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Review Article

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Recent advances in antiretroviral therapy for HIV/AIDS

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Abstract

Acquired Immune Deficient Syndrome (AIDS) is a deathly human viral infectious disease caused by Human Immune Deficient Virus (HIV) infection. Started as Mono therapy using treatment of HIV, then multiple drugs in schedule given where patients had to eat up 11-16 tablets per day. To apply test and treat policy assisted by WHO, supply of cost effective antiretroviral drugs regularly and newer drugs get approved and challenge for developing countries. Hence we tried reviewing upcoming new molecules which showed potential to be good drugs in various phases of clinical trial. AIDS. First disease killer in US was AIDS in 1993. After one decade hard work, antiviral drug cocktails-high active antiretroviral therapy (HAART) have been invented for almost all HIV infection treatments. HAART medications regularly need to take HIV/AIDS patients and even life-long. Future trends are highlighted.

Keywords: Newer Antiretroviral drugs, HIV, US FDA approved ARV drugs, HAART, antiviral therapy.

Introduction

AIDS is a deadly human disease caused by HIV infections. Due o lack of effective therapeutics at that time, almost every AIDS patient losses his/her life before mid-1990s. HIV/AIDS was once the 1st disease killer in US (1993). Primary treatment using HIV/AIDS patients was chemicals or vaccines. Before the invention of high active antiretroviral therapy (HAART, cocktail therapy), the therapeutic responses of HIV/AIDS patients were very limited. Almost every AIDS patient losses his/her life before mid 1990s-all of the AIDS patients died within 2 years after AIDS episode emergence. At that time, it looks like a capital punishment when a patient infects with HIV.

HIV infected person becomes a easy target for opportunistic infections and diseases. T-helper cell (CD4) multiplies this virus and gradually depletes them. The Two main types are HIV-1 and HIV-2. HIV-1 is the most common type found worldwide And HIV-2 is found mainly in Western Africa, with some cases in India and Europe [1].

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Different treatments regimens to treat HIV infections around 15 molecules are used. However, issues like treatment failure due to drug resistance and toxicity remain crucial issues. The purpose of this review is to brief about newer antiretroviral drugs (Pharmacokinetics and pharmacodynamics) for HIV, which are recently approved and newer promising drugs in pipeline i.e. phase 2 and phase 3 trials.

Basic Facts about HIV

10 to 15 years which is last clinical stage in HIV infected person would develop AIDS. HIV mainly found in breast milk, anal fluids, semen, vaginal and blood. But, it cannot be transmitted through saliva, sweat or urine. Currently, there is no cure for HIV but with early diagnosis and effective Antiretroviral (ARV) treatment, people with HIV can live a long and normal, healthy life. So, we can take treatment regularly and it is important. The drugs currently available for HIV blocks the replication by interfering at various stages of the life cycle. These drugs own toxicities and many reported development of resistance.

Antiviral Drug Targets and HIV Virus Life Cycle (Figure 1)

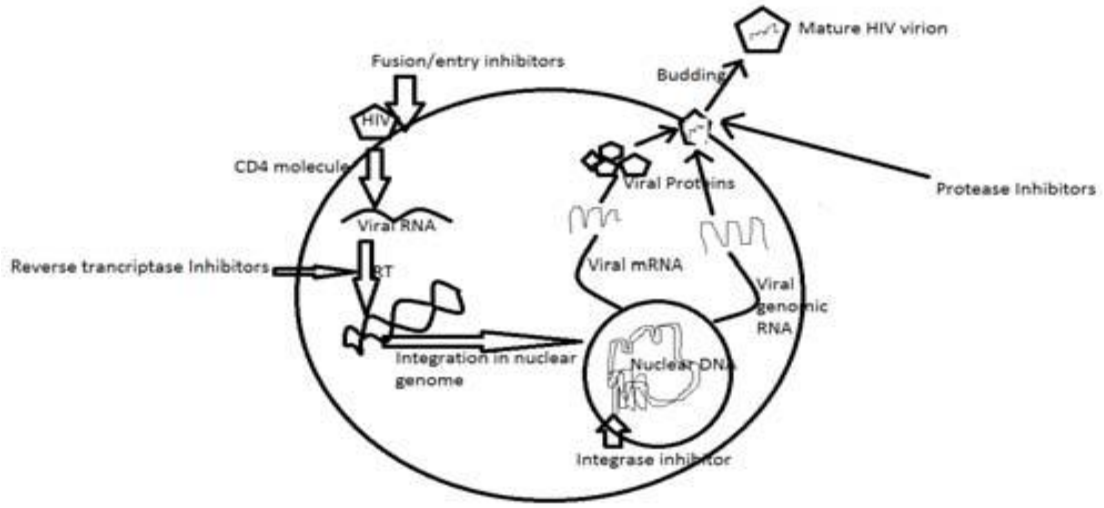

Figure 1: Antiviral Drug Targets and HIV Virus Life Cycle.

Classification of antiretroviral (ARV) drugs [2]

Classification of antiretroviral drugs in following tables.

There are divided each class depending on the FDA approval of the drugs before and after 2012. It is number of Drugs approved after 2012 has dropped down is quietly evident. Increased prise of clinical trials and decreased profit margin. (Table 1, Figure 2).

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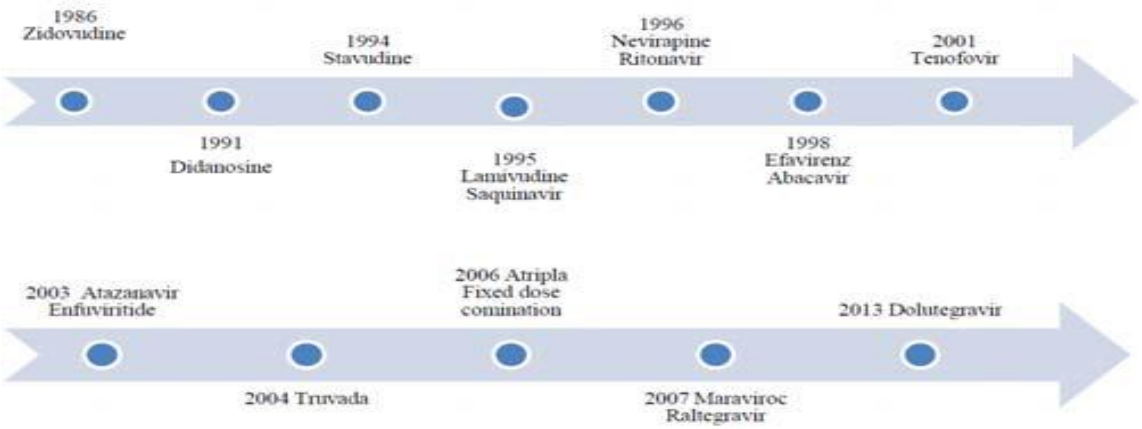

Figure 2: Timeline for ARV development [3].

Table 1: Classification of antiretroviral (ARV) drugs.

	Nucleoside reverse transcriptase inhibitor (NRTI)	**Non-Nucleoside reverse transcriptase inhibitor (NNRTI)**	**Protease Inhibitor(PI)**	**Fusion inhibitor**	**Entry inhibitor**	**Integrase inhibitor**
ARV drugs approved by FDA before 2012	Didanosine	Rilpavirine	Amprenavir	Enfuvirtide (T-20)	Maraviroc (MVC)	Raltegravir
	Abacavir	Nevirapine	Darunavir			
	Lamivudine	Etravirine	Tipranavir			
	Tenofovir	Delavirdine	Indinavir			
	Zidovudine	Efavirenz	Nelfinavir			
	Stavudine		Atazanavir			
	Zalcitabine		Ritonavir			
	Emtricitabine		Saquinavir			
			Fosamprenavir			
			Lopinavir			
ARV drugs approved by FDA before 2012	TenofovirAlafenamide					Dolutegravir Elvitegravir Cabotegravir
	*Cobicistat acts as Pharmacokinetic Enhancers which do not have any antiviral activity.					

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In patients experiencing virological failure, assessment of adherence to treatment is helpful to determine the mechanisms of failure and to choose an alternative therapeutic option [4]. Treatment of HIV with medicines is called as Highly Active Anti- Retroviral Therapy (HAART). HIV positive as per new who guidelines for ART is recommended for everyone. Combinations that are optimal to use as first-line therapy for various clinical trials determined. Exact investigations are needed to establish the value of simplified regimens in an attempt to increase the adherence. A combination of HIV medicines every day take people on ART. Three HIV medicines from at least two different drug classes generally a person initial HIV regimen. ARV drug treatment cannot cure HIV, but help people with HIV live longer and healthier lives. Reduce the risk of HIV transmission and ARV medicine.

Guideline for initiation of antiretroviral drugs [5]

Treatment of HIV/AIDS which mainly include Centre for Disease Control (CDC), World Health Organization (WHO), British HIV association (BHIVA), HIV clinical guidelines programme, New York and National AIDS Control Organization (NACO), India exists different guidelines. Though ART is recommended for all HIV-infected individuals in most of the guidelines, regardless of CD4 count, NACO India is yet to implement this policy. ART is also recommended for HIV-infected individuals to prevent HIV transmission (PreP). Patient education and counseling is very important before initiating ART to overcome the challenges with the improper use of ART and to maximize the benefits.

Challenges with the use of ARV Drugs

Figure 3: Challenges with the Use of ARV Drugs [6].

Newer anti-retroviral drugs

Newer anti-retroviral drugs which have shown promising result to rising the challenges for HIV infection are following (Figure 3).

Tenofovir Alafenamide

Other Names: A prodrug of tenofovir, tenofoviralafenamide fumarate, GS-7340, TAF, TFV alafenamide etc.

Drug Class: (NRTI) Nucleoside Reverse Transcriptase Inhibitors

Phase of Development [7]: The following TAF-containing FDC regimens are in Phase III studies:

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1) Emtricitabine/TAF
2) Rilpivirine/emtricitabine/TAF
3) Darunavir/Cobicistat/Emtricitabine/TAF and
4) Rilpivirine/ Emtricitabine, GS-9883/ Emtricitabine/TAF and Emtricitabine/TAF and TAF FDC tablets are currently under review by the U.S. Food and Drug Administration (FDA) for marketing approval.

Mechanism of action: TAF belongs to a class (group) of HIV drugs called nucleoside reverse transcriptase inhibitors (NRTIs). NRTIs prevent HIV from multiplying and can reduce the count of HIV in the body, by blocking reverse transcriptase.

Pharmacokinetic details

TAF is a prodrug. TAF prodrug does not work until the body converts it into an active form. In the body, TAF is converted to tenofovirdiphosphate (TFV-DP). The prodrug and undergo turning to tenofovir intracellularly and Tenofovir Alafenamide designed to circulate consistently, achieving higher active metabolite composition in peripheral blood mononuclear cells and lower plasma tenofovir exposures than TDF. [8] (Table 2).

Table 2: Distinguish between Tenofovir Disoproxacil Fumarate and Tenofovir Alafinamide.

Parameters	Tenofovir Disoproxacil Fumarate (TDF)	Tenofovir Alafenamide (TAF)
Clinical trial phase	Approved	Phase III
Dose	300 mg OD	25 mg OD with food
Protein binding	< 0.7% very low to human plasma proteins and < 7.2% to serum proteins	~80%
Half-life (T½)	The median terminal elimination half-life is approximately 17 hours.	The median terminal half-life is 0.51 hours. The tenofovirdiphosphate, active metabolite, has an intracellular half-life of 150 to 180 hours.
Metabolism	Cytochrome P450 enzyme system is not involved	Cytochrome P450 3A (CYP3A)-mediated metabolism of TAF is minor
Excretion	By IV administration, 70-80% of the dose is recovered in the urine as unchanged drug within 72 hours	Mainly excreted in Feces upto 31.7% and in urine ‹ 1%
Adverse Events	Rash, diarrhea, headache, pain, depression, asthenia, nausea, and nephrotoxicity.	diarrhea, upper respiratory tract infection, fatigue, nausea, and rash

The adjuvant with ART: Cobicistat

The anti viral drugs are basically used to target virus entities, However being non-specific sometimes and also having problems with metabolism due to host drug metabolizing genes makeup issues like non-adsorption and toxicity are of major concern. It is a potent CYP inhibitor but cobicistat dose not have Antiretroviral activity. By decreasing the metabolism, it increases the concentration of antiretroviral drugs. Gives an opportunity to use drugs which would be long acting at a lower dose can turns. Following characteristics are Cobicistat has been adapted in practice.

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Table 3: After 2012 under the class of integrase inhibitors Comparison of drugs approved.

Parameters	Elvitegravir	Cabotegravir [9]	Dolutegravir [10,11]
Synonym/Other Names:	EVG	cabotegravir sodium, cabotegravir LA,744 LA, CAB, GSK-1265744, GSK1265744, GSK744, GSK744 LA, GSK744 LAP, S-265744, S/GSK1265744, etc.	DTG, S/GSK 1349572 or 572
Drug Class:	Integrase Inhibitors	Integrase Inhibitors	Integrase Inhibitors
Molecular Weight:	447.88 g/mol	405.35 g/mol	441.36 g/mol
Pregnancy category:	B (No risk in non-human group)	Not available	B (No risk in non-human group)
Approval status:	EVG approved as fixed dose combination in 27 AUG 2012 as "Stribild" and as single pill formulation in 24 SEP 2014.	IIb	DTG is approved on 13 AUG 2013 for adult and children above 12 years of weight atleast 40kg or more.
Dosage form:	Tablet formulation which always take 85mg and 150mg with food and should be used with combination with other HIV medicines.	CAB is available in Tablet formulation as Oral carbotegravir and in Parenteral formulation as long acting injection/ carbotegravir LA or CAB LA, Oral CAB	Tablets: 50 mg oral.
Absorption:	Oral administration with food increases three fold absorption and reaches Cmax within 3-4 hours.	Intramuscular and subcutaneous administration followed by LA cabotegravir is readily absorbed	Oral administration of DTG gives peak plasma concentrations 2 to 3 hours post-dose.
Protein binding:	EVG shows 98% protein binding.	High protein binding.	High protein bounding i.e. greater than or equal to 98.9%
Metabolism:	Mainly via Liver by Cytochrome P450 (CYP)3Aenzyme	CAB is primarily metabolized via glucoronidation by UGT1A1 (main pathway) and UGT1A9 (minor pathway).	Dolutegravir Primarily metabolized via UGT1A1 with some contribution from CYP3A enzymes.

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Half-life:	12.9 hr.	Long-acting parentral [LAP] nanosuspension administered for 21-50 days via intramuscular [IM] or subcutaneous [SC] injection 40 hours for oral dosing.	Dolutegravir has a terminal half-life of approximately 14 hours.
Excretion:	Renal 7% and 93% in liver through occur.	CAB is eliminated in feces primarily as unchanged drug and in urine as a glucuronide metabolite.	(Feces up to 53% and in urine 18.9%) Major route of excretion is feces followed by urine
Warning and Precaution:	Care should be taken If you are allergic to EVG or have liver problem and if pregnant or breast feeding condition.	Injection site reaction may be observed.	Fat redistribution and hypersensitivity Reactions can be seen also Immune Reconstitution Inflammatory Syndrome (IRIS) is also observed. Contraindication: Co-administration with dofetilide is contraindicated it can be life threatening also.
Side effects/ Adverse Events:	Immune reconstitution inflammatory syndrome (IRIS) and the common side effect is diarrhea	For oral route, most AE seen is Headache. And for parenteral route is Injection Site Reaction (ISR) is predominately mild (93%) and Grade 1	Allergic reaction and abnormal liver function in patient infected with Hepatitis B or C
Storage:	Store at room temperature below 86°F (30°C).	-20ºC for long term storage of dried powder and -80ºC for short term storage of solution (as available from commercial supplier).	Store at room temp. 68 to 77°F (20 to 25°C)

Other Names: COBI, GS-9350 etc.

Drug Class: Pharmacokinetic Enhancers (CYP3A Inhibitors)

Approved Use: It is used as pharmacokinetic enhancer in combination with other ARV agents for the treatment of HIV-1 infection [12].

Molecular Weight: 776.03 g/mol

Molecular Formula: C_{40} H_{53} N_7 O_5 S_2

Dosage form: Tablets: 150 mg orally with meal and renal dose should be adjusted if creatinine clearance is less than 70ml/ min.

Mechanism of action: Including important CYP3A4 subtype, COBI is a potent inhibitor of Cytochrome P450 3A enzyme. It also inhibits intestinal transport proteins which also increases overall absorption of several ARV drugs.

Pharmacokinetic properties

Protein binding: 97 to 98 %.

Half-life: Terminal half-life is ~3 to 4 hr.

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Indication and usage: COBI is a CYP3A inhibitor indicated to increase systemic exposure in combination with other ARV agents for the treatment of HIV-1 infection

Side effect: COBI with Atazanavir gives yellowing of eyes (Jaundice) and nausea. Also, severe allergic reaction and symptom of kidney problems are also observed.

Precaution: Safety and efficacy are not being established patient younger than 18 yr. as it decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting the actual renal glomerular function also testing prior to Initiation of cobicistat is necessary

Contraindication: Co-administration with tenofovir is not recommended due to renal toxicity.

Storage: Cobicistat is stored at 25°C

One or more drug classes, combination HIV medicines contain two or more HIV medicines from (Table 4).

Table 4: FDA approval dates and ARV drug combination.

Generic Name (Acronyms and other names)	Brand Name	FDA Approval Date
DTG , and Lamivudine, Abacavir	Triumeq	August 22, 2014
Atazanavir and Cobicistat	Evotaz	January 29, 2015
Darunavir and Cobicistat	Prezcobix	January 29, 2015
Cobicistat, Elvitegravir, Emtricitabine, and TAF	Genvoya	November 5, 2015
Emtricitabine, Rilpivirine, and TAF	Odefsey	March 1, 2016

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Newer drugs for HIV in Phase 1 and Phase 2 trials: [13] (Table 5).

Table 5: Newer drugs for HIV in phase 1 and phase 2 trials.

Name	Class
Amdoxovir	Nucleoside Reverse transcriptase inhibitors
Lersivirine Doravirine	Non Nucleoside Reverse transcriptase inhibitors
Cenicriviroc	Entry Inhibitor
Ibalizumab	Monoclonal antibody, entry inhibitor
Beverimat	Maturation inhibitor
AMD070	CXCR4 inhibitors.
HGS004 is a human immunoglobulin (Ig)	G4 monoclonal antibody against CCR5
Apricitabine	NRTI that is active against the M184V mutation
PRO 140	CCR5 monoclonal antibody
Vicriviroc	CCR5 antagonist
Vivecon (MP-9055)	HIV maturation inhibitor
BMS-663068	binds directly to the gp120 , Attachment inhibitor
	Active unheeding of whether an HIV strain uses CCR5 or CXCR4 co-receptors.

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HAART in HIV/AIDS Treatments

HAART Invention

Approximately 20 years ago HAART was developed, which was to combine utilities of antiviral chemicals of different types or categories and displayed prolonged HIV/AIDS patient survival a great deal (approximately 7 to 10 years survival benefits is there) comparing with single antiviral drug utilities. This is a great therapeutic advancement for viral managements in HIV/AIDS patients and a great medical achievement.HIV infected patients live longer and HIV patients eventually die of causalities that are unrelated to HIV infection or HIV-induced cancer.

Now HAART become a standard of medical care for HIV infection and AIDS symptom control [14-16]. An enormous therapeutic benefit was achieved after this invention in HIV/AIDS managements.

Major protocols of HAART

Different Types of Anti-HIV Chemothera peutic Agents

Till date, more than twenty anti-HIV chemicals have been licensed for formal viral therapeutic utilities worldwide, which have been now divided into six classes of therapeutic mechanisms and categories (Table 6).

Table 6. Different types of antiviral drugs for HIV treatments.

Drug Type	Mechanisms
Fusion Inhibitors	Virus penetration through host cell membrane inhibitors
NNRTIs	Bind at position distant from active sites of RT
NRTIs	Competitively inhibit reverse transcriptase
Chemokine recetor antagonists	HIV fusion to host cells (CCR5)
Protease inhibitors	HIV formation
Integrase inhibitors	HIV into host genome

Future trends

Today, HIV/AIDS therapeutics means for HAART is the only workable. But we must not satisfy with previous achievement. New attempts must be sought after from this therapeutic achievement. (Table **7**).

Table 7. Possible drug targets different from current HAART for HIV/AIDS treatments.

Drug Categories and Disciplines	Drug Targets and Types	References
Free radical	Antioxidant NO interference	[17]
Epigenetic agents	HIV latency activations	[18]
Pharmacology	Choice of optimal drug combinations in different clinical occasions and settings	[19-21]
Immune Promotions	Polysaccharide	[23]
Medicinal chemistry	Drug therapeutic index gains	[23]
Other Viral Inhibitors	Avian flu seasonal flu Ebola	[25-26]
Pathology	Viral-induced pathway mediate	[27]
Pharmaceutical	Nano-particle drug developments HIV reservoirs penetrations	[28]

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A number of efforts have been done for decisive changes. But progresses are limited in bedside. Facing this challenge, open discussion about pathologic study (HIV-induced pathogenesis and human mortalities) and technical capabilities (diagnostics and therapeutics) for therapeutic improvements as many as possible are proposed [27]. New generations of therapeutic establishments must be placed in priority position. From Fig. (**4**) and Tables **8** & **9**, we can see a long process of HIV-induced detriment steps. They are much complicated comparing with present available/licensed therapeutic drug categories. There are two types of HIV-induced pathogenesis (biological/pathological processes vs clinical period of symptom emergence) (Tables **8** & **9**).

By these kinds of biomedical research, new drug targets, such as HIV latency [18], genomic editing [22] and so on are under investigations. Though indecisive nowadays, they may become fruitful if new discovery is available in the future. Like many wonderful technical advances, their widely utilities are not on initial stages, other new scientific findings can greatly promote their applications.

Table 8. Clinical aspects of HIV progression and active immunity counteractions.[24]

Major Disease Phases	Symptomatic Characters	Time after HIV Infections	Possible Immune-activities
HIV transmissions	Detectable HIV viremia in human Blo	4-11 days	Cellular membrane molecule and receptors
Infected symptoms	Fever, rash, fatigues, diarrhea and elevated liver enzyme level etc	2-6 weeks	Cytokine or inflammatory Mechanisms
Peak of HIV viremia	Highest viral copies and load in human blood	3-8 months	Cytotoxic T lymphocytes; CTL
Establish of chronic infections	Stable RNA copies in patient's Blood	1 years	Neutralizing antibodies or balance of human defensive
AIDS occurrence	Co-infection and cancer	No definite time-scale	Dramatic immune-decline
Mortality	Unknown mechanisms	After two years AIDS	No treatment

Initial HIV infection
↓
The distributions of HIV in human bodies
(Different vascular routes-lymphatic or blood)
↓
Parasite in different human cells, tissues or pathologic reservoirs.
↓
Critical pathways to inducing dysfunction of human immune systems.
↓
Emergence of AIDS symptom/episodes
↓
Human mortalities

Figure 4. General pathways of HIV-induced pathologic cascade and human mortalities.

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Table 9. The relationship between pathogenesis and therapeutics.

Pathologic Processes	Affected Molecules or Symptoms	Therapeutic Targets
Viral attachments	Membrane ligands and so on	Cell signal inhibitors/promoters HIV vaccines Fusion inhibitors
Viral cell entry	Membrane receptors Membrane channel	Proteasome inhibitors Fusion inhibitors
Transcription/viral replica	Reverse transcriptase	Nucleotide antagonists NNRTIs Reverse transcriptase inhibitors
Human HIV reservoirs	Tissue & cell membrane	Nano-particle HIV inhibitors Combine antibody
HIV latency	Histone deacetylase NF-kB Bromodomain-containing protein Protein kinase C (PKC)	Anti-body + activators HAART + activate or inhibitors
DNA integration	Host cell genome	Integrase inhibitors
Viral egress	Host defensive systems	Cytokine Interferon
Cell lysis	Host defensive systems	Cytokine Interferon HIV vaccines
Physiological abnormality	Fever, wasting, metabolic illness	Traditional Chinese medicine
Human immune dysfunction	No of active lymphocytes	HAART
AIDS	Co-infections or cancer	HAART
Human mortalities	Loss of physiological functions	Too late

New compound/molecular structural identifications
(Different spectra & X-ray crystallography)

↓

Biological/pathologic assays
(Biochemical analysis)

↓

Pathology & Pharmacology study
(Tolerance, ADME, efficacy and so on)

↓

Drug combinational paradigms
(Rule discovery)

↓

Update diagnostics
(Genetic/bioinformatics)

↓

Personalized therapies (Optimal therapeutics)

Figure 5. Outlook of future HIV/AIDS therapeutic studies.

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Conclusion

Acquired Immune Deficient Syndrome (AIDS) is a deathly human viral infectious disease caused by Human Immune Deficient Virus (HIV) infection. Mono therapy using treatment of HIV. High active antiretroviral therapy (HAART) have been used all HIV infection treatments. Recently drug are potentially used for antiretroviral therapy.

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