**A Concise Review of Existing Therapies and Recent Advances in the Management of HIV Infection**

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**ABSTRACT**

Human immunodeficiency virus (HIV) is an RNA retrovirus capable of replicating its genome by the DNA dependent RNA polymerase (DdRp). The virus infects the lymphocytes with the help of viral glycoproteins like Gp 120 and Gp 41. The entry of virus leads to the release of viral RNA inside the host cell, which is further replicated, and assembly of virion particles leads to the release of viral particles that further infect the other host cells. Established therapies include those that inhibit the entry of virus in the host cell, those inhibiting the integrase activity, those acting as protease inhibitors and also we have Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-Nucleoside reverse transcriptase inhibitors (NNRTIs) with NRTIS being the competitive inhibitors of DdRp also show mitochondrial toxicity. Protease inhibitors are known for their adverse effect profile and several drug interactions due to their enzyme inhibitory property. The most effective approach in the management is the highly active antiretroviral therapy containing the combined use of drugs having varied mechanisms of action. Still, long term use of these agents can end up in resistance against these agents. Well documented adverse effect profile along with various drug interactions associated with anti-HIV drugs mandates the need for the development of newer drugs against HIV. Newer molecules provide a better safety profile and better alternatives for drug-resistant cases. Therefore, this review focuses on existing therapies along with various newer pipeline drugs with their mechanisms and advantages over the existing therapies.

**Keywords:** HIV; Antiretroviral; Recent advances; AIDS; Drugs.

**INTRODUCTION**

HIV (Human Immunodeficiency Virus) infection has been a major cause of concern in the health care scenario for a long time. Recent data from United Nations AIDS (UNAIDS) reported that in 2019, approximately 38 million people were living with HIV in the world out of which 36.2 million were adults, 1.8 million were below 15 years and about 7.1 million HIV positive were unaware of their positive status for HIV infection. With time, HIV gradually leads to the development of Acquired immunodeficiency syndrome (AIDS) with decreased CD4 count with increased susceptibility to opportunistic infection which have been found to be a major contributor to mortality in AIDS patients. A great deal of improvement have been made in antiretroviral therapy (ART) for the treatment of HIV infection since starting potent combination therapy. These aggressive and combined interventions have dramatically reduced the morbidity and mortality of these patients along with an improved lifestyle of HIV positive individuals by transforming HIV infection into a manageable chronic condition. The prophylactic use of ART has been found to be highly effective in preventing HIV infection in exposed individuals. The development of resistance to ART is a major hurdle faced in the treatment of HIV patients.

With the rise in the number of cases, a simple, rapid, economical, accurate diagnostic method for the detection of new cases and follow up of infected one is a need of the hour. Various modalities are currently available to screen and diagnose HIV infection which includes serological assay (ELISA, Rapid agglutination test, Dot blot assay), molecular assay (PCR, P24 antigen assay) and confirmatory assay (western blot assay, indirect immunofluorescence assay). Laboratory tests should be performed along with confirmation of HIV infection during the initial patient visit to act as a baseline to guide the selection of ARV drug regimens and follow up on the patient. These tests include CD4 T lymphocyte cell count, Plasma HIV RNA count, serologies for hepatitis virus, Complete blood count, transaminase levels, blood urea nitrogen, creatinine, urinalysis, fasting blood glucose and serum lipids. Genotypic resistance testing along with a test for the sexually transmitted disease should also be performed. Structure of HIV

HIV is a single-stranded RNA retrovirus. The virus particle contains two identical RNA strands along with enzymes such as integrase, reverse transcriptase, and protease in the capsid core. The nucleocapsid protein stabilizes the RNA of the virus and the mature virion particle is conical in shape. It is surrounded by lipid envelope embedded with transmembrane proteins. Various proteins in HIV are utilized as targets by the drugs to control the infection in an individual. The various protein components of HIV and their function and applications are summarized in table 1.
Table 1: Overview of various protein in HIV and their function

| Genes | Proteins | Function and application |
|-------|----------|--------------------------|
| gag    | Caspid protein (p24) | Capsid formation, used in diagnosis |
|       | Matrix protein | Coats the inner surface of virus, early stages of virus replication as well as envelope incorporation into virions and assembly. 10 |
|       | Nucleocapid | Nucleic acid binding, condensing and chaperoning 11 |
| pol   | Protease | Cleavage of translated proteins into mature structural proteins and enzymes |
|       | Reverse transcriptase | Conversion of RNA into proviral DNA |
|       | Integrase | Integrate the transcribed DNA into host genome |
| env   | Surface glycoprotein (gp120) | Attaching of virus to host cell |
|       | Transmembrane protein (gp41) | Fusion of virus into host cell |

PHARMACOTHERAPIES IN THE MANAGEMENT OF HIV

From the inception of therapy against the HIV, there have been many additions in the management of HIV infection. We do have a wide array of drugs acting against HIV and are used accordingly in patients in a case to case basis. The various drugs used in HIV management are summarized as follows:

A) Existing therapy in the management of HIV

1) Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI)-

These drugs inhibit the enzyme reverse transcriptase to prevent the transcription of viral RNA to proviral DNA by getting incorporated into the replicating DNAs and terminate the elongation prematurely. 12 These drugs need to be triphosphorylated by the host cell to have activity against the virus except for tenofovir which requires 2 phosphorylation only. 12,13 The nucleoside reverse transcriptase inhibitors include Zidovudine, Stavudine, lamivudine, Emicitarabine, Abacavir, etc. The only nucleotide reverse transcriptase inhibitor is tenofovir. 12

2) Nonnucleoside reverse transcriptase inhibitor (NNRTIs)-

The NNRTIs bind to p66 subunit of the reverse transcriptase to induce a conformational change structure of the enzyme thus acting as noncompetitive inhibitors of NNRTIs are virus-strain specific which is active only against HIV-1 12,14 The approved NNRTIs are nevirapine, efavirenz, etravirine, rilpivirine, and delavirdine. 12

3) HIV protease inhibitors-

The protease inhibitors (PIs) competitively inhibit the enzyme aspartyl protease in a virus with cleavage at the N-terminal side of proline residues. These inhibit the cleavage of large polypeptide into structural proteins and enzymes. 12,15 These are saquinavir, ritonavir, fosamprenavir, lopinavir, atazanavir, darunavir, indinavir, nelfinavir, tipranavir. Low dose ritonavir is mostly used as pharmacokinetic enhancer. 12,16

4) Integrase inhibitors-

These inhibit the integration of Viral DNA into the host DNA by inhibiting the catalytic activity of integrase to form a covalent bond between them. These agents are active in the virus which has become resistant to other antiretrovirals. 12,17 The drugs available are Raltegravir, Elvitegravir, Dolutegravir. Dolutegravir is active against a virus which is resistant to even raltegravir, elvitegravir and can act without a booster. 18

5) Entry inhibitor–

The drugs that are approved and available in this category have a varied mechanism of action. Enfuvirtide binds to gp41 subunit to prevent the fusion of viral and host cell membranes. 12 It is the only antiretroviral agent given parentally. Maraviroc blocks the binding of gp120 to CCR5 chemokine receptors which is an important step in the entry of the virus into the host cell. It is mainly active against CCR5 tropic virus with no effect on CCR4 topic or dual tropic virus. 12,19,20

The National technical guidelines on anti-retroviral treatment recommend Tenofovir + Lamivudine + efavirenz as the first-line therapy for HIV patients. 21 For HIV-2 infection efavirenz is recommended to be replaced by Lopinavir/ ritonavir. 21

B) Recent advances in the therapy of HIV

The newer molecules developed for the therapy of HIV can be divided into two parts. Firstly, the new drugs developed on existing or known viral targets and secondly, newer drugs on novel targets. The various newer drugs developed are summarized as follows:

I. Newer drugs on existing targets:

The newer drugs on existing targets should be better than their previous counterparts hence the main focus of development of such molecules was directed towards either development of long-acting congeners, better safety profile, or overcoming the current resistance faced by already available drugs.

1) Newer NRTI

Islatravir- It is an NRTI with high potency. The islatravir-triphosphate intracellular half-life has been found to be about 78-5–128.0 hour thus making weekly dosing of this drug possible. 22 The drug-eluting implants of this molecule are hypothesized to provide HIV prophylaxis for about 1 year and phase 1 trials have shown that the implants were...
well tolerated. Other molecules of this class are MK-8504 and MK-8583 which are long-acting prodrg of tenofovir have been tried in phase 1 and the data from the trials have raised questions about the feasibility of these molecules in extended-interval dosing regimens.

2) Newer NNRTI

Rilpivirine- A injectable long-acting nanosuspension has been formulated with dosing every 4-8 weeks either singly for preexposure prophylaxis or can be given as two-drug injectable maintenance therapy with cabotegravir for maintenance regime. Studies have shown that it has got a better safety profile as compared to efavirenz in terms of neuropsychiatric and neurological side effects.

Doravirine- It is a novel once-daily NNRTI with good efficacy and safety profile. It has demonstrated a good in vitro activity against resistant HIV-1 mutants associated with the use of other NNRTIs, including newer agents such as etravirine, rilpivirine.

Elsulfavirine- It is a prodrug of VM-15000A which reversibly binds to carboxic anhydrase in red blood cells (RBCs) with a half-life of 9 days in RBC. The RBCs serve as a natural slow-release depot for this molecule which can provide a prolonged plasma exposure and slow elimination of this drug which can help the drug to be tried for once a month dosing.

3) Integrase inhibitors-

Cabotegravir LA- It is a dolutegravir analog and integrase strand transfer inhibitor. It has long elimination half-life of 40 days and is currently under phase 3 trials as a single agent for both HIV treatment and HIV prevention.

4) Entry inhibitor-

Combivir- It is a multi-specific entry inhibitor of HIV and contain anti CD4 adnectin and an adnectin targeting gp41 with an inhibitory domain for fusion inhibition. Adnectin are 10th fibronectin type III domain-based small therapeutic proteins with high affinity and specificity.

II. Drugs on Novel Targets

Novel mechanism of action can help in the development of newer drugs with less or no cross-resistance with existing available therapy and with lesser side effects. The main focus of newer targets is mainly directed towards trying to cure the disease instead of just managing the disease or associated morbidity.

Broadly neutralizing monoclonal antibodies (bNAbs)-

Ibalizumab- It is a humanized monoclonal antibody which acts by impeding the conformational change in CD4 – gp120 complex causing post attachment inhibition by a stearic hindrance to stop interaction of CCRX4 and CCRX5 with gp120 and causes rearrangement of gp41 to inhibit fusion of viral particle.

Leronlimab- It is an anti CCR5 monoclonal antibody active against HIV-1 virus. It is seen that Leronlimab act synergistically with other small molecule CCR5 inhibitors with the first causing competitive inhibition and other causing allosteric inhibition which can lay a path for novel combination for resistant HIV treatment.

CD4 binding antibodies-

UB-421 is a humanized anti Cd4 antibody that binds to the site of gp 120 attachment without affecting the function of the immune cell. These are active against all subtypes regardless of resistant status or tropism with 50-100 times more affinity for CD4 cells as compared to HIV. Other CD4 binding monoclonal antibodies are under trials are VRC01, 3BNC117, VRC01-LS and VRC07-523LS.

Elipovimab- It is an effector enhanced monoclonal antibodies against HIV infected cell which targets gp120/41 on the surface of infected cell and FcγRs of the immune cells such as phagocytes, macrophage simultaneously.

Capsid Inhibitors-

GS-6207 and GS-CA1 are capsid inhibitors under investigation. These act through interference with assembly and disassembly of capsid along with inhibition of nuclear transport and formation of new virion particles for release. Effective drug concentration has been detected after 12 weeks of a single dose for GS6207 in healthy individuals giving it a potential for long-acting action with easy dosing regimen.

Maturation inhibitor-

Beverimut - It causes the production of immatures capsid proteins by interfering with the processing of polyprotein Gag leading to the release of the noninfectious immature virion particle. It is active against all HIV resistant to all of the currently available drugs.

Attachment inhibitor-

Fostemsavir- A recently approved prodrug that acts on the first step of the viral life cycle by attaching itself to viral gp120 and inhibiting its entry into CD4 cells. No cross-resistance to other drugs have been demonstrated invitro, including entry inhibitors.

ABX464- It is an investigational drug having both anti-inflammatory and antiviral activity by interfering with pre mRNA splicing and have been investigated for a wide range of diseases such as HIV, Ulcerative colitis, COVID 19 and Rheumatoid arthritis etc.

A wide array of molecules have been developed for the therapy of HIV infections. Yet, we are still away from developing a complete cure from this long ailing morbid and mortal condition. The diseases needs a combination of drugs to combat the illness and with increase in number of medications the chances of development of adverse effects increases. The adverse effects whether new ones or known, should be reported to the respected pharmacovigilance centers so as to minimize the further risk of development of such incidences. Rational use of
medication would prevent the frequent development or emergence of side effects with these medications.61 However, the development of newer drugs on novel targets can definitely help in the management of the condition in a better way.

CONCLUSION

Early screening, diagnosis, and treatment of the infection have led to a decrease in morbidity and mortality due to associated complications with this disease. Despite the recent development in antiretroviral therapy, there is still need of new alternatives that are equally efficacious and cheaper as compared to the contemporary treatment available. Even after plenty of development, we still have a long way to go to find a permanent cure for this condition.

REFERENCES

1. Global HIV & AIDS statistics — 2020 fact sheet. UNAIDS. Cited on 18 July 2020. Available At: https://www.unaids.org/en/resources/fact-sheet

2. Kim YJ, Woo JH, Kim MJ, Park DW, Song JY, Kim SW et al. Opportunistic diseases among HIV-infected patients: a multicenter-nationwide Korean HIV/AIDS cohort study, 2006 to 2013. Korean J Intern Med. 31(5), 2016 Sep, 953-60. doi: 10.3904/kjim.2014.322.

3. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2014. HIV Surveillance Supplemental Report, 2016, 21(No.4). Available at : https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-21-4.pdf

4. Cohen MS, Chen YQ, McCauley M. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. Aug. 365(6), 2011, 493-505. Available at https://www.ncbi.nlm.nih.gov/pubmed/21767103.

5. Arya S, Lal P, Singh P, Kumar A. Recent advances in diagnosis of HIV and future prospects. Indian J Biotechnol, 14, 2015, 9-18.

6. Aberg JA, Kaplan JE, Libman H, Emmanuel P, Anderson JR, Stone VE et al. HIV Medicine Association of the Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 49(5), 2009 Sep, 651-81. doi: 10.1086/605292.

7. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. 2017. Cited on 22 July 2020 from URL: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oip.pdf

8. German Advisory Committee Blood (Arbeitskreis Blut), Subgroup ‘Assessment of Pathogens Transmissible by Blood’. Human Immunodeficiency Virus (HIV). Transfus Med Hemother, 43(3), 2016, May, 203-22. doi: 10.1159/000445852.

9. Muriaux D, Darlix JL. Properties and functions of the nucleocapsid protein in virus assembly. RNA Biol, 7(6), 2010 Nov-Dec, 744-53. doi: 10.4161/ma.7.6.14065.

10. Fiorentini S, Elena M, Caracciolo S, Caruso A. Functions of the HIV-1 matrix protein p17. The new microbiologica 29, 2006, 1-10.

11. Ganser-Pornillos BK, Yeager M, Sundquist WI. The structural biology of HIV assembly, Curr Opin Struct Biol. 18, 2008, 203–17.

12. Flexner CW. Antiretroviral Agents and treatment of HIV infection. In: Brunton LL, Dandan RH, Knollmann BC, editors. Goodman and Gilman’s pharmacological basis of therapeutics. 13th ed. New York, McGraw-Hill Medical, 2018, p. 1137-57.

13. Robbins BL, Wilcox CK, Fridland A, Rodman JH. Metabolism of tenofovir and didanosine in quiescent or stimulated human peripheral blood mononuclear cells. Pharmacotherapy, 23(6), 2003 Jun, 695-701.

14. Usach I, Melis V, Peris JE. Non-nucleoside reverse transcriptase inhibitors: a review on pharmacokinetics, pharmacodynamics, safety and tolerability, J Int AIDS Soc, 16(1), 2013 Sep, 4, 1-14. doi: 10.7448/IAS.16.1.18567.

15. Lv Z, Chu Y, Wang Y. HIV protease inhibitors: a review of molecular selectivity and toxicity. HIV AIDS (Auckl). 7, 2015 Apr, 95-104. doi: 10.2147/HIV.S79956.

16. Aarnoutse RE, Kleinijnenhuis J, Koopmans PP, Touw DJ, Wieling J, Hekster YA. Effect of low-dose ritonavir (100 mg twice daily) on the activity of cytochrome P450 2D6 in healthy volunteers. Clin Pharmacol Ther., 78(6), 2005 Dec, 664-74. doi: 10.1016/j.cpt.2005.09.001.

17. Hajimahdi Z, Zarghi A. Progress in HIV-1 Integrase Inhibitors: A Review of their Chemical Structure Diversity. Iran J Pharm Res., 15(4), 2016, 595-628. PMID: 28243261; PMCID: PMC5316242.

18. Temesgen Z, Talwani R, Rizza SA. Dolutegravir, an HIV integrase inhibitor for the treatment of HIV infection. Drugs Today (Barc), 50(1), 2014 Jan, 7-14. doi: 10.1358/dot.2014.50.1.2097790.

19. Perry C.M. Maraviroc. Drugs 2010,70, 1189–213. https://doi.org/10.2165/11203940-000000000-00000

20. Lalezari JP, Lubert AD. Enfuvirtide.Drugs Today (Barc), 40(3), 2004 Mar, 259-69. doi: 10.1358/dot.2004.40.3.820089.

21. National technical guidelines on anti retroviral treatment. National AIDS Control Organization, Ministry of Health and Family Welfare, Government of India. Cited on 20 July 2020, Available at: https://lms.naco.gov.in/frontend/content/NACO%20National%20Technical%20Guidelines%20on%20ART_October%202021%20%20(1).pdf

22. Schürmann D, Rudd DJ, Zhang S. Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration to treatment-naïve adults infected with HIV-1: an open-label, phase 1b, consecutive-panel trial. Lancet HIV, 7(3), 2020, e164-e172. doi:10.1016/S2352-3018(19)30372-8.

23. Matthews R.P., Barrett S.E, Patel M,Zhu W, Fillgrove KL, Haspeslagh L. First-in-human trial of MK-8591-eluting
implants demonstrates concentrations suitable for HIV prophylaxis for at least one year. Merck & Co. cited on 3 Jul 2020, Available from: http://programme.ias2019.org/Abstract/Abstract/4843

24. Matthews RP, Hsieh S.J., Nussbaum J.C., Jajamovich G.H., Zhao T. Mk-8504 and mk-8583 (tenofovir prodrugs) single-dose pk and antiviral activity in HIV. Merck Research Laboratories. Cited on 9 July 2020. Available at: https://www.croiconference.org/abstract/mk-8504-and-mk-8583-tenofovir-prodrugs-single-dose-pk-and-antiviral-activity-in-hiv/

25. Williams PE, Cruwels HM, Bastanie ED. Formulation and pharmacology of long-acting rilpivirine. Current Opinion in HIV and AIDS 10(4), (2015), 233–8.

26. Mills A, Antinori A, Clotet B, Fourie J, Herrera G, Hicks C, et al. Neurological and psychiatric tolerability of rilpivirine (TMC278) vs. efavirenz in treatment-naive, HIV-1-infected patients at 48 weeks: Tolerability of rilpivirine vs. efavirenz. HIV Med, 14(7), 2013 Aug, 391–400.

27. Lai MT, Feng M, Falgueyret JP, Tawa P, Wittmer M, DiStefano D et al. In vitro characterization of MK-1439, a novel HIV-1 nonnucleoside reverse transcriptase inhibitor. Antimicrob Agents Chemother, 58(3), 2014, 1652-63. doi: 10.1128/AAC.02403-13.

28. Feng M, Sachs NA, Xu M, Grobler J, Blair W, Hazuda DJ. Doravirine Suppresses Common Nonnucleoside Reverse Transcriptase Inhibitor-Associated Mutants at Clinically Relevant Concentrations. Antimicrob Agents Chemother, 2016 Mar, 60(4), 25, 2241-7. doi: 10.1128/AAC.02650-15.

29. Smith SJ, Pauly GT, Akram A, Melody K, Ambrose Z, Lynch RM, Boritz E, Coates EE, DeZure A, Madden P, Costner P et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Sci Transl Med, 7(319), 2015 Dec, 23, 319ra206.

30. Liu Y, Cao W, Sun M, Li T. Broadly neutralizing antibodies for HIV-1: efficacies, challenges and opportunities. Emerg Microbes Infect, 9(1), 2020 Jan, 194-206. doi: 10.1080/22221751.2020.1713707.

31. Thomsen ND, Balakrishnan M, Pace CS, Zhang X, Hung M, Nagel MR. GS-9722: First-in-Class, Effector-Enhanced, Broadly Neutralizing Antibody for HIV Cure. Gilead Sciences, inc. cited on 15 July 2020. Available at: https://www.croiconference.org/abstract/as-9722-first-class-effector-enhanced-broadly-neutralizing-antibody-hiv-cure/

32. Singh K, GallazzI F, Hill KJ, Burke DH, Lange MJ, Quinn TP. GS-CA Compounds: First-In-Class HIV-1 Capsid Inhibitors Covering Multiple Grounds. Front Microbiol., 10, 2019 Jun, 1227. doi: 10.3389/fmicb.2019.01227.

33. Wensel D, Sun Y, Davis J, Li Z, Zhang S, McDonagh T et al. GSK3732394: a Multi-specific Inhibitor of HIV Entry. J Virol. 93(20), 2019 Sep, 30, e00917-19. doi: 10.1128/JVI.00917-19.

34. Cabotegravir. AIDS info. U.S. Department of Health and Human Services. Cited on 30 July 2020. Available at: https://aidsinfo.nih.gov/drugs/513/cabotegravir/0/patient.

35. Lipovek D. Adnectins: engineered target-binding protein therapeutics. Protein Eng Des Sel. 24(1-2), 2011 Jan, 3-9. doi: 10.1093/protein/gz097.

36. Beccari MV, Mogle BT, Sidman EF, Mastro KA, Asagio-Reddy E, Kufel WD. Ibalizumab, a novel monoclonal antibody for the management of multidrug-resistant HIV-1 infection. Antimicrob Agents Chemother 63, 2019, e00110-19. doi: https://doi.org/10.1128/AAC.00110-19.

37. Jacobson JM, Lalezari JP, Thompson MA, Fichtenbaum CJ, Saag MS, Zhang BS, et al. Phase 2a study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. Antimicrob Agents Chemother, 54(10), 2010 Oct, 4137-42. doi: 10.1128/AAC.00086-10.

38. Wang CY, Wong WW, Tsai HC, Chen YH, Kuo BS, Lynn S et al. Effect of Anti-CD4 Antibody UB-421 on HIV-1 Rebound after Treatment Interruption. N Engl J Med. 380(16), 2019 Apr, 1535–45.

39. Williams PE, Cruwels HM, Bastanie ED. Formulation and pharmacology of long-acting rilpivirine. Current Opinion in HIV and AIDS 10(4), (2015), 233–8.

40. Lynch RM, Boritz E, Coates EE, DeZure A, Madden P, Costner P et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Sci Transl Med, 7(319), 2015 Dec, 23, 319ra206.

41. Deeks ED. Doravirine: First Global Approval. Drugs 78, 2018, 1643–50.

42. Rogovoy B, Koryakova A, Volosova E, Karapetian R, Nikoulin I et al. Pre-clinical Development of Elsufavirine/VM1500A Long Acting Injectable Formulations. Viroim Inc. cited on 9 July 2020. From URL: https://static1.squarespace.com/static/5a20396b90b9ade9e464cc7a1/t/5afa4d327758d468560f59b07/1525994281734/EACS+2017+Poster+Final.pdf

43. Trezza C, Ford SL, Spreen W, Pan R, Piscitelli S. Formulation and pharmacology of long-acting cabotegravir. Curr Opin HIV AIDS, 10(4), 2015 Jul, 239-45. doi: 10.1097/COH.0000000000000168.

44. Whitfield T, Torkington A, van Halsema C. Profile of cabotegravir and its potential in the treatment and prevention of HIV-1 infection: evidence to date. HIV AIDS (Auckl), 8, 2016, 157-64.b doi: https://doi.org/10.2147/HIV.S97920

45. Wensel D, Sun Y, Davis J, Li Z, Zhang S, McDonagh T et al. GSK3732394: a Multi-specific Inhibitor of HIV Entry. J Virol. 93(20), 2019 Sep, 30, e00917-19. doi: 10.1128/JVI.00917-19.
49. Martin DE, Salzwedel K, Allaway GP. Bevirimat: a novel maturation inhibitor for the treatment of HIV-1 infection. Antivir Chem Chemother., 19(3), 2008, 107-13. doi: 10.1177/095632020801900301.

50. Martin DE, Blum R, Wilton J, Doto J, Galbraith H, Burgess GL et al. Safety and Pharmacokinetics of Bevirimat (PA-457), a Novel Inhibitor of Human Immunodeficiency Virus Maturation, in Healthy Volunteers. Antimicrob agents chemother., 51(9), 2007, 3063-66.

51. Cahn P, Fink V, Patterson P. Fostemsavir. Current Opinion in HIV and AIDS, 13(4), 2018, 341-5. doi:10.1097/coh.0000000000000469

52. Nowicka-Sans B, Gong YF, McAuliffe B. In vitro antiviral characteristics of HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068. Antimicrob Agents Chemother 56, 2012, 349.

53. Li Z, Zhou N, Sun Y, et al. Activity of the HIV-1 attachment inhibitor BMS626529, the active component of the prodrug BMS-663068, against CD4-independent viruses and HIV-1 envelopes resistant to other entry inhibitors. Antimicrob Agents Chemother, 57, 2013, 4172-80.

54. Kozal, M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina JM et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. New England Journal of Medicine, 382(13), 2020, 1232–43. doi:10.1056/nejmoa1902493.

55. Vautrin A, Manchon L, Garcel A. et al. Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing. Sci Rep, 9, 2019, 792. doi: https://doi.org/10.1038/s41598-018-37813-y

56. Efficacy and Safety Study of ABX464 as Maintenance Therapy in Patients with Moderate to Severe Ulcerative Colitis. ClinicalTrials.gov Identifier: NCT04023396. Cited on 18 July 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04023396

57. ABX464 in Treating Inflammation and Preventing Acute Respiratory Failure in Patients With COVID-19 Mir-Age. ClinicalTrials.gov Identifier: NCT04393038. Cited on 18 July 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04393038

58. Study of Two Doses of ABX464 in Participants With Moderate to Severe Rheumatoid Arthritis. ClinicalTrials.gov Identifier: NCT03813199. Cited on 18 July 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT03813199

59. Dutta S, Chawla S, Banerjee S. Pharmacovigilance in India: A Need of the Hour. Acta Scientific Medical Sciences, 2(8), 2018, 98-100.

60. Dutta S. Pharmacovigilance in India: Evolution and Change in Scenario in India. Int. J. Sci., 7(10), 2018, 976-8.

61. Dutta S. Rational use of medicines: a review. World j. pharm. med. 5(3), 2019, 129-32.