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Review Article

Antiretroviral Therapy: A Compendium of the Evolving Treatment Paradigm for HIV infection

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Abstract

Guidelines on Antiretroviral Therapy (ART) are updated regularly and it is important to be abreast with the increasing knowledge. Recent international recommendation suggests initiating the ART to all those individuals who have detectable viremia. While it is imperative to perform baseline $CD4^+$ counts, viral loads and resistance testing before starting treatment, non-availability of any of these tests should not delay treatment initiation. Currently, ART in the form of daily administered triple-drug combination therapy consisting of 2 NRTIs plus 1 INSTI/PI/NNRTI, is recommended for newly diagnosed patients. The regimen should be selected based on virological efficacy, adverse effects, drug-drug interactions and cost. This article is an attempt to give an overview of existing and upcoming antiretroviral drugs and recent recommendations in the management of people living with human immunodeficiency virus infection.

Introduction

The realm of Human Immunodeficiency Virus (HIV) began with sickness, panic and death as the world faced a new virus. However, over time, the world has turned the corner for this virus– it has halted and even begun to reverse the spread of the disease, which has gone on from being a deadly disease to a chronic but manageable condition. This can largely be attributed to a better understanding of virus morphology, its pathophysiology, introduction of new and effective antiretroviral treatment regimes, development of more powerful tools for measuring HIV RNA levels in the blood and the adoption of People-First Language by the clinicians as envisaged by WHO [1]. Furthermore, the complete elucidation of the molecular and replicative pathways of the HIV virus has opened many floodgates in the field of HIV therapeutics. This article aims to review treatment of HIV infection with special emphasis on newer drugs and recommendations in the management.

Replication Cycle of the Virus with the Mechanism of Action of Antiretroviral Drugs

The virus belongs to Retrovirus family and the genus, *Lentivirus*. It has single stranded RNA that infects cells of immune system such as macrophages, T-helper cells and dendritic cells. The summary of HIV cycle and the action of antiretroviral drugs at various stages of the cycle is shown in the **(Figure 1)**. Entry of the virus in to the cell is a multistep process that involves attachment i.e. receptor binding, followed by co-receptor binding, fusion, reverse transcription of the genetic material, integration with the host DNA, synthesis of viral particles, assembly and budding [2]. The first step in the attachment involves high affinity binding of the viral envelope glycoprotein complex gp160 (consisting of gp120 and gp41) with its receptor, CD4+ on the host cell. Subsequently, gp120 with the help of co-receptors CCR5 or CXCR4 on leucocytes induces a material change in the HIV gp120/gp41 complex and exposes gp41. The peptide gp41 penetrates the cell membrane, bringing viral particles closer to cell membrane and fusion of the viral membrane with that of host. T-cell tropic HIV strains use mainly CXCR4 as their co-receptor and are referred to as X4 strains, whereas macrophage-tropic strains that use CCR5 as co-receptor are called as R5 strains. Early after HIV infection, most patients harbor R5 strains and later in the stage, X4 strains become prominent with decreasing CD4+ counts [3,4]. Viruses with dual tropism (R5/X4) and mixed tropism (R5 + X4) can also be found with a significantly increased risk of disease progression among such patients [5]. Once fused to the host cell membrane, the viral RNA and various enzymes are injected into the cell. Inside the cytoplasm, the reverse transcriptase enzyme transcribes viral RNA into complementary DNA (cDNA), which subsequently forms Double Stranded DNA (dsDNA). The dsDNA enters cell nucleus and integrates with host DNA with the help of an enzyme, integrase. Treatment with nucleoside or Non-Nucleoside Reverse Transcriptase Inhibitors (NRTI/NNRTI) inhibit reverse transcriptase and prevent transcription to cDNA, while integrase inhibitors inhibit the integration of dsDNA with the host chromosome. The integrated DNA is dormant until the host immune cell is activated by activation factors. The proviral DNA is then transcribed into mRNA and viral genomic RNA, which in turn is translated into long polyprotein chain that harbors viral enzymes and structural proteins. The final step of the viral cycle, i.e. assembly of viral particles, begins at the cell's outer membrane where they assemble into actual matrix and capsid and form an immature, non-infectious viral particle or bud. No existing drug can inhibit this step. The viral bud is then released from the host cell. The viral enzyme, protease, cuts the long HIV polypeptide chain into smaller functional units and finally a mature infectious viral particle. This step can be inhibited by the antiretroviral drugs of protease inhibitor class. **Table 1** shows the classification of the currently available antiretroviral drugs based on their site of action.

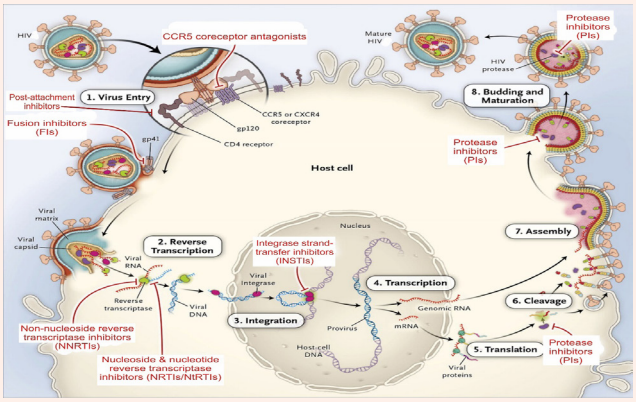

Figure 1: Life cycle of HIV and site of action of Antiretroviral drugs

Adapted from the National HIV Curriculum of AETC National Coordinating Resource Center and the University of Washington (Available at https://cdn.hiv.uw.edu)

Table 1: Currently Available Antiretroviral Agents

Category/Agents
Reverse Transcriptase Inhibitors (RTIs)
i) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
Zidovudine (AZT or ZDV)
Zalcitabine (ddC)
Stavudine (d4T)
Didanosine (ddI)
Abacavir (ABC)
Lamivudine (3TC)
Emtrictabine (FTC)
ii) Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)
Tenofovir Disoproxil Fumarate(TDF)
Tenofovir Alafenamide (TAF)
iii) Non - Nucleoside Reverse Transcriptase Inhibitors(NNRTIs)
Delavirdine (DLV)
Efavirenz (EFV)
Nevirapine (NVP)
Etravirine (ETR)
Rilpivirine (RPV)
Doravirine (DOR)
Protease Inhibitors (PIs)
Indinavir (IDV)
Ritonavir (RTV)
Lopinavir (LPV)
Saquinavir (SQV)
Nelfinavir (NFV)
Atazanavir (ATV)
Amprenavir (APV)
Fosamprenavir (FVP)
Tipranavir (TPV)
Darunavir (DRV)
Integrase Inhibitors (INIs)
a. Integrase Strand Transfer Inhibitors (INSTIs)
Raltegravir (RAL)
Dolutegravir (DTG)
Elvitegravir (EVG)
Bictegravir (BIC)
Cabotegravir (CAB)
b. Integrase Binding Inhibitors (INBIs)
Entry Inhibitors
a. Attachment Inhibitors
Fostemsavir
b. Post attachment Inhibitors
Ibalizumab (TMB-355)
c. Chemokine Receptor Inhibitor
Maraviroc (MVC)
d. Fusion inhibitors
Enfuvirtide (T-20)
Pharmacokinetic Enhancers (PKs)
Cobicistat (COBI)
Low dose ritonavir (r)

Evolving Antiretroviral Therapy: Addressing Tolerability and Barrier to Treatment Adherence

Reverse Transcriptase Inhibitors

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs were the first class to get regulatory approval for treatment of HIV. These are prodrugs and undergo activation by intracellular phosphorylation mediated by several host cellular kinases. The active triphosphate form competitively binds to reverse transcriptase and blocks the synthesis of cDNA of both HIV-1 and -2 and inhibits the viral replication. Current standard of care requires a combination of NRTI with others. However, many NRTIs have largely fallen out of favor because of drug associated toxicities. The first antiretroviral drug licensed for use was zidovudine (AZT). It has, for long, formed the backbone of ART regimes; being used as monotherapy, dual therapy and as part of the three drug regimens but has now been replaced by drugs with better safety profiles. In some resource-poor settings, it still continues to be used as part of combination ART regimes. Other NRTIs include didanosine, zalcitabine, stavudine, abacavir, lamivudine and emtricitabine. There is little cross-resistance between these agents and therefore most of these agents are usually given in pairs. Didanosine is inactivated by the low pH of stomach; therefore, it is available in combination with a buffer, which increases the gastric pH. However, it is less active clinically than zidovudine. But because we have better drugs available, didanosine and zalcitabine are no longer recommended in any of the guidelines. With the recognition that Integrase Strand Transfer Inhibitors (INSTIs)-based therapy yield better results, the role of AZT, stavudine and abacavir in the first line regimeis limite [6]. Lamivudine and emtricitabine are structurally similar dideoxycytidine analogs with emtricitabine offering an advantage of having longer half-life, higher oral bioavailability and greater *invitro* activity against HIV when compared to lamivudine [7].

Resistance

Long-term application of NRTIs has resulted in resistance to these drugs mainly from the mutations at reverse transcriptase codons. The reverse transcriptase enzyme cannot proof-read its own errors that allows amino-acid substitutions and causes structural or functional changes at its active sites. Thymidine Analogue Mutations (TAM) confer cross-resistance between AZT and stavudine, an important aspect in previously treated patients. M184V mutation with single amino acid substitution in the reverse transcriptase shows high level resistance to commonly used lamivudine and emtricitabine. However, M184V greatly restores sensitivity and partially reverse TAM-mediated resistance to AZT, stavudine and tenofovir, producing long-term suppression

of HIV.

Side Effects

The most common and significant toxicity of this class is mitochondrial toxicity that manifests as myopathy, peripheral neuropathy, pancreatitis, lipodistrophy, and/or hepatic steatosis [8]. AZT also causes bone marrow toxicity which presents as life threatening anemia and neutropenia in nearly 30% patients. The risk of developing these adverse effects is more in patients with full blown disease as compared to other HIV infected patients. Macrocytosis occurs in almost all patients but it does not predict the occurrence of anemia. Chronic use of AZT is also associated with blue nails. Lamivudine and emtricitabine are very well-tolerated drugs with rarely causing pancreatitis and skin changes. Lamivudine causes rash, nausea, headache and neutropenia, while emtricitabine causes hyperpigmentation at sun exposed areas. Painful peripheral neuropathy, lactic acidosis and fatty change in the liver (hepatic steatosis) are more common with stavudine, zalcitabine and didanosine. Therefore, these agents should be avoided in patients with fatty liver and pre-existing neuropathy and in patients taking drugs that cause peripheral neuropathy. Abacavir causes a potentially fatal hypersensitivity syndrome in patients who carry HLA-B*5701 allele. Screening for this allele, which is found in about 8% of the population[6], is now routinely recommended, and patients who are positive for this allele should not receive abacavir.

Drug Interactions

NRTIs are devoid of clinically significant drug interactions because they are neither the substrates nor inhibitors, or inducers of hepatic CYP-450 enzymes[9]. However, certain important interactions do exist. Combination of zidovudine and ganciclovir is poorly tolerated due to their combined hematological adverse effects. Zidovudine should be stopped when the patient is on high dose of ganciclovir and may be restarted when the dose of ganciclovir is reduced during the maintenance phase of CMV treatment. Zidovudine also decreases phenytoin levels, warranting monitoring in patients receiving both. AZT and stavudine compete each other and hence they should never be combined together.

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

Tenofovir is an analog of adenosine monophosphate, administered orally as a prodrug in the form of tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF). These forms are taken up by the cell and converted to pharmacological active moiety, tenofovir-diphosphate, intracellularly. Tenofovir in its isolated form reaches the plasma in lesser quantity and hence, this drug is less susceptible to side effects compared to NRTIs. Like lamivudine and emtricitabine, tenofovir has antiviral activity against hepatitis B virus; therefore, exacerbation of hepatitis B virus after discontinuation of tenofovir is possible and patients should be screened for hepatitis B virus prior to initiation of tenofovir[1,7].

Resistance

Tenofovir has a high barrier to resistance. It is effective against NRTI resistant HIV, thereby making it an attractive drug for first line treatment of HIV[1,10].

Side Effects

The most common side effects of tenofovir are nausea, vomiting, diarrhea and flatulence. Tenofovir is less likely to cause mitochondrial toxicity when compared to NRTIs [8] but it can cause bone loss and kidney injury. TAF is associated with lesser incidence of bone and renal toxicities compared to TDF. On the contrary, TAF is associated with greater weight gain and dyslipidemias.

Drug Interactions

Different transporters are involved in the transport of TAF and TDF, making TAF more susceptible to drug interactions. Co-administration with anticonvulsants and rifampicin decreases TAF concentrations but not TDF levels. Hence, TAF should not be used if the patient is receiving rifampicin. TDF should be used with caution in patients receiving amphotericin B and vancomycin due to the increased risk of nephrotoxicity [1,9].

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The NNRTIs are typically administered with a dual NRTI combination. These drugs directly bind to the reverse transcriptase enzyme at its active site non-competitively and cause allosteric inhibition. In addition, cDNA elongation is reduced, which ultimately leads to a decline in viral replication. There are six members in this group, divided into two generations. First generation NNRTIs include delavirdine, efavirenz and nevirapine whereas rilpivirine, etravirine and doravirine are second generation NNRTIs. All the NNRTIs are highly active against HIV-1 but not against HIV-2. They are highly bound to plasma proteins and extensively metabolized by cytochrome P450 enzymes. The toxicity and resistance do not overlap with NRTIs and NtRTIs, hence they were most commonly used in combination regimes. Currently, efavirenz and rilpivirine are the most commonly used NNRTIs for treatment-naïve patients,. Etravirine is generally reserved for individuals with an evidence of drug-resistant virus. Delavirdine requires higher doses and frequent administration. In the modern era of consolidated and streamlined ART, the pill burden and dosing schedule of delavirdine has limited its use. Nevirapine, for long, had been the preferred NNRTI for the treatment of HIV infection, but now efavirenz is being increasingly used, as it leads to a more durable viral suppression. Rilpivirine is approved for use in ART naïve patients with pretreatment viral loads <1,00,000 copies/mL. Doravirine, the most recently approved NNRTI has been shown to provide a more durable viral suppression. Etravirine offers the advantage of being effective in the treatment of HIV resistant to other available NNRTIs.

Resistance

Development of resistance and cross-resistance are major problems with the first generation NNRTIs, as a single mutation, K103N in the NNRTI binding pocket may confer high level resistance to all NNRTIs. The second generation NNRTI, etravirine, can however be used in patients with resistance to first generation NNRTIs[1,11].

Side effects

The most common side effects associated with this class of drugs are skin rash, nausea, headache and hepatic enzyme elevation. Skin rash develops in about 25% of people taking nevirapine [12]. It is recommended that if a patient develops a rash during the lead-in (lower dose) period of nevirapine, further dose increment should not be done. Nevirapine may also cause Stevens-Johnson syndrome in some individuals. Patients should also be carefully monitored for development of hepatotoxicity while taking nevirapine. Important adverse effects of efavirenz and rilpivirine include psychiatric symptoms (insomnia, confusion, memory loss, depression), skin rash, and headache [13]. QTc interval prolongation has been observed with efavirenz. The concerns about the teratogenicity of efavirenz were unfounded and its use is no longer prohibited during the first trimester of pregnancy. Severe immune reconstitution can occur in patients taking doravirine [1,14].

Drug interactions

Nevirapine can interact with other drugs having predominant hepatic metabolism. These drugs include anti-histamines, sedatives and anti-fungal agents. Nevirapine also increases the metabolism of protease inhibitors and therefore, should not be combined with them. Efavirenz is broken down in the liver by CYP3A4 and CYP2B6, while etravirine is metabolised by CYP3A4, CYP2C9, and CYP2C19. These drugs can decrease the metabolism of other drugs that require the same enzymes. In addition, they are moderate inducers of CYP3A4 and weak to moderate inhibitors of CYP2C9 and CYP2C19. Significant drug-drug interactions can be seen between these two drugs and rifabutin, clarithromycin, atorvastatin, azole group of antifungals, carbamazepine and other anti-convulsants[9]. Pharmacological boosting or increased doses of dolutegravir is recommended if these drugs are prescribed with it. Efavirenz also lowers the blood levels of most protease inhibitors. Efavirenz and saquinavir should never be used together since efavirenz lowers the blood levels of saquinavir dramatically. Concomitant administration of acid-lowering agents such as proton-pump inhibitors and H2-receptor antagonists with rilpivirine decrease the oral drug absorption, causing decreased viral suppression. Caution is also advised when rilpivirine and efavirenz are to be co-administered with drugs causing QT prolongation as this may result in *torsades de pointes*.

Protease Inhibitors (PIS)

PIs are the second class of drugs developed against HIV infection. They are active against both HIV-1 and HIV-2. Members of this class include saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir and darunavir. They inhibit the enzyme, protease and prevent proteolytic cleavage of polypeptide chain necessary for the formation of infectious viral particles.

Resistance

PIs have a higher genetic barrier to resistance and require multiple mutations to substantially lose antiviral activity. However, the development of resistance to pharmacologically boosted PIs in previously antiretroviral-naïve individuals is uncommon, even with less than optimal adherence, so PI-based regimens are a good choice for patients in whom adherence is a concern. Darunavir is the newest among PIs and do not possess cross-resistance with other PIs. It demonstrated activity against PI-resistant viruses and hence, it can still be used in second line and savage regimens [1,8].

Side Effects

Several side effects like insulin resistance, hyperglycemia, diabetes, hyperlipidemia, lipodystrophy, hepatotoxicity, bleeding in patients with hemophilia, and PR interval prolongation appear to be PI class effects, while others are agent-specific. Saquinavir can cause QTc prolongation. Indinavir can produce a transient increase in indirect bilirubin and renal calculi can develop in 3–15% of treated patients. Hence, patients on indinavir should be asked to maintain adequate hydration. Ritonavir causes dysgeusia, dyspepsia, abdominal pain and peripheral paraesthesias. Oral numbness is also seen in some patients. Atazanavir causes hyperbilirubinemia, renal stones, kidney injury and cardiac conduction abnormalities (asymptomatic AV blocks). Tipranavir is associated with severe hepatotoxicity and intracranial hemorrhage. Both tipranavir and darunavir have sulpha moiety in their structure and possess cross-allergy with sulphonamides [1].

Drug Interactions

CYP3A4 metabolizes all PIs except nelfinavir and therefore, drug interactions are frequent. Strong enzyme inducers like rifampicin, phenytoin, carbamazepine and phenobarbitone can reduce the concentration of these PIs. Inhibitors of microsomal enzymes like ketoconazole and itraconazole increase serum levels of these agents. This is most significant with saquinavir whose concentration is increased by up to 80% when combined with ketoconazole. Co-administration of rifampicin with indinavir leads to sub-therapeutic concentrations of indinavir and is therefore not advised. Most of these drugs also inhibit CYP3A4 at their usual dosage, although the magnitude of inhibition differs greatly, with ritonavir being the most potent inhibitor and hence used for pharmacological boosting. Ritonavir is available both in solution and capsule forms. Oral solution contains 43% alcohol, while capsules contain small amount of alcohol. Therefore, patients on ritonavir must avoid metronidazole and tinidazole to prevent disulfiram-like reaction. HMG-CoA reductase inhibitors like simvastatin and lovastatin should not be used in patients on PIs due to increased potential of myopathy and rhabdomyolysis. Atorvastatin and rosuvastatin can however be used, but with caution [9].

Integrase Inhibitors (INIs)

Integrase Stand Transfer Inhibitors (INSTIs) have opened a new era in the treatment of HIV infection. The outstanding data on efficacy and safety have made this class popular and are increasingly used as starting agents. Members of this class include raltegravir, elvitegravir, dolutegravir, bictegravir and cabotegravir. The other group of INIs such as Integrase Binding Inhibitors (INBIs) still remain experimental [15,16]. INSTIs act by inhibiting integrase enzyme that catalyzes the integration of viral dsDNA with host DNA. This step is specific to HIV (both HIV-1 and -2) and has no human homolog. The unique mechanism of action also makes them retain activity against multi-drug resistant HIV viruses. Raltegravir was the first approved INSTI followed by elvitegravir, dolutegravir, bictegravir and recently cabotegravir. Raltegravir and dolutegravir are metabolized by UGT enzymes and have less drug interaction potential compared to previous classes of drugs. They can be taken with food and no dose adjustment is needed for raltegravir and dolutegravir in patients with mild to moderate renal and hepatic dysfunction. On the other hand, elvitegravir-based regimens should be used with caution in patients with renal failure. Given the safety, efficacy and convenience, dolutegravir is recommended as first-line agent in most recommendations. It does not require pharmacologic boosting except for efavirenz- and etravirine-based regimes and can be used in treatment-experienced patients with genotypic resistance to raltegravir or elvitegravir. The claims about teratogenicity in the form of neural tube defects with dolutegravir were unfounded and currently it is recommended as first-line drug even for pregnant patients. This drug has also received approval for paediatric patients of at least 4 weeks old and weighing 3 kg. Data from antiretroviral pregnancy registry indicate no major concerns with raltegravir as well while sufficient data is lacking for bictegravir and cabotegravir. Elvitegravir produces sub-therapeutic levels and decreased viral suppression in pregnant women and hence, until sufficient data is available on its boosting, it is not recommended in pregnancy.

Resistance

Raltegravir and elvitegravir have low genetic barrier to resistance and have cross-resistance. In contrast, dolutegravir resistance is very uncommon among patients failing an initial regimen that contains dolutegravir. It is also uncommon for such individuals to develop resistance to the NRTIs that are administered in combination with dolutegravir. Even if there is 100% resistance to NRTIs, NRTI based regimen with dolutegravir can be safely administered as this has shown equal efficacy in such patients [17]. Thus, dolutegravir is well suited for use in those who require treatment before the results of genotype testing become available [18]. Data is lacking for resistance to bictegravir. This drug has not been evaluated in patients with prior INSTI use or any documented INSTI- resistance, and so it should not be used for these individuals until more data becomes available.

Side Effects

All INSTIs are generally well tolerated. Nausea, diarrhea, weight gain, insomnia, dizziness and rarely depression and suicidal ideation in psychiatric patients have been noted with INSTIs. Raltegravir ande dolutegravir are also known to cause myopathy and rhabdomyolysis occasionally [19].

Drug Interactions

A decrease in INSTI concentrations is possible when administered with polyvalent cation-containing antacids and supplements. With regards to specific agents, there are relatively few problematic interactions with raltegravir and dolutegravir as they are metabolized by glucuronidation and neither inducers nor inhibitors of CYP enzymes. Bictegravir is metabolized by CYP3A and its plasma levels are affected by concomitant medication which affect CYP system. In contrast, elvitegravir is associated with more drug-drug interactions since it is administered with the boosting agent cobicistat, which is a potent inhibitor of CYP3A [20]. Elvitegravir containing formulations are contraindicated in patients taking lovastatin, simvastatin and rifampicin.

Entry Inhibitors

Encouraging progress is seen in the development of entry inhibitors in recent times. Their mechanism of action is unique and act at different levels of viral entry into the cells, providing an advantage of acting against resistant viruses. However, the development of viral resistance to these agents is common and significant toxicity and adherence issues still occur. The various drugs under this class are fostemsavir, maraviroc, enfuvirtide and ibalizumab.

a. **Attachment inhibitors**: These drugs target the first step in the viral entry into the cells. In July 2020, fostemsavir became the first in the class to get approval. It is indicated in the management of multidrug-resistant HIV-1 infection in combination with other antiretrovirals. Inside the body, fostemsavir is hydrolyzed to produce active moiety temsavir that binds to gp120 and prevents viral attachment to CD4+ receptor and subsequent processes. Caution is recommended while choosing drugs for combination regimen as fostemsavir is a substrate of CYP3A4 and it produces adverse drug reactions such as renal toxicity, hepatotoxicity, QT prolongation and immune reconstitution syndrome.

b. **Post-attachment inhibitors**: The only member of this class, ibalizumab is the first monoclonal antibody and the latest antiretroviral drug to receive regulatory approval. The drug binds to CD4+, decreases the flexibility of CD4+ and hinders access of CD4-bound gp120 to CCR5 and CXCR4.Ibalizumab does not appear to interfere with immunological functions that involve antigen presentation and viral attachment, but does block viral entry [21]. Similar to fostemsavir, it is indicated for the management of multidrug resistant HIV-1 infections. The drug is administered intravenously every 14 days and infusion related reactions are common.

c. **Chemokine receptor antagonists**: These include CCR5 antagonists and CXCR4 antagonists which bind to CCR5 and CXCR4 receptors respectively and prevent viral entry. The development of CXCR4 inhibitors has proceeded more slowly than that of the CCR5 antagonists as X4 viruses usually are present along with R5 viruses (in contrast to R5 viruses which are found on their own in majority of the HIV patients). Inhibition of just the X4 component of the virus population may not lead to decrease in plasma viremia, thereby complicating drug activity assessment. Maraviroc is a CCR5 antagonist which is currently approved for the treatment HIV-1 but its clinical usefulness in HIV-2 infection is still an unaddressed issue. If maraviroc is being considered, a tropism assay is essential prior to initiation of therapy. This assay determines whether a response from a CCR5 antagonist should be expected since maraviroc is not active against X4 or dual-mixed tropic viruses [2-4]. The drug may cause dizziness, immune reconstitution syndrome and hypersensitivity reactions and increase the risk for upper respiratory and herpes infections and malignancy due to its mechanism of action. Hence, it is not used commonly but it may have a role in multidrug-resistant HIV-1 infections. However, the dose has to be adjusted with concomitant antiretrovirals that influence CYP3A4 as maraviroc is a substrate for this cytochrome.

d. **Fusion Inhibitors (FIs)**: Fusion inhibitors bind to the gp41subunit of the viral envelop glycoprotein; this interferes with viral fusion to the CD4+ T cell. Enfuvirtide is the only approved drug in this class. It is active against HIV-1 but HIV-

2 is intrinsically resistant to enfuvirtide [2]. Enfuvirtide is an oligopeptide and has to be administered *via* subcutaneous route, which often leads to injection-site reactions; thereby precluding its long-term use.

Pharmacokinetic Enhancers (PEs)

PEs are used to boost the effectiveness of another drug. Cobicistat and low dose ritonavir are the two approved PEs in combination regimens with protease inhibitors and elvitegravir. Full-dose ritonavir is never used alone to treat HIV infection because of potential adverse reactions and drug interactions associated with the inhibition of CYP3A, allowing PIs/INSTIs to remain in the body longer and at a higher concentration. Cobicistat, although chemically similar to ritonavir, does not have any HIV activity of its own [22].With the significant antiretroviral drug development, we now have much safer and efficacious drugs that are highly recommended as first line regimen, while combination regimen with PEs are in the alternate list.

A summary of commonly used antiretroviral drugs is given in **Table 2**.

Table 2: Characteristics of Commonly Used Antiretroviral Drugs

Drug	Administration	Adverse effects	Common drug interactions
Zidovudine (ZDV)	200 mg q8h or 300 mg q12h Take without regard to meals	Bone marrow suppression, GI intolerance, headache, lactic acidosis, myopathy	Avoid with ribavirin, ganciclovir
Zalcitabine (ddC)	0.75 mg q8h Take without regard to meals	Peripheral neuropathy, stomatitis, lactic acidosis	Avoid with antacids
Didanosine (ddI)	> 60 kg : 200 mg q12h < 60 kg : 125 mg q12h Take 30 min before or 2 h after meals	Pancreatitis, peripheral neuropathy, GI intolerance, lactic acidosis, optic neuritis	Avoid with i/v pentamidine, ganciclovir
Stavudine (D4T)	> 60 kg : 40 mg q12h < 60 kg : 30 mg q12h Take without regard to meals	Pancreatitis, peripheral neuropathy, lactic acidosis, stomatitis, lipoatrophy	Avoid with zidovudine
Abacavir (ABC)	300 mg q12h or 600 mg q24h Take without regard to meals	Hypersensitivity reaction (features may include fever, rash, nausea, vomiting, fatigue, anorexia, malaise, cough, respiratory difficulty) may be fatal	No clinically significant interactions
Lamivudine (3TC)	>50 kg: 150 mg q12h < 50 kg: 2 mg/kg q12h Take without regard to meals	Acute hepatitis, lactic acidosis, pancreatitis	Caution when using with other treatments for HBV
Emtricitabine (FTC)	200 mg q24h Take without regard to meals	Lactic acidosis hyperpigmentation of skin and hepatic steatosis;	No clinically significant interactions
Tenofovir (TDF/TAF)	TAF 25 mg/ TDF 300 mg q24h Take without regard to meals	Asthenia, headache, nausea, vomiting, lactic acidosis,hepatic steatosis, osteomalacia, depression, renal failure	Monitor for toxicity of cidofovir, ganciclovir
Delavirdine (DLV)	400 mg q8h Take without regard to meals	Skin rash, fat redistribution, headache, nausea, diarrhea, tiredness	Caution when using with didanosine
Efavirenz (EFV)	600 mg HS Avoid taking after high fat meal	Skin rash, CNS effects (dizziness, insomnia, abnormal dreams, confusion, agitation, hallucinations), hepatitis	Avoid with astemizole, cisapride, midazolam
Nevirapine (NVP)	200 mg q24h for 14 d (lead in), then 200 q12h Take without regard to meals	Skin rash, hepatitis Do not restart after severe hepatitis or skin reaction	Avoid with ketoconazole, rifampicin, oral contraceptives
Etravirine (ETR)	200 mg q12h Take following a meal	Skin rash including Stevens- Johnson syndrome, nausea, peripheral neuropathy	Avoid with unboosted protease inhibitors
Rilpivirine (RPV)	25 mg q24 h Take with meals	Skin rash, depression, insomnia, hepatotoxicity, QTc prolongation	Caution when using with drugs known to cause torsades de pointes
Doravirine (DOR)	100 mg q24 h Take without regard to meals	Headache, tiredness, abdominal pain, abnormal dreams, IRIS	Avoid with rifampicin, anticonvusants
Indinavir (IDV)	800 mg q8h Take 1 hr before or 2 h after meals	Nephrolithiasis, GI intolerance, headache, asthenia, blurred vision, dizziness, hyperglycemia, redistribution of fat and lipid abnormalities	Avoid with lovastatin, simvastatin rifampicin, astemizole, cisapride, midazolam Caution when using with atorvastatin
Ritonavir (RTV)	Day 1-2 : 300 mg q12h; Day 3-5 : 400 mg q12h; Day 6-13: 500 mg q12h; Day 14 onwards: 600 mg q12h Take with meals	GI intolerance, paraesthesias, hepatitis, hyperglycemia, redistribution of fat, lipid abnormalities, taste perversion	Avoid with amiodarone, lovastatin, simvastatin, astemizole, cisapride, midazolam, oral contraceptives, metronidazole Caution when using with atorvastatin, ketoconazole, theophylline, lovastatin,
Nelfinavir (NFV)	750 mg q8h Take with meals	Diarrhoea, hyperglycemia, redistribution of fat, lipid abnormalities, flatulence	Avoid with lovastatin, simvastatin, rifampicin, rifabutin, astemizole, cisapride, midazolam, oral contraceptives Caution when using with atorvastatin
Saquinavir (SQV)	SQV 500 mg +RTV 100 mg q12h for 7 days then SQV 1000 mg + RTV 100 mg Take with meals	GI intolerance, headache, hepatitis, hyperglycemia, redistribution of fat, lipid abnormalities, rhinitis, QTc prolongation	Avoid with lovastatin, simvastatin, rifampicin, rifabutin, astemizole, cisapride, midazolam Caution when using with atorvastatin

Amprenavir (APV)	APV 1200 mg + RTV 200 mg q24h or APV 600 + RTV 100 mg q12h Take without regard to meals	Hepatotoxicity, fat redistribution, hyperlipidemias	Avoid with preparations containing Vitamin E, ergot derivatives, cisapride
Fosamprenavir (FPV)	FPV 1400 mg + RTV 200 mg q12h or FPV 700 mg +100 mg RTV q12h Take without regard to meals	Skin rash, GI intolerance, headache, hyperglycemia, redistribution of fat, lipid abnormalities, hepatitis	Avoid with lovastatin, simvastatin, rifampicin
Lopinavir (LPV)	LPV 400 mg + RTV 100 mg Take with meals	GI intolerance, headache, hepatitis, hyperglycemia, redistribution of fat, lipid abnormalities	Avoid with lovastatin, simvastatin, rifampicin, astemizole, cisapride, midazolam Caution when using with atorvastatin
Atazanavir (ATV)	ATV 300 mg + RTV 100 mg q24h Take with meals	GI intolerance, nausea, vomiting, diarrhoea, abdominal pain, skin rash, pruritis, renal stones	Avoid with cisapride, ergot derivatives
Tipranavir (TPV)	TPV 500 mg + RTV 100 mg q12h Take without regard to meals	Hypersensitivity, skin rash, hyperlipidemia, hyperglycemia, fat maldistribution	Caution when using with in patients with known sulfonamide allergy
Darunavir (DRV)	DRV 800 mg + RTV 100 mg q24h (In ART naïve patients or ART experienced patients without DRV mutation) DRV 600 mg + RTV 100 mg q12h (In ART experienced patients with one/more DRV mutation) DRV 800 mg + COBI 150 mg Take with meals with RTV and without regard to meals with COBI	Skin rash, SJS, TEN hepatotoxicity, diarrhea, nausea, fat maldistribution	Caution when using with in patients with known sulfonamide allergy
Raltegravir (RAL)	RAL 400 mg q12h (In ART naïve patients or ART experienced patients) RAL 1200 mg q24h (In ART naïve/ experienced patients who are virologically suppressed on RAL 400 mg q12h) Take without regard to meals	Skin rash, SJS, TEN, headache, diarrhea, nausea, pyrexia, CPK elevation, insomnia, depression, suicidal ideation	Avoid with aluminium/ magnesium hydroxide containing antacids Caution when using with rifampicin

Dolutegravir (DTG)	DTG 50 mg q24h (ART naïve or ART experienced INSTI patients) DTG 50 mg q12h (INSTI experienced patients with certain INSTI mutations or with clinically suspected INSTI resistance) Take without regards to meals	Hypersensitivity reactions, insomnia, headache, hepatotoxicity, depression and suicidal ideation	Avoid with Dofetilide Caution when using with drugs that are metabolic inducers
Elvitegravir (EVG)	Fixed dose combination (EVG 150mg + COBI 150 mg + FTC 200 mg + TAF/TDF 25/300 mg) Take with meals	Nausea, diarrhoea, depression, suicidal ideation	Avoid with cobicistat boosted protease inhibitors
Bictegravir (BIV)	Fixed dose combination (BIC 50 mg + TAF 25mg + FTC 200 mg) Take with meals	Nausea, diarrhoea, vomiting	Avoid with Dofetilide Caution when using with polyvalent cations
Cabotegravir (CAB)	Intramuscular injection CAB 300 mg, RPV 600 mg	Injection site reaction, weight gastrointestinal disturbances, depressive disorders, hepatotoxicity	Antacids and Histamine H2 Receptor Antagonists may decrease the concentration of RPV. Caution when using with carbamazepine, phenytoin, phenobarbitone
Ibalizumab	Loading dose 2000 mg Maintenance dose 800 mg every 2 weeks dissolved in 250 mg NS	Nausea, diarrhea, dizziness, rash	No clinically significant interactions
Maraviroc (MVC)	MVC 150 mg q12h when given with strong CYP3A inhibitors MVC 300 mg q12h when givenwith drugs that are not strong CYP3A inhibitors or inducers MVC 600 mg q12h when given With CYP3A inducers Take without regard to meals	Abdominal pain, cough dizziness, pyrexia, rash, upper respiratory infections, orthostatic hypertension, hepatotoxicity	Caution when using with carbamazepine, phenytoin, phenobarbitone
Enfuvirtide (T20)	90 mg q12h Subcutaneous injection	Local injection site reactions (nearly 100%), increased rate of bacterial pneumonia, hypersensitivity reactions	No clinically significant interactions

Fostemsavir	600 mg per oral q12h Take without regard to meals	Kidney injury, nausea, transaminase elevation, QT prolongation, Conjugated hyperbilirubinemia, anemia, dyslipidemia	Significant interactions with carbamazepine, rifampicin, phenytoin and efavirenz. Contraindicated to use with these drugs.

When to start ART?

ART is recommended for all individuals with HIV who have detectable viremia regardless of the CD4+ count [1,23-26]. However, ART may have to be deferred in some patients because of psychological factors or in patients with cryptococcal/tubercular meningitis, where little delay before ART initiation is warranted to reduce the risk of IRIS. Such patients should be evaluated individually and attempts should be made to initiate therapy as early as possible [1,23-25]. Combination ART regimen with 2 to 3 drugs from >2 different drug classes is recommended. The benefits of ART have been demonstrated in widely divergent socioeconomic settings. Thus, indications for therapy do not generally differ in high and low resource regions. Clinicians should explain to patients that the currently available regimens do not cure HIV and once initiated ART has to be continued indefinitely. The patient must also be explained that ART is not a substitute for behavioral modification(s), and ART does not provide protection against other sexually transmitted infections, but, it is very important to adhere to treatment regimen to heal and prevent occurrence of drug resistance.

Evaluation before starting ART

Complete clinical and laboratory evaluation and counselling regarding the implications of HIV diagnosis should be made at the first visit post diagnosis [1]. The objective is to confirm the HIV infection, determine the clinical stage and the presence of co-infections, and assess overall health condition.

The evaluation includes the following:

- CD4+ cell counts
- Plasma HIV RNA (viral load)
- HIV antibody testing
- Genotypic resistance testing
- Complete blood counts, aspartate and alanine transaminase levels, renal function tests, Mantoux test, Chest X-ray, urinalysis, VDRL, serology for hepatitis A, B and C viruses
- Fasting blood glucose and serum lipids
- Pregnancy test
- Screening tests for sexually transmitted infections and opportunistic infections
- Viral tropism assay (if there is a plan to start CCR5 antagonist or when there is a virological failure with CCR5 antagonist)
- HLA-B*5701 testing (before initiating Abacavir)

Updated Recommendations on Initial Choice of ART

Bictegravir and dolutegravir based INSTI-regimens are the currently recommended initial ART regimen for most people with HIV as these regimens have shown better efficacy in terms of virological suppression and safety than PI or NNRTI based regimen [1, 25-27] (Table 3). However, a regimen should be selected based on availability, cost, adverse drugs reactions, concomitant medications, potential drug interactions, comorbidities, efficacy, pill burden and resistance test results. The regimen for a treatment-naïve patient should consist of two NRTIs usually tenofovir & emtricitabine or abacavir & lamivudine plus a drug from one of the three classes namely INSTI, NNRTI or PE- PI. Recently a "two-drug" based regimen consisting of dolutegravir and lamivudine has also shown comparable efficacy and can also be considered as an initial therapy.30Dolutegravir as a three drug regime can be started even when resistance test results are not available as it has a higher barrier to resistance and no transmitted resistance has yet been identified.1A recent trial concluded that dolutegravir in combination with NRTIs is effective even in those with extensive NRTI resistance and there is no need to switch from tenofovir to zidovudine in such cases [18]. Of late, novel injectable ART regimens consisting of long-acting cabotegravir and long-acting rilpivirine given once every four weeks and potentially every eight weeks have also been found effective for the treatment [26].

Table 3: Recommended ART Regimens

Preferred ART Regimes (not in the order of preference)
Bictegravir + Tenofovir alafenamide + Emtricitabine (BIC + TAF + FTC)
Dolutegravir+ Abacavir+ Lamivudine (DTG+ABC+3TC)—if HLA-B*5701 is negative
Dolutegravir + Tenofovir alafenamide + Emtricitabine (DTG + TAF + FTC)
Dolutegravir + Tenofovir disoproxil fumarate + Emtricitabine (DTG + TDF + FTC)
Dolutegravir + Tenofovir disoproxil fumarate + Lamivudine (DTG + TDF + 3TC)
Dolutegravir + Lamivudine (DTG+3TC)

*Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

Table 4: Alternative ART Regimes(not in the order of preference)

INSTI – based regimens
Elvitegravir/cobicistat + Tenofovir + Emtricitabine (EVG/c + TAF or TDF + FTC)
Raltegravir + Tenofovir Disoproxil Fumarate + Emtricitabine (RAL +TDF + FTC)
Raltegravir + Tenofovir Disoproxil Fumarate + Lamivudine (RAL + TDF + 3TC)
Raltegravir + Tenofovir Alafenamide + Emtricitabine (RAL + TAF + FTC)
Raltegravir + Tenofovir Alafenamide + Lamivudine (RAL + TAF + 3TC)
PI - based regimens: boosted DRV is preferred over boosted ATV
Darunavir/cobicistat or Darunavir/ritonavir + Tenofovir + Emtricitabine or Lamivudine (DRV/c or DRV/r + TAF or TDF + FTC or 3TC)
Atazanavir/cobicistat or Atazanavir/ritonavir + Tenofovir + Emtricitabine or Lamivudine (ATV/c or DRV/r + TAF or TDF + FTC or 3TC)
Darunavir/cobicistat or Darunavir/ritonavir+ Abacavir or Lamivudine—if HLA-B*5701 negative (DRV/c or DRV/r + ABC/3TC)
NNRTI – based regimens
Doravirine + Tenofovir + Emtricitabine or Lamivudine (DOR + TAF or TDF + FTC or 3TC)
Efavirenz + Tenofovir + Emtricitabine or Lamivudine (EFV + TAF or TDF + FTC or 3TC)
Rilpivirine + Tenofovir + Emtricitabine (RPV + TAF or TDF + FTC)
Regimens to consider when ABC/TAF/TDF cannot be used
Dolutegravir + Lamivudine (DTG + 3TC)
Following are less preferred
Darunavir/ritonavir + Raltegravir (DRV/r + RAL)
Darunavir/ritonavir + Lamivudine (DRV/r + 3TC)

*When compared with Recommended regimens, Alternative regimens may have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as greater toxicities, higher pill burden, drug interaction potential, or limitations for use in certain patient populations.

Alternate regimens (INSTI or PI or NNRTI based) as shown in **Table 4** are recommended in specific clinical situations, where the use of the recommended regimens is precluded [1,27-29]. Elvitegravir is now the least preferred INSTI as it causes significant drug-drug interactions due to pharmacologic boosting with cobicistat. Raltegravir-based INSTI regimens containing tenofovir and lamivudine are also part of alternate regimes as they have increased pill burden and decreased barrier to resistance. Currently, dolutegravir and boosted darunavir are recommended as first line agents for patients with virologic failure or unsure adherence or with resistance testing results pending as they have increased barrier to resistance. Boosted atazanavir with tenofovir and emtricitabine has also demonstrated excellent virological efficacy and fewer side effects as compared to other PIs and can be used during pregnancy [1,27-29]. Efavirenz based regimens have excellent virological efficacy but are limited due to high incidence of CNS related side effects. Rilpivirine has fewer adverse effects

but is inferior in patients with high baseline HIV RNA (>1,00,000 copies/ml) or low CD4+ counts (<200 cells/mm3). In patients in whom abacavir and tenofovir both are contraindicated, a combination of ritonavir boosted darunavir and raltegravir is recommended if the CD4+ count is >200 cells/mm3and HIV RNA level is <1,00,000 copies/ml, while in the rest, ritonavir boosted lopinavir and lamivudine is used [1,27-29]. The drugs not recommended upfront for the treatment of HIV patients are shown in **Table 5** and the regimes not recommended are shown in **Table 6**.

Table 5: Agents not Recommended for use as Initial Therapy

Reason for avoidance	Agent
Increased rate of virological failure	Didanosine Nelfinavir Saquinavir (unboosted) Tipranavir (ritonavir boosted) Delavirdine Etravirine
Higher incidence of toxicities	Zalcitabine Stavudine Didanosine Nevirapine Indinavir Nelfinavir Ritonavir Saquinavir (unboosted) Indinavir (unboosted)
Increased pill burden and dosing frequencies	Nelfinavir Saquinavir (unboosted) Indinavir (unboosted) Lopinavir (unboosted) Amprenavir (boosted or unboosted) Fosamprenavir ((boosted or unboosted)
Lack of data	Etravirine Ibalizumab Maraviroc Enfuvirtide

Table 6: ART Regimens Not Recommended

Regime	Reasons for avoidance
Monotherapy	Suboptimal virological potency
	Virological rebound
	Development of resistance
Dual-NRTI Regimes	Suboptimal virological potency
	Development of resistance
Triple-NRTI Regimes	Suboptimal virologic activity
	Drug toxicities
	Lack of data

Adherence to ART

Many factors decide adherence to ART, including the adverse drug reactions, co-morbidities, patient's social situation and the patient-provider relationship. Adherence should be evaluated and attended at every visit. Patients should be informed about the clinical course of HIV infection with and without the therapy, details of the prescribed regimen and development of drug resistance due to suboptimal adherence [1]. Given the efficacy of currently available antiretroviral drugs, a detectable viral load in a patient with a good access to drugs indicate poor adherence [1]. Strategies to improve the adherence in people with HIV infection are summarized in **Table 7**.

Table 7: Strategies to Improve Adherence to ART

Strategies to Improve Adherence to ART
Provide an accessible, trustworthy, non-judgmental multidisciplinary health care team
Strengthen early linkage to care and retention in care
Evaluate patient's knowledge about HIV infection, prevention and treatment and based on this assessment, provide HIV related information
Identify facilitators, potential barriers to adherence, and necessary medication management skills
Provide needed resources and involve the patient in ARV regime selection
Assess adherence at every visit and use positive reinforcement to foster adherence success
Identify the type and reasons for poor adherence and target ways to improve adherence
Enhance clinic support and structures to promote linkage and retention
Record and follow up on missed visits

Table 8: Defining Treatment Failure

Defining Treatment Failure	
Clinical failure	New or recurrent WHO stage 4 condition, after at least 6 months of ART
Immunological failure	Fall of CD4+ count to pre-therapy level
	50% fall from the 'on-treatment' peak value
	Persistent CD4+ levels below 100 cells/mm3
Virological Failure	Plasma viral load > 1,000 copies/mlafter at least 6 months of ART

Monitoring the Therapy

Monitoring should be done by assessing clinical condition of the patient and measuring plasma HIV RNA and CD4+ T cell count. The CD4+ cell count indicates overall immune status and helps to determine prophylaxis for opportunistic infections. It is also considered as the most important predictor of disease progression and survival. The CD4+ counts should be measured at the beginning of the therapy and throughout the treatment phase. In patients in whom ART is not started because of IRIS risk, CD4+ counts should be measured every 3-6 months to decide on ART initiation and prophylaxis for opportunistic infections. "A significant decrease in CD4+ cell count is defined as a decrease of >30% from baseline for absolute cell numbers and a decrease of >3% from baseline in percentage of cells." For most patients on therapy, "an adequate response is defined as an increase in CD4+ counts in the range of 50-150/mm^3 during the first year of ART followed by increase of approximately 50-100 cells/mm3/year until a steady state level is reached." Most guidelines recommend monitoring CD4+ counts every 3-6 months for the first two years from the time of initiation of ART. Thereafter for patients on a suppressive regime whose CD4+ counts range between 300-500 cells/mm3, testing is recommended annually and testing is optional for patients with CD4+ counts of >500 cells/mm3.

Plasma HIVRNA levels, on the other hand, indicate initial viral load and response to ART. Plasma RNA levels should be measured before starting ART and within 2-4 weeks of initiation but not later than 8-weeks. thereafter, viral load should assessed every 4-8 weeks until the patient documents viral suppression. "A minimally significant change in plasma HIV RNA is considered to be a 3-fold or 0.5 log10 increase or decrease". "Optimal viral suppression is defined generally as a viral load persistently below the lower level of detection (HIV RNA < LLOD) of the assay used". Once viral suppression is achieved, viral load should be repeated every 3-4 months to ascertain viral suppression or early if clinically warranted. If the patients are adherent to ART and have documented viral suppression for >2 years, viral load testing can be done at 6-monthly intervals. However, it is important to note that the decline in viral load is affected by the initial viral load, baseline CD4+ cell count, potency of regimen used and presence of any opportunistic infections and prior exposure to ART. Inability to

achieve viral load decline should prompt the clinician to reassess the patient, check for treatment compliance and possible drug interactions. If compliance and optimal drug absorption are assured, a change in the regimen should be considered after resistance testing [30].

Drug Resistance Testing

Testing for viral resistance to antiretroviral drugs may help to maximize the benefits of ART. Drug resistance is identified by both genotypic and phenotypic assays. Genotypic assays detect drug resistance mutations in rev and pro genes responsible for coding reverse transcriptase and protease enzymes respectively. The results are obtained within 1-2 weeks usually. Genotypic assays for INSTIs have to be ordered separately. Withholding ART while awaiting resistance testing results is not recommended. Phenotypic assays that assess the ability of HIV virus to grow in different concentrations of antiretroviral drugs, are more costly and difficult than genotypic assays and the results can be obtained in 2-3 weeks. Similar to CD4+ counts and viral load, drug resistance testing is recommended for all patients at the beginning of the therapy, when the patients has virologic failure and has a viral load of >1000 copies/mL and within 4-weeks of discontinuing therapy [1,30,31]. In patients with virologic failure and HIV RNA levels between 500 and 1000 copies/ml, resistance testing may be unsuccessful, but may still be considered. In patients who have discontinued therapy for more than 4 weeks without undergoing resistance testing at the recommended time, resistance testing is still recommended although the test may not pick previously selected mutations [1].

Changing drugs or ART regimen

Change in ART is required if there is a suboptimal reduction in HIV RNA after initiating the regimen, re-appearance of virus in the plasma after initial suppression and decline in CD4+ cell counts. "Less than a 0.5-0.75 $\log_{10}$ reduction in HIV RNA at 4-weeks or less than 1 log10 reduction at 8-weeks of therapy or failure to suppress HIV RNA to undetectable levels at 4-6 months of therapy indicate inadequate response and warrant change of therapy." If diagnosed as failure of therapy, it is recommended to change the drugs or use an entirely new regimen [1].

Conclusions and Future Directions

The myriad of treatment advances, as well as widespread knowledge of the virus and how it is transmitted has permitted a consideration of the possibility of 'HIV cure'. The major challenge which still remains is how to provide lifesaving ART medications to the vast majority of the patients. A lot more still needs to be done to make sure that such treatments are available to all if we intend to see the end of the HIV pandemic and achieve the dream of an 'AIDS free generation'.

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