ISSN: 2476- 2334

Review Article

International Journal of Nanotechnology & Nanomedicine

Recent Development in the Biomarkers and Drugs for Acquired Immune Deficiency Syndrome (AIDS)

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Submitted: 2023, Oct 12; **Accepted**: 2023, Nov 04; **Published**: 2023, Nov 22

Citation: Singh, H., Garima, V. (2023). Recent Development in the Biomarkers and Drugs for Acquired Immune Deficiency Syndrome (AIDS). *Int J Nanotechnol Nanomed, 8*(1), 186-196.

Abstract

In recent times, rigorous efforts have been made, oriented on the elucidation of the pathogenesis, detection, progression and treatment of HIV. HIV has two main types HIV-1 & HIV-2, both the forms originated in primates from Africa, later transmitted to humans. HIV-2 is not as aggressive as HIV-1 and restricted to the African continent. However, both are equally problematic owing to recurrent recombination and can lead to a state of Acquired Immunodeficiency Syndrome (AIDS). The AIDS leads to high mortality rate but the progression can be restricted by in time detection and commencement of proper treatment. There are approximately 38 million HIV infected cases worldwide and 8 million people still do not have the access to testing services. The numerous HIV testing kits are based on different types of biomarkers. This review is mainly focused on the various biomarkers along with the detailed discussion on available FDA approved drugs.

Keywords: AIDS, Biomarkers, Active Drugs, Virus.

1. Introduction

AIDS is a type of retrovirus which is caused by Human immunodeficiency. This virus alters the immune system of the patient in such a way that it suppresses normal functionalities of the defense mechanism of organism and the sufferer become more prone to get affected by other fatal diseases [1]. At the early stages, this condition will not show any peculiar symptoms. Its early stage symptoms are influenza-like which is typically subsequent to a long period of no symptoms. Due to this, most people with such conditions are not aware of the disease. Lately, the suppression in the immune system leads to unintended weight loss and catching common opportunistic infections like tuberculosis [2, 3]. The transmission is caused by unprotected sex with multiple partners or the infected one, blood contamination, breastfeeding and childbirth.

There is no treatment for the disease that stays for life-long duration [1, 2]. Although, antiretroviral therapy is somehow proven to be very helpful in the cases as it controls its transmission. Basically, antiretroviral therapy uses multiple drugs that targets multiple and different viral levels in the body known as Antiretroviral Therapy [4-6]. There are six classes of drugs being used in HAART, with distinctive groupings of two NRTI, one NNRTI, Protease inhibitor or INSTI which is used as base. Some examples of these drugs are: Maraviroc, Zidovudine, Lamivudine, Nevirapine, Etravirine, Dolutegravir, Atazanavir, Bevirimat etc [7, 8].

Ever since the outbreak of this epidemic in the 1980s, more than 32 million lives have been claimed by the same since then. According to the Global HIV and AIDS stats 2019 by UNAIDS about 8.1 million HIV infected population is unaware of their health status whereas 79% of all people living with HIV are aware of their condition. By the end of 2018 there were 54% children, 62% adults and majority of the pregnant or breastfeeding women with 82% were under HIV coverage and receiving antiretroviral therapy. By June, 2019 people receiving antiretroviral therapy were around 24.5 million. According to one of the surveys conducted by the World Health Organization in 2018 global estimation for the key population considering for over half of all new HIV infections were estimated for 54% with eastern Europe, central Asia, Middle eastern and north African regions around 95% new infection cases. Moreover, in the time between 2000 to 2018 mortality rate due to HIV decreased by 45% and new infection (HIV) by 37%. Over 13.6 million lives were saved by Antiretroviral Therapy (ART) [9, 10].

Drugs

HIV, resultant of the multivariate viral levels consumes a diverse range of drugs. In 1987, FDA approved first drug for the treatment of AIDS that was Azidothymidine, also acknowledged as zidovu-

dine, belonging to the reverse transcriptase inhibitor category for HIV treatment, used to slow down the syndrome development in the infected patients [11]. Since then, till today, the drugs for the HIV and their efficiency, mode of action, and dosage has been evolved drastically. This evolution of drugs and therapy for HIV is being discussed below (Table 1).

DRUG	DOSAGE	ORAL BIOAVAILABILITY	FDA APPROVANCE
ZIDOVUDINE	500 to 600 mg/day	60%	1987
LAMIVUDINE	150mg twice daily for >50kg	80%	1995
SAQUINAVIR	1000 mg +100 mg ritonavir twice daily	30%	1995
NEVIRAPINE	Interchangeable doses up to 200 mg for neonates, children, adults and pregnant ladies	90%	1996 Extended release (2011)
RITONAVIR	600 mg twice daily	60%	1996
ABACAVIR	Children- 8 mg/Kg twice daily Generally- 300 mg twice a day i.e. 600 mg/day	83%	1998
EFAVIRENZ	Efavirenz 400 or 600 mg once daily + existing combination of zidovudine plus lamivudine	30% less in HIV infected patients than healthy persons. Not specified.	1998
TENOFOVIR DISOPROXIL FUMARATE	300 mg once daily (not approved for children)	25%	2001
ATAZANAVIR	300 mg +ritonavir 100 mg once daily	60-68%	2003
EMTRICITABINE	200mg once daily	93%	2003
ENFUVIRTIDE	90 mg twice daily	84.3%	2003
FOSAMPRENAVIR	700mg twice daily	Not established	2003
TIPRANAVIR	500mg +200mg ritonavir twice daily	Increases 30% with high fat meal	2005
DARUNAVIR	Treatment-experienced- 600 mg+100 mg ritonavir once daily Treatment naïve- 800mg +100 mg ritonavir with food	30%increase with food	2006
MARAVIROC	300 mg twice daily	33%	2007
ETRAVIRINE	200mg twice daily with other antiretroviral agent	Absolute bioavailability unknown.	2008
RILPIVIRINE	100mg twice per day	Not determined	2011
DOLUTEGRAVIR	50mg twice daily	Has not determined	2013
COBICISTAT	a) Should not be given alone b) Should be taken with food c) Dosage not defined.	Depend on co-administered medicine	2014
RALTEGRAVIR	400mg twice daily with or without food.	Has not been established	2017
DORAVIRINE	(a) A single dose of 100mg doravirine (b) Combination of 100 mg ritonavir or 800 mg darunavir with emtricitabine 200 mg/tenofovirDF 300 mg (c) Abacavir 600 mg/ lamivudine 300 mg	Bioavailability is affected by gender and age. Not specified.	2018
IBALIZUMAB-UIYKLK	Initially 2000mg then 800 mg once every 2 weeks	Latest(not known)	2018

Table-1: FDA Approved Drugs with Suggested Dose.

Drug	Pharmacodynamic properties	Pharmacokinetic properties	Therapeutic efficacy	Tolerability
Abacavir	● Antiviral activity in HIV-1 infected T-lymphocyte cell line (in-vitro), also in MT-4 cells infected HIV2 ● Resistance for associated mutations for RT coding region. ● Not much toxic except inhibits mitochondrial DNA synthesis in Molt-4 cells along with in-vitro Chromosomal abnormalities	● Oral administration with rapid absorption, Cmax (0.64 to 4.38 mg/L) ● Mean elimination half-life is less than 2 hours. ● For its drug interaction, alcohol increases the area under the curve by 41%, does not inhibit human liver cytochrome P450 enzyme	Combining with NRTIs and protease inhibitors, shows significant viral load reduction.	Nausea, vomiting, fatigue. In 7-17% patients also had adverse effects of headache, cough, diarrhea, sleep disorders, anorexia and rash leading to discontinuation of the drug which results in the hypersensitivity of the drug whose further continuation could lead to death. (12,13)
Emtricitabine	● In-vitro antiviral activity in lymphoblastoid, peripheral blood mononuclear cells, MAGI-CCR5 cell lines infected with HIV. ● Emtricitabine-safe secludes are cross impervious to lamivudine, impervious to the two medications related with methionine to valine or isoleucine replacement at codon 184 in HIV genome M184V/I. ● Not toxic as such, only affects various lipid levels.	● Rapid extensive absorption by gastrointestinal tract, within 2 hours of administration, steady peak for Cmax is observed which is decreased by 23% and time prolonged to 2.8 hours if administered with high fat meal. ● Mean elimination half life is 8 to 10 hours through renal pathway. ● The drug is neither metabolized nor an inhibitor of cytochrome P450 and has limited interaction with co-administered agents.	Triple combination therapies successfully suppressed the viral load.	Headache, diarrhea, nausea, rash. general to mild to moderate intensity asthenia but no adverse effect.(14)
Lamivudine	● Exhibited good inhibition against both HIV-1 & 2 in human PBL monocytes/ macrophages and various cell lines. ● Resistance to lamivudine, mutation at codon184 of HIV pol gene, receiving drug in the form of monotherapy or combination therapy ● Minimal toxicity observed in PBL cell lines.	● 10.5-15.5 hours as half-life intracellular elimination half-life in infected cells. ● Coadministration of lamivudine and cotrimoxazole in asymptomatic patients.	Monotherapy of the drug leads to improved surrogacy in children and adolescents with HIV.	Gastrointestinal abnormalities were most common adverse effect reported.(15)
TenofovirDisoproxilFumarate	● 0.04 - 8.5 mmol/L as EC50 values against lab strains and isolation of HIV-1 and 1.6 – 5.5 mmol/L'EC 50 values for HIV – 2. ● Amino acid K65R substitution shows resistance to tenofovir. Tenofovir susceptibility shows reduction with HIV-1 strain having mutations at 3 thymidine analogue associate mutations including HIV reverse transcriptase substitutions M41L or L210W ● Not toxic to humans.	● Absorbed after oral administration AUC and Cmax values were 35% & 15% higher in high fat meals as compared to fasted state. ● Elimination through kidneys, renal clearance >> 307 and >> 210 mL/min. 18.5 hours as elimination half-life. ● No significant drug interaction.	----------	Nausea, Diarrhea, headache, depression, fatigue, upper respiratory tract infection, vomiting and back pain are most common. Although discontinuation could lead to nervous system and psychiatric adverse effect.(16)
Zidovudine	● Completely inhibits DNA synthesis. With ~1 mol/L concentration, it reduces HIV induced, reverse transcriptase activity, cytopathogenicity, viral replication, antigen expression, and particle release in T lymphocytes. ● Zidovudine-resistant against HIV strains emerge after 60 days of therapy having HIV isolate susceptibility. Its variant has been detected in genital fluids too. ● Hematological toxicity. Toxicity extends during pregnancy depending on the dosage.	● Highly lipophilic drug. Lipid based protein meals show no effect of drug absorption whereas high fat meals lowers AVC and Cmax with delaying time of maximum absorption. ● Means elimination half life is 1 to 2 hours. ● Zidovudine administration with other agents inhibit glucuronidation including probenecid, valproic acid, naproxen, indomethacin and oxazepam. Organic based transport systems secrets drugs in the kidneys, leading to reduced renal clearance.	Increased survival rates upto 36 months and decreases opportunistic infections, which delays ARC and AIDS.	Anemia and neutropenia are common but serious adverse effects. However, in advanced stages headache, myalgia and insomnia occur more frequently. Showed long term toxicity.(17,18)

DORAVIRINE	● Shows potent antiviral activity in lab strains (wild type) of HIV-1 in vitro along with concentrations resulting in 95% of viral replication. shows activities against M group subtypes and various mutants. ● Data supported findings that doravirine can produce better results than efavirenz or rilpivirine in suppressing breakthroughs of HIV-1 with the common NNRTI resistance.	● Rapid absorption after oral administration, Maximum plasma level in 1 to 4 hours. ● CYP3A enzymes metabolize doravirine majorly, half-life of is 15 hours, mean clearance of 106 mL/min.	----------	Nausea, headache, fatigue and diarrhea.(19)
EFAVIRENZ	● Inhibition constant (Ki) of efavirenz against reverse transcriptase wild type HIV-1 was found to be 2.93 nmol/L with very good inhibition against the same with inhibition concentration (IC) = 1.5 to 3.0 nmol/L resulting in 95% inhibition. ● A study reported that using two cell types (MT-2 T Cell lines and peripheral blood mononuclear cells results in two highly efavirenz-resistant HIV-1 variant production.	● Cmax (0.51 to 2.9 mg/L) 5 hours after single oral dose showing 99.5 to 99.75% plasma bounding, mainly albumin. ● Elimination half-life reported was 52-76 hrs after single dose & 40-55 hrs after multiple dose oral. Shows metabolism through the liver mainly by cytochrome P450. ● Efavirenz metabolism can be induced by CYP3A4. Using efavirenz with saquinavir as combination is not recommended as is decreases Cmax and AUC	HIV RNA plasma levels brings down by 1.68 log10 duplicates/mL from the gauge demonstrating 98% viral concealment and the tally of CD4+ cells was expanded by 96 cells/uL in HIV-1 patients treated with this medication. Parameters show no huge changes among patients randomized to the fake treatment patients.	Nervous system and dermatological effects included nausea, vomiting, dyspepsia and diarrhea related to the combination with efavirenz. Although bedtime administration of the efavirenz reduced severity of nervous system-related symptoms and rashes were effectively managed by antihistamines and topical corticosteroids.(20)
ETRAVIRINE	● The median EC50 for HIV -1 group M isolates ranging 0.29 to 1.65 nmol/L and 5.2 to 7.2 nmol/L for wild type HIV-1. For HIV-2 etravirine is not recommended due to lack of clinical data. ● Etravirine seems to introduce a higher hindrance than other original NNRTIs against improvement of medication opposition. To support the statement, 2 mutations are prior to develop resistance against the drug which makes it better than earlier NRTIs ● Fatal cases have been reported during post marketing use of etravirine	● It took 4 hours to achieve maximum plasma concentration when administered with food otherwise AUC reduced to 50% when taken in the fasted state. Highly plasma bound (99.9%) majorly to albumin and 1-acid glycoprotein. ● Basically used in the liver through cytochrome P450 (CYP) proteins CYP3A4, CYP2C9 and CYP2C19, followed by glucuronidation. Mean half-life is roughly 30-40 hrs. ● When administered with other drugs which alter the CYP3A4, CYP9C9, CYP9C19 enzyme expression may alter pharmacokinetic profile of etravirine as this drug is a substrate for the same enzymes.	Similar response rates were also observed across OBT groups that accommodate darunavir/ ritonavir/ raltegravir in co-administration.	Unfavorable impacts are demonstrated prompting treatment end in 7% of the etravirine gatherings. Events like rash, diarrhea, nausea, anemia, peripheral neuropathy, abdominal pain and fatigue. Hypersensitivity was observed the same as in placebo trials. (21)
NEVIRAPINE	● This medication demonstrated restraint in-vitro replication of different HIV-1 strains and their clinical disconnects with IC50 in refined human T-cells at 40 nmol/L. ● Completely suppresses viral replications within 24 hours, for cultured- cells infected with HIV-1. The activity get limited when administered later. ● The susceptibility gets lesser by 100 times in variant to nevirapine as compared to wild-type virus with cross-resistance to other NNRTIs. ● Almost negligible cytotoxicity in non-cancerous human cells	● Shows extremely high oral absorption and distribution among all parts of the body. 0.3 to 2.9 mg/L as Cmax in 4 hours. ● Nevirapine shows its own metabolism enhancements by itself through iso-enzymes cytochrome P450 . Mean elimination half-life is approximately 40 hours. ● Protease inhibitors do not show any visible effect on the pharmacokinetics of nevirapine.	The Nevirapine portion of 240mg/ day quickly decreases antiviral action, However, 120 to 400 mg/ day can repress HIV p24 antigen creation in mellow to direct HIV malady in pediatric patients.	Most frequent adverse event was rash and granulocytopenia in children. Some other common events were vomiting, diarrhea, pain, fever, occurred in rare cases.(22)

RILPIVIRINE	● Exhibits antiviral action against wild sort HIV-1 in vitro (middle EC50 0.73 nmol/L against HIV 3B) and shows higher power against HIV-1. Whereas, shows limited activity against HIV-2 (EC50 = 2.510 – 10.830 nmol/L). ● Resistance to rilpivirine by various amino acids substitutions may be shown, most commonly L100I, K101E, and M230I/L. in cross resistance, among HIV-1 with 2 or 3 NNRTI RAMs, 38 & 60 % showed diminished susceptibility to rilpivirine.	● Rapidly absorbed reaching Cmax within 4-5 hours. Absolute bioavailability has not been determined yet. Oral bioavailability increased when administered in fasted state. ● Half-life is approximately 45 to 50 hours. ● Rilpivirine is used by CYP3A, its plasma restricting can be adjusted by coadministration of CYP3A inducers or inhibitors. Also, the MATE2K transporter is also inhibited by rilpivirine in vitro	Virological concealment was kept up through week 100 in 89% of the patients in which rilpivirine is co-controlled with dolutegravir.	Insomnia, depression, anxiety, and abnormal dreams including headache and depressive disorders. Also, shows severe skin and hypersensitivity reactions. Not recommended during pregnancy. (23)
ATAZANAVIR	● Shows very high potency for HIV-1, as it prevents mature virion formation by restricting the cleavage of gag/gag-pol polyproteins. At higher concentration there was nil antagonistic anti-retroviral activity, or enhancement of cytotoxicity. ● Toxicity observed in-vitro was 6500- to 23800- times higher in concentrations than as much required for antiretroviral activity.	● Rapid absorption with reaching plasma concentrations at peak within 2-3 hours of oral administration. The AUC of unboosted atazanavir 400 mg concentration increased by 35% and 70% with low and high fat meals respectively. It is +86% protein bound. ● It is a liver metabolized drug mainly by CYP3A4 resulting in elimination mainly by biliary route, with very less to minor elimination by kidneys. For un boosted atazanavir, mean steady state half-life for HIV-1 was 6.5 and 8.6 hours when boosted with ritonavir.	Un-supported atazanavir show fewer viral concealment than a daily containing lopinavir/ritonavir in patients.	Most common adverse events reported were nausea, jaundice and diarrhea. while when administered in boosted form, it showed jaundice and hyperbilirubinemia. (24)
DARUNAVIR	● Non-peptidic HIV-1 PI is an oral administrator, which selective inhibitor of gag and gag-pol polyproteins, also prevent viral maturation, along with dimerization inhibition of HIV-1 protease which inhibit HIV-1 replication and proteolytic activity. Have EC50 value 1-5 nmol/L ● In-vitro studies added that resistance of HIV-1 was slower than amprenavir, nelfinavir or lopinavir. Do not show cross resistance with other PI, although may display some potential cross resistance to amprenavir.	● When boosted with low dose ritonavir, show rapid absorption reaching peak plasma level in just 2.5-4 hours. 30% increase in bioavailability when taken with food although meal type does not affect exposure. Darunavir is about 95% plasma protein bound. ● This drug shows oxidative metabolism and is metabolized by the CYP3A and P450 enzymes. Mean elimination half-life of boosted darunavir is >>15 hours. ● When boosted, other inducer or inhibitor drugs for CYP3A exhibit potential drug interaction leading to differential plasma concentrations.	Patients with boosted darunavir show viral load reduction form by 1 log 10 copies/mL from the baseline.	This drug is well tolerated in patients with HIV-1 in clinical trials with mild to moderate severity. Diarrhea, nausea, headache, upper respiratory tract infection and nasopharyngitis. Increased triglyceride and cholesterol levels were also involved in some cases. (25)
FOSAMPRENAVIR (It is a pro drug of amprenavir thus, shows similar properties as that of the amprenavir)	● This drug inhibits virions by blocking the viral protease and prevents infection causing HIVvirions formation with 50% inhibition In-vitro at 0.012-0.08 umol/L concentrations. ● Patients treated with fosamprenavir showed no cross-resistance to other drugs (PI) and mutations. ● No significant toxicity for B & T-cell.	● When regulated orally, fosamprenavir shows quick hydrolyzation in gut epithelium to amprenavir which is the dynamic moiety as it isn't consumed itself fundamentally. The mean plasma level focuses (Cmax) of 4.26ug/mL happened at 1.5 hours. Shows no effect of high fat meal and is plasma protein binding type. ● Show primary metabolism through cytochrome P450 (CYP) 3A4 pathway. ● As the drug shows metabolism, inhibition and may induce CYP3A4 pathway thus can interact with other drugs that are inducer, substrate, or inhibition of this enzyme.	At the point when co-directed with abacavir results into momentary antiviral adequacy to that of the amprenavir-based-routine.	By and large, very much endured in antiretroviral treatment. Low no. of patients ceased treatment because of unfavorable impacts. Most normal unfriendly occasion in general in two preliminaries experienced by patients is the runs. Other adverse effects with least to moderate severity were drug hypersensitivity, nausea, gastrointestinal disturbance, skin rash. (26)

RITONAVIR	● Its action against 7 HIV 1 clinical isolates in peripheral blood lymphocytes produces 50% inhibition against disease at 0.045µmol/L concentration. ● In patients treated with ritonavir monotherapy, resistance has arisen via an ordered accumulation of mutations of HIV protease, beginning at amino acid 82.	● In a fasting single-dose study, ritonavir 100 to 1000 mg showed a nonlinear pharmacokinetic profile in 16 patients with HIV infection. ● In patients who received ritonavir 600 mg twice daily Cmax was 11.2 mg/L, time to Cmax (tmax) was 4 hours and AUC24 was 156 mg/L. h, with a steady-state total clearance of 8.9 L/h. ● Its bioavailability in humans is at least 60%. ● Its half-life elimination is from 3 to 5 hours. ● Drugs inducing CYP3A increases its metabolism. Apart from this drug such as dexamethasone, itraconazole, ketoconazole, loratadine, methadone, nefazodone, quinine and sertraline also interact with ritonavir and clarithromycin and 14-0H-clarithromycin increase its AUC by 34% but drugs such as didanosine, fluconazole or Zidovudine do not interact with it.	Plasma HIV RNA load was significantly reduced in ritonavir recipients after 4 weeks' therapy [IO.25] and was below the limit of detection (10000 copies/ml) in 38% of patients. results from a dose-ranging study indicate ritonavir is well tolerated and has significant antiHIV activity in children.	Adverse events occurring in ritonavir recipients are generally reversible and tolerated. In a decreased manner in %age of patients the events of nausea, diarrhea, vomiting, asthenia, abdominal pain, headache, anorexia, circumoral paraesthesia, taste perversion and peripheral paraesthesia respectively had been observed with 17 to 6% patients to discontinue due to these adverse effects. (27)
SAQUINAVIR	● Highly active as per in-vitro studies, against HIV in acutely or chronically affected by the virus. ● Cross resistance may occur between the saquinavir and other protease inhibitors, but it is very difficult to predict the same as this resistance is not specific.	● 98% bound to the plasma protein. ● Mean half-life elimination time is 2.6 hours.	Saquinavir was changed from the SGC to HGC detailing in both MaxCmin1 and MaxCmin2, on the off chance that antagonistic gastrointestinal unsettling influences.	By and large, saquinavir was very much endured in clinical preliminaries for as long as 48 weeks in both helped or twofold supported structures. None of the 69 patients involved in the trials discontinued the therapy due to the adverse events. Only lipodystrophy was reported in some patients. (28)
TIPRANAVIR	● Effectively inhibits most of the HIV-1 group M non-clade B isolates H, G, F, D, C, A, CRF12 BF, CRF02 AG, and CRF01 AE, but shows lesser activity against group O isolates in-vitro. EC50 of tipranavir against laboratory strains and replication for HIV-1 ranged from 0.03 to 0.07 umol/L ● Tipranavir resistance is slowly developed in-vitro and is quite complex. Its resistance increases with increase in the mutations.	● In the absence of ritonavir, its absorption gets limited. Tipranavir is a weak inhibitor & inducer of the P-gp as being a substrate for the same. ● Reaches to Cmax within 1-5 hours of administration. Bioavailability increases with high fat meals. Shows maximum plasma protein binding. ● Mean elimination half -life is 6 hours. Mode of elimination through faecal route. ● Inducer, inhibitor and substrate of CYP3A. also, shows increase in metabolism when administered with P-gpand CYP3A inducing drugs.	Showed confirmed viral load reduction of _>1 log 10 copies/mL among a larger proportion of the patients. Showed no long-term failure in comparison to other CPIs.	Increase in the cholesterol levels, triglyceride levels, and liver enzymes. Patients having increased liver enzyme abnormality and hepatitis should cautiously recommend this as treatment. Patients with increased bleeding risks should be administered cautiously with the drug as tipranavir could be associated with the fatal or non-fatal intracranial hemorrhage. Gastrointestinal adverse events were most common, and rashes have also been reported. (29)

ENFUVIRTIDE	● This drug inhibits HIV-1 mediated cell-free virus transmission and cell fusion. The inhibitory concentration (50%) that is IC50 of the drug against laboratory isolates and virus loads have a rage of <0.001-7.53 ug/mL and for HIV-2 was ~103- to 104- fold greater concentration then for HIV-1, needed for the inhibition. ● HIV isolates having one amino acid substitution at 36, 38, 40, or 43, tends to decrease enfuvirtide susceptibility 3.1- to 450- folds.	● Oral bioavailability is 84.3% of the drug. Male patients who failed to respond to the treatment in a trial showed that the drug showed resistance against the blood test barrier. Bounds to plasma protein by 92%. ● Mean maximum level concentration was achieved after 4.73 hours was 6.35 ug/mL. Mean Elimination half-life was 3.8 hours. ● Does not significantly affect the activity of the CYP enzyme or N-acetyltransferase thus does not really affect the other antiretroviral drugs.	Optimized background therapy including enfuvirtide showed significant reduction in viral load and increased cell count of CD4+ improved treatment outcomes on virological and immunological parameters.	98% of the receivers faced injection-site reactions, as a result 4.4% of them discontinued the treatment. Further, 11% of the total observed severe injection-site reactions. Other than these reactions the drug is well tolerated by the patients. Enfuvirtide boosted background therapy can cause pneumonia and lymphadenopathy. (30)
MARAVIROC	● Mean grouping of maraviroc hindering half and 90% of the replication was 0.51 & 2.0 nmol/L. ● Maraviroc is particular for R5 tropic infections, in this manner strain choice that utilizes CXCR4 instead of the CCR5 center receptor could result in viral departure. ● Also, in comparison to the placebo the drug shows increased cardiac index and pulse rate and decreased stroke index and systemic vascular resistance.	● Total bioavailability was 33% with tolerably lipophilic nature and is consumed by the vehicle intervention process. Cmax diminishing from 2.9 hours with 30mg to 1.6 hours with 300mg progressively with time. Bound to plasma protein with very little distribution to the red blood cells. ● Mean Elimination half-life 10.6 hours in healthy men receiving it daily twice, and elimination half-life was 22.9 hours on the day 10 of the dosage. ● Maraviroc shows no inhibition or induction of the CYP3A4. Although all CYP3A4 inhibitors increase AUC and Cmax of maraviroc.	Maraviroc's other background therapy was better than the OBT with placebo in R5-tropic HIV-1 infected patients. Also, CD4+ cell count increased significantly in the therapy.	Discontinuation occurred in some of the patients while some cases of mortality were reported in some cases. Adverse events included pyrexia, musculoskeletal and connective tissue signs and symptoms, rash, upper respiratory tract infection, cough associated symptoms, dizziness, appetite disorders, disturbances, herpes, gastrointestinal and abdominal pain, bronchitis, constipation, sinusitis. (31)
DOLUTEGRAVIR	● Shows better in-vitro activity against broad spectrum subtypes of the HIV-1. ● Shows higher genetic barrier to resistance than raltegravir isolates with Q148 with other integrase mutations had reduced susceptibility to the dolutegravir.	● Limits to the plasma protein jumping 98.9% all around consumed in the plasma after oral organization, arriving at greatest plasma level fixations by 2-3 hours of the organization. ● Terminal half- life of the dolutegravir is 14 hours and largely metabolized by the liver. ● Data suggested from the in-vitro studies showed that this drug has very low tendencies to interact with the other drugs involved in the therapy.	Following several weeks of the treatment, HIV-1 RNA levels in plasma diminished quickly as viral RNA levels of 50 duplicates/mL were accomplished in 85% of the patients.	Most common adverse events noted were insomnia, headache, with occasional nausea. Diarrhea was also reported in very rare cases.(32)

RALTEGRAVIR	● Raltegravir acts as a selective inhibitor of the integrase. IC95, the 95% IC of the drug in human lymphoid tissue infected with HIV-1 strain was 31 nmol/L and range from 6-50 nmol/L in blood mononuclear peripheral cells of humans. ● Oral administration with 400 mg two times every-day for 48 weeks had negligible effect on fasting serum lipids in the benchmark trials.	● Bioavailability has not been established. Shows rapid adsorption with reaching Cmax plasma concentration approximately within 1 hour. 83% of human plasma protein binding approximately. ● Shows no interaction with the cytochrome P450 and no evidence of the oxidative metabolism in human liver microsomes.	An irregular exchanging preliminary recommended that raltegravir alongside other foundation medicines (OBT) was non-mediocre compared to enfuvirtide in addition to OBT regarding the viral concealment alongside the CD4+ cells checks climbed structure gauge (102-140 cells/mm3) and by the mean estimation of 83 cells/mm3 in benchmark trails.	Most common treatment adverse event is triglyceride elevation. Other effects are diarrhea, headache, nausea, pyrexia and fatigue.(33)
IBALIZUMAB-UIYK	● This drug binds to the domain 2 of the CD4+ receptor. ● Mean maximum percent inhibition was 91% overall for viral replication. The drug achieved 50% & 80% inhibition in 92%& 65% of HIV strains.	● Steady-state achieved after the first dose of 800 mg having mean concentrations 30 lg/mL. ● Maximum plasma level concentration is 402 lg/mL, with 3.3 days as mean elimination half-life. ● Dose recommended starting with 2000 mg then 800 mg as loading dose once in 15 days.	Mean viral load reduction to 1.6 log 10 in week 24 from baseline with ibalizumab boosted therapy.	Ibalizumab can potentially cause immunogenicity with all therapeutic proteins. Most frequent adverse events are diarrhea, dizziness, nausea, rash.(34)
COMBICISTAT	● Cobicistat shows a potent inhibitory activity against CYP3A which is time and concentration dependent. ● CYP3A activity with a dosage of 50 mg, reduced by 89%, and 95% reduction with the dose of 200 mg.	● Cobicistat also inhibits transporters like P-gp, BCRP, OATP1B1 and OATP1B1. Administration of the drug in the fed, fasting or protein rich conditions do not have any effect on the adsorption of the drug. Although bioavailability is affected with food intake.	----------	Increment in the triglycerides, complete cholesterol, SCr and lessening in the CrCl levels. Other most regular unfavorable occasions detailed are sickness, loose bowels, migraine, nasopharyngitis. (35)

Table 2: FDA Approved Drugs with Their Pharmacodynamics and Pharmacokinetic Properties.

The window period for the HIV diagnoses is very vast, making it challenging for the researchers to find a better and more efficient drug. From the very first FDA approved drug Zidovudine to the last drugs being used in the ART, the therapy and efficacy of these drugs has been metamorphosed drastically.

Biomarkers

Biomarker is an indicator of a biological state or conditions. They are basically chemicals or proteins that organisms produce at particular biological conditions, which could be a response to a biological process, pathogenic response or a pharmacological response to therapeutics or some chemicals. These biomarkers are released in very trace amounts, for example, the radioactive isotope of rubidium chloride is used to evaluate perfusion of heart muscle. In other words, biomarkers are the substance whose presence conforms a specific condition or state [36-38]. In the past 30 years, the study and new surfaced research on biomarkers has contributed diversely in the fields of genomics, toxicology, medicine, and drug delivery and so on, to get a better idea on the condition, effect and susceptibilities [38]. In addition to this recently, "omics" biomarkers may be classified as Genomic, proteomic, and metabolomic/metabonomic are one of the major classes under development. These biomarkers are basically giving ideas of cell conditions such as cell death, cell growth etc [38, 39].

Prostate-specific antigen (PSA), one of the commonly used biomarkers in medicine is used to detect prostate cancer as a result of mutation in the proteins as mutant protein can only be result of already existing tumor [39, 40]. HbAc1 is one the biomarkers for Type 2 diabetes mellitus or in other words, diagnostic biomarker [41]. Galactomannan another diagnostic biomarker for invasive aspergillosis patients enrolling for clinical trials for antifungal agents [42]. Another example are sweat chloride and cystic fibrosis transmembrane conductance regulator (CFTR) i.e. Ivacaftor (VX-770), are the biomarkers for cystic fibrosis and helps in evaluation of cystic fibrosis in clinical trials [43, 44].

Types of Biomarkers:

Genomic Biomarkers (GB) Characteristics based on DNA or RNA fragmentation which acts as an indicator for a biological response, process or condition. A very trending Example for the same is MicroRNAs (miRNAs), playing key role in the various cellular processes which includes Physiological stress too. In addition, to this they are present in almost all the bodily fluids and the alterations in the expression level of stress-associated miRNAs in the brain and whole-body fluids during physiological activities concretes this point. Which also leads to the point that miRNAs also can pass Blood-Brain Barrier, that can lead to very potential drug delivery systems and toxicity hand in hand [45]. These biomarkers are more efficient in diagnosing genetic disorders, characterization, selection and therapy. So, typically a genomic biomarker should be reflecting the regulation, expression or function of a gene. Some of the examples for Genomic Biomarkers for the therapy induced response are [46].

S.No.	GB	Disease	Therapy/Drug
1.	HLA-B*5701	Hypersensitivity Syndrome	Abacavir
2.	UGT1A1	Colon Cancer	Irinotecan Therapy
3.	CYP2C9/VKORC1	Anticoagulant Treatment	Warfarin
4.	EGFR	Advanced squamous cell Carcinoma	Erbitux
5.	Her2/neu	Metastatic Breast and Stomach Cancer	Herceptin
6.	(~Bcr-abl) Philadelphia Chromosome	Chronic Myelogenous Leukemia	Gleevec

Table 3: Different Examples of Genomic Biomarkers for Specific Disease and Their Prescribed Drugs.

Proteomic Biomarkers (PB):

These biomarkers are discovered using techniques like microarrays and mass spectroscopy, which are capable of analysis of different proteins simultaneously. Protein based biomarkers are known as proteomic biomarkers [47]. OVA1 is the one and only FDA approved diagnostic multivariate index assay for PB [48, 49].

Sr. No	Proteomic Biomarkers	Analysis	Disease/ Condition
1.	CA125	Over-expressed mRNA	Ovarian Cancer [47]
2.	Prealbumin	Prealbumin concentration in blood	Phenylketonuria [50]
3.	Apolipoprotein A1	Multivariate logistic regression analysis	Acute ischemic stroke [51]
4.	β 2-microglobulin	Serum albumin levels	Chronic kidney diseases/end stage renal disease, cadmium poisoning [52]
5.	Transferrin	Saturation Level	Iron deficiency, Anemia [53]
6.	HE4 (WFDC2)	Expression Level	Ovarian Carcinoma [54]
7.	C-reactive protein	Levels of the protein	HIV [55]

Table 4: Some Proteomic Biomarkers for Specified Disease and Their Analytical Base.

Metabolomic Biomarkers (MB) These biomarkers are the defining patterns of abundance of multivariate biomarkers, rather than relying on the quantification of a particular metabolite [56].

Sr. No.	MB	Expression	Condition
1.	Glutamate	Hyperactivation	Amyotrophic lateral sclerosis (ALS)
2.	Creatinine	Hypoactivation	Amyotrophic lateral sclerosis (ALS)
3.	Antioxidant (Uric Acid)	Increased levels	Amyotrophic lateral sclerosis (ALS)

2. Conclusion

HIV infection can lead to gut microbial translocation or systemic inflammation, which is the state of chronic immune system activation, ultimately it may persist with HAART. All the conditions can get severe at some stage and can be fatal, and that is why the timely detection is of utmost importance. HIV kits used for the detections are based on various biomarkers like cytokine, chemokine, coagulopathy and vascular endothelial. However, various HIV detection kits can have diversified costs based on markers. This study takes the two very important perspectives related to HIV and AIDS, first is detection that is based on biomarkers and second is treatment so available FDA approved drugs are discussed.

Acknowledgements:

Authors are thankful to Chandigarh University for providing financial and other necessary facilities for this research

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