RECENT UPDATES IN THE MANAGEMENT OF HIV INFECTION

Abstract:

Acquired immunodeficiency syndrome (AIDS) is a lethal disease caused by the dreaded pathogen, the human immunodeficiency virus (HIV). Fortunately, antiretroviral therapy (ART) distinctly reduces plasma viral load from the blood and thus mitigates HIV-associated morbidity and mortality. Further, ART also markedly reduces the risk of HIV transmission to sexual partners and infants. Consequently, antiretroviral therapy has converted HIV infection into a manageable chronic condition, with the expectation of life approaching that for people without HIV. However, lack of adherence to treatment results in the development of drug resistance as well as quickens disease development. Therefore, conditions that encourage adherence should be maximized before and after the commencement of antiretroviral therapy. Adverse effects, drug abuse, depression, socioeconomic status, low level of literacy, less social support, and interruptible access to medications are some of the reasons for poor adherence. Frequent monitoring, adequate counselling, and proper social protection help to improve treatment adherence.

Keywords: HIV, AIDS, antiretroviral therapy, adherence

Introduction:

“Human Immunodeficiency Virus (HIV), a global threat havocking human health causes the deadly acquired immunodeficiency syndrome (AIDS) and which has been termed a curse upon humans. HIV progressively weakens the immune system in humans, particularly the CD4 T-lymphocytes (CD4 cells). Once invaded, the virus gradually gains control over the host's defence mechanisms, resulting in opportunistic infections and cancers that are otherwise unusual”. [1]

“Over 38 million people were estimated to be living with HIV in 2019 with sub-Saharan Africa bearing the maximal burden of 25.8 million infected cases. Among infants, morbidity and mortality remain excessively high with more than 160,000 infants acquiring HIV and over 100,000 dying from AIDS-related diseases. Tuberculosis (TB) is the predominant cause of death among people living with HIV. In 2019, around 10 million people developed TB worldwide, of which 8.2% were people infected with HIV”. [2, 3]

One of the major worldwide challenges of the 21st century is finding a cure for HIV. However, great progress has been made in the field of HIV medicine in this century due to which HIV-infected individuals could now enjoy a near-normal life expectancy. [4] “Antiretroviral therapy (ART) emerged as a magic bullet soon after the advent of potent combination therapy in 1996 for the treatment of HIV infection. ART has markedly reduced HIV-associated morbidity and mortality by maintaining plasma viral load below the quantification limits of commercially available assays. Prolonged viral suppression improves immune function and overall quality of life, diminishes the likelihood of both AIDS-defining and non-AIDS-defining complications (cardiovascular, renal, hepatic, and neurocognitive disorders), and enables persons with HIV to live a life duration approaching that of persons without HIV”. [5]

“However, delaying ART until CD4 counts decline puts individuals with HIV in danger of both AIDS-defining conditions and certain serious non-AIDS-defining conditions. Moreover, the magnitude of CD4 recovery is directly related to CD4 count at ART initiation. Thus, many individuals who start treatment with CD4 counts < 350 cells/mm3 do not achieve CD4 counts > 500 cells/mm3 10 years later ART and they have a shorter life span than those who initiated therapy at higher CD4 count thresholds”. [6, 7]

“Despite the advances in antiretroviral treatments, the global prevalence of HIV has expanded since its discovery and has now been disseminated across the world. Unfortunately, only 16 million people (40%) are presently receiving ART out of the estimated 37 million people living with HIV worldwide”. [3] “Furthermore, treatment cessation has been correlated with rebound viremia, deteriorated immune function, and increased morbidity and mortality.

Hence, once initiated, ART should be continued with the following major treatment goals": [5]

- Maximum and durable suppression of plasma HIV RNA.
- Restoration and preservation of immunologic function.
- Alleviation of HIV-associated morbidity and upgrade the quality of survival.
- Prevention of HIV transmission.

"A comprehensive discussion about the willingness and readiness of patients to commence ART, dosage scheduling, likely benefits, possible adverse effects, and the required follow-up, as well as monitoring visits, should be initiated by healthcare providers before people start antiretroviral therapy (ART)". [8]

Initiation of Antiretroviral Therapy:

ART should be initiated immediately after HIV diagnosis and should be continued regularly without interruption to improve immunologic function as well as to maintain viral suppression. "Initiating ART early is extremely paramount for patients with AIDS-defining conditions, those with acute or recent HIV infection, and individuals who are pregnant; delaying therapy in these subpopulations has been correlated with high risks of morbidity, mortality, and HIV transmission". [5]

Table: 1 When to start ART in people living with HIV [2, 8]

Population	Recommendation
Adults (> 19 years old)	ART should be commenced in all adults living with HIV, in any case of WHO clinical stage, and at any CD4 cell count (strong recommendation, moderate-quality evidence).
	As a preference, ART should be started in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count $\leq$ 350 cells/mm^3 (strong recommendation, moderate-quality evidence).
Pregnant and breastfeeding women	ART should be commenced in all pregnant and breastfeeding women living with HIV, in any case of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).
Adolescents (10-19 years of age)	ART should be commenced in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count (conditional recommendation, low-quality evidence).
	As a preference, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count $\leq$ 350 cells/mm^3 (strong

	recommendation, moderate-quality evidence).
Children younger than 10 years of age	ART should be begun in all children living with HIV, regardless of WHO clinical stage and at any CD4 cell count: • Infants diagnosed with HIV in the first year of life (strong recommendation, moderate-quality evidence). • Children aged 1 year to less than 10 years, living with HIV (conditional recommendation, low-quality evidence).
	As a preference, ART should be started in all children < 2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤ 750 cells/mm^3 or CD4 percentage < 25% and children 5 years of age and older with WHO clinical stage 3 or 4 or CD4 ≤ 350 cells/mm^3 (strong recommendation, moderate-quality evidence).
Adults and children with TB	ART should be received as soon as possible within two weeks of initiating TB treatment, regardless of CD4 count, among people living with HIV, except when signs and symptoms of meningitis are present. Adults and adolescents (strong recommendation, low-to moderate-certainty evidence) Children and infants (strong recommendation, very-low-certainty evidence).

"Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection" by the World Health Organization (WHO) in 2016 strongly recommends that ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count. “Initiation of ART at the point of HIV diagnosis without waiting for the CD4 count to decline has been reported to decrease HIV-associated illness and AIDS-related death”. [9, 10] “Further, studies in serodiscordant couples have shown that HIV transmission reduces significantly with early initiation of ART in addition to a reduction in viral loads”. [11, 12] “Another benefit is that with tuberculosis being one of the major opportunistic infections in patients with HIV, the early initiation of ART has proven to reduce the occurrence of TB infection by up to 67% in such patients, which is of great significance in developing countries”. [13]

Since 2013, evidence and programmatic experience have continued to prefer prior initiation of ART because it results in reduced mortality, morbidity, and HIV transmission outcomes. Moreover, growing evidence from systematic reviews and cohort analyses also suggests that untreated HIV infection could also be correlated with the progression of several non-AIDS-defining conditions and that starting ART earlier reduces such events and improves survival.

"A systematic review with Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) evidence profiles that assessed the quality and strength of the evidence from one randomized controlled trial and several observational studies with reports on clinical, immunological, and virological outcomes together with HIV transmission have recommended initiating ART at any CD4 cell count". [8]

"For children and young adolescents (1-19 years), the guidelines indicate a conditional recommendation for rapid initiation of ART as there is a lack of evidence on the advantages provided by early ART in this age group. Moreover, disadvantages of early initiation of ART in this age group may include short-term side effects which may result in sub-optimal adherence to treatment followed by the emergence of drug resistance with long-term therapy". [14, 15]

"Concerning ART initiation for adults and children with TB, several countries in Africa have moved beyond the 2016 WHO guidelines as they recommend starting ART within two weeks once TB treatment commences regardless of CD4 count. However, ART should be delayed for people living with HIV who have tuberculous meningitis, because immediate ART is associated with more severe adverse events than initiating ART two months after TB treatment starts". [2]

"A great barrier to early initiation of ART is lack of diagnosis as around 17 million people are accounted to be unaware of their HIV infection. Subsequently, this leads to submission to medical care in the later stages of HIV where the advantages of early initiation of ART will not be achieved in a substantial number of patients". [3]

Treatment Regimen:

"The Food and Drug Administration (FDA) has approved over 30 antiretroviral (ARV) drugs in seven mechanistic classes for the treatment of HIV infection. These seven classes comprise the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors, CCR5 antagonist, and a CD4 T lymphocyte (CD4) post-attachment inhibitor. Additionally, two drugs namely ritonavir (RTV) and cobicistat (COBI) are used as pharmacokinetic (PK) boosters to enhance the PK profiles of PIs and the INSTI elvitegravir (EVG)". [5]

"The initial ARV regimen for a treatment-naive patient normally consists of two NRTIs with the addition of a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI. Clinical trials and retrospective evaluation of cohorts of patients in clinical care have shown that this strategy has resulted in the suppression of HIV replication and CD4 count increases in most persons with HIV". [16, 17] Viral suppression can generally be achieved 8 to 24 weeks after ART initiation for those individuals who are adherent to their ARV regimens and do not foster resistance mutations to the component drug; though in some patients it may take longer.

Table: 2 Preferred first, second, and third-line ART regimens [5, 18]

Population	1st line regimen	2nd line regimen	3rd line regimen	Comments
Adults and adolescents	TDF + 3TC (or FTC) + DTG	AZT + 3TC + ATV/r (or	AZT + 3TC + DRV/r	• Women not using or accessing contraception or who want to be pregnant

		LPV/r)		can use DTG if they have been fully informed of the potential increase in the risk of neural tube defects. However, DTG should be initiated or continued throughout the period of pregnancy, if women identify pregnancy after the first trimester. • TDF should be used with caution or avoided in patients with renal impairment and osteoporosis. • RAL + LPV/r can be taken as an alternative second-line ART regimen for adults and adolescents.
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG	AZT + 3TC + ATV/r (or LPV/r or DRV/r)	
	AZT + 3TC + EFV (or NVP)	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)	
Pregnant and breastfeeding women	TDF + 3TC + DTG			During breastfeeding, the possibility of conception remains.
TB co-infection	TDF + 3TC + DTG			Dose adjustment of DTG needed
Children and infants	ABC + 3TC + DTG	AZT + 3TC + LPV/r (or ATV/r)	AZT + 3TC + DRV/r	• The European Medicines Agency presently only approves DTG for children weighing no less than 15kg and more widely for children weighing more than 20kg who can administer 50mg film-coated tablets. • ATV/r can be used as a substitute for LPV/r for children older than 3 months. However, the limited availability of suitable formulations for toddlers younger than 6 years, the shortage of a fixed-dose formulation and the requisite for separate administration of the ritonavir booster should be observed when choosing this regimen. • DRV should not be used alone for children younger than three years and therefore should be combined with appropriate dosing of ritonavir.
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG	AZT (or ABC) + 3TC + RAL	
	ABC (or AZT) + 3TC + EFV	AZT (ABC) + 3TC + DTG	AZT (or ABC) + 3TC + LPV/r (or ATV/r)	
	AZT + 3TC + NVP	ABC + 3TC + DTG	ABC + 3TC + LPV/r (or ATV/r or DRV/r)	

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; RAL: Raltegravir; NVP: nevirapine; TDF: tenofovir disoproxil fumarate.

"Changing to a new regimen with at least two active drugs is often required when initial HIV suppression is not achieved or maintained. Low baseline viremia, high potency of the ARV regimen, tolerability of the regimen, convenience of the regimen as well as excellent adherence to the regimen encompasses the predictors of virologic success. The increasing number of ARV drugs and drug classes facilitate viral suppression below detection limits, thereby setting an achievable goal in most patients". [5]

"The 2019 updated guidelines recommend dolutegravir (DTG) based on rapidly evolving evidence of safety and efficacy in pregnant women and people co-infected with TB. These guidelines provide further assurance of DTG as the preferred antiretroviral drug in first and second-line regimens due to the diminishing estimate of neural tube defect risk". [19] "Moreover, an updated systematic review conducted to support the guidelines reasserted that a first-line regimen of DTG combined with two nucleoside reverse-transcriptase inhibitors (NRTIs) results in higher viral suppression and lower risk of discontinuing treatment as well

as developing HIV drug resistance compared with EFV (efavirenz)-based regimens among treatment-naive adults. Lower potential for drug-drug interactions, more rapid viral suppressions, and a higher genetic barrier to evolving HIV drug resistance are some other advantages of DTG over EFV". [20, 21] "However, among people co-infected with HIV and TB, the dose of DTG should be increased to 50mg twice daily due to drug-drug interactions with rifampicin efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir. Compared with EFV, this additional dose of DTG is well tolerated and exhibits equivalent efficacy in viral suppression and recovery of CD4 cell count, However, Increased Cholesterol, triglycerides, and lipase are associated with dolutegravir". [22]

"The Food and Drug Administration (FDA) has approved DTG for use in infants and young children (aged ≥ 4 weeks and weighing ≥ 3kg) rather than being limited to children aged ≥ 3 years and weighing ≥ 25kg. Raltegravir (RAL) is considered an effective alternative option among children for whom approved dosing of DTG is unavailable and is approved for use from birth. RAL efficaciously decreases viral load among highly viraemic infants and is safe and well-tolerated among newborns and infants at high risk of infection. Furthermore, abacavir (ABC) has been approved by the FDA for use in infants aged ≥ 3 months, and the Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends abacavir (ABC) plus lamivudine (3TC) or emtricitabine (FTC) as a favored dual NRTI backbone for use in infants and children aged ≥ 1 month. Additionally, with the potential to use ABC in infants and toddlers, zidovudine (AZT) is now recommended as an alternative NRTI for use in children aged ≥ 1 month". [23]

"Recently, the FDA has accepted the first complete long-acting injectable ARV regimen, cabotegravir (CAB) and rilpivirine (RPV), as an alternative to replacing the current ARV regimen in adults with HIV who are on stable antiretroviral therapy, with HIV RNA levels < 50 copies/ml and have no history of treatment failure or suspected resistance to these agents". [24] "Further, in July 2020, the FDA approved Rukobia (Fostemsavir) for adults living with HIV, who have tried different ARV regimens and whose HIV infection cannot be effectively treated with other medications because of resistance, intolerance, or safety considerations". [25]

Adherence to Antiretroviral Therapy:

"Adherence to ART can be determined by multiple factors such as the patient's social circumstance and clinical condition, the prescribed regimen, and the patient-provider relationship. Lack of adherence is often an outcome of complex medication regimens, patient-related factors such as active substance abuse, low health literacy, depression, or the experience of adverse effects, together with health system issues including inconsistent access to medications as well as inadequate treatment education and support". [26] Poor compliance or infrequent access to ART can lead to treatment failure and the emergence of drug-resistance mutations that may adversely affect future treatment options.

"Treatment adherence encompasses initiating care with an HIV provider (linkage to care), regularly attending appointments (retention in care), and compliance with antiretroviral therapy. It is estimated that only around 55% of people diagnosed with HIV are virally suppressed due to poor linkage to care and retention in care". [27] "All healthcare professionals play vital roles in successful ART adherence programs. Clinicians should help

patients in identifying responsible factors and potential barriers to adherence and should design multidisciplinary plans to overcome those barriers. Further, each new patient must assimilate basic information about HIV infection, including therapy goals, the prescribed regimen (dosing schedule and potential side effects), the importance of compliance with ART, and the ability to develop drug resistance because of suboptimal adherence. Thus, building a trustful patient-provider relationship and maintaining good communication will help to improve compliance and long-term outcomes". [28]

Strategies to improve adherence to ART are: [5]

- Setting an accessible, trustworthy, unbiased multidisciplinary health care team.
- Establish early linkage to care and retention in care.
- Identify potential barriers to adherence and develop necessary medication management skills both before and after starting ART.
- Assess the patient's knowledge about HIV infection, prevention, and treatment. Then, based on this assessment, provide the necessary information.
- Provide required resources such as stable housing, transportation assistance, social support, income, and food security.
- Involve the ARV drug selection.
- Assess compliance with treatment at every clinic visit.
- Identify the factors for poor adherence and target ways to improve adherence.

Conclusion:

The HIV pandemic has induced a devastating impact on human lives and represents the most significant global health challenge in modern history. Though antiretroviral therapy is not curative, a combinational ART regimen can effectively control HIV replication, prolong life and reduce transmission risk. Soon after the diagnosis of HIV, ART should be initiated and continued indefinitely without interruption. The crucial element in successfully maintaining viral suppression is uninterrupted access to ART and adherence to the prescribed regimen. Hence, it is important to educate patients about the benefits of ART and to recognize barriers to treatment adherence.

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