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CONCEPTS OF ANTI-HIV THERAPY & ITS APPLICATIONS IN RESOURCE POOR SETTINGS

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ABSTRACT

HIV since its invention has become global burden. In last two decades of the HIV prevalence many anti-retroviral drugs have been developed. Poor countries like India have started central government funded programmes to tackle the menace of the HIV. These programmes have been started because many people cannot afford costly ART drugs. In this review article, we have discussed current ART regimens and the new drugs which have been introduced. Also we have discussed traditional systems of medicine which are practised in India and their potential use in the HIV treatment.

INTRODUCTION: Today, the biggest & toughest challenge in front of the global medical & non-medico community is to control & treat rapidly growing HIV/AIDS cases. In spite of global efforts on public health strategies, treatment options this disease is spreading like wildfire. This worst epidemic can be explained in terms of following figures. In 1981 first AIDS case was reported in USA. Globally 34.4 million people were living with HIV by the end of 1999 of whom 8, 00,000 are from Asia. 18.8 million people have died of AIDS since the beginning of the epidemic. 2.8 million people died of AIDS in 1999, among them 1.1 million are men, 1.2 million women and 5,00,000 children. In Asia first AIDS case was reported in 1984. In this disease more than 95% of infected persons are above 15 years. Among the total number of AIDS cases reported from Asia, more than 95% are from Thailand, India and Myanmar.

Since, the HIV was first identified as the cause of AIDS enormous research efforts have concentrated on identifying & developing compounds to suppress its replication. In 1987, Zidovudine was approved by the USFDA. In the years that followed, four other drugs of the same family were introduced.

The principle problems with these drugs of including ZDV, is their limited potency' their toxicity and their time- limited benefit- largely due to the development of resistance.

Large muticentre clinical trials then showed that double therapy with two of these drugs was superior to monotherapy in terms disease progression & survival. Significantly larger reductions in viral load were achieved by adding new class of drugs i.e. the protease inhibitors that became available in early 1996. Over the past two years the number of antiretroviral agents has expanded substantially. Trials of newer drugs particularly in the triple therapies have shown reduction in both morbidity & mortality. They offer real hope for Patients Living with HIV AIDS (PLWHA) of a longer & better life.

The recent research data indicates that even with sustained suppression of HIV replication, there are still reservoirs of HIV in patients under treatment. Viable virus has been retrieved from subjects taking adequate triple therapy for up to two years. The incidence of resistance is very high even in those with good adherence to regimen.

In recognition of these limitations, we should explore alternatives to triple therapies i.e. quadruple therapy & newer compounds with ARV activity. All these approaches are in a rapid state of evolution as newer facts evolve, results are becoming available.

The use of AZT to prevent mother to child transmission of HIV was demonstrated way back in 1994. This drug reduces the transmission by 50-70 %.

In spite of all these developments in overcoming the holocaust of HIV disease, the resource poor nations are battling at the primary level of improving the access of PLWHA to ARV drugs. The management of HIV has become more complex in view of the ethical & humanitarian issues surrounding the PLWHA. There have been many arguments over the risk faced by the HIV healthcare workers & its prevention. Much has been discussed, debated & predicted about the likely possibility of a HIV vaccine. But we need to wait for a few years before this dream become reality[1, 2]

Aims & Objectives: We intend to discuss the obstacles in getting access to ARV drugs & Measures to be taken for overcoming them. We also present a brief overview of newer drug options in management of HIV.

Epidemiology of HIV in India: HIV epidemic in India is concentrated in nature. The HIV prevalence among the High Risk Groups, i.e., Female Sex Workers,Injecting Drug Users, Men who have Sex with Men and Transgenders is about 20 times higher than the general population. Based on HIV Sentinel Surveillance 2008-09, it is estimated that India has an adult prevalence of 0.31 percent with 23.9 lakh people infected with HIV, of which, 39 percent are female and 3.5 percent are children. The estimates highlight an overall reduction in adult HIV prevalence, HIV incidence (new infections) as well as AIDS related mortality in India. It is estimated that India had approximately 1.2 lakh new HIV infections in 2009,

The total number of people living with HIV/AIDS (PLHA) in India is estimated at 23.9 lakh (19.3 – 30.4 lakh) in 2009. Children under 15 yrs account for 3.5 percent of all infections, while 83 percent are the in age group 15-49 years.

ARV drugs & Developing Nations: The treatment of HIV is still difficult in view of various issues as; morphology of the virus, availability & cost of drugs, adverse drug reactions, ethical & counselling issues, lack of training to medical staff, presence of wide north-south gap [Developed & developing nations divide] etc. In order to protect the future of mankind we need to strive hard to get a better therapeutic strategy to stop this disease spread.

Developed world scientists have easy access to most new anti-retrovirals compounds. But in resource poor settings the common problems encountered are:

1. Poor access to ARV drugs.
2. High cost of therapy.
3. Poor patient compliance.
4. Inadequate infrastructure for patients' monitoring/hospitalisation.
5. Lack of sound Training of HIV activists/physicians.

Traditional/Complimentary system of Medicine: The Traditional/Complimentary system of Medicine still a big hope to the patient community of HIV. For people living with HIV/AIDS, traditional system of medicine offers many products that can be useful for dealing with common symptomatic aliments of HIV infections. It is unfortunate that many people still look to traditional system of medicine mainly in terms of producing a magic bullet to cure HIV. In reality this system of medicine offers a wide array of techniques that can be successfully incorporated in management of HIV.

Traditional medicines are available as bewildering choices & techniques. One way of evaluating these options is to ask "SANE" questions; This includes Safety, Affordability, Need & Efficacy. There are therapies worth exploring such as Acupressure, Acupuncture, Chiropractic, Massage, Meditation, Medicinal plants, Yoga, Homeopathy, Orthomolecular medicine, Aromatherapy etc.

These type of therapies are widely employed method of HIV care in countries like INDIA. This is due to the following factors: [3]

1. Low cost
2. Easy access
3. Locally available compounds/methods.
4. Ease of Administration.
5. No potential Adverse Drug reactions.
6. Faith value.

But this system of medicine has potential failure in control of AIDS/HIV due to;

1. Lack of adequate scientific data.
2. No efficacy records available for particular therapies.
3. Spread of Quacks in isolated areas.
4. No uniform methods to monitor patient health progress to confirm results.

Many traditional & alternative systems are tricky, overlapping with religious & philosophical systems & embedded in peoples daily activities. India's Ayurveda, for example means "Science of Life" & consists of many therapeutic modes as well as advice on lifestyle. In Indonesia, medicinal plant preparations called "Jamu" are taken as daily tonics & sold by vendors like food or beverages. In Thailand traditional medicines are taught in Buddhist temples. Even within one country there are many variations in implementation of these systems. After trying hard options from allopathy, Western world is focussing its attention on traditional medicines & its scientific development. One will not wonder if this system of medicine would one day offer a concrete & scientific solution for care of HIV.

Present Therapeutic idea/concept of Rx of HIV: [Module of UNAIDS 2000]

Currently available Anti-retroviral drugs: Current anti-retroviral agents for HIV/AIDS can be divided into two major classes of drugs: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). RTIs are further divide into nucleoside (NRTI) and non-nucleoside (NNRTI) subclasses. A third class, integrase inhibitors, is under development, as are drugs with other mechanisms of action (e.g. Hydroxyurea, chemokines and interleukin 2 [4]. The newer class of drugs called integrase inhibitors is under development.

Eleven antiretroviral agents are currently available in different parts of the world. Registration of drugs differs from country to country. Ten of these agents have been shown to be useful in the treatment of HIV/AIDS by slowing the progression of the disease and prolonging survival. **Table 1** lists the currently available agents, by brand name, class and estimated market cost, based on US pricing.

TABLE 1: CURRENTLY AVAILABLE ANTI HIV AGENTS

Generic Name	Brand Name *	Class	Unit dose	Cost: Three months/US$ **
Didanosine (ddI)	Videx	NRTI	100mg	420-700
Lamivudine (3TC)	Epivir	NRTI	150mg	690
Stamivudine (d4T)	Zerit	NRTI	40mg	700-730
Zalcitabine (ddC)	Hivid	NRTI	0.75mg	630
Zidovudine (ZDV)	Retrovir	NRTI	100mg	720-860
Indinavir	Crixivan	PI	800mg	1350
Nelfinavir	Viracept	PI	250mg	1670
Ritonavir	Norvir	PI	600mg	2080
Saquinavir	Invirase	PI	600mg	1720
Delavirdine	Rescriptor	NNRTI	100mg	
Nevirapine	Viramune	NNRTI	100mg	740

* Brand names may vary between countries, ** ranges reflect dosing variations

The cost of ARV therapy: The costs of providing ARV therapy fall into two major categories: Drug costs; and Costs associated with safe and effective use.

The costs of the drugs are shown in **Table 2**. These are largely derived from USA sources, so it is important to note that under market conditions the costs of drugs may be significantly higher in developing countries. Double combination therapies range in costs from US$ 4836 to US$ 9276 per year, while the triple combination therapies range from US$ 7944 to US$ 11916, increasing to up to US$ 17,580 if ritonavir is added. Country –specific data on these costs needs to be assembled wherever possible.

TABLE 2: ANTI-RETROVIRAL DRUG COSTS (US$) AT MARKET PRICES IN 1999

Drug and dosage required	Monthly cost	Annual cost
Zidovudine (ZDV) 250 mg BD	228	2738
Didanosine (ddI) 200 mg BD	175	2102
Zalcitabine (ddC) 0.75 mg TDS	220	2640
Stamivudine (d4T) 40 mg BD	232	2788
Lamivudine (3TC) 150 mg BD	214	2572
600 mg BD	692	8308
Saquinavir 600 mg TDS	545	6540
Indinavir 800 mg TDS	533	6400
Nevirapine 100 mg BD	272	3260
Double combination therapies	403 to 773	4836 to 9276
Triple combination therapies	662 to 993	7944 to 20224

TABLE 3: PARTNERS IN ARV INTERVENTIONS. FOR OPTIMUM CARE OF PLWHA WE NEED A COMPREHENSIVE HIV CARE POLICY FORMED BY FOLLOWING PARTNERS

Partners	Roles
PLWHA support groups	Disseminate information, Develop support and counselling services, Maintain drug adherence
Community based organisations	Disseminate information, Social, emotional, spiritual support, Home care
NGOs	Disseminate information, Counselling and clinical support
Private sector	Disseminate information, Regulate existing use of ARV & referrals
Pharmacies/Pharma Industry	Correct information provision, Follow up dispensing and early referrals, Providing ARV drugs at subsidised rates

TABLE 4: EXAMPLES OF TRIPLE THERAPY REGIMENS INCLUDING A PROTEASE INHIBITOR. TABLE 4 ENUMERATES VARIOUS ARV DRUG COMBINATIONS USED IN DIFFERENT SETTINGS

Initial Regimen	Alternative Regimen
ZDV + 3TC + PI_1	d4T + ddI + PI_2 Ritonavir + Saquinavir + NRTI
d4T + 3TC + PI_1	ZDV + ddI + PI_2 Ritonavir + Saquinavir + NRTI
ZDV + ddI + PI_1	d4T + 3TC + PI_2 Ritonavir + Saquinavir + NRTI
d4T + ddI + PI_1	ZDV + 3TC + PI_2 Ritonavir + Saquinavir + NRTI

TABLE 5: PREDICTING THE EFFECTIVENESS OF SWITCHING THERAPY. AS PER THE UNAIDS GUIDELINES FOLLOWING METHODS HAVE BEEN SUGGESTED TO EVALUATE/PREDICT THE EFFECTIVENESS OF ANTI-HIV THERAPY

Switching combinations	Likely effectiveness
Switching NRTI combinations	
ZDV + 3TC → d4T + 3TC	Probably not effective
D4T + ddI → ZDV + 3TC	May be effective
ZDV + ddI → d4T + 3TC	May be effective
ZDV + 3TC → d4T + ddI	May be effective
Switching protease inhibitors	
Nelfinavir → Ritonavir / Saquinavir	May be effective
Ritonavir / Saquinavir → Nelfinavir	May be effective
Ritonavir / Saquinavir →	Probably not effective
Indinavir→ Ritonavir / Saquinavir	May be effective
Indinavir→ Nelfinavir	Probably not effective
Nelfinavir→ Indinavir	Probably not effective

All these antivirals come with a price to pay, i.e. the potential adverse reactions[ADR]. ***Table 6 shows common ADR's to ARV drugs,***

TABLE 6: ANTIRETROVIRAL DRUGS, MAIN ADVERSE REACTIONS AND FOLLOW-UP ACTION / TESTS

Drug	Adverse reactions	Follow-up action / tests
Nucleoside Reverse Transcriptase Inhibitors		
Zidovudine (ZDV, 3'-azido-2',3'-dideoxythymidine	-initial headache and nausea usually temporary -anaemia, leucopenia (neutropenia) -myopathy	-clinical examination -blood count including differential - CK
Didanosine (ddI, 2',3'-dideoxyinosine)	-gastrointestinal disturbances -polyneuropathy (long term treatment) -pancreatitis	-clinical examination -clinical examination -amylase
Lamivudine(3TC)	(few)	
Zalcitabine (ddC,)	- -ulcerative stomatitis -pancreatitis	-clinical examination -clinical examination -amylase
Stamivudine (d4T, 2',3'-didehydro-deoxy-thymidine)	-peripheral polyneuropathy (common) -abnormal liver function tests (LFT) -pancreatitis (rare)	-clinical examination -liver enzymes -amylase
Nucleoside Reverse Transcriptase Inhibitors		
Nevirapine	-skin rash (common) -elevation of liver enzymes	-clinical examination -liver enzymes
Delavirdine	-skin rash (common) -abnormal LFT	- -liver enzymes
Protease inhibitors		
Indinavir	-nausea, gastrointestinal disturbances, headache, dry skin -elevation of bilirubin -kidney stones/ flank pain -diabetes mellitus (rare) - haemolytic anaemia (rare) - liver dysfunction (rare)	-clinical examination -urinary dip tests (glucose, erythrocytes) -bilirubin, liver enzymes
Ritonavir	-nausea, gastrointestinal disturbances -paraesthesias -elevation of serum levels of liver enzymes, urate, glutamyl-transpeptidase (GT), creatinine kinase (CK), triglycerides - diabetes mellitus (rare)	-clinical examination -clinical examination -analysis of serum levels of: liver enzymes, urate, GT, CK, triglyceride -analysis of glucose in urine
Nelfinavir	-gastrointestinal disturbances (around 20% of patients) -hyperglycaemia and lipodystrophy	-clinical examination -analysis of glucose in urine -liver enzymes

Antiretrovirals in Pregnancy: Antiretroviral therapy in pregnancy, both in long course and short course regimens, has been shown to significantly reduce the rate of mother-to-child transmission for non-breast feeding mothers. The combined effects of ARV treatment, elective caesarean section, and formula feeding (or other combinations of alternative obstetric and infant feeding practices) are still to be determined. Short course ARV treatment, with ZDV alone has been shown to be effective in a non-breast feeding population [5].

Post exposure prophylaxis (PEP): Is this the hope for future high risk population?

Effectiveness of antiretrovirals for POST EXPOSURE PROPHYLAXIS: Today we know that ZDV taken after exposure to HIV can reduce risk of HIV infection post exposure. The CDC study is the only study, so far, to demonstrate effectiveness of ARV treatment as post exposure prophylaxis. In a study by UNAIDS, including 31 cases of seroconversion and 679 controls (exposed people who had not seroconverted); the exposures

had occurred between 1988 and 1994. Nine cases (29%) and 246 controls (36%) had taken ZDV. The dose in most cases was 1000 mg ZDV per day for 3 to 4 weeks. Having taken ZDV was a significant factor related to reduction of infection risk (adjusted OR 0.19-95% CL:0.06-0.52). The results show that taking into account other factors, the risk of transmission was reduced by 79% (95% CL 43-94%) for those who took ZDV [6]. Therapeutic protocol of administration of anti-HIV drugs after occupational exposure: Where does the developing nations stand?

A. **Timing of initiation of Treatment**: In most industrialised countries which have made recommendations, the optimal delay is extremely short, 2-4 hours. However, with the exception of Denmark, which recommends a maximum delay of 24 hours to a start treatment, there is no time limit in most country recommendations. Prophylaxis is sometimes given empirically up to 2 weeks in the case of severe exposure when the delay has been unavoidable.

B. **Therapeutic Regimen:** So far, ZDV is the only regimen for which data on efficacy exist. However, double or triple therapy are now being used for post exposure prophylaxis on an empirical basis in industrialised countries.

The combination and the recommended doses, in the absence of known resistance to ZDV or Lamivudine in the source patient are:

ZDV 250-300 mg twice a day OR Lamivudine 150 mg twice a day.

The protease inhibitor recommended on the basis of its acceptable tolerance and limited drug interactions is, indinavir in the dose of 800 mg 3 times a day.

In developing countries, where ARVs are not widely used and the source patients are therefore likely to be ARV naïve, ZDV monotherapy for post exposure prophylaxis is a valid option. The recommended duration of treatment is four weeks, based on the results of the CDC case control study. However, the optimal duration has never been evaluated. Certain countries propose minimum treatment of two weeks and maximum four weeks [7].

Anti-HIV drugs & the Price factor: There are many hurdles in using above range of anti-retrovirals for example severe adverse effects, high cost, non-availability, poor patient compliance, inadequate training of medical & paramedical staff etc. For developing nations like India the high cost of anti-retrovirals is still a major hurdle for all of us to overcome. This factor has eliminated the huge population of PLWHA form the treatment group. **So there is urgent need to review the cost-factor of ARV in public health sector policy:**

Here the complex issue of price control can be resolved by a uniform policy formed by,

A. International AIDS agencies like WHO, UNAIDS, IAS, UNDP.

B. Pharma industry.

C. Funding agencies.

D. Representatives of PLWHA.

E. NGO community .

Improving Access to Drugs: Multipronged strategies to improve access of PLWHA form resource poor nations thus emerge as a effective way to close the Bridging the north-south devide. This in summary includes;

- Integrate medical training of HIV activists
- Local level nation-wide CME programmes.
- Treatment funding should filter down to the grass root level.
- Pharma industry should lower down the profit margins to reduce total cost of therapy.
- Free ARV distribution from Government hospitals.
- Private hospitals should collaborate with Government to provide low-cost/free ARV therapy on quota system.

Monitoring the Impact of Currently employed Better-access strategies for better future of PLWHA:

- Follow up records of all Pharmacotherapeutic aspects of ARV's.

- Track down missing patients for finding out the cause of discontinuation of therapy.

- Adequate care of Adverse drug Reactions. ARV drugs are known to cause potential adverse reactions. This may be the cause of discontinuation of therapy.

- Improving the patient-compliance factors. This issue concerns to all over the world population of HIV. Poor compliance could be due to illiteracy, poor resources, complex schedule of ARV drugs administration, high cost etc.

- Exchange programmes of scientists, doctors, AIDS activists etc between

Developed & Developing nations. This very crucial for understanding the geographical barriers & demographic patterns.

Recent Advances in HIV treatment: New additions to the existing classes of drugs;

1. **New Nucleoside Reverse Transcriptase Inhibitors**:

Apricitabine (SPD-754): It is Active against NRTI-resistant HIV-1, including virus lamivudine resistant virus. Its side effects are Nausea, headache, dizziness, fatigue. It is currently in Phase III Clinical trial.

Elvucitabine: It is similar to lamivudine and may be effective in treating individuals infected with to lamivudine resistant HIV strains. Its adverse events are serious bone marrow suppression, Rash, headache and gastrointestinal symptoms. It has completed phase II Clinical trial.

KP-1461: It accelerates Viral Decay by increasing the rate at which HIV mutates when it replicates, so that the virus soon becomes too deformed to survive. KP-1461 performs this task by inserting faulty elements into HIV's genetic code. it is less vulnerable to drug resistance. It is in phase II trials

Festinavir (OBP-601): It is a NRTI related to stavudine but with less associated toxicity. It is shown to be active against multidrug resistant HIV strains. It is currently in Phase I trials.

Reverset (D-D4FC): It shows activity against wild-type HIV-1 and HIV-2. It has activity against virus resistant to lamivudine, zidovudine and other NRTIs. It is currently in Phase II trials.

Lodenosine: It is Effective against multi-NRTI resistant viruses. It is currently in phase II trials.

Racivir: it is active against HIV and hepatitis. Racivir shows anti HIV activity that lasts more than 2 weeks after the drug is stopped. It is currently in Phase II trials.

2. **New Non nucleoside reverse transcriptase inhibitors**:

Rilpivirine: It was Approved by FDA in May 2011. It is administered once-daily and taken in combination with other drugs. It is Effective in lowering viral load as another NNRTI, efavirenz. Rash, nervous system disorders, psychiatric events, and lipid abnormalities are its main side effects.

Lersivirine: It shows similar effectiveness in reducing viral load as efavirenz. It is effective against HIV with a certain mutation (position Y181), unlike efavirenz, etravirine and nevirapine. Its main adverse events are nausea and gastritis. It is currently in Phase II trials.

Emivirine, Capravirine & Dapivirine: Trials for these drugs were discontinued since they showed no benefits in people with NNRTI resistant viruses.

3. **New Protease inhibitors:**

CTP-518: It is a novel HIV protease inhibitor which is formed by replacing certain key hydrogen atoms of Atazanavir with deuterium. The presence of deuterium slows hepatic elimination, resulting in a longer drug half-life and higher trough levels without the use of a boosting agent, such as ritonavir. It is currently in Phase II clinical trials.

Other New Protease Inhibitors: PD 178390, AG1776, TMC-310911 these drugs are active against protease inhibitor resistant viruses. They are in early human studies.

New Classes of antiretroviral drugs:

1. **Integrase inhibitors (41)**: The mechanism of action of these drugs is to inhibit integration of viral DNA into the host cell DNA.

Elvitegravir: It requires a small dose of the drug ritonavir to boost its effectiveness. It is proposed to be used in combination with the new ritonavir derivative GS-9350. Combination of these tablets may be suitable for once-daily dosing. These two compounds, along with tenofovir/FTC, are part of a new once-daily, 4-in-1 "quad pill" that is currently being studied as initial therapy.

Dolutegravir: It is efficient against raltegravir-resistant HIV. Phase IIB clinical trials of this drug are underway to support dolutegravir in combination with abacavir and lamivudine.

2. **Entry inhibitors (41):** Mechanism of Viral attachment and entry into the host cell:

- Virus gets attached to the CD4 receptor on the surface of a cell. After that it binds to either of the co-receptors i.e. CCR5 or CXCR4. Finally fuse with the cell membrane, releasing viral components into the cell. Current novel antiretroviral drugs aim to interfere with the crucial HIV entry steps:
    - Viral attachment
    - Co-receptor binding
    - Fusion

Attachment inhibitors:

PRO-542: Binds to the viral gp120 and thus prevent the virus from interacting with CD4- bearing host cells. The drug is well tolerated and causes acute reduction in HIV-1 RNA.

Co-receptor binding inhibitors (41):

Vicriviroc & Aplaviroc: They are CCR 5 Antagonist which are Superior to Maraviroc in treatment-experienced patients. Aplaviroc development was halted after phase III trials because of potential toxic effects on the liver and Vicriviroc is in phase III trials.

Cenicriviroc (TAK-652): It is an Inhibitor of CCR2 and CCR5 receptor which prevents the virus from entering into a human cell. It also acts as an anti-inflammatory. It causes Significant reductions in viral load and its effect persisting up to two weeks after discontinuation of treatment.it is undergoing Phase II clinical trials.

PRO 140: Genetically engineered antibody against CCR5 receptor. It binds to extracellular domain of CCR5 and acts as a direct competitive inhibitor of HIV binding. Though PRO 140 requires parenteral administration, the interval of administration is long enough to be reasonably convenient. It is currently in Phase III trials.

Ibalizumab: It is a humanized monoclonal antibody of murine origin against CD4 receptor. It binds to the interface between domains 1 and 2 of CD4, away from the binding site for MHC class II molecules. It causes post-binding conformational effects that prevent CD4-bound gp120 from interacting with CCR5 or CXCR4. It is currently in phase II trials.

AMD070: It blocks the CXCR4 co-receptor. AMD070 has shown promising antiviral activity in early clinical studies, with good BA and a favorable PK. It is associated with elevated white blood cell counts and tachycardia

New Fusion Inhibitors [44]:

Cyanovirin-N, Sifuvirtide, TRI-11 [44]: Pharmacokinetic data suggests that they can be administered less frequently than enfuvirtide and have high genetic barrier resistance.

Histone deacetylase inhibitors [43]:

MOA: DNA warps around histones which is cleaved by proteasomes for transcription

Acetylation of lysine residues causes increase in spatial distance between DNA & histones which in turn increases transcription activity.Acetyl group deacetylated by Histone Deacetylases (HDACs).

Vpu Ion Channels Inhibitors (43): Vpu channels have 2 important functions :

- virion assembly and release
- CD4+ degradation.

Inhibitors of the Vpu ion channel are effective at interfering with viral replication in macrophages, a reservoir not targeted by currently available drugs.

The lead compound, BIT225, showed potent antiretroviral activity in preclinical stage

TAT antagonists [43]**:** Tat gene (Transcriptional activator) responsible for elongation of viral DNA

- 4-Phenylcoumarins
- BI-201
- Ro 24-7429

These three molecules are in priclinical stage

New FDC: Quad pill [42]**:**

- Four drugs are incorporated into one pill: They are
  - Elvitegravir (150mg/day)
  - Cobicistat (150mg/day)
  - Tenofovir (300mg/day)
  - FTC(200mg/day)

It is in Phase III clinical trial. It causes rapid reduction in HIV RNA load.

No serious adverse rection has been reported with its use.

CONCLUSIONS: As we are aware, there is tremendous development going on in identifying & applying newer compounds/molecules for combating HIV. This is a major topic of research in industrialised nations. But for resource poor nations PLWHA getting access to primary drugs Anti-HIV drugs is a big hurdle. The high mortality of AIDS patients in Asian & African continent shows that most people loose the battle against HIV due to non-affordability factor.

ZThere is no denying that the north-south gap still exists. This applies to both in terms of availability of ARV's to patients and in view of the knowledge & experience of medical & paramedical community. Inspite of Herculean efforts by the IAS, WHO, UNAIDS we are still lagging behind on this issue of access to drugs. It is the duty of all of us to try various options available to overcome this.

Development of HIV-vaccine will be pathbreaking step in our fight against AIDS/HIV control. But trials of HIV vaccines are in controversy with many issues like ethics, use of Asian population as guinea pigs by developed nations, time barrier-constraints etc. Till such as vaccine becomes available our hopes are dependent on administration of antiretrovirals.

Antiretrovirals are associated with many hurdles but availability & cost are primary issues related to our population.

We suggest a separate platform preferably organised by IAS like agencies where all aspects pertaining to this issue should be addressed & solved. Efforts should be made to form a uniform policy together by Scientists, Doctors, AIDS activists, Government, Funders, NGO community & Pharmaceutical industry. We suggest there should more stress on CME/ Conferences/ workshops at local level in resource poor nations. This will improve the skills, knowledge, awareness of participants from poor zones. These programmes can upgrade our knowledge of Anti-retrovirals as well as latest concepts in development of Anti-HIV vaccines.

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