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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.

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	BMS-378806, TNX-355
	b. CCR5 binding	Maraviroc, Aplaviroc
	c. Fusion	Enfuvirtide
2	Reverse transcriptase inhibitors	
	a. Nucleoside reverse transcriptase inhibitors (NRTI)	Zidovudine (AZT), Lamivudine (3TC), Emtricitabine (FTC), Abacavir (ABC)
	b. Nucleotide reverse transcriptase inhibitors (NtRTI)	Tenofovir (TDF)
	c. Non-nucleoside reverse transcriptase inhibitors (NNRTI)	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