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Review Article

Antiretroviral therapy: Shifting sands

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ABSTRACT

HIV/AIDS has been an extremely difficult pandemic to control. However, with the advent of antiretroviral therapy (ART), HIV has now been transformed into a chronic illness in patients who have continued treatment access and excellent long-term adherence. Existing indications for ART initiation in asymptomatic patients were based on CD4 levels; however, recent evidence has broken the shackles of CD4 levels. Early initiation of ART in HIV patients irrespective of CD4 counts can have profound positive impact on morbidity and mortality. Early initiation of ART has been found not only beneficial for patients but also to community as it reduces the risk of transmission. There have been few financial concerns about providing ART to all HIV-positive people but various studies have proven that early initiation of ART not only proves to be cost-effective but also contributes to economic and social growth of community. A novel multidisciplinary approach with early initiation and availability of ART at its heart can turn the tide in our favor in future. Effective preexposure prophylaxis and postexposure prophylaxis can also lower transmission risk of HIV in community. New understanding of HIV pathogenesis is opening new vistas to cure and prevention. Various promising candidate vaccines and drugs are undergoing aggressive clinical trials, raising optimism for an ever-elusive cure for HIV. This review describes various facets of tectonic shift in management of HIV.

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A waning pandemic

The year 2015 marked the end-date of both the 2011 Political Declaration on HIV and the Millennium Development Goals. On the occasion of the World AIDS day on 1 December, it is befitting to take stock of what this killer disease has done to humankind.

HIV/AIDS has been an extremely difficult pandemic to control. Since the start of the epidemic, 78 million people have been infected and 38 million have died. There are approximately 36.9 million people living with HIV/AIDS (PLHA) at the end of 2014 with 2.0 million people becoming newly infected with HIV in 2014 globally.¹ Ninety percent of the 4.2 million HIV-positive people in Asia live in India, China, and Thailand. India contributes 49% of this large number (2.4 million

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people).² However, the use of chemotherapy to suppress replication of the HIV has transformed the face of AIDS. The WHO launched its 3 by 5 campaign in 2004 and this has enabled more than 6 million PLHA to access antiretroviral therapy (ART) in resource-limited settings.³ Significant reductions in morbidity and mortality have been achieved. It is estimated that ART has saved an estimated 14.4 million life-years worldwide from the time of its introduction in 1996 till the end of 2009. ART has led to the stabilization of the HIV epidemic with decrease in numbers of newly infected HIV cases in the last decade.⁴ This is illustrated by the fact that 2.1 million people became newly infected with HIV in 2013 globally as compared to 3.4 million in 2001. The other significant outcome of ART has been the fall in AIDS-related mortality with a 30% decline registered since 2005.⁵ ART is so effective that a recent stochastic modeling study done estimates that the life expectancy for a 30-year-old MSM becoming HIV positive in 2010 will only be reduced by about 10% with a projected median age at death being 75 years.⁶

Encouraged by these statistics, UNAIDS launched its ambitious 90-90-90 targets in 2014. Under this program, UNAIDS would work to bring 90% of PLHA to be diagnosed, 90% to be accessing ART, and 90% to achieve viral suppression by 2020. Existing indications for ART initiation in asymptomatic patients were based on CD4 levels; however, recent evidence has broken the shackles of CD4 levels. Early initiation of ART has been found not only to be beneficial to the patients but also to the community as it reduces the risk of transmission. There have been few concerns regarding the large financial outlay required to make ART universally available to all PLHA. These fears are unfounded because early initiation of ART not only proves to be cost-effective but also contributes to economic and social growth of the community.

Evolution of therapy

ART

The US FDA approved zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI) for the treatment of AIDS in

1987. This was followed by saquinavir, a protease inhibitor in 1995 and nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor (NNRTI) in 1996. Availability of multiple classes of drugs led to introduction of combination therapy called highly active antiretroviral therapy (HAART) and this was responsible for converting HIV/AIDS to a chronic and non-fatal illness.⁷ The first decade of 21st century witnessed FDA approving many new drugs like tenofovir, lopinavir + ritonavir, emtricitabine, darunavir, etravirine, and maraviroc. Most guidelines now list tenofovir as one of the key drugs for first line ART. This is due to its potent antiviral effects and good pharmacokinetics. In 2014 two new drugs were approved, i.e. elvitegravir and Cobicistat. Table 1 lists all the available ART drugs according to their mode of action.

A key aspect to understanding ART is that almost all commonly used antiretroviral drugs act only on actively replicating viruses. This means that dormant viruses residing in T-memory cells are immune to their attack. This also means that ART, once started, cannot be stopped as there is no way of predicting when and which HIV-infected T-memory cell will get activated and the virus inside it will start replicating. By current understanding, to completely eradicate HIV, the duration of ART should be more than 60 years as T-memory cells have a long half-life.⁸ Hence, ART has to be continued life-long.

Protease inhibitors block proteolysis and have emerged as potent ARV agents. These drugs are metabolized by the cytochrome P450 system in the liver. A co-drug has to be administered to decrease this metabolism and improve the pharmacokinetics of the PI. Such a drug is called a 'booster'. Therefore, PI-containing regimens contain a fourth drug that does not directly contribute to overall antiviral activity but improves pharmacokinetics. Boosting with sub-therapeutic low-dose ritonavir achieves this goal and also permits flexibility of dosing and decreases pill burden. Cobicistat is another drug that is increasingly being used for this purpose. Its greatest advantage over ritonavir is its lower potential for off-target drug interactions. This is because it is more selective inhibitor of CYP3A and is devoid of anti-HIV activity.⁹

Table 1 – Antiretroviral therapy drugs with their mechanism of action.

S. no.	Mechanism of action	Drugs
1	Entry inhibitors a. CD4 binding b. CCR5 binding c. Fusion	BMS-378806, TNX-355 Maraviroc, Aplaviroc Enfuvirtide
2	Reverse transcriptase inhibitors a. Nucleoside reverse transcriptase inhibitors (NRTI) b. Nucleotide reverse transcriptase inhibitors (NtRTI) c. Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Zidovudine (AZT), Lamivudine (3TC), Emtricitabine (FTC), Abacavir (ABC) Tenofovir (TDF) Efavirenz (EFV), Nevirapine (NVP), Etravirine (ETV), Rilpivirine (RPV)
3	Integrase strand transfer inhibitors (InSTI)	Dolutegravir (DTG), Elvitegravir (EVG), Raltegravir (RGV)
4	Transcription inhibitors	Cortistatin A
5	Virus assembly and production Inhibitor	Beverimat, Vivecon
6	Protease inhibitors (PI)	Atazanavir (ATZ), Ritonavir, Darunavir (DRV), Lopinavir (LPV), Indinavir, Tipranavir, Nelfinavir

Evolving guidelines

In 1996, International AIDS Society-USA guidelines suggested use of combination ART on the basis of CD4⁺ cell count, plasma HIV RNA level, or clinical status.¹⁰ Since 2002, WHO guidelines on ART have kept changing as more and more evidence for early initiation of ART has been accumulating.¹¹ Table 2 demonstrates evolution of WHO guidelines with time.

Strategic treatment interruptions were at one time thought to be a method of retaining people in therapy and ensuring good adherence. The Strategies for Management of Antiretroviral Therapy (SMART) study, with a sample size of 5472 patients with a CD4 count of ≤ 350 cells/mm³, revealed that continuous ART is better than CD4 cell count-guided therapy in delaying death/opportunistic infections.¹² Since 2010, there has been increasing evidence that there is an association between untreated HIV and several non-AIDS-defining conditions like cardiovascular, renal, and hepatic diseases, neurocognitive disorders, and several types of cancer.¹³ Later evidence suggested that ART also substantially reduces sexual transmission in HIV-serodiscordant couples.¹⁴ The HPTN 052 trial published in 2011 showed that early initiation of antiretroviral treatment reduced the risk of HIV transmission by 96% among serodiscordant couples.¹⁵ The ART guidelines for adults and adolescent issued by WHO in 2013 advocated ART for¹⁶:

- a. People living with HIV having CD4 counts ≤ 500 cells/mm³ and on priority in those with CD4 counts ≤ 350 cells/mm³.
- b. People living with HIV in special situations (with active TB, with HBV and severe liver disease, pregnancy, breastfeeding, serodiscordant couple, etc.).

The TEMPRANO trial published in 2015 is a randomized controlled trial that reiterated that initiating ART at a CD4 count > 500 cells/mm³ leads to less severe HIV morbidity (combined outcome of death, AIDS, and severe non-AIDS diseases) when compared with those in whom treatment was initiated at a CD4 count ≤ 500 cells/mm³.¹⁷ Another trial published in 2015. The Strategic Timing of Antiretroviral

Treatment (START) trial, enrolled 4685 people and randomized them into two groups, the first receiving immediate ART and the second deferring ART till CD4 cell count fell to < 350 /mm³. Here also there was a 57% reduction in the rates of AIDS and serious AIDS-defining illnesses in those treated early.¹⁸

The HIV modeling consortium used national cohort data from four countries in sub-Saharan Africa to prepare a model on efficacy of early ART. It showed that expanding ART eligibility criteria to > 500 cells/mm³ or regardless of CD4 cell count could result in 6–14% fewer people dying from HIV-related causes during the next decade. They felt that this would result in programmatic gains and mortality reduction (unpublished data).¹⁹

The WHO has put up the revised 2016 guidelines on its website on 30 September 2015. As per these guidelines, ART should be initiated for all adults/adolescents living with HIV regardless of WHO clinical stage and at any CD4 cell count.²⁰ The advance warning is to enable countries to amend their national guidelines. Unfortunately, as in many poorer countries, access to ART is severely limited in India, with only about 30% receiving ART in India by 2009²¹ and has slightly improved up to 36% by 2015.² As of now, the National AIDS Control Organization (NACO) guidelines (2013) for India remain unchanged and recommend ART in following situations²²:

- a. CD4 < 350 cells/mm³
- b. ART irrespective of CD4 count
 - i. WHO Clinical stages 3 and 4
 - ii. TB coinfection
 - iii. Pregnancy
 - iv. HBV/HCV coinfection if treatment for hepatitis indicated
 - v. HIV-associated nephropathy (HIVAN)
 - vi. Opportunistic infection (OI) for which no specific treatment available
 - vii. Children < 5 years
 - viii. Serodiscordant couples

Operationalizing a program like the NACO ART one is not easy. The scale and technical limitations are many. In just a decade,

Table 2 – WHO ART guidelines changing with the times.

WHO guidelines	When to start ART	Preferred first line ART
2002	CD4 count ≤ 200 cells/mm ³ ; immediate for WHO clinical stages 3 and 4	08 options: AZT/3TC + NVP/EFV or ABC or PI. AZT preferred
2003	CD4 count ≤ 200 cells/mm ³ ; immediate for WHO clinical stages 3 and 4	04 options: d4T/AZT + 3TC + NVP/EFV. AZT preferred
2006	CD4 count ≤ 200 cells/mm ³ ; immediate for WHO clinical stages 3 and 4. Consider if CD4 count between 200 and 350 cells/mm ³ and CD4 ≤ 350 cells/mm ³ for active TB	08 options: TDF/ABC; AZT/d4T + NVP/EFV + 3TC/FTC. AZT or TDF preferred
2010	CD4 count ≤ 350 cells/mm ³ ; immediate for WHO clinical stages 3 and 4, Active TB, Chronic HBV (if need HBV treatment)	04 options: FDCs (AZT/TDF + 3TC/FTC + NVP/EFV). AZT or TDF preferred
2013	CD4 count ≤ 500 cells/mm ³ ; immediate for WHO clinical stages 3 and 4, Active TB, Chronic HBV (if need HBV treatment), serodiscordant couples; CD4 ≤ 350 cells/mm ³ as priority	01 preferred option: FDC (TDF + 3TC/FTC + EFV); TDF preferred and d4T phased out
2015	Regardless of WHO clinical stage and at any CD4 cell count	Yet to come

the NACO has established 512 ART centers catering to 8.7 lakh patients. One of the big issues in providing ART to such diverse population has been simplifying regimens. With the new NACO adult and adolescent guidelines, tenofovir, lamivudine, and efavirenz (TLE) will be the primary regime for both treatment and prevention of vertical transmission during pregnancy. Operationally, this is a good step but there are some issues with tenofovir, which have not been addressed. Poor CNS penetration of tenofovir and its consequent long-term neurocognitive dysfunction will remain a worry.²³ In such patients, an alternate regimen containing maraviroc may be required.²⁴ The other issue is that of renal and bone mineral toxicity. This will be addressed in the programme by instituting regular monitoring of renal function.

Challenges to Universal ART

The first issue will be to get all HIV-positive people onto ART. This is not as simple as it sounds. There are many barriers to accessing and accepting care. This is more so amongst the people at highest risk of transmission like men who have sex with men, transgender women, cisgender female sex workers, and injecting drug users. The reasons for their shying away from HIV testing and seeking care include HIV stigma, discrimination in health care setting, fears of adverse social behavior, and marginalized group stigma.²⁵

The next issue is to convince a large asymptomatic HIV-positive populace to commit to life-long therapy. In a disease where adherence is critical, this is a huge challenge. 60% of PLHA may be on complementary and alternative medicine.²⁶ Denial of HIV status, faith in alternative systems of medicine, and long travel times and waiting periods in clinics are disincentives to being on therapy. Respectful and helpful attitude of staff at ART clinics, maintenance of confidentiality, and availability of social support all contribute to retention in therapy.^{27,28}

Earlier regimes were complex, with food restrictions and high pill burden. Simplification of regimen with once daily fixed dose combination of ARV now being freely available has led to greatly improved compliance and decreased risk of drug resistance.²⁹ The NACO switched to a fixed dose combination of tenofovir, lamivudine, and efavirenz once a day as the preferred first-line ART regime for adults and adolescents in 2014. Other similar combinations are available and all of them have ease of dosing and are mostly free of major side-effects. Recently, US FDA has approved a fixed-dose combination tablet containing Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir alafenamide (Genvoya, Gilead Sciences) for the treatment of HIV-1 infection.³⁰

With people living longer on ART, a host of metabolic complications and non-AIDS conditions are now being recognized. Their etiology is probably multifactorial involving chronic inflammation due to HIV infection, long-term ART toxicity, lifestyle-related risks for disease, and aging. Following significant complications have been noticed in patients on long-term ART³¹:

- a. Accelerated loss of bone mineral density
- b. Cognitive dysfunction

- c. Cardiovascular disorders
- d. Metabolic disorders like dyslipidemia, lipodystrophy, etc.
- e. Renal dysfunction

Data on long-term adverse effects of ART are now emerging. Tenofovir disoproxil fumarate is known to cause decline in glomerular filtration rate and decrease bone mineral density on long exposures. As this drug is one of the anchors of first-line ART world over, there has been an effort to develop alternate, safer drugs. Tenofovir alafenamide has been developed and found to be non-inferior to conventional tenofovir and with lesser impact on bone mineral density and renal function.³²

Ensuring availability of ART to all PLHA will be a gargantuan task. But they can be overcome by a strong political will and initial financial outlay. Resch et al. published a report on the economic returns to investments in ART in low- and middle-income countries in PLoS One in 2011. They showed that the cost of keeping 3.5 million people on ART in these countries would be \$14.2 billion (using 2009 ART costs). This financial outlay should be weighed against the fact that ART would save 18.5 million life-years and return \$12–34 billion through increased economic productivity, averted orphan care, delayed medical treatment for OIs, and end-of-life care.³³

One of the most difficult problems in HIV therapy is the development of drug resistance, which commonly occurs during treatment interruptions. One in every six HIV patient will interrupt treatment by 2 years. A single interruption leads to mean CD4 loss of 94 cells/mm³. On average, there are 10⁴–10⁵ or more HIV-1 particles per mL of plasma in an untreated individual, which turn over at a rate of 10¹⁰/day. As the HIV-1 genome is approximately 10,000 nucleotides in length, 1–10 mutations can occur in each viral genome with every cycle. With this colossal potential for generating genetic diversity, HIV-1 variants with drug resistance will often pre-exist in the viral quasispecies even before initiating therapy.³⁴ Suboptimal or poor compliance to ART often leads to low-level viremia³⁵ which has greater risk of virologic failure, emergence of further drug resistance,³⁶ and immune activation. Once generated, drug-resistant strains remain archived in the T-memory cells and will start replicating once these drugs are restarted. This means that drugs that have been used in a suboptimal dose or an inappropriate regimen earlier can never be reused for fear of virologic failure.³⁷ This has a profound implication in a disease where therapeutic armamentarium is limited. Hence, great restraint should be exercised in changing ART regimens and also great effort should be made to ensure that patients get the right regime in right doses and in an uninterrupted manner. In general, treatments based on NNRTIs or unboosted PIs are more susceptible to resistance than treatment based on a ritonavir boosted PI's.³⁸ Existing ART guidelines combine drugs of various groups so that potential for emergence of clinical resistance can be mitigated and results have been successful. However, as the virus continues to evolve and escape newer drugs targeting the virus will have to be developed.

The prevalence of HIV drug resistance among people starting ART varied from 4.8% in 2007 to 6.8% in 2010. This data comes from records of 5000 subjects in 36 WHO surveys in 12 low-middle income countries. These surveys showed that

most patients (82–91%) achieved adequate viral suppression by 12 months. Among those with subsequent treatment failure, 60% and 70% had drug resistance. Though exact data are not available in India, most experts estimate primary HIV resistance in ART-naïve patients to be low approximately <5%.³⁹ Approximately 10% of patients with HIV will switch to second line ART due to treatment failure in 5 years.⁴⁰

Prophylactic measures to reduce transmission

Preexposure prophylaxis (PrEP)

PrEP is defined as use of antiretroviral drugs by HIV-uninfected people to block the acquisition of HIV before exposure to HIV. PrEP leads to 51% reduction in risk of HIV infection.⁴¹ WHO recommends (2015) oral PrEP as an additional prevention choice for people at substantial risk of HIV infection in combination with other HIV prevention approaches. PrEP is indicated for people with substantial risk, i.e. HIV incidence >3 per 100 person years. PrEP is advised for the following groups:

- a. Men who have sex with men.
- b. Transgender women in many settings.
- c. Heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection.

PrEP with daily oral emtricitabine and tenofovir (FTC/TDF) is safe and effective.⁴² There are concerns that offering PrEP to this group can lead to increased risk of drug resistance at later stages. A recent study (Partners PrEP) by Lehman et al. on 4747 serodiscordant couples witnessed 121 HIV seroconversions. It revealed that risk of drug resistance due to PrEP is rare but can occur if prophylaxis is offered to individuals who are already infected with HIV or in PrEP breakthrough infections.⁴³

Postexposure prophylaxis (PEP)

The basic aim of offering PEP is to give drugs prior to establishment of HIV reservoirs. It was earlier thought that administering PEP by 72 h after exposure could protect against infection. An elegant study published in Nature in 2014 shows that infection probably gets established earlier. It could be as early as within 1–2 days of exposure. Whitney et al. infected rhesus monkeys with SIV mac251 virus intra-rectally.⁴⁴ The monkeys were then divided into four groups and ART was started on days 3, 7, 10, and 14 respectively. ART was given for 24 weeks and then stopped. A viral rebound was noted in all groups but was slowest and least in the group starting treatment on day 3. Investigators were able to detect HIV proviral RNA in regional lymph nodes as early as on day 3 implying that transport of virus from the site of entry to regional lymph nodes is much faster than was thought so earlier.

PEP should be offered and initiated as early as possible, to all individuals with exposure that has potential for HIV transmission.⁴⁵ Exposure to HIV can be occupational or non-occupational. Exposures that may warrant postexposure prophylaxis include:

- i. Parenteral or mucous membrane exposure (sexual exposure and splashes to the eye, nose or oral cavity).
- ii. The following bodily fluids may pose a risk of HIV infection: blood, blood-stained saliva, breast-milk, genital secretions and cerebrospinal, amniotic, rectal, peritoneal, synovial, pericardial or pleural fluids.

Exposures that do not require postexposure prophylaxis include:

- i. When the exposed individual is already HIV positive.
- ii. When the source is established to be HIV negative.
- iii. Exposure to bodily fluids that does not pose a significant risk: tears, non-blood-stained saliva, urine, and sweat.

A 28-day regimen for postexposure prophylaxis for HIV with two ARV drugs is effective, but three drugs are preferred. TDF + 3TC (or FTC) is recommended as the preferred PEP for adults and adolescents. The third drug for PEP in adults and adolescents according to WHO should preferably be LPV/r or ATV/r. Where available, raltegravir, boosted darunavir, or efavirenz can be considered as alternative options.

Looking ahead

Exciting developments may change HIV care in the near future. A trial using a long-acting drug combination has shown promising results. Rilpivirine–cabotegravir combination can be used as bimonthly injections.⁴⁶

Even long-term ART does not eradicate HIV from the body. Shortly after cessation of therapy, virus in resting CD4 cells will get activated and start replicating. Any technique to eradicate this reservoir will depend on methods to measure this lurking pool of replication-capable latent viruses. A novel assay can now measure the size of this reservoir. The test is called TILDA (acronym for Tat/rev Induced Limiting Dilution Assay). A chance discovery that histone deacetylase (HDAC) inhibitor, an anti-neoplastic used to treat t-cell lymphomas can activate resting CD4 cells, thereby triggering viral replication which has potential to reduce HIV reservoir. A novel 'shock and kill' strategy has been tried to eradicate latent HIV by reactivating proviral gene expression using Rhomedeprin. Following this activation, combination ART is used to kill the virus. Many HDAC inhibitors have been tested, but Rhomedeprin seems the most promising of the lot.⁴⁷ Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-mediated gene activation provides targeted latency reactivation with enhanced efficiency and specificity.⁴⁸ Another new drug, di-dehydro Cortistatin A (dCA), is a Tat inhibitor. It breaks the tat-mediated transcriptional feedback loop that is responsible for exponential viral production and establishes a near permanent state of latency.⁴⁹ All these three strategies represent ways of achieving a 'functional cure' for AIDS.

Conclusion

Current evidence suggests that ART should be initiated in PLHA at the earliest instance irrespective of CD4 counts. This

can have profound positive impact on HIV-related morbidity and mortality and reduce HIV transmission. The considerable financial gains of reduced medical and orphan care and increased man days at work will mitigate the huge financial outlay for this ambitious programme. Though at present there is neither a proven vaccine nor assured cure, various promising candidate vaccines and drug-trials in advanced stages raise hope for the ever-elusive cure.

Conflicts of interest

The authors have none to declare.

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