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Role of pharmacovigilance in safe use of medicines

By Andy Stergachis, RPh, PhD and Sarah Staedke, MD

While the use of medicines has led to remarkable improvements in health, it should be recognised that all drugs have some risk of harm. Good patient care involves a balance of the benefits and risks of treatment. Much of what is ultimately known about the potential risks of therapy is discovered after a drug is marketed and used by the general population. Risks identified after a drug is approved and used widely may range from relatively minor problems to clinically important effects that seriously alter the risk-benefit considerations. Adverse events may lead patients to stop therapy because of poor tolerability or even result in serious toxicities leading to hospitalisation. This article considers ways in which healthcare practitioners can contribute to the collection of safety data through the reporting of suspected adverse drug reactions, also referred to as spontaneous adverse event reporting.

Our understanding about the efficacy and short-term safety of drugs comes from well-controlled studies conducted during the drug development process. However, it is not possible to detect all potential risks of drugs during their development. During clinical trials, only a small number of highly selected patients are exposed to a medication over a limited period of time, compared with the large number that might use it once it is approved for marketing. Consequently, rare and delayed adverse events and drug interactions may not be detected during clinical trials.

The terms 'adverse event' and 'adverse drug reaction' are often used interchangeably, but they differ in the implication of causality, or whether the event was actually caused by the drug. An adverse event is defined as 'any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment', whereas an adverse drug reaction is defined as 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man', which implies a causal relationship between the reaction and the drug.

The detection, assessment, understanding and prevention of adverse effects of marketed drugs is referred to

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A clinician counsels a patient on ARVs. It is important to talk with patients about the expected outcome of treatment, when to return or seek additional care, possible adverse reactions and the importance of reporting any problems to the health care workers involved in their treatment.

Triomune 30 as effective as Triomune 40

By Andrew Hill, PhD

In Uganda Triomune 40 (containing d4T 40mg) is no longer available and the Ministry of Health resolved that all patients weighing over 60kg be given Triomune 30 (containing d4T 30mg), the dose normally recommended for patients weighing below 60kg. As a result many healthcare providers were concerned about the efficacy of Triomune 30 in patients weighing over 60kg. This article addresses this issue with data suggesting that Triomune 30 is as effective as Triomune 40.

In a meta-analysis of clinical trials presented at the World AIDS Conference in Toronto, stavudine 30mg BID showed equivalent antiviral efficacy to the standard dose of 40mg BID (HIV RNA <50 copies/ml at week 24). Peripheral neuropathy was less common at lower stavudine doses. Lower doses may also lessen the incidence of other adverse events (e.g. lipoatrophy).

d4T based HAART is the cheapest available ($140 per patient-year). The fixed dose combination of d4T, 3TC and

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From the Editor

With increased availability of ARVs, more African patients are now able to access antiretroviral therapy. However, like other medication, ARVs have some adverse effects. Documentation of these side effects is important to ensure rational and effective use of medicines.

In the last year the number of queries on adverse effects, received at the AIDS Treatment Information Centre, has increased significantly. While it may be argued that health workers are now more aware of these effects and are reporting them more often, it is likely that as these drugs become more widely used, there will be more patients experiencing adverse effects.

In many parts of the developed world pharmacovigilance has been integrated into clinical practice, which is not the case in the developing world where health care systems are still struggling with inadequate staffing and funding.

Our lead article emphasises the importance of pharmacovigilance and highlights procedures that health workers can follow to report the adverse effects. Different writers, both locally and internationally, have provided insights into key issues such as pharmacokinetics and areas of research. One important issue, especially in countries that still use D4T as first line therapy, is the good news that a lower dose of the drug may be as effective and less toxic.

Happy and prosperous 2007!

Triomune 30 may be as effective as Triomune 40

From on Page 1

nevirapine is widely used in Uganda.

d4T is available alone or in fixed dose combinations. The approved dose of d4T is 40mg BID for body weight equal to or higher than 60kg and 30mg BID for body weight below 60kg. The main toxiciity of d4T – peripheral neuropathy – was the dose-limiting toxicity in Phase 2 trials. Other adverse events – lipoatrophy, lactic acidosis – may be dose related.

Lower doses of d4T have been evaluated in eight randomised clinical trials and three cohort studies, in a total of 11,729 patients. The most common low dose studied is 30mg BID, with reduction to 20mg BID for those with body weight under 60kg.

We conducted a search for published papers and conference presentations of stavudine (d4T), which identified three pre-approval studies of stavudine monotherapy (Phase 1 and 2 trials, parallel track programme), five post-approval randomised trials: two Thai trials of dual NRTI treatment (HIVNAT 002 and ARV065), three Spanish trials with HAART treatment and three cohort studies (all including HAART) (see table below).

The dose-ranging Phase 1 and 2 trials showed a clear dose effect on peripheral neuropathy. The conclusion from the Phase 2 efficacy trial was that the most favourable therapeutic index was at 0.5mg/kg/day (corresponding to 15mg BID for a body weight of 60 kg, and 20mg BID for a body weight of 80kg).

In parallel track programme 10,438 NRTI pre-treated patients were randomised to weight-adjusted dose levels of d4T: 20mg versus 40mg BID for body weight equal to or higher than 60kg (15 mg vs 30mg for body weight below 60kg). Survival was equivalent in the two groups (79%). The standard dose arm was stopped by the Data Safety Monitoring Board owing to a higher rate of peripheral neuropathy (21%) relative to the low dose arm (15%). D4T was approved in the US and Europe in 1994 at the 40mg BID dose, because the main efficacy trial had used this dosage.

Since approval of d4T, several trials have investigated doses below the standard 40mg BID dose. Summary efficacy data is shown in the table below. In a meta-analysis of the trials, the efficacy of the standard and lower doses of d4T was equivalent by US and European regulatory criteria.

Some investigators want to look at even lower doses of d4T, given the results of these dose reduction trials. For now, this meta-analysis shows that the use of the 30mg BID dose for people with body weight above 60kg, and 20mg BID for those with body weight below 60kg, should improve the safety profile of d4T without compromising efficacy.

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Summary efficacy data (HIV RNA <50 copies, ITT analysis) from randomized trials of standard versus low dose d4T

	HIVNAT 002		ARV065		ETOX		Barcelona		Madrid	
	40mg	30mg	40mg	30mg	40mg	30mg	40mg	30mg	40mg	30mg
N	30	29	110	109	27	27	22	19	37	38
ITT data										
RNA<50 w24	10%	17%	23%	18%	81%	87%	95%	95%	87%	87%
RNA<50 w48	13%	24%	5.5%	12%	53%	90%	91%	100%	n.d	n.d

Isoniazid, a critical drug for HIV-related tuberculosis

Robinah N. Lukwago, B Pharm, MPS

Introduction

Isoniazid (INH) is used in combination with other antituberculosis agents in the treatment of active tuberculosis and as a single agent in treatment of latent tuberculosis. It is considered a first-line antituberculosis agent for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* known, or presumed to be, susceptible to the drug.

Available formulations

INH is available as a single drug, in fixed combination with rifampicin, or in a fixed combination with rifampicin and pyrazinamide.

Dosage and administration

HIV-seropositive patients with tuberculosis respond well to antituberculosis therapy, as long as the intensive phase of treatment (the first eight weeks) contains INH and a rifamycin such as rifampicin. The treatment of HIV-related tuberculosis requires close monitoring because of frequent drug toxicities, possible drug-drug interactions and paradoxical reactions.

INH usually is administered orally. The absorption and bioavailability of INH are reduced when administered with food. Fixed-dose combination products containing INH should be administered either one hour before or two hours after a meal [1].

The recommended dose of INH in the treatment of HIV-related tuberculosis is 5 mg/kg daily given orally or 15 mg/kg 2-3 times a week (maximum 900 mg/dose) in combination with other TB medications. Twice-weekly dosing is not recommended in HIV-patients with CD4 counts less than 100 cells/mm^3 [2].

The Centers for Disease Control and Prevention (CDC), in association with the American Thoracic Society and the Infectious Diseases Society of America, recommends a six-month treatment regimen for tuberculosis in HIV-infected patients on antiretroviral therapy. In HIV-infected cases, the six-month regimen should be considered the minimum duration of treatment. It is very important to assess the clinical and bacteriologic response to treatment in the setting of HIV-1 infection. Patients with a cavity on initial chest radiograph and a persistently positive culture at completion of two months of therapy should receive a seven-month continuation phase. Antituberculosis therapy that contains INH should be supplemented with pyridoxine (vitamin B6) at 25-50mg per day to prevent the development of peripheral neuropathy. This is especially important in patients with a predisposition to neuropathy such as in diabetes mellitus.

The treatment regimen consists of a two-month initial phase of INH, rifampin, pyrazinamide and ethambutol, followed by a continuation phase of 4-7 months.

For patients on directly observed therapy (DOT), five day-a-week dosing may be used to replace seven day-a-week dosing. Completion of treatment should be determined by the total number of doses taken, and not solely on the length of therapy.

In contrast to streptomycin, another antituberculosis agent, INH, penetrates cells easily and is effective against intracellular bacilli as well as those growing in culture media.

Patients should be advised to avoid alcohol while taking INH. The concurrent use of alcohol may increase the potential for hepatotoxicity.

Renal disease

In patients with a creatinine clearance of less than 10 ml/min the daily dose of INH should be decreased by 50% [3]. However, some authorities recommend that normal doses be given to all patients, including patients who are anuric [4].

Liver disease

Liver disease may prolong the half-life of INH; however, this effect is less significant than the genetic predisposition for rapid or slow acetylation of the drug. However, it is suggested that INH therapy for latent tuberculosis be deferred in patients with acute hepatic disease [5].

Pregnancy

INH is not known to be harmful in pregnancy [6]. If INH is administered during pregnancy, concomitant administration of pyridoxine 25mg daily is recommended.

Mechanism of action

INH is a synthetic anti-mycobacterial agent which is bactericidal for both extracellular and intracellular organisms. The drug is thought to act by interfering with cell-wall mycolic acid synthesis resulting in loss of acid fastness and disruption of the bacterial cell wall. INH is active against susceptible bacteria only when they are undergoing cell division. Susceptible bacteria may undergo one or two divisions before multiplication is arrested. INH is the hydrazide derivative of isonicotinic acid. While INH is bacteriostatic for "resting bacilli", it is bactericidal for rapidly dividing organisms. In contrast to streptomycin, another antituberculosis agent, INH penetrates cells easily and is effective against intracellular bacilli as well as those growing in culture media.

Adverse drug reactions

Peripheral neuropathy, usually preceded by parasthesia of the feet and hands, is the most common adverse effect of INH and occurs most frequently in malnourished patients and those predisposed to neuritis, such as alcoholics and diabetics.

INH has been reported to cause mild and transient elevations in serum AST (SGOT), ALT (SGPT) and bilirubin concentrations in 10% to 20% of patients, usually during the first 4-6 months of therapy.

Hypersensitivity reactions, including fever, skin eruptions, lymphadenopathy, vasculitis and hypotension, have occurred rarely with INH, generally 3-7 weeks after the start of treatment. Other adverse effects requiring medical attention include optic neuritis, characterised by a sometimes painful blurring or loss of vision, and hematologic abnormalities such as agranulocytosis, eosinophilia,

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Genetic variations in response to ART

By Marta Boffito, MD, PhD

The use of antiretroviral (ARV) therapy has shown a variety of adverse drug effects and differing susceptibility to response among patients. Considerable heterogeneity exists between populations in the efficacy and toxicity of ARV therapy related to both genetic and environmental factors. As Sir William Osler stated in "The Principles and Practice of Medicine" in 1892, "if there was not a great variability between individuals, medicine would be a science and not an art".

Host genetics are increasingly recognised to play a role in HIV infection from the initial susceptibility to HIV infection, to the durability of the immune response and to the gravity of harm which may occur over time.

Moreover, among HIV patients there is considerable difference in the response to ARV therapy. One noteworthy aspect is the marked inter-individual variability in ARV drug plasma concentrations, despite administration of the same dose to all patients [1,2]. As a consequence, drug efficacy and toxicity vary substantially between individuals.

Although much remains unknown, a number of factors have been demonstrated to be important determinants of this variability. These include genetics, disease state, concurrent use of drugs or other pharmacoactive substances and demographic factors such as age, gender and ethnicity.

Pharmacogenetics is the study of the genetic basis of individual variations in drug response; pharmacogenomics involves genome analysis of the genetic determinants of drug efficacy and toxicity. Primary candidate genes of interest include those encoding for metabolising enzymes (e.g. cytochrome P450 enzymes, CYP450) and drug transporters (e.g. P-glycoprotein, P-gp). However, selection of optimal drug therapy may also involve disease susceptibility genes indirectly affecting drug response. Furthermore, pharmacogenomics studies the identification of suitable targets for drug discovery and development.

Inter-individual variation in human genetic sequences is quite common and this variation is due to single nucleotide polymorphisms (SNPs) at discrete nucleotide positions [3]. SNPs, which make up about 90% of all human genetic variation, are DNA sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered. This means that distinct population differences are apparent in gene product expression or activity. For a variation to be considered a SNP, it must occur in at least 1% of the population. Although more than 99% of human DNA sequences are the same across the population, variations in DNA sequence can have a major impact on how humans respond to disease and drugs [3,4].

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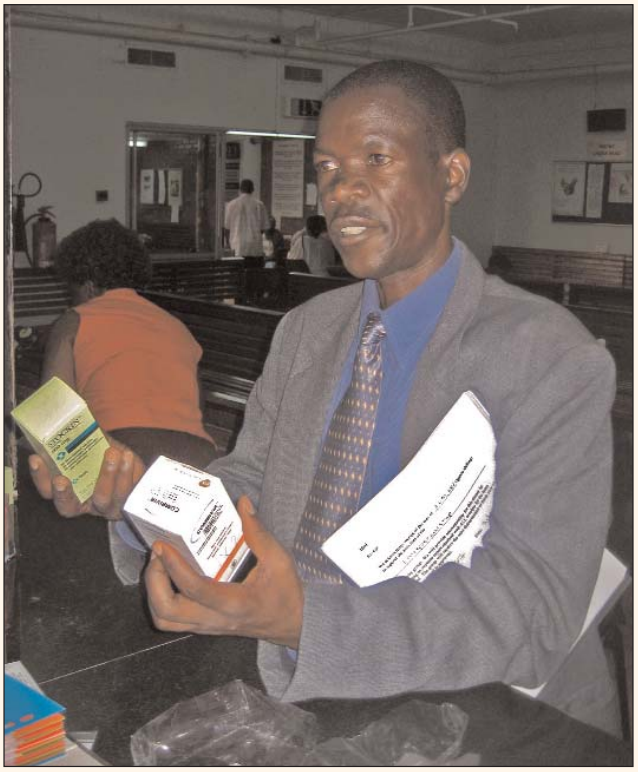
Dramatic reductions in morbidity and mortality have been documented since the advent of ARV drug combinations for the treatment of HIV infection [5]. To date, 19 ARV agents targeting HIV reverse transcriptase (nucleoside/nucleotide reverse transcriptase inhibitors, N/NtRTIs, and nonNRTIs, NNRTIs), protease, and viral entry are today available for clinical use [1].

Despite all four ARV classes being characterised by wide inter-individual variability [2] in plasma concentrations, attention has been mainly focused on NNRTIs and protease inhibitors (PIs).



A friend (patient) receives ARVs at IDI. His response to this treatment will be influenced by his genetic make-up, disease state, other drugs that he takes, as well as demographic characteristics such as age, gender and ethnicity.

CYP450 is a major set of all drug-metabolising enzymes; CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs [2]. Further knowledge on the effects of polymorphisms in the CYP450 enzyme may allow physicians to predict drug-related adverse events and adapt a drug regimen based on these genetic markers.

Furthermore, genotyping may alter the choice of drug, or the dose of the drug, especially when the drug in question has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in patients with certain polymorphisms.

To date, several polymorphisms that affect genes encoding CYP450 enzymes have been described (e.g. CYP2C9 and CYP2D6, responsible for warfarin and antipsychotic agents, respectively) [6,7].

Different studies investigated a possible role for genetic differences as the basis for developing toxicity to the NNRTI efavirenz in HIV-infected subjects.

Efavirenz is a commonly prescribed agent characterised by potent ARV activity and central nervous system (CNS) side effects during the initial weeks of therapy [1].

The relationship between efavirenz pharmacokinetic parame-

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Can Tenofovir-Didanosine combination be given together with Kaletra?

By Francis Kalemeera, BSc, BPharm, MPS

When tenofovir (TDF) and didanosine (ddI) are coadmimistered at usual doses of ddI, there is a significant increment in the plasma concentration of the latter. This increment is associated with increased side effects to ddI[1,2]. A dose reduction of ddI to 250mg in patients weighing over 60kg and 200mg in patients weighing less than 60kg is advised as this strategy produces safe and effective levels of ddI in plasma[3]. However when this combination was given with either efavirenz (EFV) or nevirapine (NVP), there was early virologic failure [4]. Later it was discovered that using a combination of TDF and ddI is also associated with a reduction in CD4+ cell count[5].

In one study which combined Kaletra (LPV/r) with TDF and ddI plus EFV, virologic potency for the combination was established[4]. In another study LPV/r-based highly active antiretroviral therapy (HAART) was associated with better immunologic and virologic responses when compared to saquinavir and nelfinavir-based HAART. It was also suggested that in salvage therapy or when a more rapid rise in CD4+ cell count is desired, LPV/r based HAART may be a better choice[6].

Whether this holds true for a TDF/ddI/LPV/r combination is the subject of this article. The question we seek to answer is: Does the CD4 cell count drop, remain static or increase when the TDF/ddI NRTI combination is administered with Kaletra?

TDF and ddI are both adenosine analogues that are metabolised by the same enzyme - purine nucleoside phosphorylase (PNP). There is a resultant imbalance in the adenosine nucleotides, exogenous and endogenous, which may explain the drop in CD4+ cell count since it resembles the Genetic PNP Deficiency Syndrome which is associated with purine nucleotide accumulation[7]. The CD4+ count drop was seen even after reducing the ddI dose; however, the drop was significantly higher with ddI standard dosing[8].

Kaletra capsules: Can they be administered together with tenofovir and Didanosine?

The question now changes to: Does LPV/RTV minimize the effect of the adenosine nucleotide imbalance within the CD4+ cells that results from the co-administration of TDF and ddI? There is no information to suggest so but this is unlikely. Note that the effect of TDF/ddI on CD4+ cell count increases in magnitude with time[8]. Initially there may be a rise in CD4+ cell count when TDF/ddI/LPV/r are given but this may start to fall at a certain point in time when an imbalance occurs within the CD4+ cells.

The TDF/ddI combination had a very promising potential for a once-daily regimen but on the basis of the findings discussed above it is not advisable to use this combination with either an NNRTI or PI.

The TDF/ddI combination had a very promising potential for a once-daily regimen but on the basis of the findings discussed above it is not advisable to use this combination with either an NNRTI or PI[9]. Whereas the DHHS Guidelines Panel recommends avoidance of TDF/ddI with an NNRTI (July 7,2004), the European Agency for Evaluation of Medicinal Products recommends avoiding TDF/ddI completely[3]. The WHO Guidelines 2006 revision state that the combination should only be used with caution and in situations where there is no alternative[10].

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Challenges of the elderly in looking after children living with HIV/AIDS

Edith Namulema, MBChB, MSc Epi

The AIDS epidemic has led to more than 14 million orphans in sub-Saharan Africa, of whom two million are HIV infected. Many of these orphans are left in the hands of elderly grandparents, who may not be able to offer optimal care. The challenge is even bigger today with the scaling up of ARV use.

As we get older, our bodies begin to show signs of wear and tear, making the elderly more susceptible to certain conditions and diseases. As human beings advance in age, they may lose many social, mental and physical abilities. Grandparents are susceptible to several conditions that affect orphan care. They may be susceptible to arthritis, which can hinder hospital visits. Cataracts may impair their vision, affecting their ability to correctly dispense medicines. Some ARV combinations are given at different time intervals, sometimes with special instructions such as food requirements. This may prove difficult for grandparents with memory problems, thereby affect adherence.

In his closing remarks at the 2006 World AIDS Conference in Toronto, Stephen Lewis, the UN special envoy on AIDS in Africa, said: *"In Africa, Grandmothers are the unsung heroes of the continent. These extraordinary, resilient, courageous women, fighting through the inconsolable grief of the loss of their own adult children, become parents again in their 50's, 60's, 70's and even 80's. We therefore need social welfare programmes that will recognise these essential caregivers' contributions to society as legitimate and difficult labor. We need to offer guarantees of sustainable incomes to the grandmothers of Africa from food to school fees and income generating activities"*.

Paediatric AIDS care remains a challenge since it involves an intermediary person, the caretaker, who acts on behalf of the children. When these caretakers are physically or mentally impaired, this may have a serious impact on the scaling up of paediatric ARV use.

The Paediatric Infectious Diseases Clinic (PIDC) was set up at Mulago Hospital to increase access to care for children and adolescents living with HIV/AIDS. It is a paediatric centre of excellence looking after approximately 5,000 children and adolescents infected with HIV, 2,000 of who are on ART. The following case highlights some of the challenges faced by the elderly looking after orphaned children living with HIV/AIDS.

Case presentation

Patient: SV is a four year old boy who lost both parents. He presented to PIDC in August 2004 with severe developmental delay (WHO IV). His CD4 at baseline was 204 (3.2%) and viral load was over 750,000 copies/ml.

Drug history: He was started on ART in March 2005, on syrups of AZT, 3TC and NVP, and placed on multivitamins and cotrimoxazole prophylaxis.

Carer: An 80-year-old grandmother, who lives in Misindye in Mukono District (approximately 15km from Kampala).

Grandma's problems

She has poor eyesight due to cataracts. She suffers from multiple body aches, yet she has to carry SV on her back to PIDC. She has four other orphans to care for, yet she has no economic support.

She has a 14-year-old granddaughter in school, supported by a charity organisation. Her granddaughter leaves home at about 6am after measuring the syrups for grandmother to give SV at 7am. Granddaughter has never come to the clinic because they can not afford transport for two persons; and grandmother cannot send the granddaughter with SV to the clinic, because she is young and cannot handle the traffic in the city.

Challenges

- There is a big age difference between grandmother and grandson.
- Due to poor sight, grandmother relies on granddaughter to measure syrups.
- Being a child, it is difficult for granddaughter to remember to measure the drugs.
- The family has no economic support.
- Though SV's viral load had become undetectable after six months of ART, at 18 months it had increased to a detectable level (90,845 copies/ml).

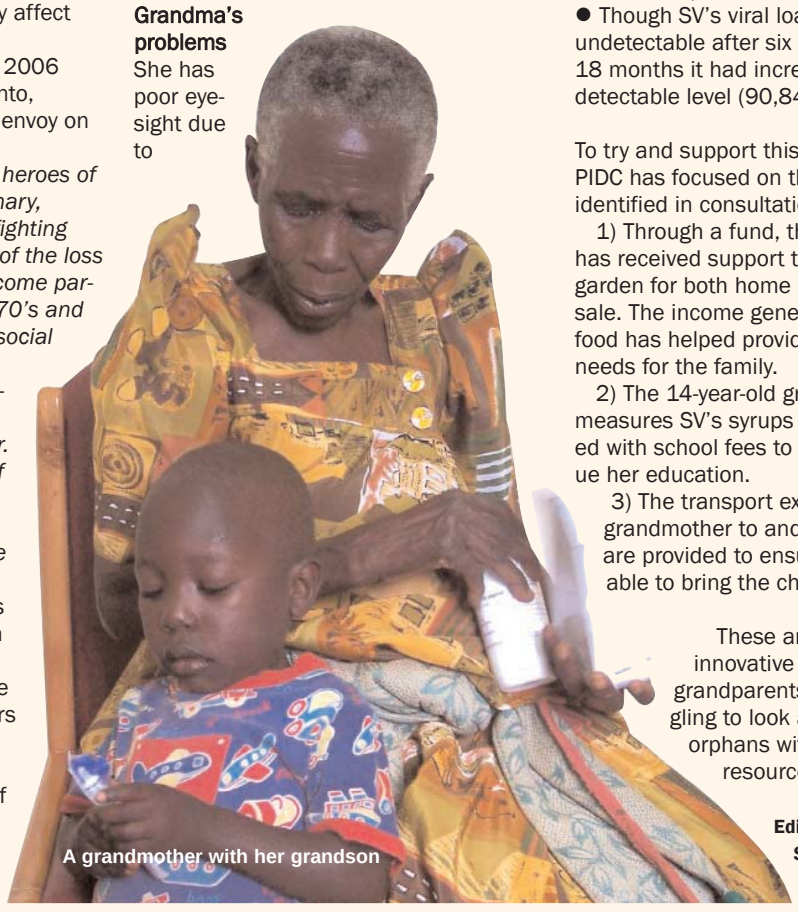
To try and support this grandmother the PIDC has focused on three key issues identified in consultation with her.

1) Through a fund, the grandmother has received support to grow food in her garden for both home consumption and sale. The income generated from selling food has helped provide some basic needs for the family.

2) The 14-year-old granddaughter who measures SV's syrups has been supported with school fees to enable her continue her education.

3) The transport expenses of the grandmother to and from the clinic are provided to ensure that she is able to bring the child to receive care.

These are examples of innovative ways to support grandparents who are struggling to look after HIV-infected orphans with meagre resources.



A grandmother with her grandson

Edith Namulema is a Senior Medical Officer at PIDC.

Ask ATIC

Robinah N. Lukwago

Q: *There is a 26 year old lady receiving care at our health centre. She was put on zidovudine, didanosine and Kaletra after failing on her first line regimen. She has now developed diarrhoea and has threatened to stop taking her antiretrovirals. Should we stop her drugs? - ZN, Tanzania*

A: Up to 50% of people with HIV will develop diarrhoea at some point and those with lower CD4 counts are at a greater risk. It is important that diarrhoea is treated, as it can lead to dehydration, lack of absorption of essential nutrients and drugs, as well as weight loss and fatigue.

Diarrhoea in HIV patients may be related to the drug therapy or infection. Before this patient's therapy is stopped, it is important to try to manage the diarrhoea. The probable cause of diarrhea in this patient is the drug Kaletra. Diarrhoea is one of the most common side effects of Kaletra therapy but tolerance often develops within a few days or weeks of therapy as the body adjusts to the medication.

Short courses of anti-diarrhoea medications such as loperamide, co-phenotrope and codeine phosphate are the drugs most commonly prescribed for diarrhoea due to Kaletra. They work by slowing gut motility. However any HIV patient experiencing diarrhoea should be evaluated for other causes, including diarrhoea due to a bacterial or parasitic infection.

To ensure patient compliance with therapy, prior to starting Kaletra, patients should be informed that diarrhoea may occur initially but that in most patients these symptoms are usually temporary and will abate.

Patients should be counselled regarding the importance of maintaining adequate fluid intake and avoiding dehydration. Patients should also be given nutritional advice such as taking small, frequent meals instead of a large meal; avoiding spicy or greasy foods and including fibre in their diet.

Isoniazid for TB in HIV infection

From P 3

thrombocytopenia, methemoglobinemia, and hemolytic, sideroblastic, or aplastic anemia.

Other adverse effects including nausea, vomiting, epigastric distress, dryness of the mouth, metabolic acidosis and urinary retention have been reported [1, 7].

Drug interactions

Carbamazepine - concomitant carbamazepine and INH therapy has been reported to produce increases in carbamazepine serum concentrations and toxicity (ataxia, headache, vomiting, and seizures) at INH doses of 200mg daily or more [8]. Carbamazepine may increase isoniazid liver toxicity.

Diazepam - there is an increased risk of benzodiazepine toxicity (sedation, respiratory depression) as INH therapy has been reported to result in a prolongation of diazepam's plasma half-life and a reduction in its clearance. The decrease in metabolism of diazepam is thought to be due to the ability of isoniazid to inhibit hepatic microsomal enzymes [9]. Some patients may require a reduction in diazepam dose.

Itraconazole - concomitant administration of INH with itraconazole may result in significant decreases in itraconazole serum concentrations and therapeutic failure. Co-administration is not recommended [10].

Phenytoin - concurrent INH and phenytoin therapy results in increased serum phenytoin levels leading to toxicity particularly in slow acetylators [11].

Resistance

Natural and acquired resistance to INH have been demonstrated *in vitro* and *in vivo* in strains of *M. tuberculosis*. *In vitro*, resistance to isoniazid develops in a stepwise manner. The mechanism of resistance may be related to the failure of the drug to penetrate or be taken up by the resistant bacteria. Resistant strains of initially susceptible bacteria develop rapidly if INH is used alone in the treatment of clinical tuberculosis; however, development of resistance does not appear to be a major problem when the drug is used alone in preventive therapy. When INH is combined with other tuberculosis agents in the treatment of clinical tuberculosis, emergence of resistant strains may be delayed or prevented.

Storage

Oral and injectable INH should be stored at temperatures below 40°C (104 °F), preferably between 15°C and 30°C (59°F and 86°F). Tablets and syrup should be stored in well-closed, light-resistant containers. The injectable product should be protected from light. The syrup and injectable products should be protected from freezing.

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Is food needed to maximise absorption

Marta Boffito, MD, PhD and Mohammed Lamorde, MBBS

All current antiretroviral drugs, with the exception of enfuvirtide, are administered by mouth. They are all absorbed in the gastrointestinal tract (stomach and intestines). Food contributes to the pharmacokinetic variability of some of the antiretroviral agents available for the treatment of HIV. The food effect on the antiretroviral agents today available for the treatment of HIV is summarized in Table 1.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Among the nucleoside reverse transcriptase inhibitors (NRTIs), didanosine and the nucleotide (Nt) RTI tenofovir have been shown to interact with food. While the enteric coated formulation of didanosine has to be taken on an empty stomach (at least one hour before or two hours after food intake) in order to ensure optimal drug absorption, administration of tenofovir following a high fat containing meal (700-1000 kcal, 40-50% fat) has been shown to increase the oral bioavailability, with an increase in area under the curve (AUC) and maximum concentration (Cmax) of approximately 14% and 40%, respectively. However, administration of tenofovir with a light meal did not have a significant effect on its pharmacokinetic parameters when compared to fasted administration of the drug. The clinical significance of the increased plasma pharmacokinetic parameters measured in the presence of a high fat meal is unclear. N/Nt-RTIs are prodrugs which require intracellular phosphorylation before they become active compounds. The antiretroviral activity of these agents depends on the active (phosphorylated) intracellular drug moiety rather than the concentration in the plasma. The amount of drug that enters the cell and the activity of the different kinases responsible for NRTI phosphorylation may be the major factors regulating formation of the active compound and therefore drug concentrations. Therefore, the different plasma concentrations observed when different meals are administered may be clinically irrelevant if enough drug is available to enter the cells harboring HIV.

All other NRTIs (zidovudine, stavudine, lamivudine, and abacavir) can be either administered with or without food since no significant change in plasma AUC was observed when comparing their pharmacokinetics in the presence or the absence of food.

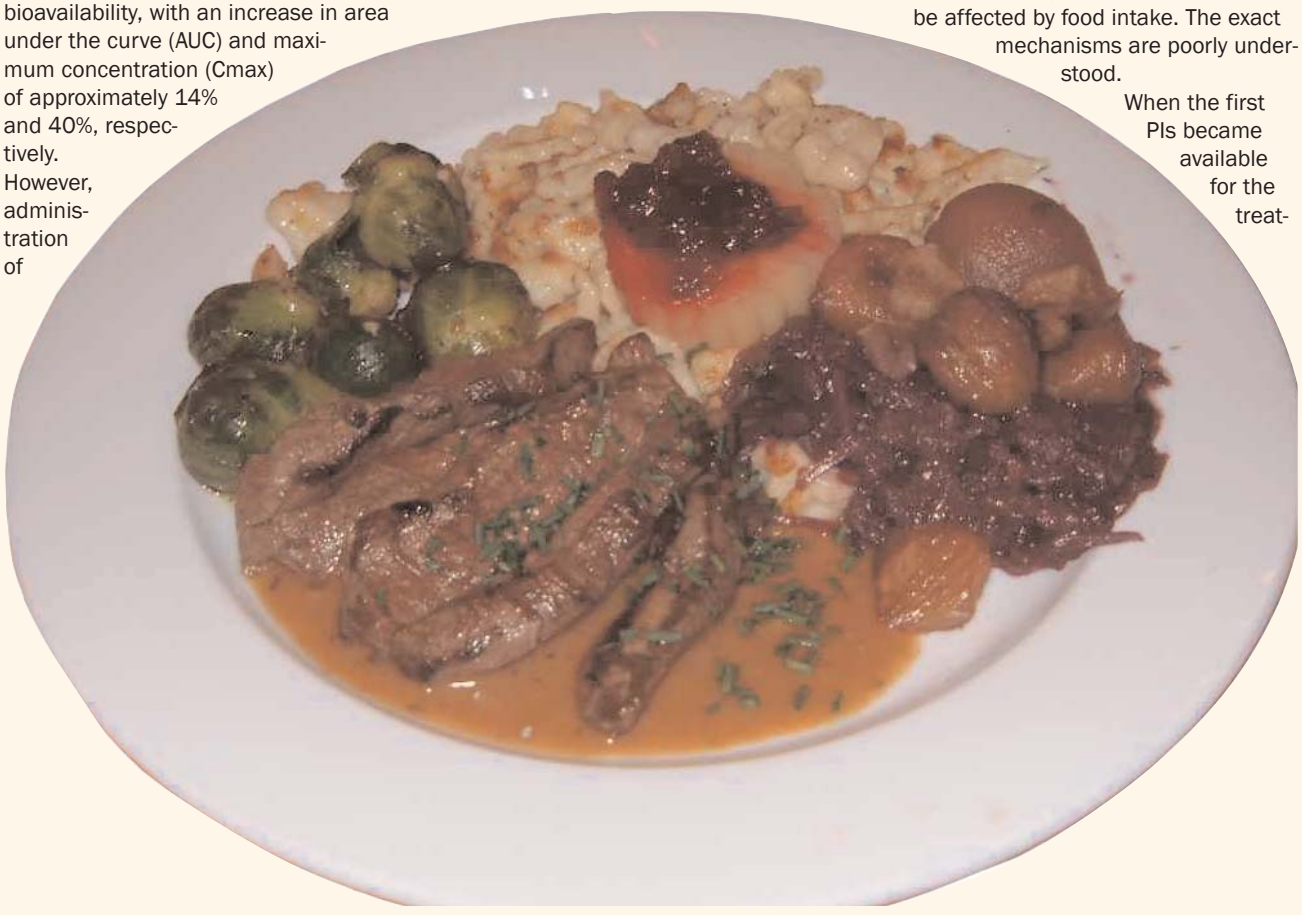
Non-nucleoside Reverse Transcritpase Inhibitors (NNRTIs)

Among the non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine absorption has been shown to be independent of food intake. However, administration of a single 600 mg efavirenz tablet with a high fat containing meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% and 79% increase in mean efavirenz AUC and Cmax relative to the exposures achieved under fasted conditions. The most common side effects of efavirenz are rash, nausea, dizziness, headache and insomnia. These have been shown to be related to high efavirenz plasma concentrations. Therefore, in order to avoid high efavirenz Cmax and adverse events, it is advisable to take efavirenz on an empty stomach at bed time.

Protease Inhibitors (PIs)

The pharmacokinetics of most protease inhibitors (PIs) has been shown to be affected by food intake. The exact mechanisms are poorly understood.

When the first PIs became available for the treat-



# of antiretroviral drugs into the blood?

ment of HIV-infected patients whether to take them on an empty stomach or with food was extremely important. Adherence to dietary requirements was considered as important as adherence to drug dosage and timing in determining the treatment response. This was because high fat containing meals had been shown to increase the bioavailability of saquinavir by approximately 670%, nelfinavir by 200-300%, and ritonavir capsules by approximately 15%. On the other hand, food decreased the bioavailability of indinavir (by 77%) when administered 800 mg three times daily without boosting by ritonavir. Therefore, strict recommendations were provided for unboosted PIs: saquinavir and nelfinavir had to be taken with food, and indinavir had to be taken in a fasted state.

The introduction of low dose ritonavir, taken not as an active anti-retroviral, but used to "boost" the plasma levels of the more potent PI, is a strategy widely used in clinical practice today, and has been shown to reduce the effect of food on the absorption of indinavir and saquinavir.

However, the addition of low dose ritonavir does not necessarily eliminate the effect of food with all PIs. For example, a high-fat meal will increase the bioavailability of saquinavir (Invirase 500 mg tablet®) 1000 mg plus ritonavir 100 mg twice a day by approximately 70%.

Darunavir (formerly TMC114) is a new PI that has been recently approved for the treatment of HIV infection in United States. It has shown remarkable potency in both antiretroviral naïve and experienced patients. Data on the effect of food on darunavir absorption were generated during drug development. The mean plasma darunavir AUC has been shown to be comparable for all administrations under a fed condition (with no differences between light snacks or high fat meals), while administration under fasted conditions resulted in a lower mean darunavir AUC (approximately 30%), suggesting again the need for food to ensure the achievement of optimal drug concentrations.

While food intake was shown to increase lopinavir/ritonavir plasma exposure following the administration of Kaletra® capsules, recent data suggest that lopinavir/ritonavir plasma concentrations seem to be consistent when Kaletra tablets® irrespective of whether they are administered with different fat-containing meals or in a fasting state, suggesting the lack of a food effect on the pharmacokinetics of lopinavir/ritonavir following the administration of the new Kaletra tablets® formulation. However, this conclusion has been drawn following a single dose pharmacokinetic study in Western HIV negative healthy volunteers and steady state data in HIV positive patients are not yet available.

While food intake was shown to increase lopinavir/ritonavir plasma exposure following the administration of Kaletra® capsules, recent data suggest that lopinavir/ritonavir plasma concentrations seem to be consistent when Kaletra tablets® irrespective of whether they are administered with different fat-containing meals or in a fasting state.

In conclusion, much information on the impact of food on the pharmacokinetic properties of antiretroviral agents has been obtained from phase I studies during drug development. These studies were primarily carried out in Western populations (mainly healthy volunteers and some HIV-infected patients). Therefore, it is important to determine the impact of food intake on drug availability in African populations with different diets and food availability. It is possible that drug-food interactions or the fasting state in African patients may result in sub-therapeutic concentrations of some antiretroviral agents. Information of the impact of food on the pharmacokinetic parameters of antiretroviral agents in African patients is lacking and formal pharmacokinetic studies aimed at investigating drug exposures are warranted.

The data on the effect of food reported in this letter have been obtained from the single drug prescribing information packages.

Table 1: Impact of food on antiretroviral drug pharmacokinetics

Drug	Common dosing	Food effect	Comments
Zidovudine (ZDV)	BID	None	None
Lamivudine (3TC)	OD or BID	↓ in C_{max} but no change in AUC	Not clinically significant
Stavudine (d4T)	BID	↓ in C_{max} but no change in AUC	Not clinically significant
Didanosine (ddI-EC)	OD	Food ↓ AUC	Empty stomach (2 h after food)
Abacavir (ABC)	OD or BID	↓ in C_{max} but no change in AUC	Not clinically significant
Tenofovir (TDF)	OD	Food ↑ AUC by 40%	Unclear clinical significance
Efavirenz	OD	Food ↑ AUC by 20%	Advised to take on an empty stomach to limit AEs
Nevirapine	OD or BID	No	Not clinically significant
Etravirine (TMC125)	BID	Mild	Fat containing snack
Indinavir	TID or BID when boosted	Fasting, ↑ in AUC by 300%*	Clinically significant interaction
Saquinavir	BID boosted	Food (high fat) ↑ AUC by 70%	Unclear clinical significance
Nelfinavir	BID	Food ↑ AUC by 200-300%	Clinically significant interaction
Lopinavir/r capsules	BID	Food ↑ AUC by 48-97%	Clinically significant interaction
Lopinavir/r tablet	BID	Food ↑ AUC by 19-27%	Not clinically significant
Atazanavir	OD	Food ↑ AUC by 35%, < CV	Unclear clinical significance, advised to take with food
Fosamprenavir	BID	None	Not clinically significant
Tipranavir	BID	High fat meal ↑ AUC by 2-fold	Clinically significant interaction
Darunavir (TMC114)	BID	Meal ↑ AUC by 30%	Unclear clinical significance, advised to take with food

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Genetic variation and ART

From Page 4

ters, CNS side effects, weight, race, virological response and treatment discontinuation was investigated in 202 subjects randomised to receive an efavirenz-containing regimen; 81% were males (53% White non-Hispanic, 32% Black non-Hispanics, 12% Hispanics and 3% other). The investigators found significant associations between drug clearance and weight, and between drug clearance and race. Efavirenz clearance was lower in Blacks and Hispanics compared to Whites, while efavirenz area under the concentration-time curve (AUC) was higher in Black and Hispanics compared to Whites. There was a trend towards an increased rate of efavirenz discontinuation with decreasing efavirenz clearance and increasing efavirenz concentration, but no apparent association between efavirenz clearance and CNS toxicity.

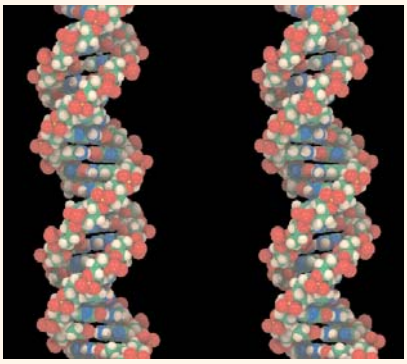
The relationship between genetic variants of the gene encoding for CYP2B6 (the isoenzyme, with CYP3A4, mainly responsible for efavirenz metabolism) and efavirenz pharmacokinetics, CNS toxicity and therapeutic effect was also studied. Twenty percent of the African Americans were T/T homozygous at the CYP2B6 516 position compared to only 3% of European Americans. Efavirenz AUC was three times higher in T/T homozygous patients relative to G/G homozygous patients. Overall, G/G and T/T homozygotes were associated with lower and higher efavirenz plasma concentrations, respectively, while those who were heterozygous (G/T) at this locus had intermediate levels. CYP2B6 position 516 TT genotype was also significantly associated with risk of CNS effects at week 1. However, the association with CNS toxicity was no longer evident by week 4, so the clinical significance of this association is unclear.

These findings corroborate the notion that drug metabolism may be affected by racial background, and suggest that CYP2B6 polymorphisms may explain some of the reported differences in efavirenz exposure and therapeutic effect in different ethnic patient populations [8].

Analysis of the interaction between genes and drugs, known as pharmacogenomics, has begun to highlight a number of genetic contributors to drug activity and side effects, including the risk of hyperbilirubinemia during atazanavir treatment.

In conclusion, there may be important genetic variations between individuals that influence the efficacy and toxicity of a drug. Ideally, through the use of pharmacogenomics, we could be able to profile variations between individuals' genes and predict responses to a certain therapeutic agent. However, despite the numerous studies presented in the past few years investigating relationships between specific SNPs and ARV drug response, conclusions from these studies may not be always clinically useful at this point because of the inadequate sample size, or the inconsistency of the results obtained from different cohort of patients.

Nevertheless, analysis of the interaction between genes and drugs, known as pharmacogenomics, has begun to highlight a number of genetic contributors to drug activity and side effects, including the risk of hyperbilirubinemia during atazanavir treatment [9], hypersensitivity during abacavir treatment [10], and central nervous system side effects during efavirenz treatment [8]. Therefore, understanding how polymorphism affects these critical proteins is becoming important to predict ARV drug efficacy and safety and knowledge about host genetics might increasingly affect care and treatment for people with HIV.



A model of DNA. Genetic structure affects susceptibility to HIV/AIDS and response to ART

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Minocycline, an old drug with new hope

By Christine Zink DVM, PhD, Dip ACVP

HIV is best known as the cause of AIDS, with its profound immunosuppression and secondary opportunistic infections and malignancies. However, in many people, it also affects the nervous system, causing motor deficits such as reduced ability to control the hands and feet, cognitive problems such as loss of short-term memory, and in severe cases, dementia.

Although these symptoms are less common and less severe in HIV-infected individuals being treated with antiviral drugs, they do occur in treated people because of the blood-brain barrier, a physical and biochemical barrier between the brain and the rest of the body. Many antiretroviral drugs are unable to cross this barrier and so do not achieve effective levels in the brain. As a result, virus replication and damage can continue in the brain of treated individuals.

Our lab at Johns Hopkins has been studying the effects of HIV on the brain, using an animal model that allows us to directly study the effects of virus on the brain at all stages of disease. In our model, macaques are inoculated with the Simian Immunodeficiency Virus (SIV), a virus isolated from African monkeys that behaves in monkeys much like HIV does in people. The inoculated monkeys experience high levels of virus replication, all of them develop AIDS and most of them also suffer nervous system damage. Using this model of aggressive HIV disease, we can study the ability of various drugs to protect the nervous system from virus-induced damage.

We have recently learnt that minocycline, a tetracycline-like antibiotic, has the ability to protect brain cells from degenerating in response to a number of different insults. This antibiotic, which is extremely inexpensive and safe when taken over long periods of time, has been on the market for over 30 years.

We have recently learnt that minocycline, a tetracycline-like antibiotic, has the ability to protect brain cells from degenerating in response to a number of different insults. This antibiotic, which is extremely inexpensive and safe when taken over long periods of time, has been on the market for over 30 years. Studies from a number of laboratories have shown that minocycline reduces the severity of nervous system damage in animal models of many different diseases including stroke, brain trauma, Parkinson's disease, Huntington's disease and multiple sclerosis. A recent study demonstrated that minocycline was also effective in reducing the damaging effects of multiple sclerosis in humans.

Using our aggressive SIV/monkey model, we decided to investigate whether minocycline would protect the nervous system from the damaging effects of SIV . We inoculated monkeys with SIV and began treating them with minocycline 21 days later, a time point equivalent to the asymptomatic stage of HIV infection. Treated monkeys had less severe pathological changes in the brain, reduced virus replication in the brain, and reduced expression of several markers of inflammation in the brain when compared with untreated monkeys. In addition, minocycline significantly decreased plasma viral load in the animals for which it had the most profound effect in the brain

These animal studies have led to the initiation of two separate clinical trials to study the efficacy of minocycline in HIV-infected humans. A multicenter trial in the United States will test the ability of minocycline to improve neurological symptoms in individuals that are undergoing antiretroviral therapy. A second trial is planned for Uganda, to investigate whether minocycline reduces the severity of neurological symptoms in HIV-infected individuals that have neurological disease but do not have CD4 counts that are low enough to qualify them for antiretroviral therapy. Scientists are hopeful that these studies will reveal that this inexpensive, readily available drug will protect HIV-infected individuals from the damaging effects of the virus on the brain and that it might also help lower viral load in the blood.

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Infectious Diseases Institute HIV/AIDS Training Programme for 2007

Course	Jan	February	March	April	May	June	July	August	Sept	Oct	Nov	Dec
Core Course		29.1. - 16th			7th - 25th				3rd - 21st		5th - 23rd	
Nurses Core Course			5th - 16th			4th -15th						
ART programmes and Epi Info			26th - 30th								26th - 30th	
Research in HIV Care		19th - 23rd			28th - 1st				24th - 28th			
Training of trainers		19th - 23rd			28th - 1st	18th - 22nd					26th - 30th	
ART clinic management for nurses/CO							16th - 20th					
Young medical officers							30th - 3rd	13th - 17th/ 20th - 24th		22nd - 26th Pharm		
Multi-disciplinary training	17th - 24th		21st -28th	18th - 25th		13th - 20th				10th - 17th		6th - 13th
Module for pharmacists and dispensers	22nd - 26th						2nd - 6th					
CME weekends				13/14th						12th - 13th		

All health workers involved in HIV/AIDS care are invited to apply for any of the above courses.
For further information visit the website www.idi.ac.ug or email sntege@idi.co.ug or call +256-41-307208.

Role of pharmacovigilance

From P 1

as pharmacovigilance. The goals of pharmacovigilance are to improve patient care and public health, to encourage safe, rational, and effective use of medicines, to contribute to the assessment of medicines, and to promote understanding, education, and clinical training of health care providers. The areas addressed by pharmacovigilance include adverse drug reactions, product quality and medication errors. The health and economic impact of each of these problems world-wide is large and, when for example they are the result of a prescribing or dispensing error or poor adherence, should be preventable.

The importance of pharmacovigilance activities for health care providers is highlighted by recent reports in the media of important safety warnings for newly marketed drugs and high profile withdrawal of drugs from the market, such as what happened with roficoxib or Vioxx the COX-2 inhibitor over concerns about increased risk of heart attacks and strokes. The primary method by which new adverse events are discovered among marketed drugs is through suspected adverse drug reaction reports from health care practitioners, although there are many different ways in which information can be collected and used for pharmacovigilance.

A number of African countries have established national programmes for reporting and monitoring of suspected adverse events to drugs, with the encouragement and assistance of the World Health Organisation. In Uganda, for example, the National Drug Authority (NDA) has established a pharmacovigilance programme that includes mechanisms for reporting of suspected adverse events to drug by health care providers. A "Report on Suspected Adverse Drug Reaction" can be found at the website http://www.nda.or.ug/ndauploads/ADR-Form.pdf, along with a guide on completing the form.

In general, if it is suspected that a patient has experienced an adverse event, it should be reported using the NDA's Report on Suspected Adverse Drug Reaction. Causality does not need to have been established for a report to be completed. Here are some examples of types of suspected adverse events are important to report:

- Events that are associated with new drugs and vaccines, particularly within the first several years of use.
- Serious reactions, including those that are fatal, life-threatening disabling or incapacitating, result in or prolong hospitalisation, congenital abnormalities, or are considered to be medically significant.
- Adverse drug reactions in children and the elderly, delayed drug effects, congenital abnormalities, and adverse events associated with traditional medicine or herbal products.

Reports of suspected adverse reactions are used as 'signals', or warning signs, of emerging drug safety problems. These 'signals' are further analysed for assessment of causality and determination of possible risk factors contributing to the reaction. Confirmatory studies may also be indicated to further explore the association between a drug and an adverse reaction. Such information can lead to changes in a drug's use, dosage, warnings and precautions. In some instances, where it is considered that the risks of a medicine outweigh the benefits, that medicine may be withdrawn from the market.

It is important for clinicians to report suspected adverse events as these programmes depend on health care providers. When administering a drug, or prescribing a treatment, it is also important to talk with patients about the expected outcome of treatment, when to return or seek additional care if their condition worsens or does not improve, what adverse reactions might be expected to occur, and the importance of reporting any problems to the health care workers involved in their treatment. Information from pharmacovigilance activities can lead to taking actions for improvements at the national and clinical level, including implementing new procedures and educational programmes. All health care workers who administer, prescribe, or distribute medications have a responsibility to participate in pharmacovigilance and to contribute to the improvement of clinical patient care and patient safety.

Andy Stergachis is a visiting professor from the University of Washington, USA.

Sarah Staedke is a Senior Lecturer at the London School of Hygiene & Tropical Medicine, UK.

In the news

Fixed-dose Triomune alternative okayed

The US Food and Drug Administration (FDA) has also granted tentative approval to a generic fixed dose combination drug containing zidovudine, lamivudine and nevirapine. This approval enables the drug to be procured and distributed among the 15 countries which currently benefit from the PEPFAR programme. It could provide a one pill twice daily option for patients experiencing toxicity to currently available combinations containing stavudine.
Source: http://www.fda.gov

One pill once a day

A low pill burden improves dosing convenience and can promote adherence. Another new drug approved by the FDA is Atripla. It is a combination of efavirenz, tenofovir and emtricitabine. The combination is the first one pill once a day treatment for HIV/AIDS and several pharmaceutical companies cooperated in its development.
Source: http://www.fda.gov

New protease inhibitor approved

A new protease inhibitor, darunavir, boosted with low dose ritonavir (formerly known as TMC114), has received accelerated approval from the FDA for use in treatment-experienced patients. It is marketed under the brand name Prevista and its approval was based on data from randomised controlled clinical trials (the POWER trials) showing marked benefit in terms of virologic suppression in the darunavir arm versus placebo. Darunavir/ritonavir is administered orally at 600/100mg twice daily with taken with food.
Source: http://www.medscape.com