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NOVEL DRUGS AND THEIR COMBINATIONS USED FOR TREATING AIDS

Mehnaz Showkat[1], Humaira Bilal[2], Bilquees[3] and Nahida Tabassum[4]*

[1-3]Research Scholar, Department of Pharmaceutical Sciences (Pharmacology Division), University of Kashmir, Srinagar, J&K-India190006.

[4]Professor Pharmacology, Head Department of Pharmaceutical Sciences, Dean School of Applied Sciences and Technology, University of Kashmir, Srinagar, J&K-India190006.

***Corresponding Author: Nahida Tabassum**
Professor Pharmacology, Head Department of Pharmaceutical Sciences, Dean School of Applied Sciences and Technology, University of Kashmir, Srinagar, J&K-India190006.

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ABSTRACT

Over past 35 years HIV/AIDS has emerged as a major global health problem across the globe. Although the Highly Active Antiretroviral Therapy (HAART) has significantly contributed to the suppression of viral load and has greatly prolonged the patient survival rate, issues such as complexity of the regimen, drug interactions, adverse effects, cross resistance between the drugs, still pose a hurdle to successful treatment. There is a persistent need of newer antiretroviral drugs (ARVs) with increased potency, improved pharmacokinetic profiles and improved activity against resistant HIV strains. Proper understanding of HIV life cycle and interaction of the virus with host cell factors has led to the development of newer and effective ARVs like, Ibalizumab, Fostemsavir, Doravirine etc. These drugs offer a number of advantages over traditional drugs and present a new choice for patients with drug resistant disease. Fixed Dose Combinations (FDC's) of currently available drugs have proven beneficial by reducing risk of emergence of drug resistant strains, less risk of medication errors, better patient compliance, reduced cost of treatment and simplified drug supply management. Besides, drugs belonging to different classes are currently in different stages of clinical trials, thus broadening the future scope of treatment.

KEYWORDS: HIV/AIDS, HAART, ARVs, Fostemsavir, Elsulfavirine, FDC's.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV), and is one of the foremost causes of mortality worldwide. AIDS represent a set of symptoms and illnesses that develop when an advanced HIV infection has destroyed the immune system.[1] It continues to be a key global health problem having claimed 33 million lives so far.[2] Nearly 38.0 million people were living with HIV at the end of 2019 and is mostly predominant in African regions(25.7 million).[2] India is home to third largest population of people suffering from HIV/AIDS (2.1 million) and is mostly seen among female sex workers, transgenders, injection drug abusers, men who have sex with men.[3,4] However, in comparison to neighboring countries, India has made an upright progress in reducing new HIV infections. Overall, India's HIV epidemic is decelerating. Between 2010 and 2017 new infections declined by 27% and AIDS-related deaths reduced more than half, falling by 56%.[5] Progress on the prevention of HIV transmission remains far too slow, with the estimated total number of new infections in 2019 more than three times higher than UNAIDS's 2020 target. However, HIV treatment access is key to the global effort to end AIDS as a public health threat.[6]

HIV and its Types

HIV is a single stranded RNA retrovirus- a type of human T leukaemia lymphoma virus (HTLV). HIV resembles other HTLVs in shape and size and both are CD4 tropic. However, HIV differs from HTLV in being cytolytic for T cells resulting in immunodeficiency while HTLV may change the target cells into T cell leukaemia.[7]

HIV has two basic forms i.e., HIV-1 and HIV-2. HIV-1 is widespread around the world and is genetically diverse, with atleast five distinct subfamilies, whereas HIV-2 is mostly confined to West Africa and parts of India and is less virulent than type 1 virus.[8,9] Both types are zoonotic contagions and their origin can be traced to species of chimpanzees who are natural reservoir of HIV and most likely source of original infection.[7] HIV-1 and HIV-2 have similar sensitivities towards most antiretroviral drugs, although the non-nucleoside reverse transcriptase inhibitors have no activity against HIV-2.[8]

Clinical Manifestations of AIDS[7]

AIDS nearly affects all body organs and systems causing progressive deterioration of body's immune system. Progression of disease occurs in all untreated patients, even if the patient is apparently latent. Various

pathological lesions and clinical manifestations of HIV/AIDS include:

1. Wasting syndrome.
2. Persistent generalized lymphadenopathy.
3. Gastrointestinal lesions and manifestations: chronic watery or bloody diarrhoea, oral, oropharyngeal and oesophageal candidiasis, anorexia, nausea, vomiting, mucosal ulcers, abdominal pain. Severe cases may develop secondary tumours of GIT (Kaposi's sarcoma, lymphoma).
4. Pulmonary lesions and manifestations: pneumonia, lung abscess, adult respiratory distress syndrome and secondary tumours.
5. Mucocutaneous lesions and manifestations: erythematous rash (at the onset of primary infection) allergic drug reactions, seborrheic dermatitis and other viral, bacterial and neoplastic infections.
6. Haematological lesions and manifestations: anemia, leucopenia, myopathy, and thrombocytopenia
7. Ophthalmic lesions: occur from opportunistic infections e.g., CMV retinitis, HIV retinopathy, and secondary tumours.
8. Musculoskeletal lesions: osteoporosis, osteopenia, septic arthritis, osteomyelitis, polymyositis.
9. CNS lesions and manifestations: HIV encephalopathy, AIDS associated dementia complex, meningitis, demyelinating lesions of spinal cord, peripheral neuropathy and lymphoma of brain.
10. Gynaecological lesions and manifestations: candida vaginitis, cervical dysplasia, carcinoma cervix and pelvic inflammatory disease.
11. Renal lesions and manifestations: HIV associated nephropathy, genitourinary tract infections including pyelonephritis.
12. Hepatobiliary lesions and manifestations: steatosis, granulomatous hepatitis and other opportunistic infections.
13. Cardiovascular lesions and manifestations: HIV associated cardiomyopathy, pericardial effusion in advanced disease as a reaction to opportunistic infection, lymphoma and Kaposi's sarcoma.
14. Endocrine lesions: lipodystrophy (buffalo hump) due to dyslipidaemia, hyperinsulinaemia, hyperglycaemia, abnormality of thyroid function, hypogonadism and inappropriate release of ADH.

These clinical manifestations develop rapidly in children in comparison to adults. Opportunistic infections, tumours along with neurological impairment causes suppression of growth and development in children. However, many of the above mentioned pathological lesions and manifestations may not become clinically apparent during life and may be noted at autopsy alone.

Diagnosis of HIV/AIDS[7,10]

HIV can be diagnosed through blood or saliva testing. Available tests to diagnose HIV in suspected patients fall into three categories:

i) Tests for establishing HIV infection include:

- Antibody tests:
  - Enzyme Linked Immunosorbent Assay (ELISA) for initial screening of antibodies.
  - Western blot or Immunofluorescence test (confirmatory test).

- Direct detection of HIV includes:
  - p24 antigen capture assay.
  - HIV RNA assay methods by reverse transcriptase (RT) PCR, nucleic acid sequence-based amplification (NucliSens).
  - DNA-PCR by amplification of proviral DNA.
  - Culture of HIV from blood monocytes and CD4+ T cells.

ii) Tests for defects in immunity

- Fall in CD4+ T cell counts.
- Rise in CD8+ T cells.
- Reversal of CD4+ to CD8+ T cell ratio.
- Lymphopenia.
- Polyclonal hypergammaglobulinemia.
- Increased β-2 microglobulin levels.
- Platelet count revealing thrombocytopenia.

iii) Tests for detection of opportunistic infections and secondary tumours

Examination of tissues/organs involved in such infections and tumours secondary to HIV/AIDS is carried by FNAC (fine needle aspiration cytology) or biopsy methods.

Treatment of AIDS

Currently, there's no cure for AIDS. If someone gets infected, the body can't get rid of it. The main goal of therapy therefore is to significantly suppress the viral replication for as long as possible. The replicative cycle of HIV offers many opportunities for the targeting of antiviral drugs. However, there are many medications that can control HIV and prevent complications. These medications are called antiretroviral therapy (ART). Everyone diagnosed with HIV should be started on ART, regardless of their stage of infection or complications.

The first Antiretroviral drug, Zidovudine, was introduced in 1987. Since then, a number a newer drugs and protocols were introduced.[11] HAART regimen has significantly contributed to suppression of HIV/RNA titre levels in blood and has greatly prolonged the patient survival rate. A key element of HAART is the coadministration of three or more drugs that impede the viral replication by various mechanisms so that proliferation of a virus with resistance to a single agent becomes inhibited by the action of other two agents. This combination therapy is primarily indicated to treat HIV-1 infected patients with no specific guideline of recommendation for HIV-2.[12] However, the drawback to HAART is that this therapy does not eradicate the virus but only inhibits it. Though the effectiveness of this therapy is >90% in infected patients, but the virus lies latent in the host genome of memory T cells and can

reactivate anytime on stoppage of therapy. Furthermore, the complexity of the regimen, adverse effects associated with the drugs, and poor compliance and lifelong therapy makes it very inconvenient to the patients.[13]

Main Classes of anti- HIV drugs and their possible mechanism is given below:

- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** turn off a protein needed by HIV to make copies of itself. Examples include efavirenz (Sustiva), rilpivirine (Edurant) and doravirine (Pifeltro).

- **Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)** are faulty versions of the building blocks that HIV needs to make copies of itself. Examples include abacavir (Ziagen), tenofovir (Viread), emtricitabine (Emtriva), lamivudine (Epivir) and zidovudine (Retrovir). Combination drugs also are available, such as emtricitabine/rilpivirine/tenofovir alafenamide fumarate (Odefsey) and emtricitabine/tenofovir alafenamide (Descovy).

- **Protease inhibitors (PIs)** inactivate HIV protease, another protein that HIV needs to make copies of itself. Examples include atazanavir (Reyataz), darunavir (Prezista) and lopinavir/ritonavir (Kaletra).

- **Integrase inhibitors** work by disabling a protein called integrase, which HIV uses to insert its genetic material into CD4 T cells. Examples include bictegravir sodium/emtricitabine/tenofovir alafenamide (Biktarvy), raltegravir (Isentress) and dolutegravir (Tivicay).

- **Entry or fusion inhibitors** block HIV's entry into CD4 T cells. Examples include enfuvirtide (Fuzeon) and sifuvirtide.

- **Chemokine Coreceptor (CCR5) inhibitors** target and block host cell CCR5 receptor preventing HIV attachment and subsequent entry of viral genome inside the host cell. Example includes maraviroc (Selzentry).

Currently Available Drugs For Treatment Of HIV/AIDS are given in **Table 1**:

Table 1: Currently Available Drugs For Treatment And Prevention Of HIV/AIDS.

Class	Drugs	References
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Tenofovir disoproxil fumarate, Tenofovir alafenamide.	[14-16]
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Nevirapine, Efavirenz, Delavirdine, Rilpivirine, Etravirine, Doravirine, Elsulfavirine.	[14,15,17]
Protease Inhibitors (PIs)	Ritonavir, Atazanavir, Nelfinavir, Indinavir, Saquinavir, Amprenavir, Lopinavir, Tipranavir, Darunavir, Fosamprenavir.	[14,15]
Fusion Inhibitors (FIs)	Enfuvirtide, Sifuviritide	[14,15]
Chemokine Coreceptor (CCR5) Inhibitors	Maraviroc.	[14,15]
Integrase Inhibitors	Raltegravir, Elvitegravir, Bictegravir, Dolutegravir	[14,15]

Newer drugs approved for treatment and prevention of AIDS

1. Ibalizumab

The alternative names are Trogarzo TM, ibalizumab-uiyk, TMB-355, TNX-355, TMB-355, Hu5A8, monoclonal antibody 5A8. Ibalizumab received its first global approval on 6 March 2018 in the US and is the first recombinant humanized IgG4 monoclonal antibody derived from a murine MAb (mu5A8) to be used for treatment of multidrug resistant HIV-1 infection in combination with other ARVs in patients with advanced disease.[18-20]

Mechanism of Action

It demonstrates a novel mechanism of action as a CD4-directed post attachment inhibitor and acts by binding to domain 2 of CD4 T cell receptors which induces steric hinderance and consequently prevents certain conformational changes within the complex of the CD4 T cell and the HIV envelope gp120.[19,20] This subsequently inhibits interaction of gp120 with the CXCR4 and CCR5 receptors,[20,21] thus preventing HIV fusion and entry without altering the immunological functions.[18,20,22] This novel mechanism makes ibalizumab effective against CXCR4- and CCR5-tropic strains and led to its classification as parenteral post attachment inhibitor.[19]

Pharmacokinetics

Ibalizumab exhibits nonlinear pharmacokinetics. It has been reported that following administration of single i.v doses of ibalizumab, the AUC increased in a greater than dose-proportional manner, clearance decreased and elimination half-life increased as the dose of ibalizumab was increased from 0.3 to 25 mg/kg. The volume of distribution was approximately that of serum volume at 4.8L. Following administration of a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg, steady-state levels were attained after the first 800 mg maintenance dose.[23] The half-life was found to be 3-3.5 days and elimination was characteristic of capacity-limited kinetics.[24]

Resistance

The primary mechanism of resistance to ibalizumab appears to be reduced expression or loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of gp120.[25,26] There is no evidence of drug–drug interactions or antiretroviral cross-resistance; the potency of the drug and its activity across genetically diverse HIV-1 isolates are superior to those of broadly neutralizing monoclonal antibodies currently in clinical development.[25,27]

Adverse effects

Diarrhoea, nausea, fatigue, pyrexia, rash, dizziness, vomiting, lymphadenopathy, nasopharyngitis, decreased appetite, excoriation, headache, upper respiratory tract infection have been reported. Most of these adverse effects (90%) were mild to moderate in severity.[19,28] However, Immune Reconstitution Inflammatory Syndrome (IRIS) was one serious effect to ibalizumab therapy, and led to a labeled warning and precaution of IRIS for ibalizumab.[23]

Dosage

The recommended dosage of ibalizumab is a single 2000 mg loading dose(10 vials-13.3ml), followed by a maintenance dose of 800 mg (4 vials-5.32 ml) once every 2 weeks.[23]

2. Fostemsavir

The alternative names are BMS-663068/GSK 3684934, Rukobia. It is a first-in-class HIV-1 attachment inhibitor approved by US FDA on 2nd July 2020 for people who have multi-drug resistant strains of HIV infections, and are left with limited options for treatment due to resistance, intolerance or safety considerations.[29]

Mechanism of Action

It exerts antiviral action by attaching directly to the glycoprotein 120 (gp120) subunit on the surface of the virus, close to the CD4+ binding site. It binds to gp120 in such a way that any conformational change necessary for interaction between virus and surface CD4+ receptors is prohibited, thereby, blocking HIV from entering host T-cells and subsequently preventing viral infection and multiplication.[30,31]

Pharmacokinetics

Fostemsavir is a prodrug of temsavir (TMR), which after oral administration is absorbed in the intestines. It has oral bioavailability of 26.9%. About 88.4% of drug is plasma protein bound. Metabolism of TMR occurs primarily by esterase-mediated hydrolysis and cytochrome P450 mediated oxidation. Excretion occurs via urine and faeces. Elimination half -life is 11hrs.[32,33]

Resistance

Fostemsavir has a unique resistance profile with no in vitro cross resistance with other classes of antiretroviral drugs, including entry inhibitors, this is because gp120 is a highly conserved area of the virus, the drug is unlikely to promote resistance to itself via generation of CD4-independent virus.[31] In addition, fostemsavir is active regardless of HIV-1 tropism and has a favorable drug–drug interaction profile. This may be attributed to four positions of amino acid substitutions in gp120 (S375H/I/N/M/T, M426L/P, M434I/K, and M475I) identified by different studies that affect the susceptibility of the virus to temsavir.[30] Among clinical isolates of HIV-1, a broad range of in vitro susceptibility to temsavir has been observed, which may be due to the substantial diversity in HIV-1 gp120, but Fostemsavir is not active against HIV-2 and another a subtype of HIV called Group O (Outlier).[34]

Adverse Effects

Most commonly reported side-effects are nausea, fatigue, diarrhoea. Rarely abdominal pain, indigestion, sleep disturbance, drowsiness and vomiting may occur.

Serious dose related adverse effects include:

- Cardiac disorders: ECG QT prolonged (asymptomatic)
- Musculoskeletal disorders: Myalgia
- Nervous system disorders: Dizziness, dysgeusia, peripheral neuropathy
- Skin and subcutaneous tissue disorders: Pruritus.[32,35]

Dosage

The recommended dosage of Fostemsavir is 600mg extended-release tablet, twice daily with or without food.[29]

Interactions

- TMR inhibits organic anion transporting polypeptide (OATP) 1B1, OATP1B3, and BCRP, indicating the possibility of drug–drug interactions between TMR and grazoprevir, voxilaprevir, ethinyl estradiol and statins.[32]
- When coadministered with oral contraceptives, doses of oral contraceptives should not contain more than 30 mcg of ethinyl estradiol per day.[29]
- Coadministration with drugs which prolong QTc interval is not recommended.[35]

Contraindications

- Hypersensitivity to fostemsavir or any of its components
- Coadministration with strong CYP3A inducers (e.g., enzalutamide, carbamazepine, phenytoin, rifampin, mitotane, St John's Wort), causes decreases in temsavir plasma concentrations, which may result in loss of virologic response.[32,33]

Precautions

- **Immune reconstitution syndrome** with combination antiretroviral therapy may occur, which may necessitate further evaluation and treatment; autoimmune disorders (e.g., Grave disease, polymyositis, Guillain-Barré) have also been reported with fostemsavir use.

- Elevations in hepatic transaminases in hepatitis B or C coinfection has been reported; liver enzyme monitoring is recommended in such patients. FDA recommends maintaining effective hepatitis B therapy when initiating fostemsavir to avoid hepatitis B reactivation.[33]

3. Doravirine

The alternative names are MK-1439, Pifeltro. It is a novel HIV-1 NNRTI developed by Merck and Co. It received USFDA approval both as a single-agent tablet (Pifeltro™) for the treatment of HIV-1 infection in adults with no prior antiretroviral treatment experience and as a fixed-dose combination tablet with the nucleoside reverse transcriptase inhibitors lamivudine and tenofovir disoproxil fumarate (Delstrigo™) for the treatment of HIV-1 infection in adults with no prior or present resistance to NNRTIs or in the case of the fixed- dose combination tablets (to lamivudine or tenofovir), on August 30 2018.[36-38]

Mechanism of Action:

DOR acts by binding allosterically to a hydrophobic pocket located in the p66 subunit of the p 66 / p51 heterodimer of HIV-1 reverse transcriptase (RT), about 10 Å away from the RT polymerase active site, causing conformational changes that inhibit HIV-1 deoxyribonucleic acid (DNA) synthesis. However DOR is not effective against HIV-2 present in peripheral blood mononuclear cells (PBMCs), exerts no cytotoxic action on resting or activated cells and does not inhibit the human cellular DNA polymerase α, β, and mitochondrial DNA polymerase γ.[39]

Pharmacokinetics

DOR is absorbed quickly after oral administration. It is almost 79% plasma protein bound. Metabolism of doravirine occurs mainly via CYP3A enzymes, and is the major route of the drug's elimination, with little of a dose being excreted unchanged via the urine (6%) Or biliary/faecal routes (no values reported). Doravirine has an elimination half-life of 15 h, a mean apparent clearance of 106 mL/ min and a mean renal clearance of 9.3 mL/min.[40] [41]

Resistance

Many studies have shown that there is very low prevalence of doravirine resistance-associated mutations in antiretroviral-naive patients, while the patients having experience of other NNRTIs like EFV (efavirenz) and ETR (etravirine) pose a higher risk of developing DOR resistance this is due to the resistance associated with the amino acid substitutions Y188L, Y188L/K103N, Y188L/V106I, V106A/ G190A/F227L and E138K/Y181C/M230L.[38,42]

Adverse effects

Most common adverse effects associated with incidence of >5% include nausea, headache, fatigue, diarrhoea, abdominal pain, dizziness, rashes and abnormal dreams.

Less than 1% incidence of interference with serum creatinine, serum transaminase, serum phosphate, urine glucose and urine protein have been reported with delstrigo which necessitates assessment of the serum levels before initiating treatment with delstrigo.[40,41,43]

Dosage forms and administration

The recommended dosage regimen of Doravirine (both as pifeltro and delstrigo) in adults is 100 mg tablet to be taken orally once daily with or without food. However, Dose modification is recommended in following conditions:

- Coadministration with rifabutin- dose is increased to 100 mg PO BID (~12 hr. apart) for the duration of rifabutin treatment.
- In Renal impairment
- In Hepatic impairment.[40,41]

Interactions

Effect of Other Drugs on Doravirine

- Co-administration of PIFELTRO with a CYP3A inducer (amobarbital, apalutamide, armodafinil, bexarotene, bosentan, butabarbital, Carbamazepine, nevirapine, phenytoin, primidone, rifampin, rifabutin, secobarbital, St John's Wort, Telotristat ethyl) decreases doravirine plasma concentrations, which may reduce Doravirine efficacy

- Co-administration of PIFELTRO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine and thus may mandate monitoring e.g.; atazanavir, cobicistat, clarithromycin, darunavir, fosamprenavir, isoniazid, Itraconazole, ketoconazole, mifepristone, tipranavir, voriconazole.
  Serious toxicity can occur when co-administered with tucatinib and voxelotor as these increase systemic exposure of sensitive CYP3A4 substrates.

Effect of Doravirine on Other Drugs

No clinically significant changes in concentration of Doravirine were observed when co-administered with

following agents: dolutegravir, lamivudine, TDF, elbasvir and grazoprevir, ledipasvir and Sofosbuvir, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, and midazolam.[40,41,43]

Contraindications

- Contraindicated with strong cytochrome P450 (CYP3A) inducers.
- It is also contraindicated in patients with a previous hypersensitivity reaction to lamivudine.[40,41]

Use in Specific Population

During Lactational period, Doravirine is not recommended due to potential HIV transmission through breastfeeding.[40,41]

Precautions and Warnings

- Immune reconstitution syndrome reported in patients treated with combination antiretroviral therapy requiring further treatment and evaluation.
- Autoimmune disorders (e.g., Grave disease, polymyositis, Guillain-Barré syndrome, autoimmune hepatitis) may occur in the setting of immune reconstitution; however, onset time may vary from patient to patient.
- New onset or worsening renal impairment: Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Avoid delstrigo administration concurrently or after recent use of nephrotoxic drugs.
- Bone loss and mineralization defects: Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss.[40,41,43]

4. Elsulfavirine

The alternative names are Elpida, elpivirine, R1206, RO 4970335, RO 5011500, VM 1500, VM 1500 LAI. It is a new generation NNRTI being developed by Viriom for treatment and prevention of HIV and received its first global approval as a daily oral formulation on 30th June 2017 in Russia for treatment of HIV in combination with other ARV drugs, however, studies for long acting injectable preparation, once daily and once weekly oral long acting formulations of elsulfavirine are still underway.[17]

Mechanism of Action

It is the prodrug of active compound VM 1500 A, a potent, highly selective NNRTI and acts by attaching to and inhibiting reverse transcriptase enzyme, thereby preventing replication of HIV and has shown a broad spectrum of activity against strains resistant to other NNRTIs.[17,44]

Pharmacokinetics

Following once daily oral administration of elsulfavirine (20 or 40 mg) in uninfected healthy subjects, the half- life was reported to be 1.7 hrs and 2.6 hrs respectively. However, in treatment naïve HIV patients, the half-life was reported to be 1.9hrs (20mg dose) and 2.4 hrs (40 mg dose). The half-life of active metabolite VM 1500 was reported to be 7.4 days and 5.4 days for 20 and 40 mg doses of elsulfavirine respectively. The tmax was reported to be 0.9 in 20 mg recipients and 1.0 and 1.1 h in 40 mg recipients; mean tmax values for VM-1500A were reported to be 6.3 and 6.2 days with 20 and 40 mg doses of elsulfavirine for 7 days.[45]

Adverse Effects

Frequent (≥ 1 to <10%) and very frequent (≥10%) side effects have been reported with elsulfavirine. These include headache, herpes simplex, leukopenia, neutropenia, sleep disorders, dizziness, vivid dreams, drowsiness, nausea, diarrhoea, dry mouth, vomiting, skin rash, itching, mild proteinuria, polyuria, asthenia, weakness, decreased appetite and increased body temperature. However, the likelihood of these side effects is slow and generally subsides without requiring discontinuation of treatment.[46]

Dosage

The recommended dosage is 20 mg capsule once a day to be taken 15 minutes before meals.[46]

Interactions

Elsulfavirine is a potent inducer of CYP3A4. Concomitant administration with substrates of CYP3A4 and CYP2B6 (e.g. amitriptyline, atorvastatin, clarithromycin, citalopram, ketoconazole, tacrolimus, tamoxifen, doxorubicin, estradiol, progesterone, venlafaxine etc.) can result in clinically significant reductions in the concentrations and effects of these agents.[46]

Fixed Dose Combinations For Treatment of AIDS

Monotherapy is seldom used to treat HIV infection. Instead, multidrug therapy is used to counteract the fast mutation rate of HIV and to curtail drug toxicity. ART is usually a combination of three or more medications from several different drug classes. This approach has the best chance of lowering the amount of HIV in the blood. There are many ART options that combine three HIV medications into one pill, taken once daily. Some fixed dose combinations of drugs approved for treatment of AIDS are given **in Table 2**

Table 2: Newer Fixed Dose Combinations Approved For Treatment of HIV.

Brand Name	Active ingredients	Manufacturer	FDA Approval Date	References
Triumeq	Dolutegravir, Abacavir, and lamivudine	ViiV Healthcare, London,United Kingdom	August 22, 2014	[47]
Evotaz	Atazanavir and Cobicistat	Bristol-Myers Squibb Company	January 29, 2015	[48]
Prezcobix	Darunavir and Cobicistat	Janssen Pharmaceuticals, Inc	January 29, 2015	[48]
Genvoya	Elvitegravir,Cobicistat, Emtricitabine, and Tenofovir alafenamide	Gilead Sciences	November 5, 2015	[49,50]
Odefsey	Emtricitabine, Rilpivirine, and Tenofovir lafenamide fumarate	Gilead Sciences, Foster City, California	March 1, 2016	[51,52]
Descovy	Emtricitabine and Tenofovir alafenamide	Gilead Sciences	April 4,2016	[53]
Juluca	Dolutegravir, Rilpivirine	ViiV Healthcare	November 21, 2017	[54]
Symfi	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate	Mylan N. V	March 22, 2018	[55]
Cimduo	Lamivudine and Tenofovir disoproxil fumarate	Mylan Pharmaceuticals, Inc	February 28,2018	[56]
Symfi Lo	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate	Mylan Pharmaceuticals, Inc	February 5,2018	[57]
Biktarvy	Bictegravir, Emtricitabine, andTenofovir alafenamide	Gilead Sciences, Inc	February 7,2018	[56]
Temixys	Lamivudine,Tenofovir disoproxil fumarate	Celltrion Inc.	November 16, 2018	[57]
Symtuza	Darunavir, Cobicistat, Emtricitabine, and Tenofovir alafenamide	Place Janssen Products, LP	July 17, 2018	[58]
Delstrigo	Doravirine, Lamivudine, and Tenofovir disoproxil fumarate	Merck & Co.	August 30, 2018	[38]
Dovato	Dolutegravir and Lamivudine	ViiV Healthcare Company	April 08. 2019	[59,60]

Drugs in Investigational Stage for Treatment of AIDS

There is no proper cure of the disease till now. Currently, research is going on for finding newer drugs which can target virus at different stages of its life cycle and can provide better resistance profile. Some drugs still in investigational stages for treatment and prevention of HIV are shown in **Table 3**.

Table 3: Drugs In Investigational Stage For Treatment And Prevention Of HIV.

Drug	Class	Sponsor	Phase	References
Islatravir (MK8591)	Nucleoside Reverse Transcriptase Translocation Inhibitor(NRTTI)	Merck Sharp & Dohme Corp.	Phase 2	[61]
Cabotegravir- LA (i.m injection)	Integrase Strand Transfer Inhibitor (INSTI)	ViiV Healthcare	Phase 3	[62]
Combinectin (GSK 3732394)	Entry Inhibitor	ViiV Healthcare	Phase 1	[63]
Leronlimab(PRO 140)	bNAb (CCR5 Antagonist)	CytoDyn, Inc	Phase 2/3	[63,64]
GSK 3640254	Maturation Inhibitor	ViiV Healthcare	Pre-clinical	[62]
Lenacapavir(GS 6207)	Capsid inhibitor	Gilead Sciences	Phase 2	[64]
MK 8504	NtRTI	Merck Sharp & Dohme Corp	Phase 1	[65,66]
MK 8583	NtRTI	Merck Sharp & Dohme	Phase 1	[67,68]
UB-421	CD4 Attachment Inhibitor	United BioPharma	Phase 3	[69]

VRC01	bNAb	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 2	[70]
3BNC117	bNAb	Rockefeller University	Phase 2	[71]
101074	bNAb (targets V3 glycan supersite on the HIV envelope protein)	Rockefeller University	Phase 2	[72,73]
10E8.4/iMab	Bispecific antibody	David Ho	Phase 1	[74]
VRC- HIVMAB091-00-AB (N6LS)	bNAb	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 1	[75]
PGDM1400	bNAb	International AIDS Vaccine Initiative	Phase 1	[76]
Elipovimab(GS9722)	bNAb	Gilead Sciences	Phase 1	[77]
PGT121	bNAb	International AIDS Vaccine Initiative	Phase 1	[78]
VRC07523LS	bNAb	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 1	[79]
ABX464	Rev Inhibitor	Abivax S.A	Phase1/2	[80,81]
BIT225-VPU	HIV-1 Vpu protein inhibitor	Biotron	Phase 2	[82]
VM 2500	Undefined	Viriom	Preclinical	[83]
VM 3500	Immunomodulator	Viriom	Preclinical	[84]
GSK 1349572	Integrase Inhibitor	ViiV Healthcare	Phase 2	[85]

CONCLUSION

Current HIV treatment and prevention regimens are potent, safe and tolerable. It can be challenging to identify where and to what extent further improvements can be made. However, newer agents in the existing classes (non-nucleoside reverse transcriptase inhibitors, integrase inhibitors and protease inhibitors) and newer mechanistic classes (HIV-1 attachment inhibitor, recombinant monoclonal antibodies) have presented a new choice for patients with drug resistant disease and have offered a number of advantages over traditional drugs. Fixed Dose Combinations (FDC's) of currently available drugs have also revealed promising results against HIV isolates resistant to monotherapy. Further advancement in the treatment and prevention of HIV infection will result from development of newer antiretroviral drugs which are currently being assessed in clinical trials. Additionally, treatment can be improved by developing more longer-acting HIV regimens, innovating care delivery models to ensure durable, efficacious and safe treatment for all patients with HIV.

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