (page 7).

This is a welcome move in terms of monitoring the distribution of ARVs in a country where the much-needed antiretrovirals can be mishandled. One of the pressing issues at the XV International AIDS conference in Bangkok last year was rational drug use in resource-limited settings. While some HIV/AIDS activists called for increased distribution of drugs to resource-limited settings like Africa, others argued that considering the cost and limited number of health practitioners, it would be difficult to prescribe drugs in a rational manner to patients. The debate still rages on as to whether healthcare providers in resource-limited settings would be able to prescribe and monitor patients on these drugs in a manner that would avert development of multi-drug resistant strains. In Uganda systems are being put in place to avert this. The Infectious Diseases Institute (IDI) for instance through its HIV/AIDS Training Programme for healthcare providers has various courses that enable healthcare providers to be knowledgeable about current trends regarding the epidemic. Already ATIC has reflected on having a patient/healthcare provider agreement before therapy can begin. If this is replicated elsewhere in Africa, it could forestall emergence of a wave of resistance to ARVs. For HIV as well as for many other diseases it is imperative that doctor and patient agree on the way forward. This must involve good rapport between the two parties as well as understanding disease presentation and the efforts to stop one from developing AIDS. The decision by Uganda's Ministry of Health to come up with an initial and logical framework to control dispensing of these drugs therefore, shows that there are ways and mechanisms that can be put in place in Africa to avoid adverse drug reactions and resistance.

Grappling with viral resistance

From page 1

The fear is that resistance mutations will accumulate at an ever-increasing speed ("mutations will snowball" seems inappropriate here).

So at first I grew alarmed at our practice here to rely on "clinical" monitoring.

In fact, at this time in Uganda we have only two chances at a regimen.

The first is NNRTI based, with 3TC, and either AZT or D4T. No matter how early we catch ARV failure, or how we do it, we are likely to have lost two drugs with low barriers to resistance (single mutations): 3TC and the NNRTI. Yes, over time the patient's virus will further accumulate the resistance mutations to AZT or D4T (TAM's or thymidine analogue mutations), but this process is slow. And the 3TC resistance mutation (m184v) actually sensitises the virus to the thymidine analogue. Since we only have one more regimen to try, the Kaletra-based one, maybe it is good we are not in a hurry to use it (and use it up). In fact the real question is one of strategies: When, in this war against HIV in a specific patient, do we choose to use our last effective weapon (Kaletra)? Perhaps it is fine that we halt our haste and save it until we really need it. The occurrence of a serious new opportunistic infection like cryptococcal meningitis would prompt me to consider starting the second line therapy, but recurrent mild thrush might be worth just treating with nystatin. If CD4s are available, maybe we should save our Kaletra regimen until we are approaching the <100 "danger zone." There is often a good long time of "virologic" failure where the CD4s do not drop. This is still immunologic and clinical success. The "failing" regimen is working well enough to partially suppress the virus, or make it less fit and less pathogenic, so that the immune system is able to hold its own, for a while. With a limit on regimens available, this is not the time to use up our last one.

Other strategic options include continuing dual therapy with 3TC and either AZT or D4T as long as the patient is clinically stable. It makes sense to stop the NNRTI component if we are sure there is resistance, since (different from 3TC) there is no residual antiretroviral value to current NNRTI's once the K103N mutation develops. Or even consider a treatment interruption if the CD4 has increased enough. It will gradually come down, but the patient may get months, or even years, off therapy. These are important considerations to discuss with your patient, and together decide what is best.

Many of these questions, including the need for CD4 counts and the value and safety of treatment interruptions, are being studied in Uganda and Zimbabwe in the Development of Antiretroviral Therapy (DART) trial.

Until the results of DART and other trials are available, our clinical judgement, in partnership with our patients ideas and wishes, will have to guide us. But please remind your patients that it is not "they" who are failing, it is the drugs.

A look at Stavudine (d4T)

By Jennifer Walker, Pharm.D

STAVUDINE, also known as d4T or Zerit®, is a nucleoside reverse transcriptase inhibitor (NRTI) that is used in combination with other ARVs to treat the Human Immunodeficiency Virus type 1.

Dosage/Administration[1-4]

Stavudine can be taken with or without food.

Adults and adolescents

> 60 kg: 40 mg (1 capsule or 40 mL of oral solution) by mouth every 12 hours

< 60 kg: 30 mg (1 capsule or 30 mL of oral solution) by mouth every 12 hours

Pregnant Women

No change in dosage recommended.

Renal Impairment Dosing

Elimination may be reduced in patients with renal impairment.

Adults

Creatinine clearance 26-50 mL/minute: 20mg every 12 hours if weigh > 60 kg and 15mg every 12 hours if weigh < 60 kg

Creatinine clearance 10-25 mL/minute: 20mg every 24 hours if weigh > 60 kg and 15mg every 24 hours if weigh < 60 kg

Hemodialysis: 20mg every 24 hours in adults who weigh > 60 kg and 15mg every 24 hours in adults who weigh < 60 kg administered after each hemodialysis session, given at the same time of day as on the days when the patient does not undergo hemodialysis

Paediatrics

There are no specific dosage recommendations for paediatrics but manufacturers state that since renal clearance is expected to be altered, the dosage should be decreased and/or the time interval between doses increased.

Contraindications/Precautions[1-3] Hypersensitivity to d4T or any of the components contained in the formulation.

Use with caution in patients with known risk factors for hepatic disease; d4T can cause lactic acidosis and severe hepatomegaly with steatosis which has been fatal. Therapy should be suspended if the patient develops symptomatic hyperlactatemia or pronounced hepatotoxicity. If lactic acidosis is confirmed, discontinuation of d4T treatment permanently should be considered.

Side Effects[1-3]

Nausea, diarrhoea, vomiting, headache, and rash are commonly experienced side effects of d4T. Potentially severe peripheral neuropathy can occur with d4T and may be dose-related. Numbness, tingling, or pain in the hands or feet has been reported mostly in patients with advanced HIV disease, patients with a history of peripheral neuropathy, or patients receiving other neurotoxic drugs such as didanosine. Patients experiencing peripheral neuropathy may tolerate d4T therapy at a lower dose (20-30 mg bid). However, if the symptoms return upon reinitiation of d4T, or worsen during treatment, consider alternative therapy.

Fatal lactic acidosis, severe hepatomegaly with steatosis, and pancreatitis have all occurred with the treatment of d4T and may occur more commonly when used in combination with ddI. Fat redistribution, specifically lipoatrophy of the face, has been reported with use of d4T.

Monitoring Parameters[1-3]

The manufacturers recommend monitoring serum creatinine, complete blood count with differential, liver enzymes, amylase, lipase and lactate levels during treatment with d4T. However, due to limited resources in some settings, patients may be clinically monitored for signs of peripheral neuropathy, liver toxicity (malaise, nausea, vomiting, right upper quadrant pain, and/or jaundice), lactic acidosis (nausea, vomiting, general abdominal pain, fatigue and weakness), acute pancreatitis.

Interruption of Therapy[1]

If a patient misses a dose, they should take it as soon as they remember. However, if it is almost time for the next dose, they should skip the missed dose and continue the regular dosing schedule. Treatment should be interrupted for any serious adverse effects including lactic acidosis, pancreatitis, and peripheral neuropathy.

Significant Interactions[1-3]

Zidovudine should not be used in combination with d4T due to antagonism secondary to competition for cellular thymidine kinase which is needed for phosphorylation of both drugs. In addition, ribavirin and doxorubicin have also been shown to inhibit the phosphorylation of d4T in vitro and should be used with caution. Didanosine and/or hydroxyurea should be used with caution in patients taking d4T due to increased risk of pancreatitis, peripheral neuropathy, and liver function abnormalities.

Pregnancy and Lactation[1-4]

Stavudine should be used when the benefit outweighs the associated risk. Cases of lactic acidosis including some that were fatal have been reported when d4T was used in pregnant women in combination with ddI, therefore use of this combination should be avoided unless there are no alternatives. In addition, although it is unknown if d4T is excreted in human breast milk, it has been shown to be excreted in the milk of lactating rats. Due to potential risks of adverse effects and transmission of HIV, breast-feeding is not currently recommended in mothers taking d4T.

Storage[1,2]

Stavudine capsules and oral solution prior to constitution should be stored in tightly closed containers between 15°C and 30° C.

Stavudine oral solution should be protected from excessive moisture and after constitution, tightly closed containers should be stored in a refrigerator, at 2° C to 8° C, with any unused portion discarded after 30 days.

Presentations[1,2]

Stavudine capsules are available in 15mg, 20mg, 30mg, and 40mg strengths.

Stavudine oral solution provides 200 mL/50ml of a 1 mg/mL.. Shake well before measuring a dose.

Additionally, d4T is an active component in the generic drug Triomune® 30 (D4T 30mg, 3TC 150mg, and NVP 200mg) and Triomune® 40 (D4T 40mg, 3TC 150mg, and NVP 200mg).

References

1. Bristol-Myers Squibb Company. Zerit® (stavudine) package insert. Princeton, NJ, USA; 2004.
2. American Society of Health-System Pharmacists. American Hospital Formulary Service Drug Information. Bethesda, MD: ASHP; 2004.
3. Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents [Internet]. 2004 Oct 29 [cited 2004 Nov 18]. Available from: http://www.aidsinfo.nih.gov//guidelines/adult/AA_102904.pdf
4. Perinatal HIV Guidelines Working Group: Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States [Internet]. 2004 June 23 [cited 2004 Nov 18]. Available from: http://www.aidsinfo.nih.gov/guidelines/perinatal/PER_062304.pdf

Cut here

IN BRIEF

Epidemic surge

SUB-SAHARAN Africa is the region of the world that is most affected by HIV & AIDS. Large variations exist between individual countries. In some African countries, the epidemic is still growing despite its severity. Others face a growing danger of explosive growth. The sharp rise in HIV prevalence among pregnant women in Cameroon (more than doubling to over 11% among those aged 20-24 between 1998 and 2000) shows how suddenly the epidemic can surge.— **UNAIDS**

HIV trend

Based on its sample of more than 16,000 women attending antenatal clinics across all nine provinces, the South African Department of Health Study estimates that 27.9% of pregnant women were living with HIV in 2003. The provinces which recorded the highest HIV rates were KwaZulu-Natal, Mpumalanga and Free State.Until 1998 South Africa had one of the fastest expanding epidemics in the world. The 2003 survey shows that the level of HIV prevalence is now growing more slowly. — **UNAIDS**

CME/CPE Corner

Can Septrin prophylaxis be given in pregnancy to HIV-positive mothers?

Female patient who has been on Triomune for one year. She is 49 years old and weighs 72kg. She has developed fat depositions on the shoulders while taking Triomune. What could be causing this?

Website: www.atic-africa.org

HIV clinical trials expanding in Africa

By Izabela Tolowinska BSc MPH

A laboratory worker in Africa

DISEASE and ill health are global issues, and HIV in particular is a worldwide pandemic. Therefore, it is encouraging that significant developments are occurring with regard to expansion of clinical trials into the developing regions of the world (Africa, Asia and Latin America). This is illustrated by pharmaceutical industry data showing that clinical trial spending in the Middle East and Africa rose from $10 billion in 1998 to $75 billion in 2002[1].

Since the highest incidence of HIV/AIDS in the 21st century is in Africa, with 25.4 million people living with HIV and AIDS in sub-Saharan Africa[2], it is therefore logical that there should be an increase in the number of HIV clinical trials being conducted in this region.

Furthermore, it is an international regulatory requirement for many products to be thoroughly investigated in all ethnic environments before they are available on the market.[3] South Africa was the first country where clinical trials were started but at last there is an expansion into the other African countries.

Despite the potential for doing clinical trials in Africa, it is not possible to simply set and run a clinical trial. The reason for this is that clinical trials carried out in Africa must be run to the same high quality and ethical standards as those in the USA and Europe. This specific standard is known as International Conference on Harmonisation - Good Clinical Practice (ICH GCP) [4]. The essential principle of this standard is to ensure that the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials provides assurance that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of the subjects in the trial are protected [4].

Conducting global trials according to ICH GCP is necessary for the generated data to be acceptable to the international regulatory authorities of the US, Europe and Japan as well as national governments. Nevertheless, certain African countries (South Africa, Namibia, Zimbabwe and Botswana) do have, to some extent, medicines control bodies that carry out application evaluations, inspections and licensing procedures [3]. No doubt as more African countries become involved in clinical trials, such organisations will be set up in the other countries.

As more clinical trials have been undertaken in South Africa, ICH GCP is now widely recognised but this is not yet the case in the other African countries.

This can be achieved however, by investing time and money in training research staff at the selected sites on the requirements and procedures of ICH GCP. Other key challenges for clinical trials include no standard regulatory requirements within Africa (although this has been the case for Europe until recently), wide range of culture customs, languages, poor access to possible sites and operational logistics (e.g. transport of blood samples, import of study medication). All of these factors can and should be overcome as Africa has huge potential both in terms of patient population (especially for HIV naïve studies) and eagerness of staff to learn about clinical trials.

References

1. M.J Lamberti (2004) The Changing Climate of Clinical Research. Presentation at the February 2004 The Association for Clinical Trial Data Management (ACDM) Meeting, UK.
2. UNAIDS (2004) 2004 Report on the global AIDS Epidemic.
3. Rouse S, Mosqueria B and Kermani F. (2004) Approaching Africa Applied Clinical Trials, March 2003 pgs 50 - 58
4. ICH Harmonised Tripartite Guideline for Good Clinical Practice.

Izabela Tolowinska is a Clinical Research Consultant, England

QUESTIONS
with
Robinah Nganwa

A report I received says my patient has the K103N mutation. What does this mean? P.K Ghana

The HIV virus has the ability to quickly develop resistance to antiretroviral drugs. When this happens, the drugs are no longer effective in controlling viral multiplication.

This results in increased multiplication of the virus in the patient's body causing more damage to the patient's immune system. The patient then is more prone to attacks by opportunistic infections that decrease the patient's quality of life.

Resistance testing may either be done by genotypic or phenotypic assays. The genotypic test costs between US$350-480 but is still cheaper than the phenotypic testing.

The genotypic assay detects mutations in target proteins that are associated with drug resistance. Reporting of mutations for each gene is done using a letter-number-letter standard in which the first letter indicates the amino acid at the designated codon with the wild type virus, the number is the codon, and the second letter indicates the amino acids substituted in the mutation e.g. K103N indicates that asparagines (N) has been substituted for lysine (K) on codon 103.

Due to the great expenses involved, resistance testing may not be an option in many developing countries. It is however important to understand the basic concepts involved in interpreting resistance results and their application to clinical practice.

NVP with AZT leads to a further reduction of MTCT

TITLE: Single-Dose Perinatal Nevirapine plus Standard Zidovudine to prevent Mother to Child Transmission of HIV-1 in Thailand

Published by:The Infectious Diseases Institute Journal Club

Date of publication: July 2004 in the NEJM.

Background:

The study was conducted in Thailand where 1.3% of pregnant women are infected with HIV.

- Since 1999, the national programme provides AZT during 3rd trimester, at delivery and to newborns.
- Transmission rates remain at about 6%.
- Single dose Nevirapine during labour and to the new born already shown to be effective .

Hypothesis

Without additional toxicity, logistic complications,or significant cost, perinatal nevirapine therapy added to AZT could further reduce transmission of HIV in Thailand.

Trial design

- Double blind, random placebo-controlled trial

Objective

Phase 3 to assess safety and efficacy of single dose NVP at onset of labour and to infants 48-72hours post-delivery added to AZT for PMTCT.

Secondary objective

Evaluate incremental effect of perinatal NVP to newborns

Trial design

- Eligible patients- pregnant women receiving AZT at any of 37 study sites in Thailand between Jan 2001 and February 2003. Pre enrollment evaluation.
- Randomised into three groups

1.NVP-NVP; single dose to mother at onset of labour and oral suspension to baby 48-72 hrs after birth.

A Nevirapine tablet

2.Placebo-Placebo; women received placebo at onset of labour and neonates received placebo 48-72hrs after birth

3.NVP-Placebo;women received single dose NVP at onset of labour and neonates received placebo 48-72hrs after birth.

- Matched Placebo used
- List of Random Numbers
- There is good randomisation except adherence

Is is significant?

- Confounding factors -taken care of by stratification
- Follow up
- Primary end point - HIV infected infant; Positive PCR (DNA assay) on 2 separate occasions. Blood taken at birth, 6 weeks, 4 and 6 months.

Results

- Interim analysis was done when study was half way done. Analysis was as per protocol- considering the actual drug taken at the specific times.
- The DSMB stopped enrollment in Placebo-Placebo Group because rate of transmission in NVP-NVP was significantly lower than PLB-PLB; 1.1 (95% CI 0.3-2.2) compared to 6.3 (95% CI 3.8-8.9). P<0.001 CI not very wide = sample size was adequate.
- Rate of transmission in NVP -PLB gp was higher than in NVP-NVP
- In final analysis; with bigger numbers the difference in rates of transmission were not statistically significant
- NVP-NVP was somewhat superior in most subgroups

Safety

- Serious adverse events among pregnant women were similar across the groups;related to pregnancy, infection and possibly AZT and NVP
- Adverse effects similar in both groups; related to neonatal or obstetric complications.

Conclusion

- NVP at delivery added to third trimester AZT results in very low transmission rates with minimal medical and financial burdens
- It is similar to multi-drug maternal regimen that are expensive and potentially toxic

Comments

- Good study; findings can be applied in resource limited settings (monotherapy for PMTCT) to further reduce MTCT (is affordable, available, minimal adverse effects.)
- Mothers who participated agreed not to breastfeed. Our mothers usually want to breast feed because of cultural issues like in-laws opinions in addition to lack of money for artificial feeds
- Already evidence that HAART reduces viral load in HIV+, although this was not a policy for PMTCT in Thailand, needs to be investigated.
- Prediction of transmission in placebo-placebo group. Is this ethical?
- Because of the predictability of the placebo-placebo group, was this an ethical design?

Clinical implications of NNRTI resistance

By Kristin Hurt, Pharm.D.

DESPITE advances in antiretroviral (ARV) therapy and increased worldwide availability, many challenges in HIV treatment remain, including emerging ARV resistance. Resistance is of particular concern within the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of ARVs, including nevirapine, efavirenz, and delavirdine.

Although potency, safety, and pharmacologic properties are favourable characteristics of the NNRTIs, there are several limitations within the class, such as a low genetic barrier to resistance and an ability to select for mutations with minimal effects on viral fitness.

Unlike the protease inhibitors, a single mutation can confer resistance to the NNRTI agent on hand, as well as cross resistance within the entire class. The most common NNRTI mutation, K103N, has been attributed to treatment failure with all three NNRTIs.[2]

Cross-resistance intuitively makes sense because each agent binds at a common site on the reverse transcriptase. Common mutations such as K103N, or Y181C, which confers high-level resistance to nevirapine, work directly or indirectly, respectively, to reduce the binding affinity. However, the mutations do not reduce the reverse transcriptase enzymatic activity.[3]

As a result, these mutations are associated with only minimal effects on viral replication capacity, and the mutated strain retains viral "fitness."[4]

Clinically, these limitations allow for rapid development of NNRTI resistance, as well as persistence of the mutation even in the absence of the drug. An example of the former is nevirapine resistance following a single dose to prevent mother-to-child transmission. This was well described in an analysis of ARV-naïve Ugandan women receiving nevirapine for prevention of vertical transmission. Of the 15 women studied, three developed the K103N mutation after the single 200mg dose.[5]

Although not clearly defined, some risk factors for development of NNRTI resistance and virologic failure have been proposed.

In a European cohort of 71 patients on efavirenz or nevirapine-based regimens, investigators found repeated drug holidays to be a significant risk factor for developing a major NNRTI mutation.[7] This makes pharmacologic sense, as NNRTIs have a much longer half-life and will persist longer than other ARVs after treatment discontinuation.

These findings demonstrate the need for careful evaluation of NNRTI treatment interruptions in order to prevent unintentional NNRTI monotherapy.

Since suboptimal adherence is frequently linked to development of resistant virus, as well as virologic failure, it is useful to examine the adherence/resistance relationship of the NNRTIs, specifically. In general, ARV adherence has been likened to a bell-shaped curve where either complete adherence or non-adherence is associated with a low probability of resistance selection. [8]

However, the level of adherence required specifically for NNRTIs to maintain full viral suppression is less clear.

In a recent cohort study, investigators identified adequate viral suppression (HIV RNA < 400 copies/ml) in patients on NNRTI-based regimens in the top three quartiles of adherence (54 to 100%).[9] However, these data are far from definitive and recommendations at this time are to aim for nearly complete adherence in order to maximise the probability of full viral suppression.

Clearly there are various pharmacologic aspects to consider for the use of NNRTIs in ARV regimens.

Despite their favourable pharmacologic properties, there are still many limitations and challenges to overcome in hopes of achieving superior viral suppression with minimal resistance.

Characteristics such as the low genetic barrier, maintenance of viral fitness, and adherence levels create specific challenges for NNRTI therapy and must be carefully considered when initiating, switching, and stopping ARV therapy.

References:

1. Grant RM, Hecht FM, Warmerdam M, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. JAMA 2002;288(2):181-8.
2. Deeks SG. International perspectives on antiretroviral resistance: Nonnucleoside reverse transcriptase inhibitors. JAIDS 2001;26:S25-S33.
3. Arts EJ, Wainberg MA. Mechanisms of nucleoside analog antiretroviral activity and resistance during human immunodeficiency virus reverse transcription. Antimicrob Agents Chemother 1996;40:527-40.
4. Collins JA, Thompson MG, Paintsil E, et al. Competitive fitness of nevirapine-resistant human immunodeficiency virus type 1 mutants. J Virol 2004;78:603-11.
5. Jackson JB, Becker-Pergola G, Guay LA, et al. Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. AIDS 2000;14:111-15.
6. Joly V, Descamps D, Peytavin G, et al. Evolution of HIV-1 resistance mutations in NNRTIs in HIV-1-infected patients switched to antiretroviral therapy without NNRTIs. Antimicrob Agents Chemother 2004;48:172-5.
7. Parienti J, Massari V, Descamps D, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis 2004;39:1311-6.
8. Friedland GH and Williams A. Attaining higher goals in HIV treatment: the central importance of adherence. AIDS 1999;13(Suppl 1):S61-72.
9. Bangsberg D, Weiser S, Guzmn D, et al. 95% adherence is not necessary for viral suppression to < 400 copies/ml in the majority of individuals on NNRTI regimens [abstract 616]. In Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, February 22-25, 2005.

The author is an Infectious Diseases/ HIV Specialist Resident Northwestern Memorial Hospital Chicago, IL

Scaling up ARV delivery

By Barbara Bitangaro
Editor ATIC News

THE AIDS Treatment Information Centre (ATIC) is now the official national referral consultation centre for all Ministry of Health (MOH) antiretroviral (ARV) therapy sites. The centre was chosen to provide correct and timely information to healthcare providers dispensing ARVs in the country.

ATIC is also the national authorisation centre for all patients switching from first line to second line ARV therapy for MOH.

A letter dated October 14, 2004 by Dr Elizabeth Madraa, the programme manager, STD/ACP-MOH, says there is need to promote rational drug use in view of the limited product availability and the rapidly changing clinical recommendations.

"Ministry of Health is working with ATIC to ensure that accurate and up-to-date information is available for healthcare providers. In addition, MOH has availed guidelines to ensure optimal availability of drugs for patients," she wrote.

In an interview with Elizabeth Namagala, a Senior Medical Officer in the Antiretroviral Therapy (ART) Ministry of Health Programme, she said, due to the increased number of ARVs coming into the country, MOH with partners in HIV care were scaling up provision of antiretrovirals countrywide.

STD/ACP-MOH manager, Dr Madraa

In June 2004, Government procured ARVs under the Public Sector Free ART Programme, which have been distributed to 26 private and public health facilities.

She said, at that time, this included all regional referral hospitals, the national referral hospital (Mulago) and some district hospitals, and health centre IVs that were ready at the time the programme was launched.

"Now with funds from the Global Programme on AIDS, Malaria and TB, another 12,000 patients have been added and there is need to scale up. We have added ARVs to the initial 26 centres and the number has shot up to 116 centres receiving ARVs under the Public Sector Free ARVs Programme. Most centres are now on board," she revealed.

Namagala said starting a patient on ARVs requires a lot of care and healthcare providers dealing with HIV/AIDS care and management need comprehensive training.

In this light, therefore, it was important to have a centre where healthcare providers could get the right information on HIV whenever they needed it. And this is why she said,, the ATIC was identified as the most appropriate centre for giving out HIV information.

"We needed to link up with people who are more experienced in the field. The centres providing these drugs are so many and information is needed all the time. So we are trying to tell the health worker that there is a free service where you can get information on care and management of HIV regularly.

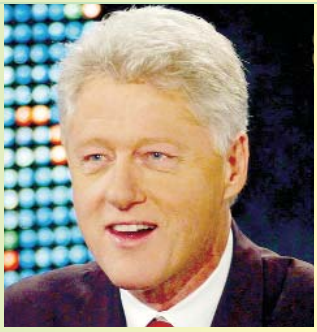
The ATIC has since its inception in February 2004, answered over 400 queries from different parts of Africa. It has done this through a call-in centre and via email. Over 12,000 copies of the four editions of *ATIC News* have also been distributed in Africa and Europe.

Clinton Foundation Initiative applauded

THE Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organisation (WHO) applauded the announcement made on April 11 by the Clinton Foundation HIV/AIDS Initiative of two new programmes to help expand AIDS care and treatment to children and to people living in rural areas.

These initiatives represent critical efforts to accelerate the delivery of ARV treatment to populations who have limited access to these life-saving medicines.

his foundation will donate $10 million to expand treatment for children with AIDS in the developing world.



Former President Bill Clinton

The new initiative will deliver AIDS drugs, known as antiretroviral treatment, or ART, and technical assistance for an estimated 10,000 children in at least 10 nations by the end of the year.

UNAIDS Head, Dr Peter Piot

The pediatric AIDS medication will be made available at half the normal cost, with the help of India-based drug company Cipla.

Former President of USA Bill Clinton has made the battle against HIV/AIDS a focal point of his Foundation's activities. He believes deeply that until we combat the pandemic in the developing world, where an estimated 40 million people are infected with the disease, lives that could be spared will be lost and it will be impossible for these countries to achieve social and economic development goals.

Clinton Foundation
HIV/AIDS Initiative
UNAIDS

ATIC News

Send your queries to contact@atic.idi.co.ug, queries@atic.idi.co.ug or call 031-307245/307258

Irish delegation visits Mulago hill

AN Irish delegation comprising Pfizer officials, academicians, senior government officials, politicians and journalists visited the AIDS Treatment Information Centre (ATIC)and the Infectious Diseases Institute (IDI) at Mulago Hospital in April.

Their visit among other things aimed at informing them about ATIC's role in HIV/AIDS care and management in the African region.

Professor David Serwadda, Principal Investigator ATIC said that by providing HIV information to healthcare providers, ATIC was averting adverse drug reactions and resistance that may arise as a result of improper drug use.

Dr David Serwadda, Principal Investigator ATIC (right) tells the delegation about ATIC

Every mother, child counts– WHO

HUNDREDS of millions of women and children have no access to potentially life-saving care with often fatal results, the World Health Organisation (WHO) says in a report published in April.

The report says the resulting death toll could be sharply reduced through wider use of key interventions and a "continuum of care" approach for mother and child that begins before pregnancy and extends through childbirth and into the baby's childhood.

About 530 000 women a year die in pregnancy or childbirth, more than three million babies are stillborn, more than four million newborns die within the first days or weeks of life, and altogether 10.6 million children a year die before their fifth birthday, according to WHO's latest figures.In *The World Health Report 2005 - Make Every Mother and Child Count.*

WHO estimates that out of a total of 136 million births a year worldwide, less than two thirds of women in less developed countries and only one third in the least developed countries have their babies delivered by a skilled attendant.

A HIV-positive mother with her children

The report says this can make the difference between life and death for mother and child if complications arise.

According to the report, almost 90% of all deaths among children under five years of age are attributable to just six conditions. These are: acute neonatal conditions, mainly preterm birth, birth asphyxia and infections, which account for 37% of the total; lower respiratory infections, mostly pneumonia (19%); diarrhoea (18%); malaria (8%); measles (4%); and HIV/AIDS (3%).

Most of these deaths are avoidable through existing interventions that are simple, affordable and effective. They include oral rehydration therapy, antibiotics, antimalarial drugs and insecticide-treated bednets, vitamin A and other micronutrients, promotion of breastfeeding, immunisation, and skilled care during pregnancy and childbirth.

World Health Organisation

ATIC News is published by The Academic Alliance For AIDS Care and Prevention In Africa-Gates Grant, P. O. Box 40008, Kampala, Tel: 256-41-542352-542283 / 256-31-307245/307228