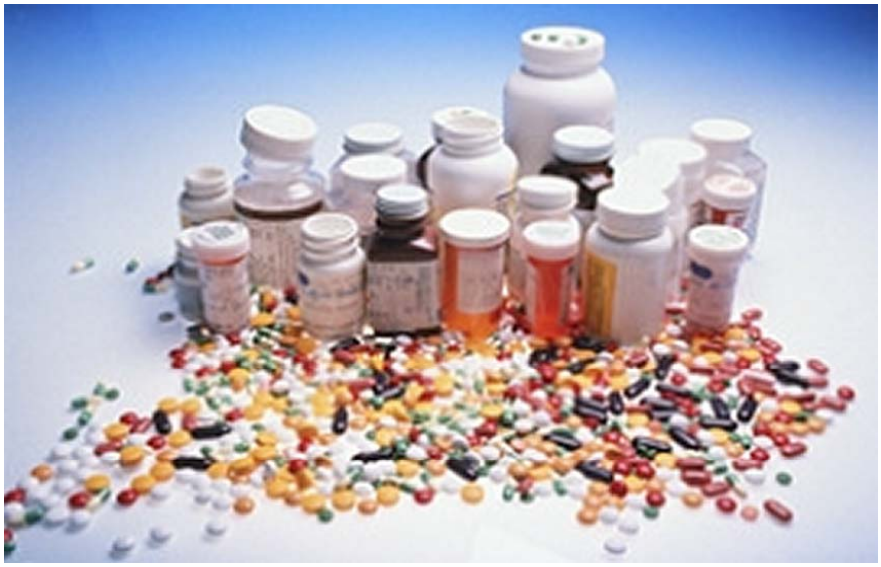
DRUG INFORMATION BULLETIN

QUARTERLY BULLETIN PUBLISHED BY DRUG ADMINISTRATION AND CONTROL AUTHORITY OF ETHIOPIA

Volume 1, Issue 3 | October 2003



Contents

Special points of interest:

* Do you know that Ethiopia Radio is transmitting Drug Information and activities of DACA every Wednesday night (21:45)?
* Daca's website is under development
* Drug Information centers will be established.

Guidelines Under Process

In line with the mandates entrusted to it, DACA is currently finalizing the following guidelines /directives,. These are guideline for-

- Prescription control,
- Adverse drug reaction reporting,
- Promotion control ,
- OTC drugs for Veterinary use.

ADR monitoring division of DACA has received Five ADR Cases

Adverse Drug Reaction monitoring and promotion control division of the Drug Administration and Control Authority of Ethiopia received five suspected ADR case reports in the month of August 2003. These cases were three skin allergic manifestations, one extra-pyramidal effect and one non-specific manifestation. (see page No. 16)

Editorial

What kind of problems do antiretroviral drugs cause?

People with HIV must take complicated treatment regimens, often taking several drugs on a daily basis. Patients may forget to take their medicine, find the food restrictions difficult to deal with, and may experience unpleasant side effects.

Aside from the complicated dosing regimens, antiretroviral drugs themselves may cause serious medical problems. Metabolic changes are occurring in people with chronic HIV infection. One of these changes causes HIV-associated lipodystrophy syndrome (HIV-LS). This condition results in abnormal fat distribution and cholesterol and glucose abnormalities. Gender and HIV infection itself can influence cell metabolism, making it difficult to distinguish adverse drug effects from the natural progression of the disease.

Some anti-HIV drugs are toxic to mitochondria, the energy-producers in cells. Tissues that require high levels of energy, like muscles and nerves, are most susceptible to the effects of damaged mitochondria. A disrupted mitochondrial energy supply can result in muscle wasting, heart failure, peripheral nerve damage causing numbness and pain, low blood cell counts, swelling and fat degeneration of the liver, and inflammation of the pancreas. Other more general signs include fatigue, depression, and high lactic acid levels in the blood.

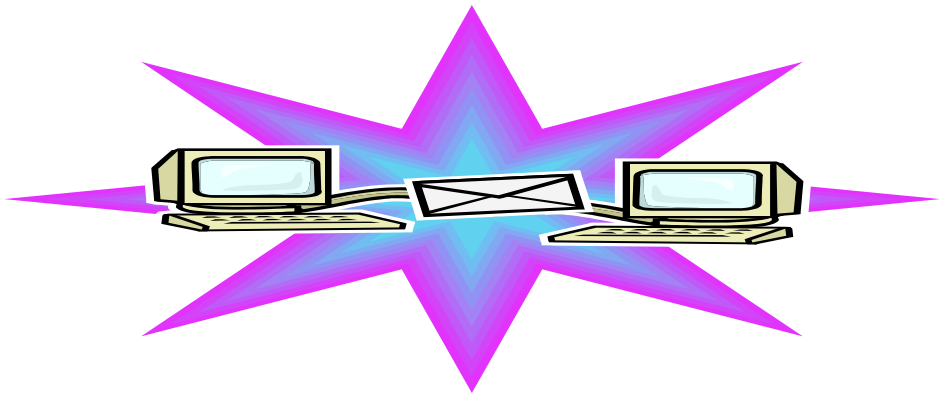
Osteonecrosis, or weakened bones, is another condition that is being seen more frequently in persons with HIV infection that may be a side effect of anti-HIV drugs.

In this issue....

Information on the adverse effects, complications and possible drug interactions related to antiretroviral therapy, which is the main part of this issue, is presented in the scientific information up date column. News and recent activities of the authority are presented on the second column and the current issue column describes different cases of ADRs and Drug interactions which have been reported recently to Australian Adverse Drug Reaction Advisory committee and another topic states about new investigation on neovastat, promising for cancer therapy, is also included in this issue. The Regulatory tips column states about the regulatory matters of the Authority.

The tutorial part of this issue comprises seven self-test questions and it is believed that it measures our readers participation. Again, we kindly invite you to send your answers for the questions that appear on this column and in the coming issue; we will give the possible answers including the list of participants who will give the correct answer.

The other column, which makes this issue unique from the previous issues is 'The readers' view'. In this column one of our reader's suggestion and comments on the bulletin content along with our response is presented.



READERS' VIEW

This Column is open for the readers. All are invited to give suggestions, comments or any inquiries regarding drug information. Please address any comments or questions to the editors. Drug Administration and control Authority of Ethiopia; Planning, Drug information Establishment and Distribution Department; P.O.Box, 5681; Addis Ababa.

I would like to say congratulations to the Authority staff as well as the editors for preparing such Drug information Bulletin that provides current and up to date information for health care professionals.

I am very much interested in your bulletin contents especially the tutorial part. The self-test questions posted in this part are so important because it initiates me to read a lot. But sometimes, since you put the answer for the questions in the same issue, I am eager to see the answer with out referring other books. So I suggest that the answer shall be given in the next issue so that the readers will have a chance to see other books till the answer is posted.

In addition to the above I suggest that the editors should also give emphasis to other chronic diseases such as Cancer, Hypertension, Diabetic mellitus e.t.c. besides to HIV/AIDS.

Ato Ashenif Tadele, EHNRI-DDR,
A.A

Dear Ashenif, First of all we would like to express our gratitude to you for the constructive suggestions forwarded through your letter.

We found your suggestions very useful to improve the content of the bulletin and encourage the readers to read more. According to your suggestion, the answers for the questions posted in the tutorial part will be given in the next issue.

In response to your suggestions, information on the therapy for cancer is presented in this issue, and more information will be also disseminated in the next issues. We will also try to accommodate information on other chronic diseases in our next issues.

Tell us what you think!

As a reader, you are the most important critic and commentator of our bulletin. We value your opinion and want to know we're doing right, what we could do better, what areas you'd like to see us published in, and any other scientific drug information you're willing to pass our way. You can help us make strong bulletin that meet your needs and give you the rational drug use guidance you require.

You can fax, e-mail, or write us directly to let us know what you did or didn't like about this bulletin as well as what we can do to make our bulletin stronger. Here's the information:

Fax: 251-1-521392
Tel.: 251-1-524122/23
E-mail: daca@telecom.net.et

Mail: Drug administration and control Authority of Ethiopia
Planning, Drug information establishment and dissemination department
5681
Addis Ababa

Antiretroviral Agents

HIV continues to have enormous global impact, particularly in the developing world. Around 42 million people are infected worldwide and new infections occur at a rate of 14000 per day. Eradication of HIV by continuous therapy is highly unlikely, due to the very long half-life and latency of some immune cells infected with HIV. No cure is in sight and a preventive vaccination will not be available in the near future.

From the late 1990s to the present time, HIV treatments have come under increasing scrutiny. However, treatment success did not come without a price and unpleasant adverse effects were relatively common with the new classes of medications. The protease inhibitors often cause gastrointestinal adverse effects such as significant nausea and diarrhoea. Drug interactions between protease inhibitors and other medications were frequent and problematic. The non-nucleoside reverse transcriptase inhibitors had the potential to cause rash, hepatotoxicity and occasionally Stevens-Johnson syndrome. Treatment regimens with Highly Active Antiretroviral Therapy (HAART) were more complex than monotherapy or dual therapy and typically required numerous tablets to be taken multiple times a day with rigid dosing intervals and restrictions around food. Adherence to these schedules was difficult and needed to be sustained for treatment to be effective.

General information on the twelve ARV drugs included in the national drug list of Ethiopia has been covered in the first two issues. In this issue some information on the adverse effects, complications and possible drug interactions related to antiretroviral therapy is presented by summarizing first the information of each class of ARV drugs disseminated in the previous two issues.

Table 1. Nucleoside Analogs

Drug	AZT, ZDV Zidovudine	DDI Didanosine	DDC Zalcitabine	d4T Stavudine	3TC Lamivudine	ABC Abacavir
How Supplied	100 and 300 mg tabs; 300 mg + 3TC 150 mg as Combivir; 300 mg + 3TC 150 mg + ABC; 300 mg as Trizivir 10 mg/mL oral solution	25, 50, 100, and 150 mg buffered tabs; 100, 167, and 250 mg powder packets; 200 mg buffered tabs for 1-2x daily dosing; 120, 200, 250, and 400 mg enteric coated cap (Videx EC); Pediatric powder with 4 g/240 mL	0.375 and 0.75 mg tabs	15, 20, 30, and 40 mg caps 1 mg/mL oral sol'n	150 mg tabs; 150 mg with AZT 300 mg as Combivir; 10 mg/mL oral solution; 150 mg with AZT 300 mg and ABC 300 mg as Trizivir	300 mg tabs; ABC 300 mg + AZT 300 mg + 3TC 150 mg as Trizivir
Dosing Recommendations	300 mg bid (or with 3TC as Combivir 1 tab bid or with 3TC + ABC as Trizivir 1 tab bid)	Tablets or oral sol'n* >60kg: 200 mg bid or 400 mg qid (tabs) or 250 mg bid or 500 mg qid (powder); 400 mg cap (Videx EC) qid <60kg: 250 mg qid or 125 mg bid (tabs) or 167 mg bid or 250 mg qid (powder) or Videx EC 250 mg qid	0.75 mg tid	>60kg: 40mg bid <60kg: 30mg bid	150 mg bid or with AZT as Combivir (1 tab bid) or with AZT + ABC as Trizivir (1 tab bid)	300 mg bid or with AZT + 3TC (1 tab bid)
Oral Bioavailability	60%	30% to 40%	85%	86%	86%	83%

Food Effect	None; may be better tolerated with food	Levels ↓55% Videx - Take 1/2 hour before and 2 hours after meal; Videx EC - take 1 hour before and 2 hours after meal	None	None	None	None Alcohol ↑ABC levels 41%
Serum Half-life	1.1 hours	1.6 hours	1.2 hours	1.0 hour	3 to 6 hours	1.5 hours
Intracellular Half-life	3 hours	25 to 40 hours	3 hours	3.5 hours	12 hours	3.3 hours
CNS Penetration (% serum levels)	60%	20%	20%	30% to 40%	10%	30%
Elimination	**M**etabolized to AZT Glucuronide (GAZT) **R**enal excretion of GAZT	Renal excretion - 50%	Renal excretion - 70%	Renal excretion - 50%	Renal excretion unchanged	**M**etabolized **R**enal excretion of metabolites - 82%
Major Toxicity Class Toxicity†	**B**one marrow suppression: anemia and/or neutropenia **S**ubjective complaints: GI intolerance, headache, insomnia, asthenia	**P**ancreatitis **P**eripheral neuropathy **G**I intolerance - nausea, diarrhea. Videx EC has fewer GI side effects Avoid combination with d4T in pregnancy #	**P**eripheral neuropathy **S**tomatitis	**P**eripheral neuropathy **A**void combination with ddI in pregnancy#	**M**inimal toxicity	**H**ypersensitivity (2% to 5%), fever, nausea, vomiting, anorexia, cough, dyspena, malaise, morbilliform rash. Rechallenge may be life-threatening.
Drug Interactions	Ribavirin may reduce AZT activity	Methadone↓ ddI levels 41%; consider ddI dose increase	None	Methadone ↓ddI levels 27% No dose adjustment.	None	None

*For adults, ddI pediatric oral solution can be mixed by the pharmacist with liquid antacids. See package insert for instructions.

^Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity probably seen with all NRTIs, but most frequently with d4T, ddI, and AZT.

#The combination of d4T + ddI should be avoided in pregnancy due to risk of lactic acidosis and hepatotoxicity.

Table 2: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Drug	**NVP Nevirapine**	**DLV Delaviridine**	**EFV Efavirenz**
Form	200 mg tabs; 50 mg/mL oral solution	100 mg and 200 mg tabs	50, 100, 200 mg caps
Dosing Recommendations	200 mg PO qid x 14 days, then 200 mg PO bid	400 mg PO tid	600 mg PO qid (in the evening)
Oral Bioavailability	>90%	85%	42%
Food Effect	No effect	No effect	Absorption increased 50% with high-fat meal; avoid after high-fat meal
Serum Half-life	25 to 30 hours	5.8 hours	40 to 52 hours
Elimination	Metabolized by cytochrome P450 (3A4 inducer); 80% excreted in urine (glucuronidated metabolites, <5% unchanged), 10% in feces	Metabolized by cytochrome P450 (3A4 inducer); 51% excreted in urine (<5% unchanged), 44% in feces	Metabolized by cytochrome P450 enzymes (3A4 mixed inhibitor/inducer); 14% to 34% excreted in urine, (<1% unchanged) 16% to 61% in feces
Major toxicity Class Toxicity	•Rash (15% to 30%); discontinuation required in 7%; rare cases of Stevens-Johnson syndrome •Hepatitis with hepatic necrosis	•Rash (10% to 15%); discontinuation required in 4% •Increased transaminase levels	•CNS: dizziness, "disconnectedness," somnolence, insomnia, abnormal dreams, confusion, amnesia, agitation, hallucinations, poor concentration - 40% to 50%, usually resolves within 2 to 3 weeks; take in evening; discontinuation of EFV for CNS toxicity in 2.6% •Rash (5% to 10%); discontinuation required in 1.7%; rare reports of Stevens-Johnson syndrome •Teratogenic in cynomalgus monkeys. Avoid in pregnancy and women should use adequate contraception methods. •False-positive drug screening test for cannabinoids (marijuana).

Table 3. Protease Inhibitors			
Drug	**IDV Indinavir**	**RTV Ritonavir**	**NFV Nelfinavir**
Form	200, 400, 333 mg caps	100 mg caps 600 mg/7.5 mL PO solution	250 mg tablets 50 mg/g oral powder
Usual Dose	800 mg q8h Separate buffered ddI dose by 1 hour	600 mg bid* Separate buffered ddI dose by 2 hours	1250 mg bid or 750 mg tid
Food effect	Levels decreased 77%; take 1 hour before or 2 hours after meals; may take with low-fat snack or skim milk	Levels increased 15%; take with food if possible to imporve tolerability	Levels increase 2x to 3x; take with meal or snack

Table 3. Protease Inhibitors (con't)			
Drug	**IDV** **Indinavir**	**RTV** **Ritonavir**	**NFV** **Nelfinavir**
Bioavailability	65% (on empty stomach)	Not determined	20% to 80%
Storage	Room temperature	Soft-gel cap and liquid formulation - room temperature	Room temperature
Serum Half-life	1.5 to 2 hours	3 to 5 hours	3.5 to 5 hours
CNS Penetration	Moderate	Poor	Moderate
Elimination	Biliary metabolism P450 cytochrome, CYP 3A4 inhibitor	Biliary metabolism P450 cytochrome, 3A4>2D6; most potent 3A4 inhibitor	Biliary metabolism P450 cytochrome, 3A4 inhibitor
Side Effects	•GI intolerance (10% to 15%) •Nephrolithiasis or nephrotoxicity (10% to 20%) take >1.5 L/day; Misc. - headache, blurred vision, thrombocytopenia, paronychia, hepatitis, asthenia, dizziness, rash, metallic taste, ITP, alopecia, dry skin, chapped lips •Lab - increase indirect bilirubinemia (inconsequential)	•GI intolerance (20% to 40%) - nausea, vomiting, diarrhea; •Circumoral and extremities (10%) •Taste perversion (10%) •Lab - increased triglyceride levels in 60% and increased transaminase levels in 10% to 15%, increased CPK and uric acid •Misc. - asthenia, hepatitis, alcohol content of oral solution contains ETOH, possible disulfiram reaction	•Diarrhea (10% to 30%) •Increased transaminase levels

Table 3. Protease Inhibitors (con't)			
Drug	**SQV Saquinavir**		**LPV/RTV Lopinavir/Ritonavir**
Form	200 mg caps (hard-gel caps)	200 mg caps (soft-gel caps)	133 mg LPV + 33 mg RTV caps; 80 mg LPV + 20 mg RTV/mL oral solution
Usual Dose	400 mg bid with RTV (only use of Invirase)	1200 mg tid	400/100 mg (3 caps or 5 mL) bid
Food effect	No food effect when taken with RTV	Levels increase 6x; take with large meal unless taken with RTV	Fat increases AUC 50% to 80%; take with food
Bioavailability	4%	Not determined (estimated to be 13x higher than Invirase)	Not known
Storage	Room temperature	Room temperature or refrigerate	Room temp - stable x 2 months
Serum Half-life	1 to 2 hours	1 to 2 hours	5 to 6 hours
CNS Penetration	Poor	Poor	Not known
Elimination	Biliary metabolism P450 cytochrome, 3A4 inhibitor	Biliary metabolism P450 cytochrome, 3A4 inhibitor	Biliary metabolism P450 cytochrome, 3A4 inhibitor
Side Effects	•GI intolerance (10% to 20%) •Misc. - headache, transaminase levels increase	•GI intolerance (20% to 30%) •Misc. - headache, increased transaminase levels, hypoglycemia in diabetes	•GI intolerance - nausea, vomiting, •Diarrhea •Asthenia •Hepatitis •Oral solution is 42% ETOH - possible disulfiram reaction

- Dose escalation for RTV: days 1 and 2: 300 mg bid; days 3 to 5: 400 mg bid; days 6 to 13: 500 mg bid; day 14: 600 mg bid. Combination treatment regimen with SQV (400 mg as *Invirase* or FTV PO bid) plus RTV (400 mg PO bid).

CLASS ADVERSE DRUG REACTIONS (ADRs) TO ANTIRETROVIRAL AGENTS

Several class-related adverse events have been recognized with antiretroviral drugs during the postmarketing period. For NRTIs, lactic acidosis with hepatomegaly and hepatic steatosis has been reported. For PIs reports of hyperglycemia/diabetes mellitus, increased bleeding episodes in patients with hemophilia, and lipodystrophy with and without serum lipid abnormalities have been received. Because these events were identified based on spontaneous reports and other uncontrolled data, the actual incidence of these events and the causal association with these drugs have not been definitively established. Controlled and/or population-based epidemiologic studies evaluating these potential class adverse events are warranted.

NUCLEOSIDE ANALOGS

Lactic Acidosis/Hepatic Steatosis

Lactic acidosis and severe hepatomegaly with steatosis during use of NRTIs appear to occur at a low frequency, but with a high case fatality risk (*Lancet* 1994;343:1494). One retrospective database analysis showed an incidence of 1.3 per 1000 patient-years among patients who received NRTIs. The incidence of elevations in serum lactate may be as high as 5% to 10% with more aggressive diagnostic evaluations based on serum lactate levels (39th ICAAC, San Francisco, Calif., September 1999, Abstract 1285; 7th CROI, San Francisco, Calif., February 2000, Abstract S21, 42, 55, 56, and 57). Patients typically present with fatigue, nausea, vomiting, abdominal pain, weight loss, and dyspnea. Evaluation reveals elevated serum lactate with or without metabolic acidosis, and may show elevated CPK, ALT, and/or LDH, increased anion gap, and low bicarbonate. Abdominal CT scan or liver biopsy often shows steatotosis (*Ann Intern Med* 2000;13:192). The initial clinical manifestations of lactic acidosis are variable and may include nonspecific GI symptoms without dramatic elevation of hepatic enzymes, and in some cases dyspnea. Fatalities have been reported despite intensive supportive treatment; in other cases, the adverse event has resolved after discontinuation of NRTIs. All NRTIs have been implicated, although some studies suggest higher rates with d4T or ddI/hydroxyurea (HU). The frequency with 3TC and with ABC appears to be low, but data are inconsistent. It is possible that other clinical expressions of mitochondrial toxicity include myopathy, cardiomyopathy, neuropathy, pancreatitis, asthenia, and/or lipoatrophy (7th CROI, San Francisco, Calif., February 2000, Abstract S21). The most important therapeutic intervention is discontinuation of NRTIs. Lactic acidemia resolves slowly usually over a period of 3 to 6 months. The safety of substituting alternative drugs in the NRTI class is not known, but preliminary data suggest that substitution of regimens that don't contain 3TC or ABC in place of d4T and/or ddI may be successful. There is limited experience with antiretroviral regimens that don't contain nucleosides, but the largest (and best) experience has been with IDV + EFV + SQV + RTV; also attractive is LPV/RTV + EFV. One report suggests that lactic acidosis may respond to 50 mg riboflavin (*Lancet* 1998;252:292). Other suggested treatments (without established merit) are coenzymes (thiamine), antioxidants (compound Q), electron acceptors (vitamin C), and L-carnitine (*Lancet* 2000;356:1424). Other toxicities that may be ascribed to mitochondrial toxicity are presented in the table below:

Table 4: Known and Possible NRTI Complications Possibly Ascribed to Mitochondrial Toxicity (Adapted from Carr A, Cooper DA. *Lancet* 2000;356:1423)

Drug	Organ	Rate	Features	Lab	Rx
AZT	Skeletal muscle	17%	Fatigue, myalgias, proximal muscle wasting	CPK↑	Discontinuation
AZT	Cardiac muscle	Rare	Dilated cardiomyopathy	Echocardiogram	Discontinuation
AZT	Marrow	5% to 10%	Anemia and/or neutropenia	CBC	G-CSF Erythropoietin (EPO), discontinuation
d4T ddI ddC	Peripheral nerve	10% to 30%	Painful peripheral neuropathy with paresthesias, reduced reflexes (ankle jerks)	Axonal degeneration on biopsy	Tricyclic antidepressants, gabapentin, lamotrigine, discontinuation
ddI (d4T, 3TC)	Pancreas	1% to 6%	Abdominal pain	amylase ↑	Discontinuation
d4T (AZT, ddI)	Tissue (lipoatrophy)	50%	Fat loss - face, extremities, buttocks	None	Discontinuation (may be irreversible)

NNRTIs

Rash

Rash is a relatively common toxicity encountered during use of NNRTIs. A significant minority of these rashes are severe, and potentially fatal cases of Stevens-Johnson syndrome have been reported. The median time of onset is at 1 to 3 weeks. The frequency is 15% to 20% with NVP and DLV, and 8% to 10% with EFV; severity sufficient to require discontinuation is 7% with NVP and 2% with EFV.

PIs

Lipodystrophy, hyperlipidemia, and insulin resistance have been associated with PI use with variable frequency. These changes may occur together or as isolated observations. The etiologic role of PIs is not considered established by some, and the long-term consequences are generally unclear. Recommendations for monitoring and intervention are also unclear at the present time.

Hyperglycemia

Insulin resistance decreased glucose tolerance, hyperglycemia, new-onset diabetes mellitus,

diabetic ketoacidosis, and exacerbation of existing diabetes mellitus in patients receiving PIs have been reported (*Lancet* 1997; 350:317; *Ann Intern Med* 1997; 127:947; *Ann Intern Med* 1997; 127:948). Among these reports, symptom onset occurred a median of 63 days (range 2 to 390 days) following initiation of PI therapy. Hyperglycemia resolved in some patients who discontinued PI therapy; however, the reversibility of these events is currently unknown due to limited data. Some patients continued PI therapy and initiated treatment with oral hypoglycemic agents or insulin. Clinicians are advised to monitor HIV-infected patients with preexisting diabetes closely when PIs are prescribed, and to be aware of the risk for drug-related new-onset diabetes in patients without a history of diabetes. Patients should be advised about the warning signs of hyperglycemia (i.e, polydipsia, polyphagia, and polyuria) when these medications are prescribed. Some authorities recommend routine fasting blood glucose measurements at 3- to 4-month intervals during treatment. Routine use of glucose tolerance tests to detect this complication is not recommended. There are no data to aid in the decision to continue or discontinue drug therapy in cases of new-onset or worsening of diabetes; however, most experts would recommend continuation of HAART, but not necessarily with PIs in the absence of severe, life-threatening diabetes.

Lipodystrophy

Changes in body fat distribution, sometimes referred to as "lipodystrophy syndrome" or "fat redistribution syndrome" have been observed in 13% to 84% of patients taking protease inhibitors (*AIDS* 1999;13:2493). The frequency with which this change is noted by the patient and confirmed by the care provider with PI-based HAART and an 18-month follow-up in one large study was 17%. Clinical findings include central obesity and peripheral fat wasting. The changes may include visceral fat accumulation, dorsocervical fat accumulation ("buffalo hump"), loss of buttock fat and subcutaneous fat in the extremities with venous prominence, facial thinning, breast enlargement, and lipomatosis (*Lancet* 1998;351:871; *Lancet* 1998;351:867; *Lancet* 1997;350:1596; *Lancet* 1998;352:1881; *J AIDS* 1999;21:107). Some patients with both fat accumulation and fat atrophy may have a cushingoid appearance despite the absence of measurable abnormalities in adrenal function. It is unclear whether the various clinical manifestations represent distinct entities with different etiologies, or whether they occur as a result of a single pathologic process. Similar findings have also been reported in HIV-infected patients not receiving PIs (*Lancet* 1998;351:867); however, the number of reports has increased concomitantly with the widespread use of PI-containing antiretroviral regimens. Some experts believe that fat atrophy is due to NRTI-associated mitochondrial toxicity, especially as a result of d4T, ddI, and AZT while fat accumulation is due to PIs, and is often associated with insulin resistance and hyperlipidemia. A review of published reports in 1999 showed the frequencies of various changes as follows: buffalo hump (2% to 5%), breast enlargement (1% to 13%), abdominal paunch (1% to 21%), face atrophy (1% to 22%), and extremity wasting (8% to 13%) (*AIDS* 1999;13:2493). There are sparse data on management recommendations.

Hyperlipidemia

Changes in triglycerides and/or cholesterol have occurred with or without the clinical findings of fat redistribution. In clinical studies, all PIs have been implicated, but RTV has been shown to produce substantial increases in triglycerides and cholesterol. Although the long-term consequences of fat redistribution

are unknown, substantial increases in triglycerides or cholesterol are of concern because of the possible association with cardiovascular events and pancreatitis. In this regard, case reports have appeared describing premature coronary artery disease, cerebrovascular disease, and cholelithiasis in patients receiving PI therapy. Some authorities recommend monitoring of serum levels of cholesterol and triglycerides at 3- to 4-month intervals during PI therapy. Assessment should include evaluation for independent risks for cardiovascular disease (i.e, family history, medical history, smoking, diet, weight, etc.) and the magnitude of lipid changes. Intervention is often recommended for triglyceride levels >750 to 1000 mg/dL and/or LDL cholesterol levels >130 mg/dL (in individuals without known coronary disease or with two or more coronary risk factors) or >160 mg/dL (in individuals without known coronary disease and with fewer than two coronary risk factors). The effectiveness of dietary modification and lipid-lowering drugs such as gemfibrozil and niacin is not clear. Some patients have had resolution of serum lipid abnormalities with discontinuation of PIs; however, this decision requires a risk-benefit analysis.

Management of dyslipidemia (Recommendations of the ACTG, Dubé et al. *Clin Infect Dis* 2000;31:1216)

Monitoring: Fasting (8 to 12 hours) cholesterol, HDL cholesterol, and triglycerides at baseline and at 3 to 6 months. Frequency of monitoring thereafter depends on results and risk profile. Note that RTV may cause significant increase in cholesterol levels within 2 weeks.

Risk: Risk of premature cardiovascular events with hyperlipidemia with PI therapy is not known but is suspected (*Lancet* 1998;351:1328; *Lancet* 1998;351:1958,*Lancet* 1998;351:1959).

Magnitude: Mean increase in cholesterol with PI therapy is reported at 32 mg/dL at 3.4 months with LDL increase of 18 mg/dL.

Switch: Data are incomplete, but one study shows a favorable response to PI substitution with NVP (*AIDS* 1999;14:805), EFV (*Clin Infect Dis* 2000;31:1266), or ABC (7th CROI, San Francisco, Calif., February 2000, Abstract 51).

Recommendations: Treatment is (*Circulation* 1994;89:1329) based primarily on LDL levels and risks, with particular emphasis on patients with diabetes or prior cardiovascular disease (*Ann Intern Med* 2000;133:549).

Triglycerides: Drug therapy if triglyceride levels are >500 mg/dL. Usual treatment is a fibrate (genfibrozil 600 mg bid or fenofibrate 201 mg/day or nicotonic acid).

Drugs

Statins: Concern is that many are metabolized by cytochrome P450 pathways and cases of rhabdomyolysis have been reported with simvastatin (40th ICAAC, Toronto, Canada, September 2000; Abstract 1297). Cytochrome P450 3A4/5 isozymes are responsible for metabolism of most statins and most PIS and NNRTIs.

Table 10: Drug Interactions Requiring Dose Modifications or Cautious Use

Drugs Affected	IDV	RTV	SQV*
Antifungals **Ketoconazole**	Levels: IDV ↑68% Dose: IDV 600 mg tid	Levels: ketoconazole ↑3x Dose: use with caution; do not exceed 200 mg/day	Levels: SQV ↑3x Dose: Standard
Antimycobacterials **Rifampin**	Levels: IDV ↓89% Contraindicated	Levels: RTV ↓35% May increase hepatotoxicity (?)	Levels: SQV ↓84% Contraindicated unless using RTV + SQV then RIF 600 mg qid or 2x to 3x/week
Rifabutin	Levels: IDV ↓32% RBT ↑2x Dose: ↓RBT to 150 mg qid or 300 mg 2x to 3x/week; IDV 1000 mg tid	Levels: RBT ↑4x Dose: ↓RBT to 150 mg qid or dose 3x/week RTV - standard dose	Levels: SQV ↓40% Not recommended
Clarithromycin	Levels: Clarithromycin ↑ 53% No dose adjustment	Levels: Clarithromycin ↑77% Dose: Adjust for renal insufficiency	Levels: Clarithromycin ↑45% SQV ↑177% No dose adjustment; with RTV + SQV use clarithromycin 150 mg 2x tp 3x/week
Oral Contraceptives	Levels: Norethindrone ↑26% Ethinylestradiol ↑24% No dose adjustment	Levels: ethinyl estradiol ↓40% Use alternative method	No data
Anticonvulsants Phenobarbitol Phenytoin Carbamazepine	Unknown but may decrease IDV levels substantially. Use alternative antiretroviral therapy or RTV + IDV	Unknown Use with caution	Unknown, but may decrease SQV levels substantially
Methadone	No change in methadone levels	Methadone ↓37%, May require dose increase	No data
Miscellaneous	Grapefruit juice ↓ IDV levels by 26% Sildenafil: Do not exceed 25 mg/48 hours	Desipramine ↑145%, reduce dose Theophylline ↓47%, monitor theophylline levels Many possible interactions (see product insert) Sildenafil: Do not exceed 25 mg/48 hours	Grapefruit juice increases SQV levels Dexamethasone decreases SQV levels Sildenafil: Do not exceed 25 mg/48 hours

*Some drug interaction studies were conducted with *Invirase*. Results may not necessarily apply to use with FTV.

Table 11: Drug Interactions Requiring Dose Modifications or Cautious Use (*Continued*)

Drugs Affected	NFV	APV	LPV/RTV
Antifungals **Ketoconazole**	No dose adjustment necessary	Levels: Ketoconazole ↑44% APV ↑31%; combination under investigation	Levels ketoconazole ↑3x LPV ↑13% Dose:?
Anti-Mycobacterials **Rifampin**	Levels: NFV↓ 82% Contraindicated	Levels: APV ↓82% Contraindicated	Levels LPV ↓75% Avoid
Rifabutin	Levels: NFV ↓32% RBT ↑2x Dose: ↓RBT to 150 mg qd NFV ↑1000 mg tid	Levels: APV ↓15% RBT ↑193% Dose: ↓RBT to 150 mg qod, APV dose-standard	Levels: LPV ↓17% RBT: ↑3x, ↓RBT dose to 150 mg qod LPV/RTV - standard
Clarithromycin	No data	Levels: APV ↑18% Clarithromycin no change Dose: usual	No data
Oral Contraceptives	Levels: Norethindrone ↓ 18%, ethinylestradiol ↓ 47% Use alternative method	Not studied Use alternative method	Levels: Ethinylestradiol ↓42%; use alternative method
Anticonvulsants Phenobarbitol Phenytoin Carbamazepine	Unknown, but may decrease NFV levels substantially	Unknown, but may decrease APV levels substantially Monitor anticonvulsant level	Unknown Monitor anticonvulsant level
Methadone	NFV decreases methadone significantly but has minimal effect on maintenance dose. Monitor	No data	Methadone ↓53% Titrate methadone dose
Miscellaneous	Sildenafil: Do not exceed 25 mg/48 hours	ABC: APV ↑30% Sildenafil: Do not exceed 25 mg/48 hours	Sildenafil: do not exceed 25 mg/48 hours

Table 12: Drug Interactions Requiring Dose Modifications or Cautious Use

Drugs Affected	NVP	DLV	EFV
Antifungals **Ketoconazole**	Levels: Ketoconazole ↓ 63% NVP ↑15% to 30%: Not recommended	Not studied	Not studied
Antimycobacterials **Rifampin**	Levels: NVP ↓37% Not recommended	Levels: DLV ↓96% Contraindicated	Levels: EFV ↓25% No dose adjustment
Rifabutin	Levels: NVP ↓16% No dose change	Levels: DLV ↓80% RBT ↑100% Not recommended	Levels: EFV unchanged RBT ↓35% Dose: ↑RBT to 450 mg/day or 600 mg 2x to 3x/week EFV dose - standard
Clarithromycin	Levels: NVP ↑26% Clarithromycin ↓30% Dose: standard	Levels: clarithromycin ↑100% DLV ↑44% Dose: adjustment for renal failure	Levels: clarithromycin ↓39% Alternative recommended
Oral Contraceptives	Ethinylestradiol ↓20%, use alternative method	No data	Levels: Ethinylestradiol ↑37% Use alternative method of birth control
Anticonvulsants Phenobarbitol Phenytoin Carbamazepine	Unknown Monitor anticonvulsant level	Unknown, but may decrease DLV levels substantially Monitor anticonvulsant levels	Unknown Use with caution Monitor anticonvulsant levels
Methadone	NVP unchanged Methadone ↓60% Titrate methadone dose	No data	Methadone levels decreased - titrate methadone dose
Miscellaneous		May increase levels of dapsone, warfarin, and quinidine Sildenafil: Do not exceed 25 mg/48 hours	Monitor warfarin when used concomitantly

Awareness Creation on ADR reporting

Experts from the ADR monitoring and promotion control division are promoting ADR reporting. The division has been conducting an onsite video show in each and every health institution followed by discussion on ADR monitoring participating all health professionals. So far, 61 Physicians, 13 Pharmacy Technicians, 70 Nurses and 40 Health Assistants from 6 Hospitals and 4 health centers have attended the program.

The program is believed to create awareness among the professionals as to the need for Monitoring ADR, what an ADR is, and How to monitor ADRs. Market authorization, counterfeit and substandard drug, illicit drug control and the need for post marketing surveillance with particular emphasis on ADR monitoring were some of the issues on which hot discussions were made. The program is to be extended to other health institution out of Addis in the forthcoming schedule.

ADR case reports coming!

Adverse Drug Reaction monitoring and promotion control division of the Drug Administration and Control Authority of Ethiopia received five suspected ADR case reports in the month of August 2003. These case reports were from ALERT hospital, St. Peter's hospital, Tibebu General hospital (private) and Yergalem hospital.

These cases were three skin allergic manifestations, one extra-pyramidal effect and one non-specific manifestation. The type of drugs suspected to cause these ADRs are antibiotics, antimalarial and antifungal. In some cases the reporter neither use the brand name nor mention the manufacturers which makes it difficult to identify the specific product.

It is really encouraging to see suspected ADR case reports in such short period of time since the launching of monitoring. The authority has acknowledged to all on the receipt of the reports. Each one of these case reports may generate a signal for serious ADR. Therefore, all health professionals are encouraged to report any suspected ADRs to any pharmaceuticals, biologicals and medical supplies.

Experts in the ADR monitoring division are currently working on the causality assessment of each ADR cases. After being categorized as unlikely/remote, possible, probable/likely, certain/definite, conditional and un-assessable, the information will be entered in to the national and international database. For such reports to be sent to the international center, the information on the report should be as complete as possible and be sent to the division using the address on the back of the form. The ADR report form is available at the departments, pharmacy and nurse stations of all the health institutions.

Half of Africa has no medicines

04-09-2003

Half of Africa's population, mostly the poor and disadvantaged, do not have access to existing essential medicines and many more are denied new medicines for treating common diseases like malaria and HIV, says a report released on Monday.

"Only 50 000 of the 4.5-million people who need antiretroviral therapy have access to treatment despite significant reductions in cost," states the annual report for 2002 of the regional director of the World Health Organisation.

Only six percent have access to voluntary counselling and only one percent to services for the prevention of mother-to-child transmission, it says.

"The HIV/AIDS epidemic continues to spread relentlessly in the African region."

About 29-million HIV-positive people, 70 percent of the global total, are in Africa, and an estimated three million died of AIDS last year.

The overall adult HIV-prevalence is about nine percent, while in different regions it varies from one to over 30 percent. Botswana, Lesotho, Swaziland and Zimbabwe have adult infection rates exceeding 30 percent.

Due to HIV/AIDS, tuberculosis has become a growing problem. The average treatment success rate is 68 percent, compared to the target of 85 percent.

"Frequent shortages of anti-TB drugs, inadequate human resource capacity and insufficient diagnostic and treatment facilities are some of the challenges which are frustrating control efforts."

Effective vaccines are available but diseases that they could prevent still constitute major public health problems in Africa, the report says.

"For example, measles-related deaths are still extremely high at 445 000 annually; pertussis causes 106 000 to 190 000 deaths annually; yellow fever is still endemic in 34 countries, causing about 30 000 deaths annually; and mortality from neonatal tetanus is about 510 per 1 000 live births."

Malaria makes 270 000 people in Africa acutely ill every year, kills over 900 000 and causes significant loss in household earnings.

The annual economic loss from malaria is estimated at $12-billion," the report reads."Due to drug resistance and difficulties with implementation in the African region, tools, methods and technologies once considered effective for the management of communicable diseases are failing rapidly.

"At the same time, the acceptance of new and effective drugs and vaccines by national health systems has been slow due to inadequate investments."

Non-communicable diseases, mental disorders and substance abuse, including tobacco consumption, are becoming major problems in the region.

Countries do not give such diseases enough attention, and treatment is not universally available or affordable.

The lack of long-term commitment, coupled with the progressive increase in non-communicable diseases, contributes to widening health gaps between and within countries, the document states.

"All of this is threatening development in the African region." At 940 per 100 000 live births, Africa has the highest maternal mortality ratio in the world. The average lifetime risk of maternal death is estimated at one in 14.

"More than 75 percent of the 600 000 annual deaths from pregnancy and childbirth-related causes can be prevented through timely access to essential obstetric care."

The prevalence of female genital mutilation varies, ranging from 10 percent in Niger to over 98 percent in Guinea.

"The extent and depth of poverty as well as threatening environmental conditions represent major threats to health development in the African region."

According to the report, over 450-million poor Africans do not have access to safe water, 490-million do not have adequate sanitation and one out of five children dies from a communicable disease linked to environmental conditions.

Poverty causes food insecurity and the consumption of unsafe food.

"Together, these factors contribute to the complex natural and human-made emergencies occurring on a large scale in the region.

"The regional office aims to support member states to make health central to sustainable development through promoting a strategic, systematic and integrated approach to poverty and other determinants of health."(Source: SAPA, 1 September 2003).

PREGNANCY DESPITE DEPOT MEDROXYPROGESTERONE

Australian, Adverse drug reaction advisory committee (ADRAC) has received 27 reports of women becoming pregnant despite using depot medroxyprogesterone products (Depo-Provera, Depo-Ralovera) for contraception. In ten of the cases, the women was confirmed as becoming pregnant 2-10 weeks after administration of the drug. An interaction with carbamazepine may have been a factor in two of these cases. In another nine cases, the injections were given late or at borderline times.

These depot progesterone contraceptives have a high level of efficacy. However, prescribers and other health care professionals who administer these drugs need to avoid the following situations which contribute to the risk of contraceptive failure:

- Incorrect timing of the injection- injections must be commenced during the first five days after the onset of a normal menstrual period, within five days postpartum if not breastfeeding or, if breastfeeding, at six weeks postpartum, after having excluded pregnancy. Injections are given at 3-monthly intervals, no more than 14 weeks apart. If the interval is greater than 14 weeks, a pregnancy test should be conducted prior to administration.
- Failure to properly suspend the microcrystals by not adequately shaking the vial. Storing vials on their side may allow the microcrystals to cake and fail to suspend when shaken.
- Failure to give the full dose- inadequate drawing up or full dose injected.
- Incorrect injection technique with deposition of the suspension in tissues superficial to the muscles.
- Incorrect drug being administered- there has been one case of Depo-Medrol being used instead of Depo-provera.

IMPLANON AND VAGINAL BLEEDING

Since August 2001, Australia, ADRAC has received 130 adverse reaction reports for Implanon (subdermal Etonogestrel contraceptive implant), including 37 reports of vaginal bleeding, most of which described prolonged bleeding (duration 2-26 weeks; median 8 weeks). The bleeding generally started soon after insertion, but the time to onset was up to 16 weeks. Thirty-three of the 37 patients required implant removal. One patient was hospitalized, and transfused 4 units of packed red blood cells. In a published 3-years study, 2.8% of patients experienced heavy or prolonged bleeding with Implanon.

Unacceptable vaginal bleeding may occasionally occur with Implanon, and often requires implant removal.

Reference: Australian Adverse Drug Reactions Bulletin, Volume 22, Number 3, June 2003.

Patterns of resistance mutations to antiretroviral drugs in extensively treated HIV-1-infected patients with failure of highly active antiretroviral therapy

Resistance-mutation patterns in the reverse transcriptase (RT) and protease genes of HIV-1 were analyzed in 22 patients who had been extensively pretreated and who failed to respond to highly active antiretroviral therapy (HAART). The number of mutations ranged from 8 to 19 (median, 13): 4 to 12 (median, 6) mutations in the RT gene, and 4 to 8 (median, 7) mutations in the protease gene. In the RT gene, the most frequent resistance mutations were found at codons 215 (100%), 41 (95%),

67 (91%), and 210 (77%). Multidrug-resistant mutation patterns including Q151M and insertion mutations at codon 69, which confer cross-resistance to the different nucleoside analogue RT inhibitors were detected in 1 and 3 patients, respectively; 1 patient with insertion mutation displayed a NGQGV [corrected] sequence at codons 67 to 70. In the protease gene, the most frequent mutations were found at codons 63 (95%), 10 (86%), 90(86%), 71(77%), 46 (50%), 36 (45%), and 84 (45%). Genotypic resistance to zidovudine, saquinavir, and indinavir was found in 100% of the patients. All patients showed also resistance or possible resistance to stavudine, abacavir, ritonavir, and nelfinavir. Mutations conferring genotypic resistance to nonnucleoside analogue RT inhibitors (NNRTIs) were found in 12 (80%) of the NNRTI-experienced patients and 1 of 7 NNRTI-naive patients. Our results indicate that failure of HAART in the patients extensively pretreated results from the multiplicity of RT and protease mutations that confer genotypic resistance to almost all available antiretroviral drugs. In these patients, genotypic resistance tests confirm the lack of alternative salvage therapy strategies based on the currently available antiretroviral drugs.

Adapted from: http://www.ncbi.nlm.nih.gov /entrez/query.fcgi

Miconazole oral gel: interaction with warfarin

Attention has previously been drawn to the possibility of an interaction between miconazole oral gel (Daktarin Oral Gel®) and warfarin resulting in elevation of International Normalized ratio (INR). The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 18 reports describing this interaction in the year 2002, which is the most serious and important of the reactions described in the 32 reports to ADRAC involving oral miconazole. In most cases there was a clinically significant increase in the INR of patients who had been stabilized on warfarin. This usually occurred within a week or two of commencing miconazole. In the 17 patients in whom the INR values were documented, the INR rose to between 7.5 and more than 18. In 9 cases, there were no symptoms but in the other 8 cases, the patients presented with bruising, haematuria or mucocutaneous bleeding. Most patients required the withdrawal of one or both drugs. At least 9 patients were given vitamin K and 5 of these required fresh frozen plasma. Miconazole oral gel is absorbed to a sufficient extent to affect warfarin metabolism and hence increase its blood concentration and activity. This may occur through inflamed oral mucosa or from the bowel after swallowing the gel. An interaction is probably less likely when miconazole is administered to the skin or vaginally but ADRAC has received one report of an interaction involving topical miconazole cream. Prescribers should be aware that the possibility of an interaction with warfarin is the most important adverse effect of oral miconazole. It is mentioned in the product information and the consumer medicine information for both oral and vaginal miconazole products. It should also be noted that pharmacists as well as doctors need to be alert to a possible interaction. Adapted from: WHO Drug Information Vol. 16, No. 4, 2002.

New Class of Drugs Brings Hope to Cancer Patients

This is an exciting time in cancer research. Recent information on angiogenesis -- the growth of new blood vessels -- is providing researchers opportunities to find new ways to slow or stop a tumor's growth by cutting off the blood supply it needs.

Angiogenesis performs a critical role in the development of cancer. To grow, solid tumors need oxygen and nutrients provided by new blood vessels. Once a vascular network has been generated, cancer cells can also invade the rest of the body, a process called metastasis. Currently, researchers believe that more than 90 percent of all cancer cases are angiogenesis-dependent.

The good news is that a novel class of drugs, which acts as angiogenesis inhibitors, shows great potential in fighting more than 20 different diseases, including many types of cancer.

These "anti-angiogenesis" drugs being developed and tested block the formation of new blood vessels, starving cancerous cells and stopping tumor growth. One drug being tested, Neovastat, was discovered in 1994 and is derived from cartilage tissue. Neovastat is the only angiogenesis inhibitor being developed in the biotechnology and pharmaceutical universe that has four mechanisms of action to combat blood vessel growth. Furthermore, Neovastat is taken orally, making it convenient for patients who need long-term treatment, and it has shown minimal side effects in clinical trials. This means that unlike standard chemotherapy, Neovastat is not likely to interfere with a patient's immune system, or cause adverse gastrointestinal symptoms or hair loss.

In addition, because most cancer cells are genetically unstable and more prone to mutations, resistance is a major problem with many chemotherapy agents. But since anti-angiogenesis drugs target normal endothelial cells that are not genetically unstable, drug resistance is less likely to develop and has not been a problem so far in clinical trials.

Another hope is that angiogenesis inhibitors can be used in combination with therapies that directly target tumor cells. Because anti-angiogenic drugs and chemotherapy are aimed at different cellular targets, it is possible that the combination will prove even more effective than either therapy is as a stand-alone.

Currently, Neovastat is the subject of three clinical trials, targeting three forms of cancer for which there are urgent needs for new therapies. For multiple myeloma, the second most common form of blood cancer, the drug is in phase two trials with 125 patients in the United States, Canada and Europe. This trial should be completed by the end of 2002. For

progressive renal cell carcinoma, the drug is in phase three trials with 280 patients in the United States, Canada and Europe, which should be completed in early 2003. For non-small cell lung cancer, Neovastat is in a phase three trial sponsored by the National Cancer Institute with 760 patients in the United States and Canada. This trial should be completed in 2005.

Once the clinical trials are complete, health authorities in various countries can then assess test results and make decisions on approval.

Neovastat is being developed by Aeterna Laboratories of Quebec, Canada. For more information about current trials.
Adopted from:
http://www.cancer.gov/clinical_trials.

In the Next issue . . . .

Information on how to manage moderate to severe cancer pain will be released.
When pain is not controlled by opioids administered by mouth, other options must be considered. This topic will review the options, considers the benefits and the risks associated with alternative methods of administration and presents recent evidence about their effectiveness in providing relief and comfort to the patient.

WHO regards Ethiopia as an "associate member" for the international collaborating center.

Assessing the activities undertaken by the ADR monitoring and promotion control division of DACA of Ethiopia, the WHO drug monitoring program regarded Ethiopia as an "associate member" for the international collaborating center.

Letters from WHO Quality Assurance and Safety Medicines , Dr. Mary R. Couper and the head of the external affairs of the UMC, Mr. Sten Olsson made it clear that our national center would have access to routine products and services made by the UMC. Full membership for formal participation in the WHO Program on international drug monitoring will be granted when a solid working relationship is established between the UMC and our national center.The Authority is working hard to ensure the safety of product in our market. In so doing the

contribution of all health professional has paramount importance towards detecting any potentially hazardous, unsafe, counterfeit and substandard drugs. Thus we would like to call-upon every health professional to report all suspected adverse reaction to:

ADR monitoring and promotion control division
Planning, Drug information department
Drug Administration and Control Authority of Ethiopia
P.O. Box
Addis Ababa
Ethiopia
E-mail: daca@telecom.net.et

Drug Registration

Drug evaluation and registration is one of the major tasks of the Drug Administration and Control Authority which is given emphasis both in the National Drug Policy (NDP) and the new Drug Administration and Control proclamation (proclamation No. 176/1999). From 1964-1986 a number of attempts were made to enforce drug registration in the country. But, the registration procedure was merely an administrative formality consisting of nothing more than "entry in a register". Comprehensive evaluation and registration procedure was started in 1986. In these years, the first written guideline was revised three times in line with

the international trend and the latest one is the September 2002 revise version. This guideline covers not only drugs but also requirement for the registration of manufacturers of pharmaceuticals, medical supplies and medical devices.

Document evaluation is done by a committee composed of experts from pharmacy and other disciplines. A product can be registered only after it has passed the evaluation process through a laboratory test.

The Drug Evaluation and Registration Department is staffed with 5 pharmacists, 2 veterinary doctors, 1 Agronomist and 1 druggist. The department is well equipped with latest model soft ware (WHO recommended soft ware for registration process) called foxpro (siamed) which facilitates registration process.

Drug Evaluation and Registration Department so far registered 4200 products representing 400 chemical entities. Due to the free economy policy of the government, now a day the number of applicants is increasing. And it is expected that the number of registered products will increase significantly in the future.

Currently

- 5,235 dossiers for registration have been submitted and evaluated.
- Out of these, 4200 drugs have passed the evaluation process and registered.

- 350 manufacturers are registered as manufacturers of pharmaceutical products.
- 88 manufacturers are registered as manufacturers of medical devices
- 8 companies are registered as manufacturers of medical supply.

DRUG INFORMATION: COMMUNITY EDUCATION

Drug Information (DI) is an essence of Pharmacy practice whether community or hospital, whereby a registered pharmacist provides accurate to precise information on drugs to other health professionals. It is any objective scientifically derived and documented data of knowledge, pharmacological, toxicological and therapeutic use of drugs. Drug information includes but not limited to identification, Availability, Dosage, Pharmaceutical Compatibility, Side effects/or Contraindications, Adverse Reactions, therapeutic Compatibility, Therapeutic Use, Metabolism and Toxicity. Drug information does NOT include Advertisement Advertising material, Drug detailing, Clinical impression, "Testimonial" type reporting, Inventory control and purchasing Information.
The role of the pharmacist as a drug information specialist is mainly to utilize the knowledge and experiences of pharmacist together with his ability to analyze and interpret drug information to form the basis of professional services. These consultative services should be designed to meet the needs of the practitioners who present a drug or therapeutic problem concerning a specific patient. The drug information specialist should be able to communicate to the practitioner the clinically relevant information that can be used to facilitate the practice of rationed therapeutics.

Using a broad definition Drug Information service (DIS) encompasses the activities of specially trained individuals (i.e. clinical pharmacists) to provide accurate, unbiased, factual information or consultations which are primarily given in response to patient oriented drug problems received from physicians, pharmacists, nurses and other health professionals. Note that these services need not be limited to formalized DIC. A well staffed and equipped community pharmacy can and should provide drug information.

Drug information implies the ability to communicate to the practitioner the clinically relevant information that can be used to facilitate the practice of rational therapeutics. The activities of a drug information service are communicative and the scope of these communication activities can be divided in to the collection and dissemination of drug information. The only real measure of the success of a drug information service is its utilisation and this dwindles to a point where the continuing existence of the service cannot be justified if it is without a clinically oriented existence.

Information on drugs and pharmaceutical products is essential at all health care levels and the quantity of information supplied to each level must vary.

The patient/consumer has to be informed on the effects and risks associated with these pharmaceutical products at the time the drug is prescribed, when it is handed over to him at the pharmacy as well as with the drug itself. The patient must have clear and definite information on the dose of the drug, any possible reaction with common food and beverages. How much of the side effects should be tried to cope with before discontinuing the drug or report back to his doctor or pharmacists. Any ambiguity in giving information can negate the efficacy of the drug and in some cases can be fatal.

Drug Information is also useful in the preventive education on Drug Abuse, when a community is well informed about the dangers inherent in careless or excessive use of drugs, it reduces the pressure which the patient i.e. the public exerts on the doctor and pharmacist by way of demand for more and newer drugs. In other words it reduces drug Abuse among such community.
Community education enhances the decision making skill of the general public and also clarifies values and translates them into and develop coping skill motivation, attitudes values and translates them in to and develop coping skill motivation, attitudes and behaviour are influenced by community education.

Drug abuse is a form of symptom of community malaise, and as such the whole community has to be involved in the preventive education process directed at correcting or controlling this defect. Various groups of people are involved in this community education and these are: the parents, pharmacists and medical professionals, teachers, religious leaders and journalists in the mass media. Parents should avoid over emotional reactions and develop good relationship with their children, so as to share with them the decision they face about drug use. The pharmacists and Medical professionals should be very knowledgeable in the prescription, distribution and use of drugs. These groups need to know all the manifestation of all types of drug-related problems, including societal responses and the treatment and rehabilitation of drug dependent persons. Mass media should be used to get at the grass roots but caution should be exercised in order not to misuse or give out wrong information. Posters, printed materials films etc can be used so as to convey short, factual messages which leave lasting impression on people's mind.

Lectures, talks and workshop can also be used achieve in a community, members of the community must be fully educated

Finally, for drug information to be effective in a community, members of the community must be fully educated.

Adverse Drug Reaction Reporting Form

Patient's Name: (Initials only)_____ Card Nº: _____ Age: _____ Sex: _____
Weight:_____ Habit: _____
Address: _____
Adverse Drug Reaction Description (Including Laboratory test results): Date of onset of Reaction: _____/_____/_____
_____
_____
_____
_____
_____
_____
_____

Reaction necessitated: Discontinuation of drug/s/ ☐Yes ☐No
Prolonged Hospitalization☐Yes ☐No

Information on Suspected Drug

Drug Name (use Brand Name . if generic name are used Please indicate manufacturer and batch no. if applicable.)	Route	Dose	Frequency	Date Drug		Therapeutic Indication
				Started	Stopped	
				D|M|Y	D|M|Y	
Other Drugs Taken Including self-medication						

Reaction subside after D/C of Suspected Drug ☐Y ☐ N ☐NA
Reaction reappear after Restart of Suspected Drug ☐Y ☐N ☐NA
Treatment of reaction: _____
_____
_____

Outcome: ☐Died due to adverse reaction ☐Died, drug may be contributory ☐Died Unrelated to drug
☐Not yet recovered ☐Recovered with out sequelae ☐Recovered with sequelae ☐Unknown
Sequelae:_____
Additional information: (e.g. relevant history such as allergies, chronic disease, pregnancy etc.)
_____
_____

Reported by:_____ Name _____ Profession: _____ Signature: _____ Date: _____
Name of health Institution: _____ Address: _____ Tele Nº: _____

Continued

For office use only

Received On: _____ Registration Nº: _____

Key: D|M|Y Date |Month |Year; D/C Discontinue Treatment; Y Yes; N No; NA Not available

What to report

All suspected reactions to drugs
Unknown or unexpected ADRs
Serious adverse drug reactions
Unexpected therapeutic effects
All suspected drug interactions

From _____

_____

_____

_____

_____

¾Ñ<ÇÃ S M e S eÝ ›ÑMÓKAƒ ðnÉ lØ ` HQ2
Business Reply Service Licence No.HQ2

Postage

Prepaid

Drug Administration and Control Authority
ADR Monitoring & promotion control Division,
P. O. Box 5681,
Addis Ababa,
Ethiopia.

Tutorial

Effectiveness

We assume that all your P-drugs have already been selected on the basis of efficacy. However, you should now verify that the drug will also be **effective** in this individual patient. For this purpose you have to review whether the active substance is likely to achieve the therapeutic objective, and whether the dosage form is convenient for the patient. **Convenience** contributes to patient adherence to the treatment, and therefore to effectiveness. Complicated dosage forms or packages and special storage requirements can be major obstacles for some patients.

Safety

The safety of a drug for the individual patient depends on contraindications and interactions; these may occur more frequently in certain high risk groups. **Contraindications** are determined by the mechanism of action of the drug and the characteristics of the individual patient. Drugs in the same group usually have the same contraindications. Some patients will fall into certain high risk groups (see Table below) and any other illnesses should also be considered. Some side effects are serious for categories of patients only, such as drowsiness for drivers. **Interactions** can occur between the drug and nearly every other substance taken by the patient. Best known are interactions with other prescribed drugs, but you must also think of over-the-counter drugs the patient might be taking. Interactions may also occur with food or drinks (especially alcohol). Some drugs interact chemically with other substances and become ineffective (e.g. tetracycline and milk). Fortunately, in practice only a few interactions are clinically relevant.

High Risk Factors/Groups	• Pregnancy • Lactation • Children • Elderly • Hepatic failure	• Renal failure • History of drug allergy • Other diseases • Other medication

Exercise: patients 1-4

Verify in each of these cases whether the active substance and dosage form of your P-drug is suitable (effective, safe) for this patient. Different cases are discussed below.

Patient 1:

Man, 45 years. Suffers from asthma. Uses salbutamol inhaler. A few weeks ago you diagnosed essential hypertension (145/100 on various occasions). You advised a low-salt diet, but blood pressure remains high. You decide to add a drug to your treatment. Your P-drug for hypertension in patients under 50 is atenolol tablets, 50 mg a day.

Patient 2:

Girl, 3 years. Brought in with a severe acute asthmatic attack, probably precipitated by a viral infection. She has great difficulty in breathing (expiratory wheeze, no viscid sputum), little coughing and a slight temperature (38.2°C). Further history and physical examination reveal nothing. Apart from minor childhood infections she has never been ill before and she takes no drugs. Your P-drug for such a case is a salbutamol inhaler.

Patient 3:

Woman, 22 years, 2 months pregnant. Large abscess on her right forearm. You conclude that she will need surgery fast, but in the meantime you want to relieve the pain. Your P-drug for common pain is acetylsalicylic acid (aspirin) tablets.

Patient 4:

Boy, 4 years. Cough and fever of 39.5°C. Diagnosis: pneumonia. One of your P-drugs for pneumonia is tetracycline tablets.

Exercise: Patient A-C

Review the following prescriptions and list the most important instructions and warnings that should be given to the patient. You may consult your pharmacology books. Cases are discussed below.

Patient A

Man, 56 years. Newly diagnosed depression. R/amitriptyline 25mg, 1 tablet daily at night for one week.

Patient B

Women, 28 years. Vaginal trichomonas infection. R/metronidazole 500mg, 1 vaginal tablet daily for 10 days.

Patient C

Boy, 5 years. Pneumonia. R/amoxicillin syrup, 5 ml (=250mg) three times daily.

Answer for the questions posted in the previous issue (Vol.1 Issue 2)

1.B 2.D 3.A 4.C 5.C 6.A 7.D 8.B 9.B

Drug Resistance

Drug resistance and the consequences for treatment

IV is highly variable, it is an RNA virus and the reverse transcriptase has no proofreading function (this means at when the DNA copy is made no checks are made to ensure the sequence is exactly right–mistakes, or utations, are consequently often encountered). Although some mutations may kill the virus it is inevitable that ug resistant strains will emerge over long term treatment. For example, with continued use of zidovudine, the rus develops resistance to the drug due to mutations resulting in amino acid substitutions in the viral reverse anscriptase.

he introduction of potent combinations of antiretroviral drugs (highly active antiretroviral therapy, HAART) has elped to reduce the incidence of opportunistic infections, and improved survival. With HAART, resistance should ke longer because a virus strain resistant to one drug could still be sensitive to another. This means that the rus has to develop multiple mutations to overcome the actions of two or more drugs, this is certainly not as kely to occur.