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Current concepts in management of HIV in adults

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Abstract
The human immunodeficiency virus remains a global health problem since its discovery in 1983. The number of people living with HIV in India is estimated to be a little over 21 lakhs. Paucity of resources and manpower make the management of this disease a greater challenge in our country. In September 2015, the World Health Organization made its recommendations based on several peer reviewed sources and studies which stated that anti-retroviral therapy must be initiated for all patients, irrespective of CD4 counts. UNAIDS estimated that early ART might avert 28 million AIDS related deaths and prevent 28 million infections across all age groups by 2030. Various guidelines have been instituted for effective management. This article aims to consolidate current concepts for management of HIV/AIDS and also give a glimpse into future research in the field of management of HIV/AIDS.

Keywords: HIV, AIDS, ART, opportunistic infections, vaccine

Introduction
The human immunodeficiency virus remains a global health problem since its discovery in 1983. The people living with HIV in India is estimated to be a little over 21 lakhs. Various guidelines have been instituted for effective management. Keeping up to speed with changing recommendations and rapid advances, is challenging, even for the most astute clinician. Paucity of resources and manpower make the management of this disease a greater challenge in our country. This article aims to consolidate current concepts for management of HIV/AIDS.

When to start anti-retroviral therapy?
In September 2015, the World Health Organization made its recommendations [(1)] based on several peer reviewed sources and studies (the START trial and TEMPRANO, to name a few) which stated that anti-retroviral therapy must be initiated for all patients, irrespective of CD4 counts. This was based on the finding that early initiation of therapy resulted in lower rates of mortality and morbidity due to both serious AIDS related and serious non-AIDS related causes. Additionally, no significant increase in drug related adverse events due to early ART was found. The quality of evidence for initiation of ART in the 1-10 years' age group, was, however, less compelling. Nevertheless, the UNAIDS estimated that early ART might avert 28 million AIDS related deaths and prevent 28 million infections across all age groups by 2030. Earlier in 2013, a study [2] showed that in patients with a CD4 of 351-500, the deferral of anti-retroviral therapy was associated with an increase in the risk of death by 69%. This was attributed to earlier control of viral replication and viral diversity and faster immunological recovery. Analysis of the CD4 trajectory in patients with recent HIV infection showed that patients who started early ART (<4 months after HIV infection) had a faster spontaneous rise in CD4 (about 200 cells/micro litre on an average) and a much slower decline in CD4. For each month of delay in starting of ART, there was a progressive reduction in the chances of CD4 + T cell recovery by 10 %. Furthermore, starting therapy at progressively higher CD4 counts has shown to lower the risk of some toxic effects associated with anti-retroviral therapy. Early ART initiated also prevents neurocognitive declines, increases chances of CD4 normalisation, and lowers the risk of development of IRIS [3]. As on date, we have enough data to suggest that all PLHIV should be started on ART. Anti-retroviral therapy must be started for all patients irrespective of WHO clinical stage and CD4 status [1, 4]. This applies to pregnant and breastfeeding females as well. The long-term feasibility, cost-effectiveness and implementation consideration in our resource limited setting needs evaluation. While the recent recommendations include a greater percentage of people living with HIV into the ART umbrella, the importance of commencing ART for patients with advanced disease or low CD4 still remains a priority [5].

Pre-treatment evaluation
A detailed history and physical examination is essential to assess baselines status. Unearthing of co-existing infection may also be possible on history and examination alone. The patient's nutritional status, family and household structure and understanding of HIV/AIDS must also be assessed [5].
Baseline laboratory evaluation aims to assess stage of the disease, rules out concurrent infections and determines baseline safety parameters. These include a complete haemogram, liver and renal function tests, VDRL, CD4 count and a plain chest radiograph [3, 5]. Additional tests such as sputum examination, USG abdomen and CSF analysis may be carried out based on the physician's discretion, based on the clinical presentation. Special tests like surface antigen for hepatitis B or Anti HCV may be undertaken if ALT > 2 ULN.

PAP smear and fundus examination may also be undertaken. CD4 must be evaluated once every 06 months. Special investigations like HLA B5701 prior to ABC or coreceptor tropism prior to prescribing Maraviroc may be taken up on a case to case basis [6]. Their cost and availability generally preclude their frequent use in a major fraction of our patients. Tests for monitoring purpose are summarised in Table -1. With the possible exception of baseline evaluation, initiation of ART must never be delayed pending these investigations [5].

Table 1: Tests for monitoring

AZT based regimen	Hb at 15 days, and every month for initial 03 months.
TDF based regimens	Serum creatinine every 06 months
NVP based regimens	ALT at 15 days, 30 days and then every 06 months
EFV based regimen	Lipid profile yearly
PI based regimen	Blood sugar and lipid profile every 06 months

Antiretroviral Therapy

The goals of antiretroviral therapy are summarised in Table 2. The ART team must counsel all patients prior commencing ART regarding the importance and implications of adherence and follow up. They should be briefed about the manifestation of commonly occurring OI and counselled regarding seeking attention early, if such symptoms should occur. Adequate information must also be provided about possible drug toxicities and other ADR. All patients must undergo at least two counselling sessions before ART is started. It must be understood by every care giver in this realm, that the news of being seropositive is devastating. In India, the disease has major social and familial implications. Employment, marriage and family dynamics are all significantly affected at the revelation of having this disease.

Table 2: Goals of Antiretroviral therapy

Clinical goals: Improving survival and overall quality of life
Virological goals: Greatest possible reduction in viral load for as long as possible
Immunological goals: Immune reconstitution that is both quantitative and qualitative
Therapeutic goals: Minimizing toxicity while maintaining above goals

Opportunistic infections must be managed effectively before starting ART [7]. Tuberculosis, pneumocystis carinii pneumonia, invasive fungal infections like candidiasis, cryptococcal meningitis and bacterial pneumonias must be managed as per existing recommendations prior starting ART. A general consensus is to allow two weeks after starting anti-tubercular therapy in patients with evidence of the disease. Notable exceptions to concept of treating OIs first include Mycobacterium avium complex and progressive multifocal leukoencephalopathy. In these cases, commencing ART is the preferred therapy. Additionally, conditions which preclude absorption of ART, like severe diarrhoea, must be tackled effectively before ART is exhibited.

The anti-retroviral drugs available are summarised in Table 3. National and international guidelines, with numerous meta-analyses suggest that the backbone of first line anti-retroviral therapy is Lamivudine (3TC) and Tenofovir (TDF) [5, 8]. Western literature recommends the widespread use of Emtricitabine (FTC) in the first line arsenal, something that has not translated into clinical practice in India. The use of FTC (and INSTIs, see below) in first line ART is clearly limited by its cost (in combination with Tenofovir disoproxil fumarate) with monthly costs exceeding 2000 INR per patient.

Table 3: Antiretroviral drugs

NRTI
Lamivudine (3TC)
Zidovudine (AZT)
Emtricitabine (FTC)
Abacavir [9]
Didanosine
Stavudine (d4T)
NNRTI
Efavirenz (EFV)
Nevirapine (NVP)
Delaviridine (DLV)
Etravirine [10]
Rilpivirine (RPV)
Doravirine
Nucleotide Analogues
Tenofovir disoproxil
Tenofovir alafenamide
Protease Inhibitors
Lopinavir (LPV)
Indinavir (IDV)
Nelfinavir (NFV)
Saquinavir (SQV)
Atazanavir (ATV)
Darunavir (DRV)
Tipranavir (TPV)
Integrase Inhibitors
Dolutegravir (DTG)
Elvitegravir (EVG)
Raltegravir
Pharmacokinetic Boosters
Cobicistat
Ritonavir
Entry Inhibitors
Maraviroc
Experimental Agents
Romidepsin (HDAC inhibitor)
CROI 2016 (Attachment inhibitor)
Disulfiram (activator of latent HIV infected cells)
IL-21 based therapy
Miltefosine
Portmanteau inhibitors

Second generation NNRTIs, Etravirine and Rilpivirine (approved in 2008 and 2011, respectively) are more potent, have a safer side effect profile and longer half-life when compared to the first generation NNRTIs (which were incidentally the first class of drugs against HIV). However, Rilpivirine was found to have a higher rate of virologic failure in combination with TDF and FTC when used in patients with baseline HIV viral load > 100,000 copies /mm3. As a result, its use is limited in patients with HIV viral load less than 100,000 copies/mm3. HIV viral load estimation is not routinely recommended by NACO. Making a decision in the given clinical scenario in the absence of routine HIV viral

load testing is difficult. This has made the use of second generation NRTIs limited in our context.

Integrase strand transfer inhibitors (INSTIs) have found their way into several first line regimes [6, 11]. Their mechanism of action is based on inhibition of fusion of the pre-integration complex with the host DNA. In November 2015, the US-FDA approved the combination of Elvitegravir, Cobicistat and Tenofovir alefenamide and FTC for treatment on ART naïve patients. The CDC recommends Dolutegravir, Abacavir and Lamivudine (after testing for HLA B5701 to preclude life threatening allergic reactions secondary to Abacavir) [8] The combination of FTC, TDF and Elvitegravir and Cobicistat (available worldwide as STRIBILD) as the quintessential first line combination has won several notable proponents in the past few years. However, this combination can only be used in patients with pre ART CrCL >70 ml/minute. As of January 2016, four of the five first line ART regimes for treatment naive patients are INSTI based [8].

In clinical practice, the first line regimen must be chosen on the basis of patient profile with due consideration to factors like presence or absence of OIs, baseline haemogram, renal and liver parameters, concurrent illness like Hepatitis B or C and cost and availability. The absence of recommendations on INSTI based regimes by NACO [5, 12] and other regulatory authorities in our country means that we must continue to adhere to the status quo. As mentioned before, cost and availability are great modifiers in modern clinical practice, especially in resource limited settings.

The First Line

A combination of two NRTIs (with one of them always being Lamivudine, 3TC) and one NNRTI (Nevirapine, NVP or Efavirenz, EFV) is the current accepted first line regimen. Other regimens are detailed in table 4. NRTI inhibit a variety of DNA polymerases thereby having a relatively inferior safety profile compared to other classes of drugs (see below).

Table 4: First line ART regimens

Regimen I	AZT + 3TC + NVP	Hb>9 gm/dl and not on ATT
Regimen Ia	TDF + 3TC + NVP	Hb <9gm/dl and not on ATT
Regimen II	AZT + 3TC + EFV	Hb >9 gm/dl and on ATT
Regimen IIa	TDF + 3TC + EFV	Hb <9gm/dl and on ATT, for patients with Hep B or Hep C and for pregnant females.

The second line

In the presence of reasonable indications to switch to an alternative regimen (see below) the patient may be started on second line ART. These are summarised in Table 3.

Table 5: Second line ART regimens

Regimen III*	AZT + 3TC + ATV/r	For those develop toxicity to both NVP and EFV.
Regimen IIIa*	AZT + 3TC + LPV/r	For those who develop ATV toxicity
Regimen IV*	TDF + 3TC + ATV/r	For patients on TDF containing first line regimen and for those who develop toxicity to both NVP and EFV.
Regimen IVa*	TDF + 3TC + LPV/r	For patients on Regimen IV with ATV toxicity
*NACO nomenclature		

Immunization

Table 6 summarises the recommendations for immunizations for HIV infected patients [9]. Inactivated vaccines are generally the norm, with live vaccines being contraindicated when CD4 < 200/ mm3.

Table 6: Immunization in HIV patients

Pneumococcal vaccine: PPSV 23 if CD4 is more than 200/micro litre	Once in 5 years
Hepatitis A: MSM, IVDU and persons with chronic liver disease or HBV, HCV positive.	Two doses at 0 and 6 months
Hepatitis B: 40 micrograms, a dose higher than the conventional 20 mcg.	Three doses at 0, 1 and 6 months
Influenza: Inactivated vaccine recommended for all patients	Once every year
Tetanus toxoid: Same as for HIV negative people. One time substitution with Tap at time of next booster	Vaccinate every 10 years

Drug Toxicity

Adverse drug events secondary to ART is of major clinical significance [3, 5, 6]. These determine patient compliance, affect regimen selection and eventually affect treatment outcome.

Gastrointestinal disturbances, including nausea, vomiting, diarrhoea can occur with most classes of anti-retroviral drugs, but are more specific to AZT, TDF and PIs. Anaemia and neutropenia is frequently seen with AZT, TDF and PIs as well. Hepatotoxicity is seen with NVP, EFV and PIs, and this side effect is more common with patient with Hepatitis B or C. In addition to Dizziness, confusion and vivid dreams are documented side effects of EFV.

Medium term (the first six months) drug reactions include anaemia and hyperpigmentation of skin and nails secondary to AZT. D4T and ddl have also been implicated in lactic acidosis Peripheral neuropathy may also occur due to these drugs. Pancreatitis due to ddI can occur at any time.

Long term drug toxicities include lipodystrophy due to d4T, AZT and PIs. PIs and EFV can lead to dyslipidemia. Indinavir is known to cause diabetes. TDF can cause a renal tubular dysfunction and reduction in bone mineral density.

The most notorious group among the anti-retroviral line-up to cause drug interactions are the Protease inhibitors. With statins, PIs can cause myopathy and rhabdomyolysis. Statins must therefore be initiated at the lowest possible dose. A notable exception is Fosamprenavir with Rosuvastatin. This combination does not need a dose reduction when co-administered. PIs also increase the concentrations of Benzodiazepines, antidepressants, AEDs, Antifungal, Anti-tubercular drugs, OCPs, PDE-5 inhibitors, Methadone and St John's wart. PIs can also interfere with metabolism of other anti-retroviral drugs such as Maraviroc. Also, co-administration of TDF and ddI levels result in 60 % increase in patient's serum levels of ddI, which predisposes the patient, significantly to pancreatitis. This combination is therefore best avoided.

Substitutions due to drug toxicity is summarised in Table 7. These are generally made within the same class. If the toxicity is life threatening, as in NVP induced Steven Johnson's syndrome, then all ART must be stopped and restarted when the patient stabilises. The rare case of suspected Lamivudine toxicity must be referred to SACEP further opinion and management.

Table 7: Drug substitutions [5]

Toxicity due to	Switch to
AZT	TDF
TDF	AZT if not anaemic, d4T if anaemic
Both TDF and AZT	d4T
NVP	EFV
Both NVP and EFV	ATV/r
ATV/r	LPV/r or RAL/DVG

Treatment Failure

For a patient who has been on Anti-retroviral therapy for at least 06 months a worsening clinical, immunologic or virological profile generally indicates treatment failure. Table 8 defines the indications to change therapy in patients while on ART.

Table 8: Indications to change ART

Clinical failure, as evidenced a new or recurrent WHO stage 4 condition after 06 months of ART
Persistently declining CD4 counts
Less than 1 log reduction in HIV RNA after 04 Weeks of initiation of therapy
A threefold or greater rise in HIV RNA from baseline

Once treatment failure is defined, the substitutions for each class must be determined. If AZT was used in the first line, the choice in second line is TDF and vice versa. If neither can be used, d4T is the last choice [5, 13, 14]. PIs must always be prescribed in a boosted combination. As before counselling for adherence, support services and a follow up and monitoring plan must form an integral part of management.

The Future

Several new therapies and modalities have arisen in the past few years, which show promise in preliminary testing platforms. Some of them are briefly described below.

Romidepsin

HIV-1 integrates into the host DNA, thus establishing the basis for latent infection. As ART cannot eliminate transcriptionally inactive or latent virus, adjunctive interventions that efficiently activate latent virus are needed to achieve the ultimate goal of a cure for HIV-1 infection [15]. One of the possible mechanisms to cure HIV was by activating and killing the latently infected cells, while the over-arching presence of ART prevents spread of the infection [16, 18]. This approach has been a prime target of HIV research in recent times. The depsipeptide Romidepsin was recently found to be effective latency reversing agent. Romidepsin is a histone deacetylase inhibitors (HDACi) which promises to enforce the "kick and kill" approach for HIV management or even, cure. Flow cytometry analysis for lymphocyte H3 acetylation (a marker for drug activity) subsequent to administration of 5 mg/m2 of Romidepsin was found to significantly induce HIV transcription, which makes the latent cells more susceptible to immune mediated killing. This novel mechanism is a promising new area for further research.

Vaccine for HIV/AIDS

There are primarily four basic approaches to creating a vaccine for HIV AIDS. These are summarised in Table 9. Unfortunately, none of the molecules having arisen from these strategies have received US - FDA approval.

Table 9: Strategies for a vaccine for HIV/AIDS

Incorporation of HIV genes into a plasmid and introduced into the human subject, eliciting an immune response
HIV genes are inserted into the genomes of live, but non-infectious viruses, and the protein expressed by these genes could be the target for the immune response
Chemically synthesized HIV peptides allowed to elicit a B cell response
Empty shells of the viral structure could produce a high titre of neutralising antibodies, but due to lack of genetic material fail to cause infection.

Various subtype B canary pox -HIV vector primes and booster containing subunit glycoprotein 120 or 160 (gp120 or gp160) have been under evaluation. In 2009, the ALVAC-HIV priming and AIDSVAX B/E boosting for the prevention of HIV-1 infection in more than 16000 young Thai adults at risk for the disease(19).This was the only study to show a modest protective effect (31%) of the vaccine and offers new insight for research. Four years later, the multigene, DNA prime–recombinant adenovirus type 5 vector boost (DNA/rAd5) vaccine trial was stopped due to lack of efficacy [20].

The use of broadly neutralising anti-body is a relatively new concept. The VRC01 antibody was initially found in HIV infected individuals (> 10 years) but who never developed AIDS. These patients, termed "Elite controllers" were the source for this antibody which has been shown to neutralise more than 90% of the 190 strains it has been tested against. This study, part of the HIV vaccine trials network and the Antibody mediated prevention study, has currently progressed to phase 2b of clinical trials(21).

Conclusion

The human immunodeficiency virus remains a global health problem since its discovery in 1983. The WHO now recommends that anti-retroviral therapy must be initiated for all patients, irrespective of CD4 counts. Various guidelines have been instituted for effective management. Also, starting ART at progressively higher CD4 counts has shown to lower the risk of some toxic effects associated with anti-retroviral therapy. Early ART initiated also prevents neurocognitive declines, increases chances of CD4 normalisation, and lowers the risk of development of IRIS. In India the backbone of first line anti-retroviral therapy remains Lamivudine (3TC) and Tenofovir (TDF) [5, 8]. The use of FTC (and INSTIs, see below) in first line ART is clearly limited by its cost. The current research is focused, in addition to HIV vaccine, on the latency reversing agent, Romidepsin, a depsipeptide.

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