Update Article

THERAPY AND PROPHYLAXIS IN HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

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Introduction

Some ages are defined by their epidemics. Today, we live in the shadow of Acquired Immunodeficiency syndrome (AIDS), the terrifying modern epidemic. Recent developments have brought about what looks like some hope in the form of therapy and prophylaxis in the HIV infected.

The first anti-retroviral drug to be licensed was zidovudine (AZT) in 1987 [1] in the form of monotherapy. In a very short period of time, availability of anti retroviral drugs has increased from one drug with a modest activity to twelve approved drugs with remarkable potency, particularly when used in combination [2]. AZT is a synthetic pyrimidine, a nucleoside analog and a reverse transcriptase inhibitor (NRTI). What did the monotherapy with AZT offer? In a multicentric study [2] monotherapy with AZT resulted in reduced death rate, significant difference in occurrence of opportunistic infections (OIs), improvement in Karnofsky's functional capability scores, weight gain, increased CD4 counts (although falling back after 5 months), and gain in skin test reactivity. These initial encouraging results reflected diminished viral replication in vivo. The mode of action of AZT is well elicited. Within the cytoplasm of HIV infected cells AZT gets phosphorylated to its active form, AZT-TP (AZT-triphosphate) by cellular protein kinases. This compound has got a 100-fold greater affinity for viral reverse transcriptase (RT) in comparison to affinity for cellular DNA polymerase. Thus, AZT-TP serves as a substrate for viral RT and gets incorporated into growing DNA chains in preference to thymidine, resulting in premature DNA chain termination and inhibition of viral replication [4]. Notwithstanding these benefits offered by AZT, HIV isolates from patients who received AZT for 6 months or more, showed in-

creasing resistance to the drug in vitro. Such resistance often paralleled clinical deterioration in time [3], vindicating relationship between the two parameters. Mechanism of resistance to AZT is not clear as yet.

The need for newer drugs

Thus emerged an intense investigation into other possible targets for antiviral action in the HIV replication cycle. These included potential agents to counter viral binding to cells, other inhibitors of RT besides AZT (non-nucleoside RT inhibitors-NNRTI which act to inhibit RT by non competitive inhibition at the pyrophosphate binding site of the enzyme), inhibitors of viral integration in to host cell genome, inhibitors of viral gene expression (transcription and translation), posttranslational processing inhibitors-protease inhibitors which inhibit the processing of the polyprotein products of gag and gag-pol genes in to the functional core proteins and viral enzymes, inhibitors of viral budding and release from the infected cell [5].

Many important advances have been made in the understanding of the biology and treatment of HIV infection during the past 24 months. In July 1996, at an International AIDS Conference in Vancouver, Canada, David Ho, a virologist reported on his most promising experiment. He and his team administered protease inhibitor cocktail therapy to HIV infected patients earliest possible in their course of disease. They came tantalisingly close to eliminating the virus from blood and body tissues. The mathematical models broached by them suggested that patients caught early enough following infection may be rendered virus free within 2-3 years with cocktail therapy [6]. This virological 'holy grail' dawned the concept: AIDS is not invincible. For helping lift a death sentence-for a few years or perhaps longer-on tens and thousands of

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AIDS patients and for pioneering a treatment that just might lead to a cure, David Ho was awarded a Nobel prize in Medicine for the year 1997.

Many randomised clinical trials [7,8], have suggested combination anti-retroviral therapy is superior to nucleoside analog (NRTI) monotherapy. There is a need to consider some of the broad principles which have gained a wide consensus [9] amongst HIV treating physicians:

(a) Treatment should be offered before substantial immunodeficiency ensues.

(b) Initial treatment should include combinations of at least two drugs

(c) Switches in therapy should involve substitution or addition of at least two new agents.

(d) Viral load (HIV RNA plasma load) and CD4 counts are essential measurements.

(e) Reduction in viral load to below the detection level of a sensitive assay represents the optimal treatment response and failure to achieve or sustain this control should prompt consideration of therapy modification.

Aims of therapy

These are:

(a) Delay AIDS defining clinical events

(b) Delay death

(c) Keep viral burden (as measured by plasma viral RNA levels), as low as possible and for as long as possible on a drug regimen that is compatible with long-term tolerance and compliance.

The agents

The pharmacokinetics, toxicity, dose and approximate cost of anti-retroviral agents belonging to three broad groups are presented in Table -1

Initiation of anti-retroviral therapy

Measurement of HIV RNA plasma load and CD4 counts are mandatory before initiation of anti-retroviral therapy, because these two parameters determine the risk of disease progression and response to therapy. Early initiation of therapy is vital as reduction of plasma HIV RNA to below levels of detection by this approach is viewed as optimal response to therapy. This stems from the rationale that early suppression of HIV replication limits the potential for selection of diverse HIV variants resistant to antiviral drugs. And also failure to suppress HIV replication adequately early in disease is likely to lead to virological and clinical failure besides preventing cumulative damage

to the immune system [11]. Thus the considerations for initiation of therapy are:-

- symptomatic HIV disease

- CD4 counts /cmm

- HIV RNA 5000-10000 copies/mL irrespective of CD4 count

Selected options for initial therapy are [10]:

(a) NRTI-1, NRTI-2 and PI

(b) NRTI-1, NRTI-2 and NNRTI

Both the above regimens are able to achieve plasma HIV RNA levels below the limit of detection in large majority of patients. The second regimen also permits deferral of use of a PI. However, this regimen is not recommended for patients with advanced disease. A prototype regimen as per (a) above is as follows:

Zidovudine (Zidovir)	100 mg capsules	2 tid
Zalcitabine (Epivir)	150 mg tablet	1 tid
Indinavir (Crixivan)	400 mg capsules	2 tid

(Note: The approximate present cost for the above mentioned regimen is Rs.5,20,000/- per year).

Monitoring of antiretroviral therapy

The laboratory tool that has contributed most to the increased understanding of viral pathogenesis and anti-retroviral efficacy is quantitation of HIV RNA in plasma. The level of HIV RNA in plasma has been shown to be the strongest predictor of outcome over 1-10 years period of observation [12]. The level of HIV RNA expression in lymphoid tissue may be higher and more intense than suggested by plasma concentration. Thus, even moderate levels of HIV RNA appear to reflect very active HIV replication in tissue. Decline in plasma HIV RNA concentrations during therapy are strongly associated with a decrease in risk of subsequent disease progression [13]. Despite the strength of plasma viral load quantification as a prognostic and therapeutic marker certain caveats are important:-

(a) Single determinations may be fallacious

(b) Inter assay variability,

(c) Disparity between clinical and virological cure

In view of the above independent predictors of clinical cure, although less powerful than viral load, have been identified and adhered to. These include CD4 counts and if feasible, biological phenotype (syncytium inducing-SI strains) [14].

Changing of therapy

Indications for changing therapy are:

TABLE 1

Pharmacokinetics and other relevant features of antiretroviral agents belonging to three broad groups

	Oral absorption	Elimination	Major toxicity	Dose	Yearly cost
NRTIs (Nucleoside reverse transcriptase inhibitors)					
Zidovudine(AZT) (Retrovir)	Good No interference by food	Renal	Myelodepression	200 mg PO tid 300 mg PO bid 100 mg PO 5/day	1,40,000/-
Zalcitabine(ddC) (Hivid)	Good on empty stomach	Renal(50%)	Peripheral neuropathy	0.75 mg tid	1,05,000/-
Didanosine(ddI) (Videx)	Better on empty stomach	Renal(80%)	Pancreatitis	For > 60 kg 200 mg bid For < 60 kg 125 mg bid	95,000/-
Stavudine (d4T) (Zerit)	Good No food interference	Renal(50%)	Peripheral neuropathy	For > 60 kg 40 mg bid For < 60 kg 30 mg bid	1,20,000/-
Lamivudine(3TC) (Epivir)	Good on empty stomach	Renal (100%)	Peripheral neuropathy	150 mg PO, bid	1,15,000/-
NNRTIs (Non nucleoside reverse transcriptase inhibitors)					
Nevirapine (Viramune)	Very good	Renal(80%)	Fever,rash	200 mg qid x 14 days then 200 mg bid	1,30,000/-
Delaviridine (Rescriptor)	Very good	Renal (50%) Stool (50%)	Rash	400 mg tid	1,10,000/-
Protease inhibitors (PIs)					
Saquinavir (Fortavase)	Better with food	Renal(1%)	Nausea, diarrhoea, dyspepsia	600 mg PO tid	1,70,000/-
Ritonavir (Norvir)	Better with fatty meal	Stool (98%)	Nausea, diarrhoea dyspepsia	600 mg PO bid	3,20,000/-
Indinavir (Crixivan)	Rapid on empty stomach	Stool (80%)	Nephrolithiasis	800 mg PO tid	2,15,000/-
Nelfinavir (Viracept)	Better with food	Stool (87%)	Diarrhoea	750 mg PO tid	2,75,000/-

(a) Treatment failure as suggested by a confirmed rise in HIV RNA level or failure to achieve the desired reduction in plasma viral load, declining CD4 cell count, clinical disease progression.

(b) Unacceptable toxicity of, intolerance of, or non adherence to the regimen

(c) Current use of suboptimal treatment regimens i.e. anti retroviral monotherapy

What to change to?

In the case of treatment failure the guiding principle should be to try and change all drugs in the regimen or at least to include a minimum of two new drugs in the revised regimen. The practice of adding a single drug to a prior insufficiently suppressive regimen is strongly deplored. Thus, failure with two NRTIs + one PI entails switching over to two newer NRTIs and one newer PI, or to two newer NRTIs and NNRTI, or to two newer PIs and one newer NRTI [15].

When to stop therapy?

Stopping anti-retroviral therapy may be the recourse in patients with very advanced disease in whom there is significant drug toxicity that consequently affects the quality of life. However, efforts should be

made to manage drug related toxicity before all therapy is abandoned.

Special Considerations

Perinatal transmission

Without anti-retroviral intervention, 15-35% of infants born to HIV positive mothers [16] will acquire HIV infection through mother-to-child-transmission (MTCT). Reported rates of MTCT differ significantly between developed and developing countries. Breast feeding may be largely responsible for the higher rates in developing countries [17,18]. Zidovudine prophylaxis is recommended for prevention of perinatal transmission of HIV. The regimen followed by American Control Trial Group (ATCG 076) using zidovudine monotherapy aims to intervene at all possible stages of transmission i.e. antenatal, intrapartum, postpartum & neonatal. Zidovudine has consistently resulted in reductions of 65-75% in infant infections with no immediate serious consequences to the mother, infant, or child development during the first two years of life [19]. Zidovudine significantly decreases the likelihood of vertical transmission at all observed levels of maternal HIV viral load [20]. Since no other anti-retroviral drug has yet demonstrated to significantly reduce vertical HIV transmission, zi-

Table 2.

Provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV, by type of exposure and source material:

Type of exposure	Source material**	Prophylaxis+	Regimen##
Percutaneous	Blood \$\$		
	Highest risk	R	ZDV+3TC+IDV
	Increased risk	R	ZDV+3TC +/-IDV#
	No increased risk	O	ZDV+3TC
	Fluid containing visible blood, other infectious fluid* or tissue	O	ZDV+3TC
	Other body fluid e.g. urine	NO	
Mucous membrane	Blood	O	ZDV+3TC +/-IDV \$
	Fluid containing visible blood, other infectious fluid* or tissue	O	ZDV+3TC
	Other body fluid e.g. urine	NO	
Skin, Increased risk \$	Blood	O	ZDV +3TC +/-IDV \$
	Fluid containing visible blood, other infectious fluid* or tissue	O	ZDV+3TC
	Other blood fluid e.g. urine	NO	

** Any exposure to concentrated HIV (e.g., in a research laboratory or production facility) is treated as percutaneous exposure to blood with highest risk.

+Recommend (R), postexposure prophylaxis (PEP) should be recommended to the exposed worker with counseling; Not Offer (NO), PEP should not be offered because these are not occupational exposures to HIV-1; Offer (O), PEP should be offered to the exposed worker with counseling.

Regimens: ZDV 200 mg three times a day; 3TC 150 mg two times a day; IDV 800 mg three times a day (if IDV not available, saquinavir 600 mg three times a day). prophylaxis is given for four weeks.

Possible toxicity of additional drug, may not be warranted

\$\$ Highest risk, both larger volume of blood (e.g., deep injury with large diameter hollow needle, previously in source patient's vein or artery specially involving an injection of source patient's blood) and blood containing a high titer of HIV (e.g., source with acute retroviral illness or end stage AIDS; viral load measurement may be considered, but its use in relation to PEP has not been evaluated); Increased risk, either exposure to larger volume of blood or blood with high titre of HIV; Not increased risk, neither exposure to a large volume of blood nor blood with high titre of HIV (e.g., solid suture needle injury from source patient with asymptomatic HIV infection).

*Includes semen, vaginal secretions, cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluids.

\$For skin, risk is increased for exposures involving a high titre of HIV, prolonged contact, an extensive area, or an area in which skin integrity is visibly compromised. For skin exposures without increased risk, the risk of drug toxicity outweighs the benefit of PEP.

dovudine should be included as a component of any anti-retroviral regimen during pregnancy as far as pos-

sible [16]. Zidovudine regimen used and recommended by US Public Health Service [21] for use in HIV infected pregnant women and their newborn is as follows:-

(i) Oral administration of ZDV 100 mg 5 times daily, initiated at 14-34 weeks of gestation and continued throughout pregnancy.

(ii) During labour, IV administration in one hour loading dose of 2 mg per kg body weight, followed by continuous infusion of 1 mg per kg per hour until delivery.

(iii) Oral administration to the newborn (ZDV syrup) 2 mg per kg every 6 hours for the first 6 weeks of life beginning 8-12 hours after birth.

A recently recommended [17] short course zidovudine regimen (Thailand trial) is as follows:-

(i) 300 mg ZDV PO, bid from 36 weeks gestation until onset of labour.

(ii) 300 mg ZDV PO, every 3 hours from onset of labour until delivery.

(iii) All women counselled about infant feeding options and provided with breast milk substitutes if they choose not to breast feed.

Postexposure Prophylaxis for health care workers (HCWs)

HCWs are potentially at risk for HIV infection through occupational exposure. The estimated risk for HIV infection after a percutaneous exposure to HIV infected blood is 0.3% [22]. After controlling for all factors associated with HIV transmission risk in HCWs in a large study [23], use of zidovudine prophylaxis reduced HIV transmission by 79%. In view of the proven disregard for zidovudine monotherapy, the recommendations (in detail) for chemoprophylaxis after occupational exposure to HIV, by type of exposure and source material are presented in Table 2 [24,25].

Conclusion

Starting anti-retroviral therapy is a major decision and careful thought and consideration are needed by both patient and physician if success is to be achieved. Several factors would determine the common ground on which individual patient would make an informed decision on his/her willingness to start therapy. These factors would include regimen adherence, cost, tolerability, psychological morbidity, and limitation of future therapeutic options in patients commencing early treatment. Physicians and patients when considering therapy must set realistic and achievable therapeutic

goals.

Further advances will ensue and recent advances are to be applauded. We anticipate further updates will be forthcoming and many caveats will be filled up. One such caveat is anti-retroviral prophylaxis for high risk sexual exposures on which Centre for Disease Control (CDC), Atlanta is in the process of developing recommendations. However, in view of increasing complexity of treatment it is imperative that all clinicians involved with the care of HIV infected patients continue to remain abreast of a rapidly changing knowledge base. Guidelines are useful summary statements of current knowledge and thinking and cannot substitute a well informed clinician fully aware of current data and their interpretation.

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