Editorial

Dear readers!!!
Greeting to you.

The second issue of the Drug Information Bulletin is now at your hand. In this issue, as in the first we have five regular columns. The scientific information column of this issue will be on antiretroviral drugs included in the National Drug List, which is a continuation of the first issue. News and recent activities of the authority are presented on the second column while the current issue column describes survey report about Drug Information need assessment and antimicrobial resistance. In the Regulatory Tips (fourth) column some points about Adverse Drug Reaction monitoring and other regulatory matters about drugs is presented. Last but equally important is the Tutorial column that is in the form of self-test questions and it is believed that it measures our readers active 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 and addresses of readers who participated.

One column," Readers view" which is expected to appear in this issue could not be materialized for the reason that we didn't receive letters from our readers. We are still waiting earnestly to receive your invaluable opinions in the near future. Hence, we encourage our readers to send us their views and other drug related articles, with genuine sources. Besides, we will acknowledge and support participants' effort and contribution for the attainment of our objectives.

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AIDS EPIDEMIC UPDATE 2002

AIDS EPIDEMIC UPDATE 2002

WHO has released on 26 Nov. in collaboration with **UNAIDS**, the Aids epidemic update, Dec 2002 with estimates based on the most recent available data in the spread of HIV in countries around the world. There are **42** million people living with HIV/AIDS worldwide. 38.6 million of these are adults, 19.2 million are women and 3.2 million are children under the age of 15**. Five million** new infections with HIV occurred in 2002 of which 4.2 million were adults and 2 million of them were women.
A total of **3.1** million people died of HIV/AIDS related causes in 2002.
Sub-Saharan Africa has the highest number of HIV positive individuals (29.4 million people living with HIV/AIDS) followed by south and South- East Asia (6 million). In North America there are 980,000 people living with HIV/AIDS, 570,000 in Western Europe and 1.2 million in Eastern Europe and Central Asia. The number of HIV positive individuals in Australia and New Zealand has remained constant since 2001 (15,000 people). In Latin American and the Caribbean the figure is 1.2 million and 440,000 respectively.
East Asia and pacific have 1.2 million people living with HIV/AIDS. North Africa and the Middle East have 550,000 people living with HIV/AIDS.
(Adapted from: AIDS Epidemic Update, December 2002)

Ethiopia is one of the most seriously affected countries in the world. As would be expected, HIV/AIDS is more widespread in urban rather than rural areas.
The Federal Ministry Of Health has released in December 2002, the current information available on the HIV/AIDS situation in Ethiopia in the year 2001. It is estimated that about 2.2 million people in Ethiopia are currently infected with HIV/AIDS, including 2 million adults and 200,000 children. Approximately 10 percent of these or 219,400 are full-blown AIDS cases.
The number of new AIDS cases reported to the MOH in 2001 is 15,202 and the estimated number of new AIDS cases in this year is 219,400.
The 2001 estimate of HIV prevalence in Ethiopia is 6.6 percent. Urban HIV prevalence rate continue to be high at 13.7 percent while the HIV prevalence rate for rural areas remains relatively low at 3.7 percent. HIV prevalence for Addis Ababa is estimated to be 15.6 percent.

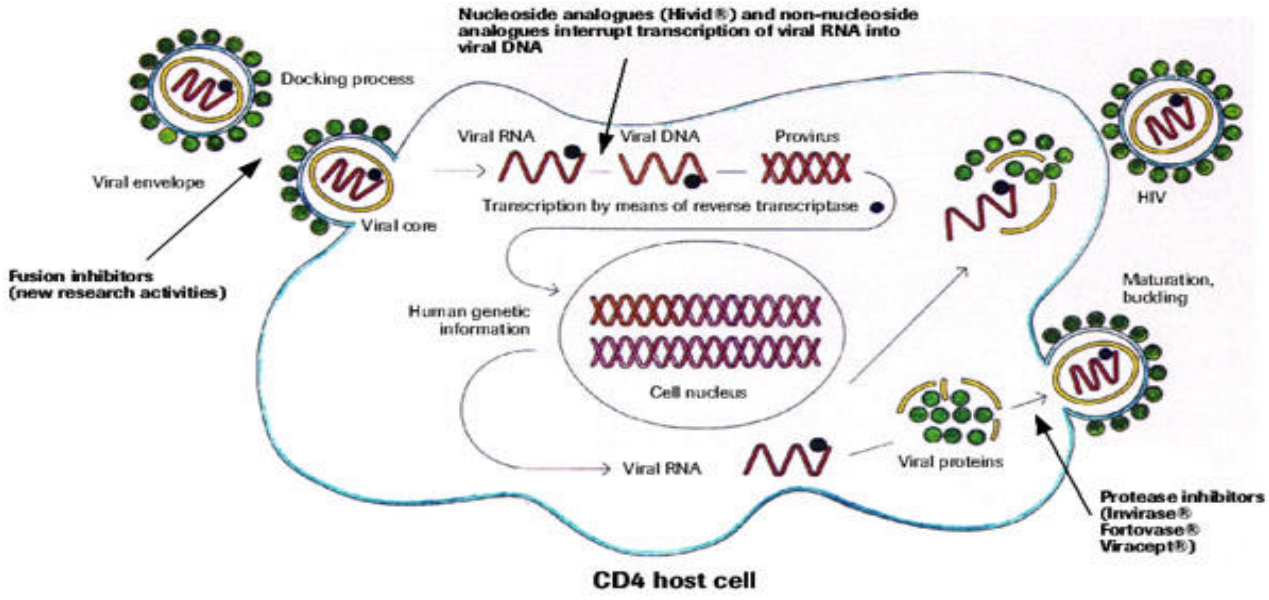
The highest prevalence of HI V is seen in the group 15 to 24 years of age, representing "recent infections". The age and sex distribution of reported AIDS cases shows that about 91 percent of infections occur among adults between 15 and 49 years. The report also reveals that the number of females infected between 15 and 19 years is much higher than the number of males in the same age groups. This discrepancy is attributable to earlier sexual activity among young females with older male partners.

The highest urban HIV prevalence in Ethiopia is reported for Bahir Dar (23.4 percent) followed by Jijiga (19 percent). A close third is Nazareth with an HIV prevalence of (18.7 percent). The current estimate for Addis Ababa is 15.6 percent. The estimated HIV prevalence for urban population is 13.7 percent and a rural prevalence rate of 3.7 percent was estimated.

Since the beginning of the AIDS epidemic, the ministry of health has received reports of 107,575 cases of AIDS. These reported AIDS case represents only the visible part of the epidemic. However there is much more to the epidemic than is revealed by the number of reported cases.
Adapted from AIDS IN ETHIOPIA, December 2002.

Antiretroviral Drugs (*continued ...from vol.1, Issue1, OCTOBER 2002*)

Antiretroviral drugs (drugs that fight against HIV) are the most effective intervention to date in managing HIV infection. These drugs have the potential to dramatically improve the health and extend the lives of many people living with HIV/AIDS.
Antiretroviral drugs work by interfering with HIV's life cycle and its ability to reproduce. Accordingly presently available drugs are classified into three categories, namely Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs),and Protease Inhibitors (PIs).



In the previous issue (vol.1, Issue1) six of the twelve ARV drugs included in the LIDE have been covered and in this issue the general information of the rest six drugs is presented below.

EFAVIRENZ

Efavirenz is non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated in combination with other antiretroviral agents for the treatment of HIV - 1 infection. NNRTIs should not be given as a single agent or added by itself to a failing regimen. Therefore Efavirenz should be initiated in combination with at least one new anti-retroviral agent to which the patient has not been previously exposed.

Pharmacokinetics

Mechanism of Action - Inhibition of HIV-1 reverse transcriptase. Efavirenze has no inhibitory effect on HIV-2 reverse trans-criptase human cellular DNA polymerases alpha, beta, gamma, or delta.

Absorption
Dose related increases in peak plasma concentration (C_{max}) and area under the curve (AUC) were seen for doses up to 1600 mg. The increases were less than proportional, suggesting diminished absorption at higher doses. Efavirenz may be taken with or without meals; however, it should not be taken with meals with a high fat content.
Efavirenz is insoluble in water, possess very high protein binding (primarily bound to albumin).

Biotransformation
Efairenz is metabolized primarily by the hepatic cytochrome P450 system into hydroxylated, inactive metabolites. These metabolites undergo subsequent glucuronation. Efavirenz is an inducer of cytochrome P450 enzymes, resulting in the induction of its own metabolism.

Half-life (Elimination)-

Terminal half-life: single dose-52 to 76hours. Multiple doses- 40 to 55 hours.

Time to peak concentration - 3 to 5 hours
Elimination - Renal and fecal

Precautions to consider

Pregnancy

- Pregnancy should be avoided (use contraceptives) in women receiving efavirenz, due to the fear of teratogenic effect. It is recommended that efavirenz not be given to pregnant woman except in situation in which there are no therapeutic alternatives.

Breast-feeding

-To avoid postnatal transmission of HIV, infected mothers are not advised for breast-feeding. Also breast-feeding is not recommended during therapy with efavirenz.

Pediatrics

-Safety and efficacy have not been established in children up to 3 years of age or those who weigh less than 13 Kg.

Drug interactions and/or related problems

Combinations containing any of the following medications, depending on the amount present may also interact with this medication. Alcohol or psychoactive drugs ⇒Additive effect on CNS. Astemazole, cisapride, midazolam, Triazolam, ergot derivatives, ⇒ efavirenz inhibit the metabolism of these medications through competition for the CYP3A4 isoenzyme resulting in prolonged adverse effects. Amprenavir, saquinavir, Indinavir, Rifabutin ⇒ efavirenz results in a decrease in plasma concentration of these drugs.

When warfarin is used concurrently with efavirenz its plasma concentrations and clinical effects may be either increased or decreased.
Efavirenz aggravates the adverse effect of ritonavir.

Other drugs like Clarithromycin, phenobarbitone, ethinylestradiol and rifampicin showed interaction with efavirenz.

Precautions
Except under special circumstances, efavirenz should not be used if hypersensitivity to the drug is expected. Risk-benefit should be considered when hepatic function impairment or hepatitis B or C is confirmed or suspected history of it. Liver enzymes monitoring are recommended for patients having history of hepatitis B or C and in patients treated with other medications associated with liver toxicity.

* Avoid potentially hazardous tasks (driving, operating machine) since efavirenz may cause dizziness, impaired concentration, and/or drowsiness.

* Alcohol or other psychoactive medications may exacerbate the CNS effects.

* Efavirenz does not reduce the risk of transmitting HIV to other sexual contact or contamination through blood.

* Using two methods of contraception, a reliable barrier method and an oral other hormonal contraceptive, when the potential for pregnancy exists.

Side/Adverse Effects

Incidence more frequent: -
Depression, dizziness, pruritis (itching), skin rash, fatigue, headache, impaired concentration, increased sweating, insomnia, nausea or vomiting, somnolence (drowsiness).

Incidence less frequent: -
Hematuria, increase in total cholesterol concentration, renal calculus, abdominal pain or dyspepsia, abnormal dreams, anorexia, flatulence, hypoesthia, nervousness.

Incidence rare: -
Abnormal vision, allergic reaction, asthma, ataxia, confusion, convulsions, diplopia (double vision), elevated liver enzymes, erythemamultiforme, fever, hepatitis, impaired coordination, migraine headache, neuralgia, pancreatitis, paraesthesia, peripheral edema, peripheral neuropathy, hallucinations, psych-ological reactions (inappropriate behavior), psychosis, speech disorder, Stevens Johnson syndrome, suicidal ideation or attempts, syncope (fainting), tachycardia or palpitations, thrombophlebitis, tremor, urticaria, vertigo, Agitation or anxiety, alopecia (loss of hair), amnesia, apathy, arthralgia or myalgia, asthemia, depersonalization, dry mouth, eczema, emotional lability (mood changes), euphoria, folliculitis, flushing, malaise, parosmia (Change in sense of smell), skin exfoliation, taste perversion (change in sense of taste), tinnitus.

Patient Consultation: -

Conditions affecting use includes:
Pregnancy - Birth defects have been observed in animal studies.
Breast-feeding - is not recommended to avoid the postnatal transmission of HIV.
Use in children - children are at increased risk for skin rash, which may be severe. The appearance of a rash should be reported to the physician as soon as possible.

- Better to avoid contra indicated medications mentioned above

- Medical problems, especially liver function impairment or history of hepatitis B or C.

Proper use of this medication: -

- Importance of not taking more medication than prescribed, importance of not discontinuing efavirenz without checking with physician.
- Compliance with full course of therapy with efavirenz and with any other medications prescribed or HIV infection. Taking efavirenz with or without meals; not taking with high fat meals because they may increase the absorption of the medication.

Being aware that the CNS and psychiatric side effects are likely to decrease with continued therapy; dosing at bedtime, especially during the

first 2 to 4 weeks of treatment, may make these side effects tolerable.

Proper dosing
Missed dose: taking as soon as possible, not taking if almost time for next dose, not doubling doses.

Proper storage

General Dosing Information

NNRTIs are not used as a monotherapy, otherwise resistance develops immediately.

Treatment with efavirenz may be reinitiated in patient whose therapy was interrupted by skin rash. The use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz is restarted.
Prophylaxis with antihistamines is recommended in children before initiating therapy with efavirenz due to the high incidence of skin rash, which may be severe, in this population.

For the treatment of adverse effects treatment consisting the following is recommended.

Discontinuation of efavirenz in patients who experience skin rash associated with blistering, desquamation, mucosal involvement or fever. Treatment with anti-histamines and/or corticosteroids may increase the tolerability of symptoms and shorten the time to resolution of the rash.

Usual adult dose (Oral - Efavirenz capsules)

- 600 mg once a day

Usual pediatric dose (oral)

- Children up to 3 yeas of age: Safety and efficacy have not been established.
- Children 3 years of age and older (by weight)
  - 10 to 15 Kg - 200 mg once a day
  - 15 to 20 Kg - 250 mg once a day
  - 20 to 25 Kg - 300 mg once a day
  - 25 to 32.5 Kg - 350 mg once a day
  - 32.5 to 40 Kg - 400 mg once a day
  - ≥40 Kg - see usual adult dose

Usual geriatric dose - see usual adult dose

Packaging and storage -

- Store at 25 ^{o}C (77 ^{o}F); brief deviation between 15 and 30 ^{o}C (59& 86^{o}F) are allowed.

Auxiliary Labeling: -

- May cause dizziness or drowsiness
- Take at bed time
- Caution with alcoholic beverages

STAVUDINE

Stavudine is nucleoside reverse transcriptase Inhibitor (NRTI) indicated for the treatment of HIV patients who have received prolonged previous treatment with zidovudine. The duration of clinical benefit from antiretroviral therapy may be limited. If disease progression occurs during stavudine treatment, an alternative antiretroviral therapy is recommended.

Pharmacokinetics

Mechanism of Action:-
Stavudine, a nucleoside analog of thymidine, is rapidly phosphorylated by cellular enzymes to its active moiety, stavudine triphosphate. Stavudine triphosphate inhibits HIV replication by competing with the natural substrate, deoxythymidine triphosphate, and by inhibiting viral DNA synthesis by acting as a terminator of chain enlongation. In addition, stavudine triphosphate inhibits cellular DNA polymerases beta and gamma, and markedly reduces the synthesis of mitochondorial DNA.
A concentration of 0.009mg/ml of stavudine is required to inhibit HIV replication by 50% invitro. The invitro potency of stavudine against HIV is similar to that of zidovudine.

Absorption: -
Stavudine is rapidly absorbed with an oral bioavailability of 78 to 86 %. Stavudine may be taken with food or on an empty stomach.

Administration with food results in a decrease in peak plasma concentration (Cmax) of approximately 45 %; however, the systemic bioavailability, as measured by the area under the plasma concentration - time curve (AUC), remains unchanged.

Distribution
Crosses the blood-brain barrier and distributes into the cerebrospinal fluid (CSF). Distributes equally between RBC and plasma.

Protein binding - Negligible

Half – life:
Normal renal function -
-Adults - 1 to 1.6 hours
-Children - 0.9 to 1.1 hours.
Renal function impairment -
Approximately 4.8 hours.
Intracellular half-life of stavudine triphosphate - Approximately 3.5 hours

Time to peak concentration - 0.5 to 1.5hours.
Peaak serum concentration-
-Approximately 1.4 μg/ml. (6.2 μmoles/litre) after a single oral dose of 70 mg.

Elimination
Renal (glomerular filtration and tubular secretion); approximately 40 % is excreted unchanged in the urine in 6 to 24 hours. Approximately 50 % of an administered dose undergoes non renal elimination. Although the exact metabolic fate is unknown, stavudine may be cleaved to thymine, and the subsequent degradation and/or utilization of thiamine may account for the unrecovered stavudine.

Drug Interactions and/or Related problems :-

Medications that may cause peripheral neuropathy, such as: Chloramphenicol cisplatin, Dapsone, Didanosine, Ethambutol, Ethionamide, Hydralazine, Isoniazide, Lithium, metronidazole, Nitrofurantoin, phenytoin, vincristine, zalcitabine or combinations containing any of these drugs, depending on the amount present, should be avoided during stavudine therapy or, if concurrent use is necessary, use with caution (since stavudine also causes peripheral neuropathy).
Zidovudine - invitro studies detected an antagonistic antiviral effect between stavudine and zidovudine.

Laboratory value alterations -
Serum values of Alanine Aminotransferase (ACT/SGPT), Alkaline phosphatase and Aspartate Aminotransferase (AST/SGOT) have increased to greater than 5 times the upper normal limit, but returned to base line when therapy was discontinued. Mean corpuscular volume (MCV) - may be increased & serum amylase and lipase values also may increase.

Contra indications

Risk-benefit should be considered when the following medical problems exist:

- Alcoholism, active or a history of, or hepatic function impairment ⇒stavudine exacerbate hepatic dysfunction.

- Stavudine may cause peripheral neuropathy; if such symptoms develop, interrupt stavudine. If symptoms resolve completely, reinstatement of therapy at a lower dose may be considered.

Patients with renal function impairment may be at increased risk of toxicity due to decreased clearance of stavudine, patients with a creatinine clearance of <50 ml/min (0.83 ml/sec) may require a reduction in dose.

Side/Adverse Effects:-

Frequently peripheral neuropathy occurs and this may need medical attention. Since complication of HIV also result in this situation, differentiation between this side effect of stavudine and the complication of the disease may be difficult. Chills and fever are also frequent incidents.
Incidence less frequent includes: -

Arthralgia, hypersensitivity & myalgia- these also need medical attention
Asthenia (weakness), GI disturbances, headache and insomnia
Rarely - anemia and pancreatitis may result.

Patient Consultation:-
Before using starvudine, conditions affecting its use; especially,
Pregnancy - Stavudine should be used during pregnancy only if clearly needed (It is not known whether stavudine crosses the placenta & reduces prenatal transmission or HIV, as does zidovudine.
Breast-feeding - not recommended, because of potential postnatal transmission of HIV to the nursing infant.
Other medications, particularly those associated with peripheral neuropathy.
Other medical problems, especially peripheral neuropathy and renal function impairment.

Proper use of this medication:-

- Importance of not taking more medication than prescribed; importance of not discontinuing medication without checking with physician.
- Compliance with full course of therapy
- Importance of not missing doses and of taking at evenly spaced times. Not sharing medication with others.

- Proper dosing
  Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses.

- Proper storage:

Precautions while using this medication:-
- Regular visits to physician for blood tests
- Importance of not taking other medications concurrently without checking with physician.
- Taking steps to avoid spreading HIV infection

General dosing information

Patients with symptoms of peripheral neuropathy or clinically significant elevations in serum concentrations of hepatic transaminases should discontinue taking stavudine. If symptoms or serum enzyme elevations resolve completely, stavudine may be reintroduced at 50 % of the regular dose.
Stavudine may be taken on a full or empty stomach.

Usual adult and adolescent dose
(Oral - Stavudine Capsules)
Body weight ≥60 Kg - 40 mg every 12hrs.
Body weight <60 Kg - 30 Mg every 12hrs.

Note: Patients with renal function impairment may require a reduction in dose as follows:

Creatinine clearance (ml/min) / (ml/sec)	Recommended dose based on patient's Body weight	
	≥ 60 Kg	<60 Kg
>50 / 0.83	Usual adult dose	Usual adult dose
26-50 / 0.43-0.83	20 mg every 12 hrs	15 mg every 12 hrs
10-25 / 0.17-0.42	20 mg every 24 hrs	15 mg every 24 hrs

Data are insufficient to recommend a dose for patients with creatinine clearance <10ml/min (0.17 ml/sec) or for patients undergoing hemodialysis.

Packaging and storage - store at controlled room temperature, preferably between 15 and 30°c (59 and 30°F) in a tight container.

Auxiliary labeling - Continue medicine for full time of treatment.

Stavudine for oral solution

Usual adult and adolescent dose - Refer to Stavudine capsules above.
Usual Pediatric dose (oral)
- Infants and children weighing ≥30 Kg - 30 mg every 12 hours

- Infants and children weighing <30 Kg - 1 mg/Kg body weight every 12 hours

Packaging and storage
Prior to reconstitution, store at controlled room temperature, preferably between 15 and 30°c (59 and 86°F), in a tight container. Protect from excessive moisture.
After reconstitution, store in a refrigerator (2 - 8°c, 36 -46°F).

Preparation of Dosage Form
To prepare stavudine for oral solution, add 202 ml of purified water to each bottle (1mg/ml) and shake vigorously to dissolve. This will provide 200 ml of dispersible solution. The solution may appear slightly hazy.

Stability
Reconstituted solutions are stable for up to 30 days when refrigerated.

Auxiliary labeling
- Shake prior to use
- Continue medicine for full time of treatment

ZALCITABINE, ddC, HIVID

Zalcitabine is used, in combination with zidovudine (Both are grouped under NRTIs), for treatment of HIV infection in patients with limited prior exposure (less than 3 months) to Zidovudine. Zalcitabine is also indicated with antiretroviral protease inhibitors, for the treatment of HIV infection.

Zalcitabine is indicated as a monotherapy for the treatment of advanced HIV infection in patients who are intolerant of, or who have disease progression while receiving, alternative anti-retroviral therapy.

The duration of clinical benefit from antiretroviral therapy may be limited. Alterations in antiretroviral therapy should be considered if disease progression occurs during treatment with zalcitabine.

Pharmacokinetics

Mechanisms of action- similar to stavudine (and other NRTIs) mentioned above. In vitro, zalcitabine is approximately 10 times more potent than zidovudine against HIV.

Absorption
Bioavailablility in adults is greater than 80 %; One small study done in children found a mean bioavailability of approximately 54 %.

Administration with food resulted in a decrease in peak plasma concentration (C_{max}) of 39 %, a decrease in the mean area under the plasma concentration time curve (AUC) of 14 %, and a two-fold increase in Time to Peak plasma concentration (T_{max}).

Distribution : -
Cross the blood-brain barrier and distributes into the CSF; the mean CSF plasma concentration ratio is 20 (range, 7 to 37).
Plasma protein binding - low (<4 %).

Biotransformation: -
Phosphorylated intracellularly to ddC TP, the active substrate for HIV reverse transcriptase. Zalcitabine does not appear to undergo significant metabolism by the liver. The primary metabolite that has been identified is dideoxyuridine (ddu).
Half-life
Normal Renal function - Adults: 1 to 3 hours
Children (ages 6 months to 13yrs): Approximately 0.8 hour.

Renal function impairment in adults (creatinine clearance <55 ml/min, 0.92 ml/sec)- up to8.5hrs
Intracellular half-life of ddcTP is 2.6 to 10 hours

Time to peak concentration - 1 to 2 hours
Peak serum concentration- 7.6 and 25.2 nanograms/ml after a single oral dose of 0.5 and 1.5 mg respectively.

Elimination
Renal; approximately 70 % of Zalicitabine is excreted in urine as the parent drug. Less than 10 % (as ddcTP and ddu) is found in feces.

Drug Interactions and/or Related Problems

Zalcitabine may cause Pancreatitis (rare occasions fatal), medications associated with the development of pancreatitis should be avoided, or if concurrent use is necessary, it should be used with caution. Such drugs include Alcohol, Asparaginase, Azathioprine, Estsrogens, furosemide, Methyldopa, pentamidine (iv), sulfonamides, Tetracyclines, Thiazide diuretics, Valproic acid, and other drugs associated with pancreatitis. Treatment with zalcitabine should be interrupted if intravenous pentamidine is required.
Aminoglycosides (parentral), Amphotericin B, Cimetidine, Probenecid or Foscarnet may increase the toxicity of zalcitabine by interfering with its renal clearance.

It is recommended that antacids, aluminium - and/or magnesium containing, not be administered together, concurrent administration resulted in a 25 % reduction in Zalcitabine absorption.

Drugs associated with the development of neuropathy should be avoided during Zalcitabine therapy or, if concurrent use is necessary, use with caution. Since Zalcitabine has been shown to cause peripheral neuropathy. Such drugs include Chloramphenicol, cisplatin, Dapsone, Disulfiram, Ethambutol, Ethionamide, Gold, hydralazine, Isoniazid, lithium, metronidazole, nitrous oxide, phenytoin, Ribavirin, Stavudine, vincristine or other drugs associated with peripheral neuropathy.

Nitrofurantoin - its concurrent use with Zalcitabine may increase the risk of pancreatitis and periphperal neuropathy.

Contra indications-
Risk-benefit should be considered when the following medical problems exist:
Alcoholism (active or history of), Hypertriglyceridemia (or history of), pancreatitis, hepatic function impairment, peripheral neuropathy.

The following laboratory results should be considered in patient monitoring
Alanine Amino transferase (ALT, SGPT), Alkaline Phosphatase, & Aspartate aminotransferase (AST, SGPT) - serum values of these may be increased to greater than five times the upper normal limit.
Elevated serum amylase, lypase, and triglyceride concentration may result from pancreatitis or zalcitabine.
Zalcitabine should be discontinued if amylase concentration is elevated by 1.5 to 2 times normal limits and/or the patient has symptoms consistent with pancreatitis.
Blood Urea Nitrogen (BUN) and serum creatinine concentrations should be monitored in patients with renal function impairment; an adjustment in dosage interval may be required.

Side/Adverse Effects
In general, patients with decreased CD_4 cell counts appear to have an increased incidence of adverse events to Zalcitabine.
Some side effects of Zalcitabine, such as peripheral neuropathy, may also be seen with severe HIV disease; therefore, differentiation between the side effects of Zalcitabine and the complications of AIDS may be difficult. Also, toxicities associated with zidovudine monotheapy are likely to occur when zidovudine is administered concurrently with Zalcitabine; these side effects should also be monitored.

Peripheral neuropathy is usually dose related and slowly reversible; however, it is potentially irreversible if Zalcitabine is not stopped promptly,

and may initially progress despite discontinuation of the drug. Zalcitabine should be discontinued as soon as there is mild progressive discomfort from numbness, tingling, burning, or pain in the hands, arms, feet or leg. Though pancreatitis is relatively uncommon with Zalcitabine monotherapy, fatal pancreatitis has also been observed when Zalcitabine was given alone and in combination with zidovudine.

Severe hepatotoxicity has occurred rarely. Lactic acidosis, in the absence of hypoxemia, and severe hepatomegaly with steatosis has been reported with the use of nucleoside analogues, including zidovudine and Zalcitabine, and are potentially fatal.

Less frequently arthralgia, hypersensitivity, myalgia, ulceration of the mouth and throat, GI disturbances and headache may be observed.

Patient consultation
Before using Zalcitabine: -
Conditions affecting its use include:
Pregnancy - Zalcitabine should not be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus; fertile women should not receive Zalcitabine unless they are using effective contraception during therapy. Unlike zidovudine, it is not known whether Zalcitabine reduces potential transmission of HIV infection.

Breast feeding - It is not known whether Zalcitabine is distributed into breast milk. Because of the potential for postnatal transmission of HIV to the nursing infant. Breast feeding is not recommended.

Use in children - well tolerated and produces clinical improvement in some children. The side effect profile is similar to that for adults.

Contraindicated drugs and disease conditions should also be considered.

Proper use of this medication -
- Importance of not taking more medication than prescribed; importance of not discontinuing medication without checking with physician.
- Compliance with full course of therapy
- Importance of not missing doses and of taking

at evenly spaced times. Not sharing medication with others.

Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses.

Proper storage

Precautions while using
- Regular visits to physician for blood tests
- Importance of not taking other medications concurrently without checking with physician.
- Taking steps to avoid spreading HIV infection

General Dosing Information

No adjustment in dose needs to be made for patients who weigh 30 Kg or more; this is based on pharmacokinetic weight - ranging data. If patients receiving Zalcitabine and zidovudine combination therapy develop what are thought to be medication related side effects, the dose of the medication associated with that particular toxicity profile should be modified. When the toxicity is more likely to be caused by Zalcitabine, the dose of that drug should be reduced or the drug should be discontinued; the same is true for zidovudine. For severe toxicity in which the causative drug cannot be identified, or side effects continue despite dose reduction or discontinuation of one medication, the dose of the other medication should also be reduced or the medication discontinued.

Patients with mild, new onset, or progressive symptoms of peripheral neuropathy should discontinue taking Zalcitabine, especially; if the symptoms last for more than 3 days and are

bilateral. Zalcitabine may be introduced at 50 % of the regular dose (0.375 mg every 8 hours) only if the peripheral neuropathy improves to very mild symptoms.

Oral dosage form, Zalcitabine tablet:-

Usual Adult and adolescent dose:
0.75 mg in combination with 200 mg Zidovudine, every 8 hours
Advanced HIV - 0.75 mg every eight hours.

Adults with acute or chronic renal impairment may require a reduction in dose of zalcitabine as follows.

Creatinine clearance (ml/min) / (ml/sec)	Dose (mg)	Dosing interval (hours)
>40 / 0.67	0.75	8
10-40/0.17-0.67	0.75	12
0-10/0-017	0.75	24

Usual pediatric dose
Safety and efficacy of zalcitabine given alone or in combination with zidovudine have not been established in children up to 13 years of age. The doses being studied in on going clinical trials are 0.005 and 0.01/mg per Kg of body weight every eight hours.

Packaging and Storage
Store between 15 and 30°c(59 and 86°F), in tight, light - resistant container.

Auxiliary Labeling
- Continue medicine for full time of treatment.

NELFINAVIR

Nelfinavir is HIV protease inhibitor (PI). Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. The potential for cross-resistance between nelfinavir and other PIs has not been fully explored.

Pharmacokinetics
Similar pharmacokinetic properties of nelfinavir had been observed in healthy volunteers and HIV infected patients.

Mechanism of action: -
Nelfinavir inhibits HIV type 1 protease. HIV protease cleaves the viral precursor proteins gag and pol, which are required to produce mature infectious virus particles. Inhibition of HIV protease results in the production of immature, noninfectious virus particles.

Absorption
Maximum plasma concentration and area under the plasma concentration time curve (AUC) values were two to three times higher under fed conditions than under fasting conditions.

Protein binding - very high (>98 %)

Biotransformation:

Following a single oral 750 mg dose, 82 to 86 % of the total plasma nelfinavir remains unchanged; one major and several minor metabolites are found in plasma; the major oxidative metabolite has in vitro antiviral activity comparable to that of the parent drug. Nelfinavir is metabolized in vitro by multiple cytochrome P450 isomers, including CYP3A.

Half-life: - Terminal half - life in plasma - 3.5 to 5 hours.

Time to peak concentration: -
Following single and multiple oral doses of 500 to 750 mg with food 2 to 4 hours.

Peak plasma concentration

Following multiple dosing with 750 mg three times a day for 28 days (steady state- Average 3 to 4 mcg/ml.

Elimination

Fecal - 87 % of an oral 750-mg dose is recovered in feces; 20 % of this portion consists of unchanged Nelfinavir, while 78 % of its portion consists numerous oxidative metabolites.

Renal - 1 to 2 % of an oral 750mg dose is recovered in urine; unchanged Nelfinavir is the major component.

Drug Interactions: -

Competition for the cytochrome P450 enzyme CYP3A by Nelfinavir may inhibit the metabolism of Amiodarone, Astemazole, Cisapride, Ergot derivatives, Midazolam, Trizolam, quinidine or terfenadine concurrent administration may result serious and/or life threatening cardiac arrhythmias or prolonged sedation. Nelfinavir causes a decrease in plasma concentrations of oral contraceptives such as ethinylestradiol or Norethindrone. Alternative or additional contraceptive measures should be taken.

Rifabutin - causes a 32 % decrease in the AUC of Nelfinavir and 207 % increase in AUC of Rifabutin. Hence when used with Nelfinavir, the dose of Rifabutin should be reduced by half of the usual dose.

Rifampicin - Concurrent use cause 82 % decrease in the AUC of Nelfinavir; concurrent use is not recommended.

Carbamazepine, phenobarbital or phenytoin causes a decrease in AUC of Nelfinavir.
Saquinavir causes 18 % increase in the AUC of Nelfinavir; the AUC for Saquinavir increases by 39.2 %, no dose adjustments are needed.

It is recommended that nelfinavir should be taken with food, and didanosine be taken on an empty stomach. Therefore, nelfinavir should be taken more than 2 hours before or 1-hour after didanosine is taken.

Contra indications:

Except under special circumstances, Nelfinavir should not be used when there is hypersensitivity to it, or in hepatic impairment. Nelfinavir is metabolized primarily by the liver.
When there is phenyl ketonuria, Risk - benefit should be considered.
Development of Hyperglycemia or diabetes may be associated with the use of protease inhibitors, close monitoring of patient glucose concentrations is recommended.

Side/Adverse effects

Diabetes, or hyperglycemia, and ketoacidosis indicates need for medical attention. Frequently diarrhea, flatulence; nausea or skin rash need medical attention only if they continue or are bothersome. For the diarrhea we can use loperamide.

Patient Consultation:
Before using Nelfinavir special conditions like: -

- Hypersensitivity to the drug should be considered
- Breast feeding - Not recommended for HIV - infected mothers
- Use in children - safety and efficacy have not been established in children up to 3 years of age.
- Consider contraindicated drugs listed above
- Other medical problems, especially hepatic impairment

Proper use of this medication: -

- Importance of taking Nelfinavir with food.
- Importance of not taking more medication than prescribed
- Compliance with full course of therapy
- Importance of not missing doses and of taking at evenly spaced times.
- Not sharing medication with others.

o Proper dosing: -

Missed dose: taking as soon as possible; not taking if almost time for next dose; not doubling doses.

- Proper storage

General Dosing Information

Dosing and strength of dosage forms available are expressed in terms of nelfinavir base (not the mesylate salt).

Nelfinavir Mesylate Oral Powder
Nelfinavir mesylate oral powder contains 11.2 gm of Phenylalanine per gram of powder.
Usual adult and adolescent
The oral powder usually is used in children.
Usual pediatric dose
Children 2 to 13 years of age: Oral 20 to 30-mg/Kg body weight three times a day with food.

Children up to 2 years of age:
Dosage has not been established.

Packaging and Storage
Store at 15 to 30°c(59 to 86°F), unless otherwise specified by the manufacturer.

Preparation of dosage form: -

The oral powder form of Nelfinavir may be mixed with a small amount of water, milk, formula, soy formula, soymilk, or dietary supplements. Acidic food or juices (e.g. apple juice, orange juice) are not recommended because the combination may result in a bitter taste. The oral powder should not be reconstituted with water in its original container. Once mixed, the entire content must be consumed to obtain the full dose.

Stability
Once reconstituted, Nelfinavir should be taken with in 6 hours.

Auxiliary labelling
- ✓ Take with food.

Nelfinavir mesylate tablets

Usual adult and adolescent dose - oral, 750 mg,

Body weight	Pediatric dose to be Administered 3times a day	
Kilograms	Number of level teaspoonfuls	Number of tabs
7 to < 8.5	1	
8.5 to < 10.5	1¼	
10.5 to < 12	1½	
12 to < 14	1¾	
14 to < 16	2	
16 to < 18	2¼	
18 to < 23	2½	2
≥ 23	2¾	3

three times a day, with food in combination with nucleoside analogs. (250 mg tab, 3 /day)

Usual pediatric dose -see the powder dosage form.

Packaging & Storage, and auxiliary labeling-similar to powder dosage form.

RITONAVIR

Ritonavir is HIV protease inhibitor (PI). Cross - resistance between Ritonavir and reverse transcriptase inhibitors is thought to be unlikely because each affects a different part of HIV replication. However, it is unknown whether there is cross-resistance between Ritonavir and other PIs.

Pharmacokinetics

Ritonavir inhibits both HIV-1 and HIV-2 proteases, which leaves these enzymes incapable of processing the gag-pol polyprotein precursor. This leads to the production of noninfectious immature HIV particles.

Absorption - may be decreased if taken with food for oral solution whereas or the capsule form food may enhance the absorption of Ritonavir to some extent.

Protein binding- very high (98 to 99 %)

Biotransformation
Hepatic: Five metabolites have been identified in the urine and feces. Isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of Ritonavir; however, plasma concentrations of M - 2 are low. The cytochrome P450 enzymes CYP3A and CYP2D6 are primarily involved in ritonavir metabolism.

Half life -3 to 5 hours.

Time to peak concentration: -

- Two hours after administration of 600 mg of oral solution under fasting conditions.
- Four hours after administration 600 mg of oral solution with food.

Peak serum concentration: -
Approximately 11 mcg/ml after administration of 600 mg every 12 hours.

Elimination

Fecal; approximately 86 % of the dose was excreted in the feces, with approximately 34 % excreted as unchanged drug.

Renal: approximately 11 % of the administered dose was excreted into the urine, with approximately 4 % excreted as unchanged drug.

Drug Interactions

Amiodarone, Astemizole, Bepridil, Bupropion, Cisapride, Clozapine, Dihydroergotamine, Encainide, Ergotamine, Flecainide, Mepridine, pimozide, Piroxicam, Propafenone, Propoxyphene, Quinidine, Rifabutin, Terfenadine, clarithromycin, clorazepate, Diazepam, estazolam, Flurazepam, Midezolam, Triazolam, Zolpidem.
These medications should not be administered concurrently with Ritonavir, due to high affinity of Ritonavir to the cytochrome P450 enzymes; it likely produces large increase in the plasma concentrations of these drugs which may result in serious adverse effects. Similarly Clarithromycin and despramine are also affected in same way; hence, if administered together dose reduction may be necessary, especially for patients having low creatinine clearance.

Concurrent administration of ritonavir with theophylline, or Estrogen containing oral contra-ceptives may decrease the AUC of the drugs.
Hence- dosage adjustment of theophylline
-a higher estrogen content or an alternative method of contraception should be considered.
Ritonavir capsules and oral solution contain alcohol, when administered concurrently with metronidazole or disulfiram, it can produce of disulfiram - alcohol reaction.

Laboratory Value Alterations

Alanine Aminotrasferase (ALT, SGPT), serum and Aspartate aminotrasferase (AST, SGOT), serum and creatine kinase (CK) and Gamma-glutamyl transferase (GGT) - values may be increased concentrations of Glucose, plasma and Triglycerides, serum uricacid, serum - may increase.

Contra indications:
Except under special circumstances, ritonavir should not be used when hypersensitivity to it exists.
Risk-benefit should be considered when there is (1) hemophilia and (2) Hepatic function impairment. Because (1) increased bleeding, including spontaneous skin hematomas and hemarthrosis, has been reported in patients with hemophilia types A and B who are receiving PIs therapy; a causal relationship has not been established. (2) Ritonavir

is primarily metabolized by the liver, it should be used with caution patients with hepatic functions impairment.

Patient's plasma glucose concentration should be closely monitored; development of hyperglycemia or diabetes may be associated with the use of PIs.

Side/Adverse Effects

Frequently, asthenia (generalized weakness); GI disturbances; taste perversion; Dizziness; headache; somnolence (sleepiness) these conditions may not need medical attention, unless they continue or are bothersome, where as the following conditions although less frequent (rare) may need medical attention: circumoral paresthesia, peripheral paresthesia, Diabetes or hyperglycemia, Ketoacidosis.

Patient Consultation

Before taking Ritonavir
Conditions affecting use, especially

- Hyper sensitivity to Ritonavir
- Use in children - safety and effectiveness have not been established in children up to 2 years of age.
- Attention should be given to avoid concurrent use of Ritonavir with drugs listed under drug interaction, contra indication and disease conditions discussed above.

Proper Use of this medication

- Importance of taking Ritonavir with food.
- Importance of not taking more medication than prescribed; importance of not discontinuing medication without checking with physician.
- Compliance with full course of therapy
- Importance of not missing doses and of taking at evenly spaced times. Not sharing medication with others.

- Proper dosing

Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses.

- Proper storage:

Regular visits to physician for blood tests and blood glucose concentrations are advisable.

General Dosing Information

If an adult or adolescent experiences nausea or other adverse events upon initiation of 600 mg two times a day, the following dose escalation may be beneficial: 300 mg two times a day, then increasing the dose by 100 mg two times a day up to 600 mg two times a day.

If a pediatric patient cannot tolerate a dose of 400 mg/m^2 of body surface area two times a day due to adverse events, the highest tolerated dose should be used for maintenance therapy in combination with other antiretroviral agents.
Patients who are initiating both Ritonavir and nucleoside analogs may improve gastrointestinal tolerance by initiating Ritonavir alone and then adding the nucleoside analog within 2 weeks.

The taste of Ritonavir oral solution may be improved by mixing with chocolate milk, within one hour of dosing.
Ritonavir capsule is not usually used in children, where as the oral solution is not usually used for adult & adolescent.

Ritonavir Capsules
Usual Adult and adolescent dose oral, 600 mg two times a day with food.
Packaging and storage

- Store in a refrigerator between 2 and $8^{o}c$, protect from light.

Auxiliary Labeling

- Take with food
- Continue medicine for full time of treatment
- Refrigerate
- Do not take other medications with out physician's advice

Ritonavir Oral Solution

Usual pediatric dose

Infants and children up to 2 years of age: safety and efficacy have not been established.

Children 2 years of age and older: oral, 250 mg/m^2 of body surface area two times a day, increasing by 50 mg/ m^2 of body surface area two times a day in two to three day intervals, up to a total dosage of 400 mg/ m^2 of body surface area two times a day, according to the following table.

Body Surface area (m^2)	250 mg/ m^2 (Given Bid)	300 mg/ m^2 (Given Bid)	350 mg/ m^2 (Given Bid)	400 mg/ m^2 (Given Bid)
0.25	0.8 ml (62.5 mg)	0.9 ml (75 mg)	1.1 ml (87.5 mg)	1.25 ml (100 mg)
0.5	1.6 ml (125 mg)	1.9 ml (150 mg)	2.2 ml (175 mg)	2.5 ml (200 mg)
1	3.1 ml (250 mg)	3.75 ml (300mg)	4.4 ml (350 mg)	5 ml (400 Mg)
1.25	3.9 ml (312.5mg)	4.7 ml (375 mg)	5.5 ml (437.5 mg)	6.25 ml (500 mg)
1.5	4.7 ml (375 mg)	5.6 ml (450 mg)	6.6ml (525 mg)	7.5 ml (600 mg)

Body surface area (m^2)= $\sqrt{\text{height (cm) x weight (Kg)/3600)}}$

Usual pediatric prescribing limits: 1200 mg per day

Strength usually available - 80 mg/ml

Packaging and Storage

Store at room temperature between 20 and 25^o c (68 and 77^o F); it should not be refrigerated.

The oral solution should be stored in the original container.

Auxiliary Labeling

- Shake well
- Take with food
- Continue medicine for full time of treatment
- Do not take other medications without physician's advice.

Continuing Education Programme EPA and DACA

The Ethiopian Pharmaceutical Association (EPA) in collaboration with Dug Administration and Control Authority (DACA) has conducted a continuing education program on veterinary drugs for pharmaceutical professionals working at different institutions, i.e. private, government, NGO, manufacturing, whole sale distribution, retail etc. EPA as a professional Association has the obligation of updating members with the growing pharmaceutical science and these educational programs were organized to fulfill this objective

The programs were conducted Jan 30 - Feb. 1 /2003, 6th and &7th Feb 2003 for pharmacy professionals drawn from Addis Ababa. According to the organizers, so far, more than 170 participants have attended the programs. DACA has played a pivotal role in supporting the program financially & materially. It is believed that the program will continue and cover at least 400 pharmacy professionals. Including Health facility staff members.

Workshop on ADR and DI

The Drug Administration and Control Authority (DACA) in collaboration with Ababa University are conducting workshops on Adverse Drug Reaction (ADR) and Drug Information (DI) to health professionals. The first round was held at Nazareth, from Jan 20 to 22, 2003 to 58 professionals (Medical doctors and pharmacy personnel) drawn from Hospitals and Health Centers in Addis Ababa, Nazareth, Debrezeit, Metehara, Wonji and Shasemene.

The second round workshop was conducted at Mekelle, similar professionals working in Tigray & Afar Administrative regions attended the workshop from 3 - 5 March 2003.

The workshops are organized with the aim of promoting the need for carefully monitoring ADR situations at Health Institutions and report the incidence promptly to DACA for further action. Moreover the workshops have also well addressed to need for the organization, screening and dissemination of quality drug information, which is the backbone of Rational use of drugs.

Group exercise on ADR & DI workshop

Proclamation Popularization

DACA is established by proclamation number 176/99 to ensure safety, efficacy and quality of drugs and to maintain the proper production, distribution and use of drugs.

To accomplish this task, the authority is conducting different popularization seminars for individuals and institutions practicing in the field, at different regions. The main objective of the seminars is to increase the awareness of professionals about the drug policy, proclamation, guidelines and directives. The topics covered include, Familiarization of National Drug Policy and Drug Administration and Control Proclamation, the need and principles of categorization of National Drug List, concepts about the different working guidelines.

The participants are professionals working in private pharmacy (human or veterinary) retail, import and wholesale distribution. Places where this popularization seminar conducted includes Addis Ababa, Awassa, Nazareth, Nekempt, Mekele, Axum, and Dessie.

CUSTOMER SERVICE TRAINING

A five days training on Quality Management was given for both administrative and technical staff of DACA at the Ethiopian Management Institute, Debrezeit from 15th to 19th Feb. 2003.

The major topics covered include Customer Service, Communication Skills, Dealing with Customer Complaints, Quality Management, Steps to Service Success and Difficult Customers Handling.

The training is believed to improve the quality of the service delivered by each member of the authority.
The process of the training was participatory that was supported by lecture, video show, group exercise and discussion.

Trainers actively participated in each subject and received certificate from the institute up on successful completion of the course.

Participants attending ADR & DI Workshop

Antimicrobial Resistance

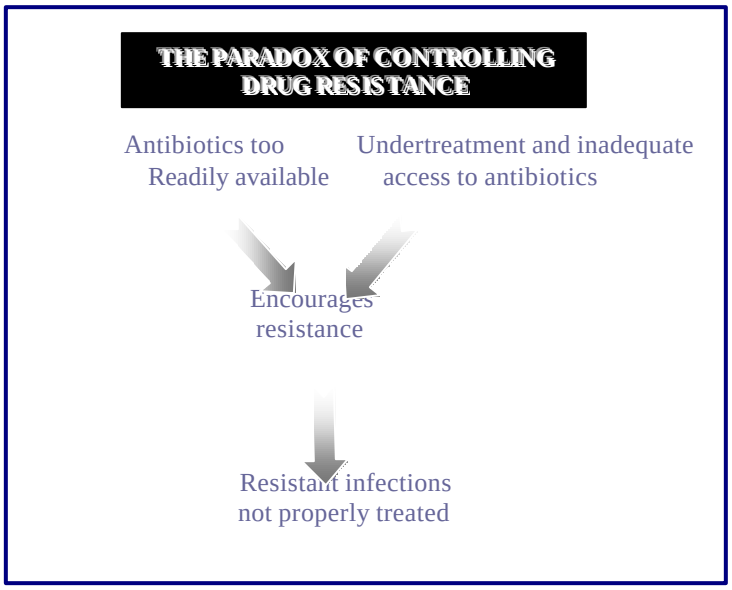
Antimicrobial resistance is on the increase threatening our ability to treat some of the infectious diseases that cause most deaths. Diseases such as tuberculosis (TB), which was once thought to be under control, are becoming increasingly difficult to treat as medicines become less effective-steadily depleting the arsenal of drugs available.
Infectious diseases still account for 45% of deaths in low-income countries and for almost one in two premature deaths worldwide. And most of these deaths (about 90%) are due to no more than six diseases: acute respiratory infections (mainly pneumonia), diarrhoeal disease, HIV/AIDS, TB, malaria and measles. Antimicrobial resistance is today challenging our ability to treat effectively at least four of these infections: acute respiratory infections, diarrhoeal disease, malaria and TB.

What is Antimicrobial resistance?
When antimicrobial resistance occurs, it is the microbe (bacterium, virus, fungus or protozoan) that is resistant; not the drug, nor the patient. Species of bacteria that are normally resistant to penicillin, for example, can develop resistance to these drugs either through mutation (vertical transmission) or through acquisition from other bacteria of resistance genes (horizontal transmission). This dual means of acquiring resistance explains why the resistance trait can spread rapidly and replace a previously drug-susceptible population of bacteria.

Are antimicrobial drugs to blame?
No. Antimicrobial drugs do not cause resistance. But the process is accelerated when antimicrobials are misused. What happens is that natural selection- a natural biological process- favours the survival of microbes that develop resistance genes by chance when exposed to antimicrobials -both appropriate and inappropriate-apply a selective pressure on microbial populations. However, the more antimicrobials are used, the greater this pressure will be. Thus it is critical to gain maximum benefit from the curative effects of antimicrobials - especially in developing countries, where they are not only misused, but often under-used due to financial constraints. At the same time, it is also essential to minimize the opportunities for resistance to emerge. In practice this means using antimicrobials both widely and wisely - - neither too little, nor too much, and never inappropriately. Inappropriate prescribing practices - including the wrong choice of drug and incorrect dosage or length of treatment - poor compliance with treatment, and the use of low quality (sometimes counterfeit) drugs all contribute to the emergence of drug-resistant microbes.

How does resistance develop?
If a person develops an acute infection such as pneumonia with a drug-susceptible strain of *streptococcus pneumoniae*, for example, and is treated promptly with penicillin, the bacteria will be killed and the infection resolved before resistance has time to emerge. However, in the treatment of chronic infections such as TB and HIV/AIDS- especially if treatment compliance is poor drug-resistant mutants have time to emerge and multiply and replace the drug-susceptible population of microbes. Under these circumstances, it is likely that the treatment outcome will be poor.
So why is it that the microbes involved in acute infections have also become resistant to

many of the first-line drug available? The problem is that antimicrobial drugs not only kill the microbe being targeted, they also "treat" other normally harmless microbes ("normal flora") in the body as well. For example, *streptococcus pneumoniae*, as well as causing otitis, pneumonia and meningitis, is also carried by many people, especially children, as part of their normal flora, without causing any symptoms. So every time they take an antimicrobial - for whatever reason - their streptococci are exposed. If a mutant emerges, it will have a selective advantage and can spread to other people. A similar process occurs when salmonella bacteria are exposed to antimicrobials incorporated into animal feed. While these bacteria may not cause the animal any harm, they can be spread to humans through the food chain.



one. In addition, a single microbial cell can carry resistance genes to a whole series of totally unrelated antimicrobial drugs. Over time, the dysentery-causing bacterium *shigella*, for example, has become resistant to each successive class of antimicrobials used in treatment. As a result, it has a string of genes, each coding for resistance for a different antimicrobial. To make matters worse, this string of genes can be transmitted from one bacterial cell to another. Thus a previously susceptible *shigella* can, in one fell swoop, acquire five or six resistance genes.

Why is antimicrobial resistance spreading so fast?

Although mutations are rare events (about one in a million bacteria may show a mutation which might lead to resistance), microbes multiply very rapidly-thereby enabling a single mutant to rapidly become dominant. Microbes also spread readily from person to person. Thus one person infected with the resistance strain may be an important source of spread, not only of the infection, but of a resistant infection. This is demonstrated in hospitals, where one patient infected with MRSA *(methicillin-resistant staphylococcus aureus)*, for example, is often the source from which many others become infected or colonized. Thus in taking action to contain resistance, both the ***emergence of resistance*** and ***the spread of resistant strains*** needed to be considered.

TACKLING THE PROBLEM

Can antimicrobial resistance be halted?

No. But it can be contained. Antimicrobial resistance is a natural biological phenomenon-the response of microbes subjected to the selective pressure of antimicrobial drug use. The main priority should be to prevent infection in the first place. After that, containment of the problem is the best we can aim for. And since it is antimicrobial use that drives resistance, the focus of any containment strategy should be on minimizing any unnecessary, inappropriate or irrational use of antimicrobial drugs.

Ideal drug usage involves:

* The correct drug
* Administered by the best route
* In the right amount
* At optimum intervals
* For the appropriate period
* After an accurate diagnosis

Problems occur in both developed and developing countries when antimicrobials are:

* Not equitably available
* Used by too many people
* To treat the wrong disease
* In the wrong dosage
* For the wrong period of time
* Not in the correct formulation or strength

Antimicrobial resistance is not a new or surprising phenomenon. All micro-organisms have the ability to evolve various way of protecting themselves from attack BUT over the last decade or so:

* Antimicrobial resistance has increased
* The pace of development for new and replacement antimicrobials has decreased

RESISTANCE MEANS THAT:

* **People can't be effectively treated**
* **People are ill for longer**
* **People are at greater risk of dying**
* **Epidemic are prolonged**
* **Others are at greater risk of infection**

Interventions To Contain Antimicrobial Resistance

Target group	Recommended interventions
Patient and the public	1.Education on appropriate use 2.Education on hygiene 3.Discourage self-medication
Prescribers and Dispensers	1.Training 2.Guidelines and formularies 3. Monitoring and supervision 4.Regulation of professionals 5.Educate prescribers about promotion
Health system	1.Therapeutic committees 2.Infection control committees 3.Guidelines for antimicrobial use 4.Antimicrobial use surveillance 5.Laboratory network and epidemiological Resistance surveillance.
Government Policies, strategies And regulations	1.National antimicrobial resistance task force 2.Drug policies e.g. essential drug list, standard treatment guideline 3.Registration of all drug outlets 4.Antimicrobials by prescription-only 5.Dispensing of antimicrobial by licensed staff only 6.Quality assurance system 7.Drug licensing to include resistance data 8.Undergraduate and postgraduate training on Antimicrobial resistance 9.Access to evidence-based drug information 10.Cut perverse rational drug use economic incentives 11.Monitor and supervise drug promotion 12.Monitor and link antimicrobial resistance and Drug use data.
Pharmaceutical Industry	1.Incentives for industry to do research and development 2.Monitor and supervise drug promotion 3.Production according to Good Manufacturing practice Standards
Non-human Antimicrobial use	1.Surveillance of resistance and use 2.Phase-out growth promoters 3.Educate farmers and Vets

Adapted from: ESSENTIAL DRUGS MONITOR, ISSUE NO. 28 & 29, 2000

Common Side Effects Of Antiretroviral Drugs

Dealing with the Side effects of antiretroviral drugs can be challenging and very difficult without adequate support. The following list shows common side effects of the various antiretroviral drugs. Each drug has its own set of possible side effects, which can vary in severity in different people.

The following is a list of common side effects of antiretroviral drugs:

- Abdominal pain
- Altered taste
- Anorexia (reduced appetite)
- Arthralgia (joint Pain)
- Chills
- Constipation
- Depression
- Diarrhea
- Fatigue
- Fevers
- Headache
- Insomnia (sleep problems)
- Malaise
- Menstrual Irregularities
- Myalgia (Muscle pain)
- Nausea
- Nephrolithiasis (Kidney stones)
- Neurologic symptoms
- Neuropathy
- Pancreatitis (Inflammation of pancreas)
- Paresthesia (numbness, prickling, tingling)
- Rash
- Seizures
- Vomiting

Adopted From: http://www.enderhealth.org/res/onc/hiv/management/hiv5table2.html

DRUG INFORMATION NEED ASSESSMENT SURVEY HAS BEEN CONDUCTED BY DACA

This is a descriptive study carried out in DI distribution and establishment division of DACA. Drug information disseminating activity had not been undertaken properly before the establishment of Drug Administration and control Authority (DACA) one year ago at a national level. But to date the Authority has put the drug information dissemination as one of its prime task in its agenda. And for the success of the activities that will be carried out in the future, the national resource center believe in need of tangible indicatives of the occurrence of drug information system in different health facilities.

This is why; the Authority has done this study of the drug information need assessment in 20 selected health institutions from A.A, East Shoa and Awassa to achieve the following objectives.

Purpose of the study

The aim of this survey is to design feasible intervention methods so as to improve the availability & quality of DI in the health institutions (H.Is).

Specific objectives of the survey were: -

- To identify the appropriate means/methods of disseminating DI in health institutions & the public.
- To assess the need of health institutions on particular areas where DI should concentrate.
- To take account of the methods or practices undertaken in different H.Is in, collecting, compiling & disseminating drug information.

Survey population

The survey population comprised two categories of informants. These are: representatives of 20 selected H.Is in the first category; and 103 different health professionals working in the selected H.I where the study was conducted in the second category.

The H.Is with different level of health facilities were included in the study.

Selected cities/towns & number of health facilities included in the survey are tabulated below.

City/ town	No.Of Hsp.	No.Of H.C	Total
A.A	6	4	10
Debrezeit	1	0	1
Nazareth	1	1	2
Modjo	0	1	1
Meki	0	1	1
Wonji	1	0	1
Zeway	0	1	1
Shashemena	1	1	2
Awassa	0	1	1
Total	10	10	20

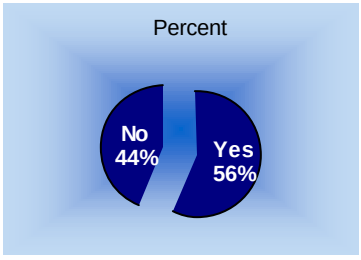
Method

Developing the questionnaire: -
Two types of questionnaires were developed by a core group comprising the staff members of the planning & drug information establishment department, with useful inputs from other departments of the Authority. One of which was to be filled by representatives of the H.Is because it directly assess the DI system of the institution. And the other one was to be filled by the health care workers.

Respondents
The number of respondents were 18 representatives of the H.Is from the first category and 92 H.Ps working in the selected institutions from the second category.
89.4% of the survey population completed and returned the questionnaire.

Results, conclusions & recommendations

Though at different level and quality, DI dissemination is practiced in 10 H.Is (55.6%) of the total.



According to the representatives' response the methods used for disseminating drug information are restricted to consumers (these are one of the three major components of drug information users). The most frequently mentioned method was - health education mentioned in approximately 47% of the responses. Others such as posters (12%), broachers (12%) & mass media (5%) were mentioned as methods employed.

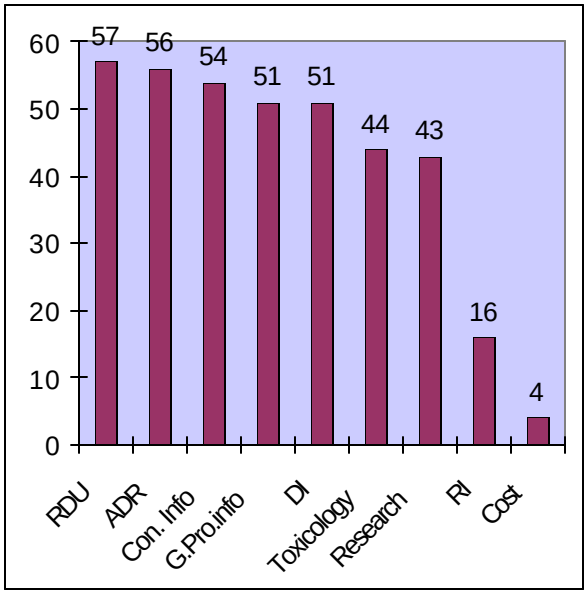
The underlying factors hindering dissemination of DI are found to be:

- Scarcity of reference materials (26.3%)
- Shortage of allocated budget (~26.3%)
- Lack of awareness on the need (~26.1%)
- Shortage of health personnel (~21.1%)

According to the second group of informants (H.Ps) about 37% do not have access to DI. It is found that most H.Ps have a personal interest in ?access to DI' but are affiliated to organizations that have little or no particular focus in this area. From the responses of the respondents it was able to know the suitable media for H.Ps that could be used for disseminating DI. According to the result Bulletin was chosen as a best means by being mentioned 29 times of the total 100 responses. Next to bulletin, seminars/workshops (21times), newsletters & magazine were mentioned 14 & 13 times respectively as a best means for disseminating DI.
With respect to the best facilities to be used for better scale of communication to the public, mass

media & written materials were mentioned 73 times of the total 95 responses.

The types of DI that should be emphasized in the publications or in any other preferred means of disseminating DI were also assessed. Rational drug use (57 times), adverse drug reaction (56 times), consumer information (54 times), general product information (51 times), drug interaction (51 times), and up to date research out comes (43 times) were among the areas suggested to be included in the publications & other media.



Generally, the survey has shown the existence of poor DI disseminating system in the H.Is that could create a great gap between the body of knowledge (current information) on existing drugs and the knowledge of H.Ps & the patients as well. Hence it is recommended that the Authority should try to fill the gap by: -

* Providing up to date drug information by giving emphasis on suggested topics and through methods preferred by the health care workers.
* Build up the awareness of health professionals on the importance of DI.
* Convincing the MOH on the necessity of DI in the healing process so as to allocate adequate budget to H.Is for facilitating the specified activity.
* Providing recently revised National drug list & encouraging the H.Is to establish P & T committee and to prepare own drug list & drug utilization profile.
* Designing a means of communicating with H.Is for eg. By motivating and supporting (technically or financially) H.Ps to establish effective DI centers in their H.Is and by preparing & issuing guideline on the establishment & operational procedures of DI centers in health institutions.

MISOPROSTOL

Major labelling changes

USA. Changes to misoprostol (Cytotec) labelling have been posted on the US FDA web site.

- The statement that misoprostol (Cytotec) is contraindicated in pregnant women has been removed from the product label. This change is based on the fact that the drug is frequently used to induce labor and delivery and the fact that it is part of the FDA approved regimen for use with mifepristone to induce abortion in pregnancies of 49 days or less.

- The label clarifies that the contraindication in pregnant women concerns those who are using misoprostol to reduce the risk of non-steroidal anti-inflammatory drug induced stomach ulcers. This does not contraindicate off-label use of misoprostol.

- A Labor and Delivery section has been added that contains safety information regarding the use of misoprostol in these areas.

- The label provides new information that uterine rupture, an adverse event reported with misoprostol (Cytotec) is associated with risk factors such as later trimester pregnancies, higher doses of the drug, prior Caesarean delivery or uterine surgery and having had five or more previous pregnancies.

TAMOXIFEN

Boxed warning added to product label

USA The labelling of AstraZeneca's tamoxifen (Nolvadex) has been revised to include a boxed warning highlighting the increased risk of uterine malignancies, stroke and pulmonary embolism, and the Warnings section has been extended. AstraZeneca has issued a 'Dear doctor' letter advising that the prescribing information now includes a new-boxed warning. The warning contains new information of particular relevance to women with ductal carcinoma in situ (DCIS) and women at high risk for developing breast cancer who are receiving or considering tamoxifen therapy to reduce their risk of developing invasive breast cancer. It states that serious and life-threatening events associated with tamoxifen in this risk reduction setting include uterine malignancies, stroke and pulmonary embolism, some of which may be fatal. Estimated incidence rates for the events are also presented. The Warnings section advises that, while most uterine

malignancies seen in association with tamoxifen are adenocarcinomas of the endometrium, uterine sarcoma, the diagnosis of which is generally associated with a poorer prognosis and shorter survival time, has been reported to occur more frequently in long term tamoxifen users than in non-users; some of these malignancies have been fatal. Patients with prior or present exposure to tamoxifen should be advised to undergo annual gynaecological examinations and to report any gynaecological abnormalities to their physician immediately. Healthcare providers are advised to discuss the potential benefits and risks of tamoxifen therapy with patients, particularly women with DCIS and those at high risk for developing breast cancer who are considering taking tamoxifen to reduce their risk. However, it is also stated that in women already diagnosed with breast cancer, the benefits of tamoxifen therapy for outweigh the risks.

Canada

Health Canada has posted a message on the use of Tamoxifen and the incidence of uterine malignancies, stroke and pulmonary embolism. The message was derived from the National Adjuvant Breast and Bowel Project Breast Cancer Prevention (NSABP P-I) study with women at high risk for breast cancer or having ductal carcinoma in Situ (DCIS) receiving tamoxifen in the prevention setting. Higher incidences of uterine malignancies, stroke and pulmonary embolism were associated with tamoxifen treatment compared to that of placenta in the treatment population of this study. Health Canada emphasized that the use of tamoxifen in the prevention setting is not an approved indication in Canada. The current approved indication for tamoxifen in Canada is in the treatment of breast cancer in Oestrogen – receptor positive tumors where the benefits of using tamoxifen have been judged to outweigh the potential risks.

Reference:

- *Summary of labeling changes by FDA, 17 Apr 2002. Available from URL: http://www. fda. gov.*

- **'Dear Doctor' letter from** *AstraZeneca, 15 May 2002. Available from URL: http://www. fda. gov/medwatch/ SAFETY/2002May 02.htm*

Adopted from WHO Pharmaceuticals Newsletter No. 3 and No. 4, 2002

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

rug Name (use Brand Name . if generic name are use 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 _____

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

Tutorial

1. The most common opportunistic infection of people with AIDS is: -
    a. Kaposi's sarcoma.
    b. Pneumocystis carinii pneumonia.
    c. Tuberculosis
    d. Wasting syndrome
2. All of the following groups presently show a rising rate of HIV infection EXCEPT:
    a. Babies born with HIV.
    b. Teenagers.
    c. Women.
    d. African-Americans.
3. An important indicator of how the immune system is functioning and how advanced the ADIS infection is:
    a. The number of helper T cells.
    b. The number of killer B cells.
    c. The number of macrophages.
    d. The number of helper B cells.
4. HIV antibodies are usually detectable in the blood how soon after the virus enters the body?
    a. 2-6 hours
    b. 2-6 days
    c. 2-6 months
    d. 2-6 years
5. Opportunistic infections are diseases that:
    a. Are not life threatening to people with HIV/AIDS.
    b. Develop the same in healthy people as in people with HIV/AIDS.
    c. Benefit from a vulnerable immune system.
    d. Are favorable side effects that help fight HIV/AIDS infections.
6. Which form of sexual interaction presents the most risk for spreading HIV among men and women?
    a. Anal intercourse
    b. Vaginal intercourse
    c. Oral sex
    d. All of the above are equally risky
7. How do most antiretroviral drugs work?
    a. They kill the HIV
    b. They cause the body to increase population of all types of T cells.
    c. They fight opportunistic infections.
    d. They interfere with replication of HIV.
8. In testing of HIV infection:
    a. The western blot is given first and the ELISA is used to recheck positives.
    b. The ELISA is given first and the western blot is used to recheck positives.
    c. The only test used now is the DNA-HIV.
    d. The DNA-HIV is given first and the ELISA is used to recheck positives.
9. How do most children contract HIV?
    a. Infected breast milk
    b. Perinatal transmission
    c. Transfusion with infected blood
    d. Child sexual abuse

Adopted from: http://highered.mcgraw-hill.com