APPROCHES TO ANTI-HIV CHEMOTHERAPY

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Summary

The causative virus of AIDS 'HIV' which was discovered in 1981. Since then it has made the situation of the human health very volatile, escalating and unstable. An extensive research has been done in last two decades to establish biology, pathophysiology and consequences of HIV infection, to design the satisfactory therapy. The development of new regimen of drugs to prevent HIV infection is still on. The review describes HIV infection with the various approaches of therapy under study. An attempt is made to provide panoramic view of the developments in the field of therapeutics strategies and treatment regimen.

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Introduction

It was 1981 that first case of a new disease called Acquired Immune Deficiency Syndrome were recognized in a number of young previously healthy homosexual men of unknown origin who were reported with rare type of cancer and with infections previously seen only. In patients with severe immune system impairment, initially called GRID (Gay related immune deficiency), AIDS was soon reported in other populations. It was initially thought to be due to immunosupression. About two years later Luc Montaiger and Robert Gallo identified the major cause to be retrovirus "HIV". Formerly called HTLV-III (Human T Lymphotropic virus Type III) by Gallo and Luv (Lymph adenopathy associated virus) by Montaiger. The term HIV was adopted by international committee in 1986 and much controversy over which group discovered the virus first. The global HIV epidemic is so far more worse than previously thought with about 1 in every 100m adults aged between 15-49 years being injected.

Structure and Function of the Enzymes:

Reverse Transcriptase (RT):

HIV-I RT exists as a heterodimer consisting of tightly associated p51 and p 66 subunits. This enzyme has 3 distinct catalytic functions.

1) An RNA dependant DNA polymerase activity.
2) Utilizing the viral RNA strand as template it synthesizes a complimentary strand of DNA. As this DNA strand is being formed, activity residing in the RNA H domain of p66 serves to digest the RNA template.
3) A DNA dependant DNA polymerase to compete the synthesis of the double stranded proviral DNA.

Hence RT is responsible for the synthesis of double standard viral DNA from proviral RNA for subsequent incorporation into the host cell chromosomes.

The function of RT is therefore essential for replication of HIV; therefore this is a suitable target for anti-HIV chemotherapeutic intervention.

Routes of transmission:

- Blood contaminated needles, Blood to blood contact such as transfusion, Sexual contact, Breast milk, Organ transplant, Artificial insemination with donated sperm.
- HIV positive mother to achild (risk of transmission is at least 30 %)

AIDs is not transmitted by

Casual Social Sharing, Glasses, Towels, Insects, Contacts, Household facilities

Diagnosis of HIV-I- Infections

Methods	**Product Measured**
Antibody detection technique a) ELISA b) Western Blot	Anti-HIV Antibody
Polymerase chain reaction PCR	Proviral DNA, Transcribe DNA
Branch chain DNA amplification	“Labelled” viral RNA

Table no 1: FDA approved drugs

Drug	Other Names	Target Enzymes	FDA Approved Treatment
Zidovudine	AZT	Reverse transcriptase	87 for treatment of adult AIDs or symptomatic HIV and CD4<200. 87 for treatment of adult infection and < 500. 90 also approved for pediatric use (3m-12 yrs). 94 approved for Perinatal transmission in HIV positive woman (14-34weeks gestation) and new borns.
Didanosine(Videx)	DD1	Reverse transcriptase	91 for treatment of adult and pediatric with advanced HIV who are intolerant to or deteriotating on AZT. 92 approved for patients with advanced HIV previously treated with AZT.
Zalcitabine (Hivid)	Ddc	Reverse transcriptase	91 for combination use with AZT treatment of selected patient with advanced HIV disease. 96 approved for monotherapy in advanced HIV for ages > 13 yrs who are intolerant to or have disease progression on AZT.
Stavudine	D4T	Reverse transcriptase	94 approved for use in adults. 96 approved for adults on prolonged AZT also for peadiatric use.
Nevirapine	Viramine	Reverse transcriptase	96 approved for use in combination with Nucleoside analogues in adults.

Table no. 2

Drug	Manufacture	Target Enzymes	FDA Approved Treatment
Invirase (Saquiravir)	Hoffman-1a Roche	Protease	95 Approved for use in combination with RT1, AZT, dd1, dd3, d4T for the treatment of advanced HIV infections.
Novir	Abbot	Protease	96 Approved for use alone or with combination or alone with nucleoside analogues of RT1, also used in pediatric infection > 2yrs.
Crixivan	Merck	Protease	96 approved for use alone or combination with nucleoside analogues of RT1 for infection in adults.
Veracept	Agouron	Protease	95 approved for treatment of HIV infection in adults and in pediatric > 2 yrs.

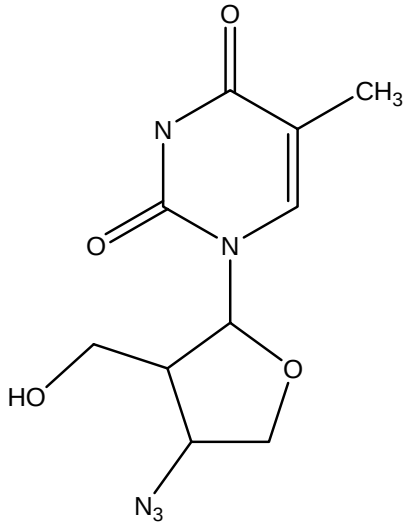
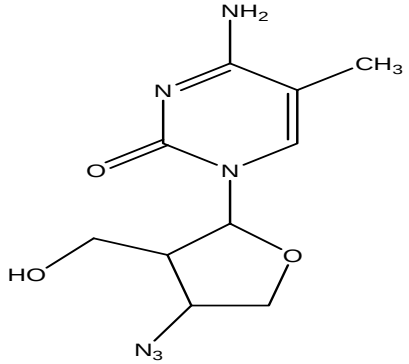
Table no 3: Protease inhibitors in early stage of development

Drug	Manufacturer	Stage of development
VX-478 141w98	919x0-welcome/Vertex	In early trials in people with HIV infection.
KN-272 (Kynostatin)	Kikko kyto pharmaceutical and national cancer institute.	In early trials in people with HIV infection.
U-103373	Upjohn	In early trials in people with HIV infection.
Cap-53437	Ciba-Geigy	In lab tests
Hee/Boy-793	Hoechst-Bayer	In Lab test
SR-41476	Sanoji	In lab tests

Table 4

Name of the Plant	Family	Target	Isolated active molecule
Xanthoceras sorbifolia	--	HIV-1-protease	29-hydroxy-3-oxitirucalla,7,24-diene-4-oic acid. Epigallocatechin[4P-8,2b-0-7] epicatechidiene-21-oic acid.
Maclura tinctoria	Moraceae	HIV inhibitory activity	Xanthones such as Maclura-Xanthone B,C Alvaxanthone Flavonoids such as Dihydrocudraylavone B.
Monotes africenus	Dipterocarpaceae	HIV inhibitory activity	Flavonol 6,8, diprenylkaempferol
Tripterygium hypoglaucum	Celatraceae	HIV inhibitory activity	Alkaloids such as Peritassine A, Hypoglaunine C, Triptonines A and B, Wifordinines A,B,C.
Syzygium claviforum	Myrtaceae	HIV-Inhibitors	3-O-acyl-betalinic acid and Oleanolic acid.
Rosa woodsil	Rosaceae	HIV-Inhibitors	3-O-(3,3-dimethyl)-succinyl betulinic acid
Prosopis glandalosa	Leguminosae	HIV-Inhibitors	3-O-(3,3-dimethyl)-succinyl betulinic acid
Phoradendron juniperinum	Loranthaceae		3-O-Glutaryl ursolic acid.
Syzygium claviforum	Myrtaceae		3-O-Isovalalanyl ursolic acid
Hyptis capitata	Laminaceae		3-O-Diglyosyl ursolic acid
Ternstromia gymmanthera	Theaceae		
Palicourea condensate	Rubiaceae	Anti-HIV	Macrocyclic peptide palicourein
Chassalia parvifolia	Rubiaceae		Circulines A-F
Psychotria longipes	Rubiaceae		Cyclopsychotride A
Oldenlandia offinis	Rubiaceae		Kalatia B1 Cycloviolins A-D
Viola spices	Violaceae	Anti-HIV	Violapeptide I and Varus A-H1
Viola arvensis	Violaceae		

Table no. 5 Natural product based Dinucleoside transcriptase inhibitors

Dideonucleoside Analog	Structure	Anti-HIV EC 50 µg	III B T 150
AZT MW=267		**0.001**	**>1000**
Dde, Dideoxycytidine MW=211		**0.010-0.061**	**200**

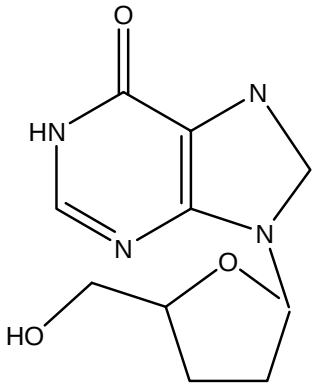
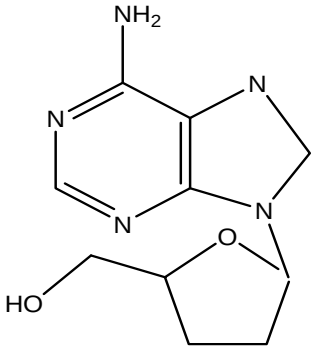
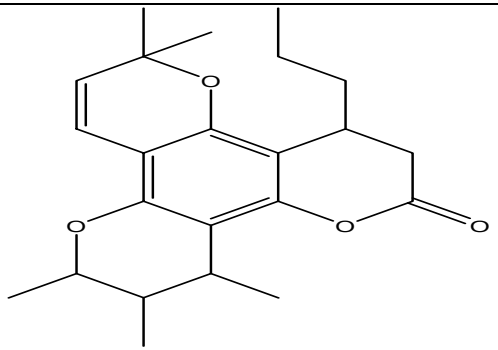
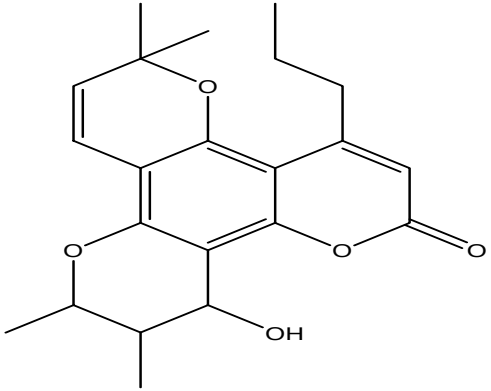
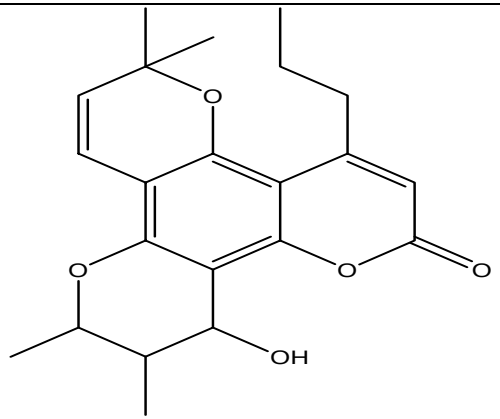
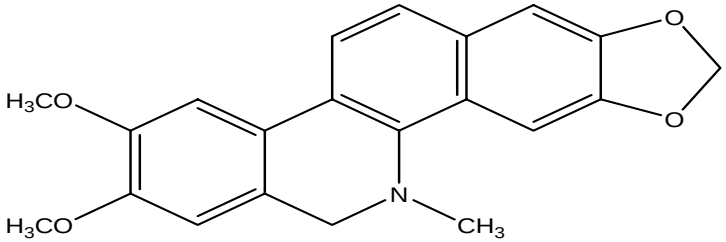
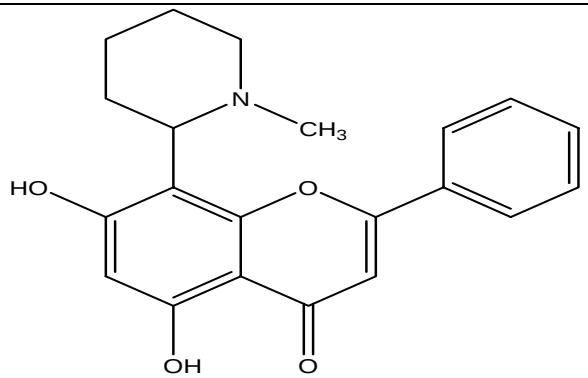
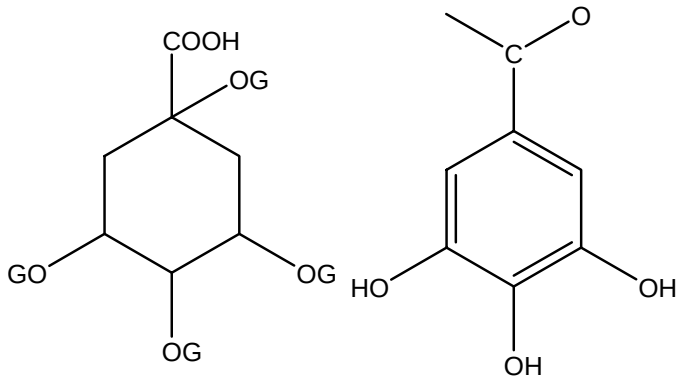
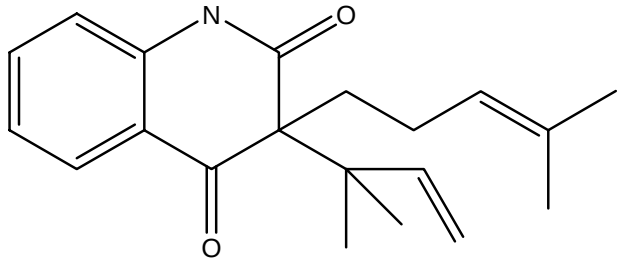
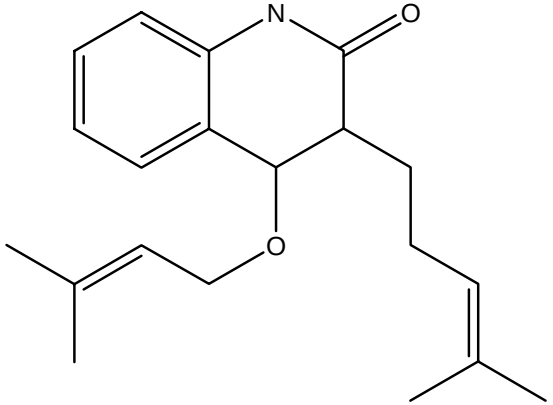
Dd1, Dideoxyinosine MW=218		**0.0056**	**10760**
β- FddA, β – Flurodideoxy adenosine MW=253		**1.16**	**>17.0**

Table no 6: Non-nucleoside Reverse Transcriptase Inhibitory-Leads Discovered by NCl, LDDRD

Common name	Structure	Taxonomy source	Anti-HIV EC50 µg	T 150
(+) Calanolide MW=370		Caophyllum lanigerum Sarawak, Malasia	0.2	103
(-) Calanolide B MW= 370		Caophyllum lanigerum Sarawak, Malasia	0.2	>20

(-) Dihydrocalanolide MW=370		**Caophyllum lanigerum Sarawak, Malasia**	**0.1**	**99.8**
Nitidine		**Toddallia asiatica, Rutaceae, Taiwan,Japan**	**14**	**3**
O-dimethyl Buchenvianine MW=351		**Buchenavia capitata, Combretaceae, Dominican Republic**	**14**	**3**

Galloyl quinic acid		**Lepidohotrys staudrill, Lepidobotryaceae**	**0.5**	**20**
Buchapine MW=310		**Euodia roxburghiana thialay**	**0.94**	**31**
Quinolone MW=297		**Euodia roxburghiana thialaians**	**1.69**	**17**

Conclusion

The review explains the various changes that have occurred in the past year in the guidelines to HIV therapy, current management strategies including movement away from ZDV monotherapy, institution of combination therapy earlier in the disease. New classes of antiretroviral such as protease inhibitor are considered to be the most potent therapeutic agents for the treatment of HIV infection to date. The other therapeutic strategies for combating AIDS are

1 Natural products
2 Non-nucleoside reverese transcriptase inhibitor
3 Integrase inhibitors
4 Gyrase inhibitors
5 Gene therapy

Protease inhibitors in the early stages and works various peptide inhibitors is presently in progress, such as peptide derived HIV-PI and non pepticle derived HIV-PI. The drugs use of which are discussed in the review at present or those which are likely to be become available in the near future, it may be that control of viral replication with a consequent delay or prevention of further immunosuppressant, is the best that can be achieved. The combination therapies have shown promising results; it is too early to say that, AIDS will soon be a chronic non-fatal disease. The preset generation of protease inhibitor and other novel therapeutic strategies and future generation of drugs under active development have recently provided potent new weapons against HIV. But successful genetic treatment is still a attractive prospects, offering among the other advantages, freedom from daily drug regimens required to keep the virus in check. Future generations of drugs under active development will probably provide HIV infected patients, a new ray of hope in life.

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