Selections from Drug & Therapeutics Letter*

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Drug Resistant Tuberculosis

Though effective antitubercular drugs have been available for more than 50 years, tuberculosis is still a basic public health problem in most developing countries. Today we have various anti-tubercular drugs that can cure tuberculosis if properly used in correct combination and doses for a proper duration of time. But it has been observed that less than 50% of the treated new infectious cases of tuberculosis are cured because of discontinuation of treatment due to various reasons. These poorly treated cases have high chances of developing drug resistance. Drug resistant tuberculosis is considered as a potential threat to the new DOTS (Directly Observed Treatment Short-course) strategy. The National Tuberculosis Programme of Nepal has been adopting DOTS strategy since 1996. Till 1999 September, 112 DOTS treatment centres have been established in 46 districts of Nepal. The cure rate achieved in these DOTS implemented areas is 89%. Cure rate with unsupervised SCC (Short Course Chemotherapy) is still quite low.

It has been said that drug resistant tuberculosis is a man-made problem. Poor management of TB patients leads to the development of drug resistant tuberculosis.

Definition of drug resistance

Acquired drug resistance is that which is found in a patient who has received at least more than a month of prior anti-tubercular drug treatment.

Primary drug resistance is the presence of resistant strains of *M. tuberculosis* in a patient with no history of such prior treatment.

Multi-drug resistance (MDR) is defined as the presence of resistant strains of *M. tuberculosis* in a patient, at least to isoniazid and rifampicin or to more drugs.

Magnitude of MDR TB

The exact extent of the problem is unknown. International Union Against Tuberculosis and Lung Diseases (IUATLD) suggests that, with a good national tuberculosis programme, acquired MDR TB is 4%-10% and primary MDR TB is 1% or less, in new cases. In Nepal a survey was conducted in 1996 with the collaboration of Global Drug Resistance Surveillance. The result showed that the primary MDR was 1.5%.

Basic principles for the management of MDR tuberculosis

Most of the MDR TB cases are virtually untreatable for developing countries. Prevention is the best measure. Every effort should be made by each prescriber to prevent such cases. The total cost of treatment is very high and may require 4,00,000-6,00,000 Rupees. In the United States it costs more than us $100,000 to treat such a case. The duration of treatment required ranges from 18 to 21 months and the drugs are quite toxic. If someone wants to treat such cases with reserve drugs, it should be made sure that the following points are taken care of.

Specialized unit

The reserve drugs should be made available only at specialized units and not in the free market. Only specialist authorities should use these reserve drugs in order to prevent further incurable tuberculosis. The patients should be under close monitoring to identify drug toxicity.

Designing an appropriate regimen

The patient should receive an effective and appropriate combination of drugs for a proper duration. This requires skillful experience. Therefore it is better to follow the WHO-recommended regimen. Never add *one* new drug to a failing regimen.

Reliable susceptibility test report

Reliable culture and sensitivity report should be available before labelling a case as MDR TB. The quality of susceptibility tests carried out in a laboratory should be supervised by national or supranational laboratory for quality control.

Reliable drug supply

Availability of reserve drugs for full course should be ensured before starting treatment with such drugs.

When to suspect MDR TB ?

Treatment failure is not always due to drug resistance. First find out whether the patient is taking regular treatment or not. Look for other associated diseases like uncontrolled diabetes mellitus. Think twice before changing the regimen. You can suspect MDR TB only when reliable culture and sensitivity report is available or smear positive patient is not responding to WHO-recommended *retreatment* regimen (2SHRZE+ 1HRZE+5HRE).

TB Epidemiology in Nepal

Infection

- Annual Risk of Infection 1.8
- 45% of total population are infected

Disease

- 80 to 90 thousand people have active TB
- 44 thousand new cases occur annually
- 20 thousand new P+ (infectious) cases per year

Deaths

- 8 to 11 thousand per year

Achievement 1998/99

- Case finding rate 62%
- Treatment success rate on DOTS 89%
- Treatment success rate (National) 79%
- DOTS coverage 51%

Formulation, acceptance, daily dosages and main characteristics of anti-tuberculosis drugs available for treatment of MDR tuberculosis

Drugs	*Formulation*	*Daily dosage (mg)*		*Acceptability*	*Tolerance*	*Toxicity*
		Mini-mum	*Maxi-mum*			
1. Aminoglycosides						
a. Streptomycin	vial, 1g	750	1000	injection	moderate	medium
b. Kanamycin	vial, 1g	750	1000	injection (painful)	poor	medium
Amikacin	vial, 1g	750	1000	injection		
2. Capreomycin	vial, 1g	750	1000	injection (painful)	moderate	medium
3. Thioamides						
a. Ethionamide	tablet, 250 mg	500	750	good	moderate	medium
b. Prothionamide	tablet, 250 mg	500	750	good	moderate	medium

4. Pyrazinamide	tablet, 400 mg or 500 mg	1200	1600	good	moderate	low
5. Fluoroquinolones						
a. Ofloxcin	tablet, 200 mg	600	800	good	good	low
b. Ciprofloxacin	tablet, 500 mg	1000	1500	good	good	low
6. Ethambutol	tablet, 400 mg	1000	1200	good	good	low
7. Cycloserine	tablet, 250 mg	500	750	good	moderate	high
Terizidone	tablet, 300 mg	600	600			
8. PAS	tablet, 500 mg	10 g	12g	bad (bulk, taste)	poor	low
	granules packet 4 g	10g	12g	good	moderate	low

Acceptable "third line" regimen for the treatment of MDR tuberculosis

	Initial phase		*Continuation phase*	
Resistance	*Drugs*	*Minimum duration in months*	*Drugs*	*Duration in months*
Isoniazid &	Ethionamide,	3	Ethionamide	18
Rifampicin	Ofloxacin,	3	Ofloxacin	18
	Ethambutol,	3	Ethambutol	18
	Pyrazinamide,	3		
	Aminoglycoside	3		
Isoniazid,	Aminoglycoside	3	Ethionamide	18
Rifampicin and	Ethionamide	3	Ofloxacin	18
Streptomicin	Pyrazinamide	3	Ethambutol	18
	Ofloxacin	3		
	Ethambutol	3		
Isoniazid,	Aminoglycoside	3	Ethionamide	18
Rifampicin,	Ethionamide	3	Ofloxacin	18
Streptomycin &	Pyrazinamide	3	Cycloserine	18
Ethambutol	Ofloxacin	3		
	Cycloserine	3		

Conclusion

We should try to prevent the development of MDR tuberculosis. There is minimal hope to cure such cases. The maximum cure rate achieved by these expensive and toxic treatments is only 50%. The best way of prevention is the proper management of new and retreatment cases with the WHO-recommended DOTS strategy.

Sources

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2. Anti-tuberculosis drug resistance in the world, WHO/TB/97/229.
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Reproduced from:

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Drugs that alter the colour of urine

Drug	**Urine colour**
Amitriptyline	greenish blue
Anthraquinone derivatives (eg, senna)	red, violet, orange
Chloroquine	brown, black
Chlorzoxazone	red, violet, orange
Deferoxamine	red
Ibuprofen	red, violet
Iron dextran	black
Levodopa	red, turns black
Methocarbamol	brown, green, blue
Methyldopa	dark on standing
Metronidazole	brown
Nitrofurantoin	brown, yellow
Phenazopyridine	orange, red
Phenolphthalein	red, orange
Phenothiazines	reddish brown
Phenytoin	reddish brown
Primaquine	brown
Quinine	brown, black
Rifampicin	red, orange
Sulfasalazine	orange
Warfarin	red, brown

Source

Aronoff GR, Abel SR. Practical guidelines for drug dosing in patients with renal impairment. In: Schrier RW, ed. Manual of nephrology, 4th edition. Boston: Little, Brown & Company, 1995: 173-185.

Reproduced from:

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UNMINDFUL USE OF ANTITUBERCULOSIS DRUGS

Contributed by **Anil Pahari**, MD, Lecturer, Dept. of Internal Medicine, Maharajgunj Campus and TU Teaching Hospital, T.U. Institute of Medicine, Kathmandu.

This is the story of a 30-year old male, who has had repeated courses of anti-tuberculosis treatment (ATT) without any bacteriological evidence.

The patient presented with haemoptysis 13 years ago to Dhangadhi District Hospital. ATT was started without bacteriological evidence. He received injection streptomycin and a tablet (name not known). He continued this treatment for 18 months. As haemoptysis persisted, he consulted a doctor in Bombay who prescribed isoniazed + rifampicin + ethambutol. Even with this treatment, he continued to have haemoptysis, so he consulted a doctor in Delhi, who also advised him to remain on ATT.

As haemoptysis still continued, he consulted TB Hospital in Nepal, where, after sputum examination and other tests, he was told that it was not TB and was advised to discontinue ATT. He remained off treatment for two years. Once again he had haemoptysis, for which he went to other doctors who all gave him different regimens of ATT for variable periods. In 13 years, this patient has had seven courses of ATT consisting of various regimens.

He was admitted to TU Teaching Hospital (TUTH) on 05/10/2056 (19 January 2000), again with the complaint of haemoptysis. His X-ray chest showed fibrocavitary lesion on the left upper zone. Sputum tests for acid fast bacilli (AFB) were repeatedly negative. High resolution computarised tomography (HRCT) was done and this was suggestive of bronchiectasis. Since the patient was morbid and has had life-threatening haemoptysis, our management of choice was surgery.

The idea behind this case report is to re-educate ourselves about TB diagnosis and management. In an era of technological advancement, it is not justified to treat diseases, particularly for prolonged periods, only on empirical basis and the confidence of 'personal experience'. Not all cases of haemoptysis or unresolved fever are due to TB.

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DRUG-INDUCED GINGIVAL HYPERPLASIA

Drug-induced gingival over-growth (gum hypertrophy) is a well-recognised adverse effect of treatment with some drugs such as phenytoin, cyclosporin and nifedipine. Apart from nifedipine, other calcium channel blockers reported to cause this problem are amlodipine, felodipine, nitrendipine, verapamil and diltiazem. Sodium valproate and oral contraceptives are also documented to cause gingival hypertrophy.

It is estimated that 25 to 80% of patients taking cyclosporin develop gingival hyperplasia. Similarly, up to 50% of patients taking phenytoin may develop this adverse effect. Although it is estimated that 15 to 20% of patients on nifedipine may be affected, severe cases tend to occur in less than 1%.

Drug-induced gingival hypertrophy has been reported to occur from a few days to more than 4 years after starting treatment. In general, it occurs within a few months of commencing treatment. Poor oral hygiene could be a contributory factor in the causation of this problem. A recent report from Australian Adverse Drug Reactions Advisory Committee indicated that, where documented, recovery from gingival hypertrophy was rather slow and ranged from weeks to more than a year after stopping the drug.

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4. *WHO Pharmaceuticals Newsletter*, Nos. 9-12, September-December 1999; page 6.

Reproduced from:

Drug & Therapeutics Letter 2000; **7** (2): 6-7.

MODERATE ALCOHOL INTAKE REDUCES CORONARY HEART DISEASE

Excessive alcohol consumption increases the risk of early death. But there is now strong evidence to suggest that light to moderate drinkers have a lower mortality than those who abstain from drinking. This is mainly due to inverse association between moderate alcohol consumption and coronary heart disease (CHD). Moderate alcohol intake provides protection against CHD in both men and women.

The CHD risk is 10 to 40% lower in persons who take one to three drinks per day than in those who do not drink. This beneficial effect of moderate drinking has been attributed to favourable changes in lipid and haemostatic factors.

A recent meta-analysis report published in the 11 Dec '99 issue of *BMJ* has also concluded similarly. The analysis included 42 experimental studies that assessed the effect of moderate alcohol consumption (up to 100g a day) on concentration of lipids and other factors. The meta-analysis shows that moderate alcohol intake increases the concentration of high-density lipoprotein cholesterol and apolipoprotein A I and decreases the concentration of fibrinogen. The meta-analysis also points out that there is a weak association between moderate alcohol consumption and increased concentration of triglycerides and this can attenuate the beneficial effects of alcohol. The study projects that, after considering association of different bio-markers that lower or raise the risk of CHD, the overall benefit provided by drinking 30g alcohol a day would cause an estimated overall reduction of 24.7% in the risk of CHD.

Based on the above findings, what should be the current public policy ? Should non-drinkers be recommended to start drinking ? In his paper Criqui writes that non-drinkers should not be advised to start drinking because most of them abstain from drinking due to certain reasons such
as previous health conditions, family history of alcoholism, and religion. Currently recommendations in the USA and UK also do not encourage drinking but do include the statement that moderate alcohol intake can be part of a healthy lifestyle.

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Reproduced from:

Drug & Therapeutics Letter 2000; **7** (2): 7-8.

CISAPRIDE WITHDRAWN

Cisapride is a prokinetic drug. It was approved in the U.S. by the FDA in 1993 for night-time heartburn. But in March 2000, the manufacturer of this drug – Janssen Pharmaceutica Inc. – withdrew it from the market. This withdrawal was because of safety concerns.

Cisapride can cause disturbances in cardiac rhythm. By the end of 1999, the FDA had received 341 reports of cardiac rhythm disturbances, including 80 reports of death, associated with the use of this drug.

Cisapride is currently available in Nepal under many brand names.

Source

Six drug withdrawals in 30 months on safety grounds: why the five-year rule is more important than ever. *Worst Pills Best Pills News* 2000; 6(5): 33-34.

Reproduced from:

Drug & Therapeutics Letter 2000; **7** (2): 8.

Drug THERAPY of HIV / AIDS

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It is estimated that worldwide approximately 16,000 people are infected with Human Immunodeficiency Virus (HIV) daily. The majority of them will not realise that they are infected until they show the unmistakable symptoms, and once they do realise, may deny or keep the information to themselves. The aim of managing HIV patients is to prolong and provide them with an acceptable quality of life. In order to achieve this, counseling, education and medical management should go hand in hand. The purpose of drug treatment in HIV infection is to suppress HIV replication, and this can be achieved by antiretroviral therapy. A few questions regarding medical management of HIV infection still remain unanswered -

1. When should the antiretroviral therapy be started ?

2. What is the best regimen to start with ?

3. When is a change of regimen indicated and what should the changed regimen be ?

In order to decide the best possible treatment of HIV infection, extensive trials are being conducted. However, the physician and the patient must discuss these treatment issues and come to a mutually agreed plan based on the best data available regarding the treatment. When the HIV enters a person's body, it weakens the immune system by destroying the CD4 cells. As an increasing number of the CD4 cells
are destroyed, the infected person
becomes vulnerable to a collection of potentially deadly diseases and infections called **Acquired Immuno Deficiency Syndrome (AIDS)**.

The common opportunistic infections are *Pnemocystis carinii* pneumonia (PCP), Kaposi sarcoma, toxoplasmosis of the brain, and candidal esophagitis. HIV infection can progress to AIDS any time from as early as less than 5 years to as long as 15 years. However, AIDS develops only when the T-cell (CD4) count drops to below 200/microL. In healthy adults, the normal CD4 count is 800-1300/microL. Hence it is best to commence the treatment for HIV infection before the CD4 cell count drops to under 200, and better still when the count lies between 200-500.

AIDS = HIV infection + CD4 count < 200 + opportunistic infections / malignancy.

Important facts about hiv/aids

• Worldwide some 16,000 people are infected with HIV daily, i.e. 11 persons per minute.

• Rate of infection is rapidly increasing in South East Asia day by day.

• Currently more than one hundred thousand people are estimated to be infected with HIV in Nepal.

• HIV infection occurs by sexual contact, transfusion of blood & blood products, peri-natal transmission from mother to child, & contact with infected needles & body fluids.

• Can be transmitted with long kissing (tongue kissing).

• Not transmitted by sharing household items or by living and sleeping together.

• Confirmatory test for HIV — positive Western Blot and/or positive PCR and/or positive two separate types of ELISA tests.

• If ELISA is negative in suspected cases, repeat after 3 and 6 months.

• CD4 count is the most important factor in classification, treatment and determining the prognosis of HIV patient.

• All HIV infections are not AIDS.

• Patients may live with HIV infection for as long as 10 years without any symptoms (before eventually developing AIDS) (asymptomatic stage).

• Suspect HIV infection if the person has prolonged fever, chronic diarrhoea, lymphadenopathy, pneumonia, skin lesions, malignancies, or STD diseases.

• More than 80% of HIV/AIDS patients die as a result of opportunistic infections.

• With multi-drug therapy, an AIDS patient may live for as long as 15-20 years.

• Zidovudine (AZT) is the best drug for prevention of perinatal transmission.

• Following accidental exposure, antiretroviral therapy should be immediately started as post-exposure prophylaxis (PEP) and continued for 28 days.

• Currently one-month course of combination therapy with zidovudine, lamivudine and saquinavir costs around Rs 40,000 in Nepal.

Reproduced from:

Mertens TE *et al*, eds. Basic Science in HIV/AIDS: an update. WHO/TRANSCRIPTASE/ UNAIDS, 1999.

Antiretroviral medicines

The drugs used for treating HIV infection are grouped according to their mechanism of action and are broadly grouped under two headings.

A) The Reverse Transcriptase Inhibitors

This group of drug works by blocking the enzyme HIV reverse transcriptase, which translates HIV RNA chromosomal information into a DNA chromosome. This group is further divided into two sub-groups; Nucleoside Analogues and Non- nucleoside Analogues

B) Protease Inhibitors

These agents inhibit the cleavage of proteins by the HIV protease and thus stop the final growth stage of the virus.

The names of individual members of different antiretroviral groups of medicines are given in Figure 1.

The goals of treatment of HIV infection are to: slow the replication rate of HIV; prevent and treat opportunistic infection; & relieve symptoms and generally improve the quality of life.

Approach to therapy:

The patient's viral load (HIV RNA) and CD4 cell count help in monitoring disease control or progression and in deciding whether or not to switch over to another treatment regimen. Initially, when the nucleoside analogues were introduced, the standard treatment then consisted of one- or two- drug regimen. The newer protease inhibitors are much more powerful drugs and are now frequently combined with one or more nucleoside analogues ("triple therapy") to produce a very powerful viral inhibition, so powerful that sometimes the viral loads are undetectable. Along with a decrease in viral loads, the "triple therapy" delays the progression of disease and consequently increases patient survival.

There are two approaches to the medical management of HIV infection.

1. *Conservative approach*

This depends upon the patient's CD4 count. If the count lies between 200-500/microL, then one of the following regimens can be given:

a. A single nucleoside, i.e. didanosine

b. Two nucleosides — zidovudine + didanosine, OR, zidovudine + zalcitabine, OR, zidovudine + lamivudine.

If the CD4 count falls below 200/microL, the treatment modality is changed to one or two nucleosides + one protease inhibitor.

2. *Aggressive Approach*

This involves using combination therapy from the time of diagnosis of HIV infection. The following combination therapies can be tried -

a. Combination of indinavir (protease inhibitor) plus zidovudine & lamivudine (nucleosides)

b. Use of other nucleosides in combination with saquinavir (protease inhibitor)

c. Combination of nucleosides, saquinavir, and ritonavir and possibly the addition of a non-nucleoside reverse transcriptase inhibitor.

The patient is monitored carefully with CD4+ T cell count and plasma levels of HIV RNA.

Highly Active Antiretroviral Therapy (HAART)

In order to minimise the occurrence of mutants resistant to a given drug therapy the residual viral replication rate should be brought down to the lowest level possible. If the average time for development of resistance can be prolonged to say more than a human lifetime, then an almost permanent therapy can be achieved. As the rate of viral replication ceases, the T cell levels rebound, the patient's immune system gets stronger and so chances of acquiring opportunistic infections decrease.

HAART therapy involves the combination of two separate nucleoside analogues (which require separate mutations to

achieve resistance) plus a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. This therapy has proved to reduce the viral replication rate sufficient enough to allow the T cell levels to rebound, thereby preventing development of opportunistic infections. The use of HAART therapy in countries with significant resources has made HIV infection a chronic, manageable disease.

Prophylaxis

The CD4 count directly reflects the immune status of the individual. As long as the CD4 count remains >200, chances of developing opportunistic illnesses are low. Individuals having thrush or persistent and unexplained fever or CD4 count of 200 or less are at high risk of contracting *Pneumocystis carinii* pneumonia (PCP). Such individuals and others who are at risk of developing tuberculosis, toxoplasmosis, mycobacterium avium infection and cytomegalovirus infection are candidates for prophylactic medications. The most common and effective regimen to prevent PCP is trimethoprim-sulphamethoxazole in a dose of 15 mg/kg/day for 21 days.

Vaccinations

In addition to prophylactic medications, vaccinations are routinely recommended for the prevention of influenza, pneumococcal pneumonia and hepatitis B. Vaccinations can be recommended as soon as HIV infection is ascertained or may be given at a particular CD4 count of the individual.

Post-exposure prophylaxis (PEP)

The term "post-exposure prophylaxis" refers to treatment of occupational exposures using antiretroviral therapy. The rationale is that antiretroviral treatment which is started immediately after exposure to HIV may prevent HIV infection. Health personnel are more prone to infection by needle prick.

There are two regimens for PEP - the Basic and the Expanded regimens.

The appropriate regimen is selected depending on the type and severity of exposure. **Basic regimen** includes zidovudine 600 mg/day + lamivudine 300 mg/day for 28 days. **Expanded regimen** includes Basic regimen + protease inhibitor for 28 days.

New advances

1. **Drugs**: - Some countries now have 15 different drugs to treat HIV infection. These antiretroviral drugs currently constitute the nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI & NNRTI) and protease inhibitors. The latest drugs are new members of the existing families, fusion inhibitors and nucleotide derivatives.

2. **Immunotherapy**: - Interleukin 2 (IL2) stimulates the activation and proliferation of CD4+ and CD8+ T cells and also their cytotoxic activity. IL2 therefore plays an important role in the regulation of cellular and humoral immunity. IL2 alone or in combination with the latest antiretroviral drug might, in the long term, improve the immunological status of the HIV patients. Trials with IL2 are being conducted on HIV patients and the clinical benefits of combination therapy can only be determined in lengthy randomised trials.

3. **Vaccine**:- The best way of preventing HIV infection is by changing human sexual behavior, which, we all know, is very difficult to change. Hence, the best way is the development of a safe and effective vaccine. This is a difficult task as the virus has a high mutation rate, and the infection can be transmitted by a cell free or cell-associated virus. Also, there should be an effective mucosal immunity. Despite these difficulties, a large number of vaccines are being explored and different types of vaccines are under trial. They are - whole inactivated vaccine, live attenuated vaccine, recombinant HIV envelope protein, virus-like particles, synthetic peptide vaccine, live vectored vaccine, and naked DNA vaccine.

Current Difficulties In Nepal

Laboratory tests for CD4 count and HIV RNA level are not yet available in Nepal. As outlined above, these two tests are very important in: determining the immune status (CD4); monitoring the disease progression; judging the efficacy of the treatment given; and deciding whether a change in treatment modality is indicated.

A few antiretroviral drugs are available. However, they are quite expensive. Their names and approximate costs are mentioned below.

Drugs current approximate cost

(for one day's therapy)

1. Zidovudine (ZDV, AZT) Rs 103.00

2. Lamivudine (3TC) Rs 110.00

3. Zalcitabine (ddc) Rs 564.00

4. Saquinavir Rs 671.00

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