

Current Status of Antiretroviral Therapy (ART) for Acquired Immunodeficiency Syndrome(AIDS) in Bangladesh

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Acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) is a threat and can be termed as a curse upon the human race. The physicians and scientists first noticed and recognized the presence of AIDS as an actual disease following an increase in the incidence of rare opportunistic infections and cancers among otherwise healthy homosexual men ¹.

The first case of an unknown syndrome was reported in USA in 1981, characterized by a profound drop in CD4+ T lymphocyte counts and subsequent immune depression of patients. In those days, the disease was called “Gay pest”, “Gay cancer” or Gay-related immune deficiency (GRID), due to its major incidence among men having sex with men (MSM)^{2,3}. Further demonstration that heterosexual patients were equally susceptible to infection led to its official definition as Acquired Immunodeficiency Syndrome (AIDS)⁴.

The etiological agent of AIDS was first identified in 1983, by the French virologist Luc Montagnier and they identified retroviral particles and reverse-transcriptase activity in cultures of lymphocytes isolated from AIDS patients. This was the first report

associating a retrovirus with AIDS, but not conclusive on their causal relationship. Less than a year later, the group led by Robert C. Gallo at the National Cancer Institute provided solid evidences in four reports, supporting the hypothesis of a new retro-virus as the causal agent of AIDS⁵⁻⁹. The corner stone in Gallo's work was to replicate the new virus in a tumor cell line of lymphoid origin (H9), providing enough viral material to characterize its proteins and to develop serologic diagnosis methods to detect antibodies specific for the virus in patient's sera ¹⁰. Consequently, the nucleotide sequences of two different but similar viruses were elucidated, markedly different from any previously identified human retro-virus^{11,12}. This was the basis for denominating the new entity as the Human Immunodeficiency Virus (HIV)¹².

Burden in Bangladesh:

In world, total no of people living with HIV is 36.7 million, 20.9 million people is receiving antiretroviral therapy, new infected HIV case is 1.8 million, deaths due to AIDS is 1.0 million.¹³

In Bangladesh the first HIV case was detected in 1989. HIV prevalence remains less than 0.01% among general population. Estimated people living with HIV is 11,700. In 2017, total number of new cases were 856. Reported cases for Rohingya crises from 25th August 2017 till now is 168. In 2015, treatment was given among 4665 people living with HIV and in the last year total no of ARV receiver was 2642. ¹³

Anti-retroviral therapy past and present:

In <30 years of antiretroviral therapy (ART), there have been more than 25 drugs developed. In 1987, the first

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antiretroviral agent, zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI), was shown to have a positive impact on clinical progression and death¹⁴

The challenges of early NRTI regimens included high pill burdens, inconvenient dosing, treatment-limiting toxicities and incomplete virological suppression. Sequential monotherapy and incomplete virological suppression resulted in the emergence of multiple resistance mutations, with long-term treatment consequences. In treatment of Human immunodeficiency virus (HIV) protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), introduced in the mid-1990s, revolutionized the management of HIV infection. Highly active antiretroviral therapy (HAART) regimens, consisting of two NRTIs plus a PI or NNRTI, were capable of virological suppression (<400 copies ml⁻¹), and widespread uptake quickly led to dramatic reductions in morbidity and mortality in the developed world¹⁵. HAART provides effective treatment options for treatment-naïve and treatment-experienced patients.

Common antiretroviral drugs: Drugs are classified into following:

Reverse Transcriptase Inhibitors

Reverse transcriptase inhibitors are a group of drugs, which can bind and inhibit the reverse transcriptase enzyme to intercept the multiplication of HIV. There are two types of inhibitors: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)¹⁶ and Nucleoside Reverse Transcriptase Inhibitors (NRTI)¹⁷. Examples of this group of drugs include Zidovudine, Didanosine, Abacavir, Tenofovir, and Combivir.

Protease Inhibitor:

Regulation of HIV protease is of high importance for the correct assembly and production of HIV. Protease inhibitors effectively block the functioning of protease enzymes in acutely and chronically HIV-infected CD4 cells. Inhibition of HIV protease enzymes results in the liberation of immature and noninfectious viral particles¹⁸. Examples of this group of drugs include lopinavir/ritonavir, Indinavir, Ritonavir, Nelfinavir, and Amprenavir.

Fusion Inhibitors :

This class of drugs acts by blocking HIV from entering the CD4 cells of infected patients. They inhibit the

fusion of HIV particles with the CD4 cells¹⁹. Enfuvirtide is an example of a fusion inhibitor used in HIV treatment.

Chemokine Receptor 5 Antagonist

This group of drugs prevents the infection by blocking the Chemokine Receptor 5 (CCR5) antagonist receptor present on CD4 cells. In the absence of vacant CCR5 receptors, HIV fails to gain entry and infect the cell²⁰. Maraviroc is an example of a CCR5 antagonist used in HIV treatment.

Integrase Strand Transfer Inhibitors

Strand transfer inhibitors prevent the integration of viral DNA into the host genome of CD4 cells by an integrase enzyme. Blocking integrase prevents HIV from replicating²¹. Raltegravir, Elvitegravir, and Dolutegravir are some medications in this category.

ART should be initiated in all individuals with HIV regardless of WHO clinical stage

or CD4 count. Adherence to treatment is of paramount importance in order to achieve the full efficacy of treatment and also to prevent the incidence of drug resistance²³.

The strategy of using two NRTIs plus a potent third agent still forms the cornerstone of current treatment principles, and is now referred to as combination antiretroviral therapy. According to WHO Guideline there are first, second, and third line treatment options²².

First-line ART

Adults: First-line ART treatment for adults consists of two NRTIs and one NNRTI. Tenofovir disoproxil-fumarate (TDF) + lamivudine (3TC) or Emtricitabine (FTC) + Efavirenz (EFV) as a fixed dose is the favored choice for this type of ART.

When this drug combination is contraindicated or is unavailable,

- 1) zidovudine (AZT) + 3TC + EFV,
- 2) AZT + 3TC + nevirapine (NVP),

or

- 3) TDF + 3TC (or FTC) + NVP is used.

Pregnant and breastfeeding patients: First-line ART in this subpopulation is comprised of a single daily dose of TDF + 3TC (or FTC) + NVP. Breastfeeding infants

of mothers who are receiving ART must receive six weeks of infant prophylaxis with a daily dose of NVP. The preventive medication should commence immediately post-delivery or when HIV exposure is identified.

Pediatric patients: Patients below three years of age should be given Lopinavir/Ritonavir (LPV/r)-based treatment, even under NNRTI exposure. When LPV/r is not a viable option, NVP based treatment should be used. For infected children who are over age three, EFV is the ideal NNRTI while NVP has been identified as the second option. For infected children younger than three years of age, who develop TB while on the Lopinavir/Ritonavir (LPV/r)-based treatment, the NRTI regimen should be switched to Abacavir (ABC) + 3TC or AZT + 3TC until the TB infection is cleared. NRTI regimens similar to that of adults (TDF + 3TC (or FTC)) or (AZT + 3TC) or (ABC + 3TC) are preferred for patients between 10 and 19 years of age who weight 35 kg or more.

Second-line ART

Adults: including pregnant and breastfeeding patients: When a first-line treatment of ART fails, a second-line ART should be utilized. The second-line ART is comprised primarily of two NRTIs and a ritonavir-boosted PI. The recommended option for second-line ART includes AZT and 3TC as the NRTI. After the failure of AZT or stavudine (d4T) + 3TC-based first-line regimen, TDF + 3TC (or FTC) as the NRTI should be considered. When first-line NNRTI-based treatment fails, two NRTIs + a boosted PI are suggested.

Pediatric patients: For children below three years of age, first-line ART is continued even when it fails. No change in treatment is recommended; instead, adequate steps should be taken to improve adherence to the ART regimen. If first-line ART fails in children ages three and up, a second-line treatment consisting of one NNRTI and two NRTIs should be given. If ABC or TDF + 3TC (or FTC) fails, the recommended option is AZT + 3TC. After a failure of AZT or d4T + 3TC (or FTC) in first-line treatment, the preferred NRTI option is ABC or TDF + 3TC (or FTC).

Third-line ART

If first- and second-line ART fails, the WHO recommends inclusion of new medicines with the least amount of risk for development of cross-resistance

towards previously used drugs (e.g. integrase inhibitors and second-generation NNRTIs and PIs).

Factors to consider when selecting ART

The major factors that deserve thorough consideration while choosing an ART for a patient include the viral load and CD4 cell count before the treatment, the result of HIV genotypic drug resistance test, HLA-B*5701 status, patient preferences, and anticipated adherence. Comorbid conditions to screen prior to ART include cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, neurologic disease, drug abuse or dependency requiring narcotic replacement therapy, pregnancy, coinfections with hepatitis C (HCV), hepatitis B (HBV), and tuberculosis (TB)²⁴.

Contraindications should also be considered:

1. Creatinine clearance is less than 50 ml per minute: Tenofovir.
2. Patients on psychoactive drug treatment: Efavirenz.
3. Patients who are pregnant or who are trying to conceive: Efavirenz.
4. ALT elevation: Nevirapine.

CD4 count monitoring for therapeutic response

Monitoring patients' viral load is critical to identify ART response. When the viral load analysis is not practical via polymerase chain reaction (PCR), branched chained DNA (bDNA), and nucleic acid sequence-based amplification (NASBA), the CD4 count is used as an indicator of HIV treatment response. During the first year of treatment, increases in CD4 count from 50 to 150 cells/mm³ with an increased response in the first trimester are considered as a positive response. CD4 count rises steadily ranging from 50 to 100 cells/mm³ per year until equilibrium is reached in the subsequent years (normal range: 500 cells/mm³ to 1200 cells/mm³)²⁵. Periodic monitoring of CD4 count is required during and even after the patient achieves normal CD4 count under ART.

A number of treatment independent factors like age, viral load, genetic make-up, lifestyle, quality of health care, etc., negatively influence the CD4 counts and HIV disease progression. Under such circumstances, a change in ART medication might be required.

Treatment available in Bangladesh:

In Bangladesh first case of HIV was diagnosed 1989. Since then upto 2011 treatment facility for the patient living with HIV depended mostly on the international NGO. From 2012 Bangladesh Government supplying drug through "AIDS/STD program" in collaboration with NGOs. This improved health care service to the patients. From the 1st October 2017, Bangladesh government start ART centre in 6 institutes. They are BSMMU, IDH, Sylhet M.A.G Osmani Medical College Hospital, Chittagong medical college hospital, Khulna medical college hospital, Cox's bazar sador hospital¹³.

In Bangladesh 2 pharmaceutical (Beximco and Square) company producing 6 different types of drugs (abacavir + lamivudine + zidovudine, efavirenz, lamivudine + zidovudine, lamivudine + zidovudine + nevirapine, Nelfinavir).

The specific objectives of an ART centre are to: 1) provide Care, Support and Treatment services to all PLHIV and monitor patients in HIV care (Pre- ART) regularly 2) Identify eligible PLHIV requiring ART and initiate them on ART in a timely manner according to ART guidelines 3) Provide ARV & OI drugs to eligible PLHIV 4) Provide treatment adherence and counselling services before and during treatment to ensure high levels of drug adherence 5) Counsel and educate PLHIV, caregivers, guardians and family members on nutritional requirements, hygiene, positive living and also on measures to prevent further transmission of infection 6) Refer patients requiring specialized services (including admission) to other departments or higher facilities 7) Provide comprehensive package of services including condoms and prevention education with a view towards "Positive Prevention" 8) Ultimately integrating HIV care into general health system for long term sustainability.²⁶

The regimen that are available in ART centre are:

1. Tab. Lamivudine (3TC) 150mg + Zidovudine (AZT) 300mg + Nevirapine (NVP) 200mg
2. Tab Zidovudine (AZT) 300mg + Lamivudine (3TC) 150mg
3. Tab Efavirenz (EFV) 600mg
4. Tab Lamivudine (3TC) 300mg
5. Tab Tenofovir (TDF) 300mg

6. Tab Lopinavir/Ritonovir (LPV/r) 200mg/50mg
7. Tab Tenofovir 300mg + Emtricitabine 200mg + Efavirenz 600mg
8. Tab Atazanavir /Ritonavir 300mg + 100mg
9. Tab Tenofovir 300mg + Emtricitabine 200mg
10. Tab Abacavir 300mg
11. Tab Lamivudine (3TC) 30mg + zidovudine (AZT) 60 mg + Nevirapine (NVP) 50 mg
12. Tab Lamivudine (3TC) 30mg + zidovudine (AZT) 60mg
13. Tab Abacavir 60mg + Lamivudine (3TC) 30mg
14. Syp Nevirapine 50mg/5ml, 100ml
15. Syp Lopinavir 80mg/Ritonavir oral Solution, 20mg/ml (160ml)

Target to end AIDS epidemic:

UNAIDS has made an ambitious target treatment to end AIDS epidemic by the year 2030. They set target 90-90-90. By 2020, 90% of all people living with HIV will know their HIV status. By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy. By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression. This target is also for Bangladesh¹³.

Conclusion:

People living with HIV in Bangladesh are getting antiretroviral drugs and all facilities are available for diagnosing, treating and monitoring treatment. Previously it was supplied through NGOs. Drugs are now available in different govt. hospital under HIV/STD control program of DGHS. By ensuring investment & commitment, increasing the HIV testing facility in different government settings, addressing the epidemic in adolescents and children, comprehensive HIV response to Migrant people, Addressing legal and social barriers we can overcome the challenges.

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