Drugs Fut 2006, 31(10): 915-934

CCC: 0377-8282/2006

Update 2006 – Treatment of HIV Infection

(Source: Prous Science Integrity®)

Treatment of HIV Infection by Mechanism

Mechanism	Phase	Drug	Source
Anti-CD11a/CD18 (LFA-1)	I/II	Cytolin®	CytoDyn
Anti-CD195 (CCR5)	I	CCR5mAb004	Human Genome Sciences
	I	PRO-140	Progenics
Anti-CD4	II	TNX-355	Tanox
	I/II	PRO-542	NIAID/NICHD
Anti-gp120	I	BMS-378806	Bristol-Myers Squibb
	I	ISIS-5320	ImQuest BioSciences/Isis Pharmaceuticals
	I	KD-247	Chemo-Sero Therapeutic Research Institute
Chemokine CCR5 antagonist	III	Maraviroc[2]	Pfizer
	II	Vicriviroc	Schering-Plough
	I	INCB-9471	Incyte
Chemokine CXCR4 (SDF-1) antagonist	I/II	AMD-070	AnorMED
HIV integrase inhibitor	III	MK-518	Merck & Co.
	II	GS-9137 (JTK-303)[2]	Gilead/Japan Tobacco
	I	S-364735	Shionogi-GlaxoSmithKline
HIV protease inhibitor	L-2006	Darunavir[2]	Tibotec
	L-2005	Tipranavir[2]	Boehringer Ingelheim
	II	Brecanavir	GlaxoSmithKline/Vertex
	I	PPL-100	Ambrilia Biopharma
HMG-CoA reductase mRNA expression inhibitor	II	SP-01A	Samaritan Pharmaceuticals
Monoclonal antibodies	II	4E10/2F5/2G12	Polymun
	I/II	2F5/2G12	Polymun
PDGFR inhibitor/dihydroorotate dehydrogenase inhibitor/inhibitor of signal transduction pathways	I	Leflunomide[1,2]	NIAID
Reverse transcriptase inhibitor	L-2006	Efavirenz/emtricitabine/ tenofovir disoproxil fumarate	Gilead/Bristol-Myers Squibb
	III	Etravirine[2]	Tibotec
	II	Amdoxovir[2]	NIAID
	II	Apricitabine	Avexa
	II	BILR-355	Boehringer Ingelheim
	II	Calanolide A[2]	Sarawak MediChem
	II	Elvucitabine[2]	Achillion
	II	Fosalvudine tidoxil	Heidelberg Pharma
	II	MIV-210	Medivir/Tibotec
	II	PSI-5004	Pharmasset
	II	Rilpivirine	Janssen/Tibotec
	I	KP-1461	Koronis Pharmaceuticals
	I	MIV-150	Medivir/Population Council
Viral fusion inhibitor	II	Sifuvirtide	FusoGen Pharmaceuticals
Viral maturation inhibitor	II	Bevirimat	Panacos
Other	III	Atvogen	HemispheRx
	III	VGV-1	Viral Genetics
	II	HE-2000	Hollis-Eden

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Treatment of HIV Infection by Source

Source	Mechanism	Drug	Phase
Achillion	Reverse transcriptase inhibitor	Elvucitabine[2]	II
Ambrilia Biopharma	HIV protease inhibitor	PPL-100	I
AnorMED	Chemokine CXCR4 (SDF-1) antagonist	AMD-070	I/II
Avexa	Reverse transcriptase inhibitor	Apricitabine	II
Boehringer Ingelheim	HIV protease inhibitor	Tipranavir[2]	L-2005
	Reverse transcriptase inhibitor	BILR-355	II
Bristol-Myers Squibb	Anti-gp120	BMS-378806	I
	Reverse transcriptase inhibitor	Efavirenz/emtricitabine/tenofovir disoproxil fumarate	L-2006
Chemo-Sero Therapeutic Research Institute	Anti-gp120	KD-247	I
CytoDyn	Anti-CD11a/CD18 (LFA-1)	Cytolin®	I/II
FusoGen Pharmaceuticals	Viral fusion inhibitor	Sifuvirtide	II
Gilead	HIV integrase inhibitor	GS-9137 (JTK-303)[2]	II
	Reverse transcriptase inhibitor	Efavirenz/emtricitabine/tenofovir disoproxil fumarate	L-2006
GlaxoSmithKline	HIV protease inhibitor	Brecanavir	II
Heidelberg Pharma	Reverse transcriptase inhibitor	Fosalvudine tidoxil	II
HemispheRx	Other	Atvogen	III
Hollis-Eden	Other	HE-2000	II
Human Genome Sciences	Anti-CD195 (CCR5)	CCR5mAb004	I
ImQuest BioSciences	Anti-gp120	ISIS-5320	I
Incyte	Chemokine CCR5 antagonist	INCB-9471	I
Isis Pharmaceuticals	Anti-gp120	ISIS-5320	I
Janssen	Reverse transcriptase inhibitor	Rilpivirine	II
Japan Tobacco	HIV integrase inhibitor	GS-9137 (JTK-303)[2]	II
Koronis Pharmaceuticals	Reverse transcriptase inhibitor	KP-1461	I
Medivir	Reverse transcriptase inhibitor	MIV-150	I
		MIV-210	II
Merck & Co.	HIV integrase inhibitor	MK-518	III
NIAID	Anti-CD4	PRO-542	I/II
	PDGFR inhibitor/dihydroorotate dehydrogenase inhibitor/inhibitor of signal transduction pathways	Leflunomide[1,2]	I
	Reverse transcriptase inhibitor	Amdoxovir[2]	II
NICHD	Anti-CD4	PRO-542	I/II
Panacos	Viral maturation inhibitor	Bevirimat	II
Pfizer	Chemokine CCR5 antagonist	Maraviroc[2]	III
Pharmasset	Reverse transcriptase inhibitor	PSI-5004	II
Polymun	Monoclonal antibodies	2F5/2G12	I/II
		4E10/2F5/2G12	II
Population Council	Reverse transcriptase inhibitor	MIV-150	I
Progenics	Anti-CD195 (CCR5)	PRO-140	I
Samaritan Pharmaceuticals	HMG-CoA reductase mRNA expression inhibitor	SP-01A	II
Sarawak MediChem	Reverse transcriptase inhibitor	Calanolide A[2]	II
Schering-Plough	Chemokine CCR5 antagonist	Vicriviroc	II
Shionogi-GlaxoSmithKline	HIV integrase inhibitor	S-364735	I
Tanox	Anti-CD4	TNX-355	II
Tibotec	HIV protease inhibitor	Darunavir[2]	L-2006
	Reverse transcriptase inhibitor	Etravirine[2]	III
		MIV-210	II
		Rilpivirine	II
Vertex	HIV protease inhibitor	Brecanavir	II
Viral Genetics	Other	VGV-1	III

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Vaccines and Other Products for HIV Infection by Name

Name	Source	Phase
825780	GlaxoSmithKline/PowderMed	I
ADMVA	Aaron Diamond AIDS Research Center/IAVI/Univ. Rochester	I
AGS-004	McGill University	I/II
Aldesleukin	NIAID	II
ALVAC vCP1452	NIAID/ANRS	II
ALVAC vCP1521	NIAID/NICHD/NIDA/NIMH	I
ALVAC vCP1521 + AIDSVAX® B/E	Walter Reed Army Institute/sanofi pasteur	III
AMZ-0026	Amazon BioTech	IND filed
AVX-101	AlphaVax	I
DermaVir™	Genetic Immunity/Res. Inst. Genetic Human Ther./NIAID	I/II
DNA/PLG microparticles + gp140/MF59	NIAID	I
DNA-HIV-C	EuroVacc Foundation	I
DNA-HIV-C + NYVAC-HIV-C	EuroVacc Foundation	I
DP6-001	CytRx	I
E1M184V peptide vaccine	NCI	II
EnvDNA	St. Jude Children's Res. Hosp./NIH	I
EP1043	Pharmexa/NIAID	I
EP1090	Pharmexa/ NIAID	I
EP1090 + EP1043	Pharmexa/NIAID	I
gp120/NefTat/AS02A	GlaxoSmithKline	I
GTU®-MultiHIV	FIT Biotech	II
HGTV43	Enzo Biochem	I/II
HIV CTL multiepitope peptide vaccine	Wyeth/NIAID	I
HIV-1 gag DNA vaccine	Wyeth/NIAID	I
HIV-1 gag DNA vaccine + HIV CTL multiepitope peptide vaccine	Wyeth/NIAID	I
HIV gp140/LTK63 + HIV gp140/MF59	St. George's Univ.	I
Interferon alfa-n3 (human leukocyte-derived)	HemispheRx	II
IR-103	Immune Response	II
LIPO-5	ANRS	II
MRKAd5gag	Merck & Co./NIAID	II
MRKAd5gag/pol/nef	Merck & Co./NIAID	II
MVA-BN® Polytope	Bavarian Nordic	IND filed
MVA-CMDR	Walter Reed Army Institute	I
MVA-HIVnef	Bavarian Nordic	II
Palifermin	NIAID	II
PEHRG214	Virionyx	I
pGA2/JS7 + MVA-HIV62	NIAID/HIV Vaccine Trials Network	I
pHIS-HIV-AE + rFPV-HIV-AE	Univ. New South Wales	I
PolyEnv1	St. Jude Children's Res. Hosp./NIAID	I
Recombinant IL-7	NIAID/Cytheris	I
Remune®	Immune Response	II
SCBaL/M9	NIAID	I
Tat toxoid vaccine	Neovacs/sanofi pasteur	I/II
TBC-M4	Therion Biologics/IAVI	I
tgAAC09	Targeted Genetics/IAVI	II
Vacc-4x	Bionor Immuno	II
Vacc-5q	Bionor Immuno	I/II
VICHREPOL	Ivanovsky Institute of Virology	I
VIR201	Virax	I/II
VRC-HIVADV014-00-VP	GenVec/NIAID	I
VRC-HIVDNA009-00-VP	NIAID	I/II
VRC-HIVDNA009-00-VP + VRC-HIVADV014-00-VP	NIAID	I
VRC-HIVDNA016-00-VP	NIAID	I
VRC-HIVDNA016-00-VP + VRC-HIVADV014-00-VP	GenVec/NIAID	II
VRX-496	NIAID/Univ. Pennsylvania/VIRxSYS	II

Vaccines and Other Products for HIV Infection by Source

Source	Name	Phase
Aaron Diamond AIDS Research Center	ADMVA	I
AlphaVax	AVX-101	I
Amazon BioTech	AMZ-0026	IND filed
ANRS	ALVAC vCP1452	II
	LIPO-5	II
Bavarian Nordic	MVA-BN® Polytope	IND filed
	MVA-HIVnef	II
Bionor Immuno	Vacc-4x	II
	Vacc-5q	I/II
Cytheris	Recombinant IL-7	I
CytRx	DP6-001	I
Enzo Biochem	HGTV43	I/II
EuroVacc Foundation	DNA-HIV-C	I
	DNA-HIV-C + NYVAC-HIV-C	I
FIT Biotech	GTU®-MultiHIV	II
Genetic Immunity	DermaVir™	I/II
GenVec	VRC-HIVADV014-00-VP	I
	VRC-HIVDNA016-00-VP + VRC-HIVADV014-00-VP	II
GlaxoSmithKline	825780	I
	gp120/NefTat/AS02A	I
HemispheRx	Interferon alfa-n3 (human leukocyte-derived)	II
HIV Vaccine Trials Network	pGA2/JS7 + MVA-HIV62	I
IAVI	ADMVA	I
	TBC-M4	I
	tgAAC09	II
Immune Response	IR-103	II
	Remune®	II
Ivanovsky Institute of Virology	VICHREPOL	I
McGill University	AGS-004	I/II
Merck & Co.	MRKAd5gag	II
	MRKAd5gag/pol/nef	II
NCI	E1M184V peptide vaccine	II
Neovacs	Tat toxoid vaccine	I/II
NIAID	Aldesleukin	II
	ALVAC vCP1452	II
	ALVAC vCP1521	I
	DermaVir™	I/II
	DNA/PLG microparticles + gp140/MF59	I
	EP1043	I
	EP1090	I
	EP1090 + EP1043	I
	HIV CTL multiepitope peptide vaccine	I
	HIV-1 gag DNA vaccine	I
	HIV-1 gag DNA vaccine + HIV CTL multiepitope peptide vaccine	I
	MRKAd5gag	II
	MRKAd5gag/pol/nef	II
	Palifermin	II
	pGA2/JS7 + MVA-HIV62	I
	PolyEnv1	I
	Recombinant IL-7	I
	SCBaL/M9	I
	VRC-HIVADV014-00-VP	I
	VRC-HIVDNA009-00-VP	I/II
	VRC-HIVDNA009-00-VP + VRC-HIVADV014-00-VP	I
	VRC-HIVDNA016-00-VP	I
	VRC-HIVDNA016-00-VP + VRC-HIVADV014-00-VP	II
	VRX-496	II
NICHD	ALVAC vCP1521	I
NIDA	ALVAC vCP1521	I
NIH	EnvDNA	I
NIMH	ALVAC vCP1521	I
Pharmexa	EP1043	I
	EP1090	I
	EP1090 + EP1043	I

Continuation

Vaccines and Other Products for HIV Infection by Source

Source	Name	Phase
PowderMed	825780	I
Res. Inst. Genetic Human Ther.	DermaVir™	I/II
sanofi pasteur	ALVAC vCP1521 + AIDSVAX® B/E	III
	Tat toxoid vaccine	I/II
St. George's Univ.	HIV gp140/LTK63 + HIV gp140/MF59	I
St. Jude Children's Res. Hosp.	EnvDNA	I
	PolyEnv1	I
Targeted Genetics	tgAAC09	II
Therion Biologics	TBC-M4	I
Univ. New South Wales	pHIS-HIV-AE + rFPV-HIV-AE	I
Univ. Pennsylvania	VRX-496	II
Univ. Rochester	ADMVA	I
Virax	VIR201	I/II
Virionyx	PEHRG214	I
VIRxSYS	VRX-496	II
Walter Reed Army Institute	ALVAC vCP1521 + AIDSVAX® B/E	III
	MVA-CMDR	I
Wyeth	HIV CTL multiepitope peptide vaccine	I
	HIV-1 gag DNA vaccine	I
	HIV-1 gag DNA vaccine + HIV CTL multiepitope peptide vaccine	I

Drugs Under Development for the Treatment of HIV Infection

N.E. Mealy, B. Lupone, M. Tell
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

4E10/2F5/2G12

4E10/2F5/2G12 is a combination of three broadly neutralizing, fully human monoclonal antibodies (MAbs) against HIV-1. The combination is currently in phase II clinical trials at Polymun for the prevention of rebound viremia in well-suppressed highly active antiretroviral therapy (HAART)-treated individuals who began therapy during acute and early HIV-1 infection.

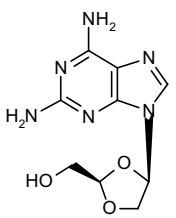
2F5/2G12

Polymun is also conducting early clinical trials with a combination of the human anti-HIV monoclonal antibodies 2F5 and 2G12.

AMD-070

AMD-070 is a chemokine CXCR4 antagonist in early clinical trials at AnorMED for the oral treatment of HIV infection. Through antagonism of the chemokine CXCR4 receptor, AMD-070 inhibits attachment of the HIV virus. The compound has also been studied at the National Institute of Allergy & Infectious Diseases (NIAID).

Amdoxovir



The reverse transcriptase inhibitor amdoxovir is in phase II clinical trials alone or in combination with mycophenolate at the NIAID for the treatment of HIV infection. Originally developed at Emory University and the University of Georgia Research Foundation, Gilead acquired rights to the compound upon its acquisition of Triangle Pharmaceuticals in 2003, but subsequently terminated the licensing agreement with the universities.

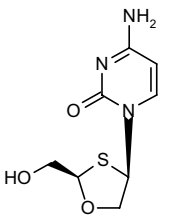
Original monograph – Drugs Fut 2000, 25(5): 454.

Atvogen

HemispheRx has filed a regulatory application in the E.U. for atvogen (Ampligen®), a double-stranded RNA drug, for the intravenous treatment of chronic fatigue syndrome (CFS). The company is currently preparing an NDA in the U.S. for the drug candidate. Atgoven is also in phase III clinical development at HemispheRx for the treatment of hepatitis C and HIV infection. Phase II trials are under way at the company for the emergency treatment of HIV-infected patients who are resistant to all available therapies. Another phase II trial sponsored by HemispheRx is evaluating atvogen as monotherapy and in combination with zidovudine for the treatment of HIV infection, and a phase II trial in Spain conducted by Esteve is studying the efficacy of the drug candidate in patients infected with HIV-1 (with or without co-infection with HCV). HemispheRx had conducted preclinical trials for the treatment of viral encephalitis. *In vitro* studies suggest that atvogen stimulates the immune system and inhibits viruses directly. In March 2002, HemispheRx established a sales and distribution agreement with Esteve, granting Esteve the exclusive right to market atvogen in Spain, Portugal and Andorra for the treatment of CFS. Esteve agreed to conduct, at its expense, certain clinical trials using the compound in the patient population co-infected with hepatitis C and HIV viruses. The following year, HemispheRx signed an agreement with Guangdong Medicine Group to organize clinical trials,

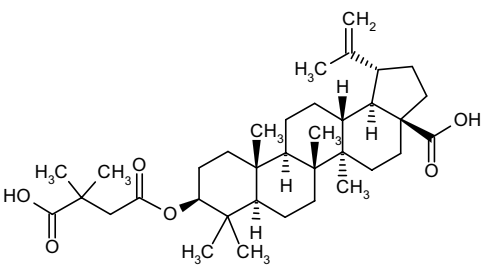
marketing, sales and distribution of atvogen in the People's Republic of China. Pursuant to the agreement, Guangdong will conduct clinical trials with atvogen for the treatment of HIV. The company will fund the trials and will be responsible for a marketing and promotional program. In 2004, Fujisawa entered into an option agreement to become the distributor of atvogen for the treatment of CFS in Germany, Switzerland and Austria. In November 2005, HemispheRx established an agreement with Defence R&D Canada - Suffield (DRDC), an agency of the Canadian Department of National Defence, to evaluate the antiviral efficacy of atvogen, as well as Alferon®, for protection against human respiratory influenza virus infection in well-validated animal models. Atvogen has been granted orphan drug designation for several indications, including the treatment of CFS, invasive metastatic melanoma (stage IIb, III, IV), renal cell carcinoma and AIDS.

Apricitabine



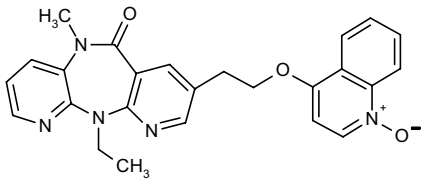
Apricitabine (AVX-754, formerly SPD-754) is a nucleoside reverse transcriptase inhibitor (NRTI) in phase II clinical trials at Avexa for the treatment of HIV infection. Originally developed at Shire Pharmaceuticals, apricitabine was licensed to Avexa in January 2005.

Bevirimat



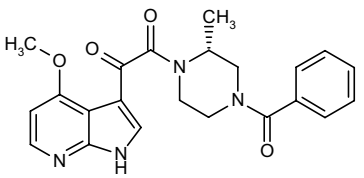
Phase II clinical trials are under way at Panacos with bevirimat (PA-457), a first-in-class viral maturation inhibitor for the oral, once-daily treatment of HIV infection. The drug candidate works by inhibiting the final step in the processing of the HIV-1 Gag protein.

BILR-355



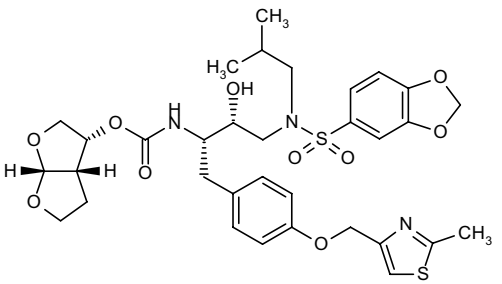
BILR-355 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) in phase II clinical trials at Boehringer Ingelheim for the treatment of HIV infection. The drug candidate is a nevirapine-like analogue that has shown antiretroviral activity against both wild-type and clinically relevant NNRTI-resistant strains.

BMS-378806



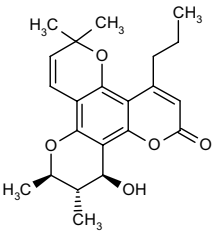
A small-molecule HIV-1 entry inhibitor, BMS-378806 is in early clinical trials at Bristol-Myers Squibb for the treatment of HIV infection. The compound blocks viral entry by binding to the HIV-1 envelope protein gp120 and inhibiting the interaction between gp120 and CD4 receptors.

Brecanavir



Brecanavir (640385, VX-385) is an HIV protease inhibitor in phase II clinical trials at Vertex and GlaxoSmithKline for the treatment of HIV infection. Protease inhibitors prevent viral replication by inhibiting the activity of protease, an enzyme used by the viruses to cleave nascent proteins for final assembly of new virions. Brecanavir was originally developed at Vertex, and a co-development agreement was later signed with GlaxoSmithKline. The drug candidate has received fast track designation in the U.S.

Calanolide A



Calanolide A is an NNRTI in phase II clinical trials at Sarawak MediChem for the treatment of HIV infection. The calanolides are a group of compounds originally isolated from the tree *Calophyllum lanigerum* and discovered by the National Cancer Institute (NCI). Calanolide A was discovered in the Sarawak rain forest by the State of Sarawak, Malaysia, which formed a 50/50 joint venture with MediChem Research in April 1997 to create Sarawak MediChem for the purpose of developing the compound. Advanced Life Sciences was created as a spin-off of MediChem Research, and also has a 50/50 joint venture agreement with Sarawak MediChem.

Original monograph – Drugs Fut 1999, 24(3): 235.

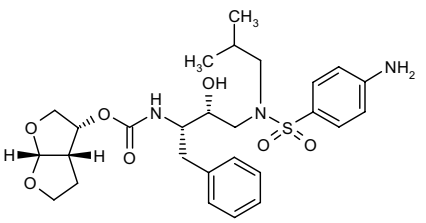
CCR5mAb004

The fully human monoclonal antibody CCR5mAb004 specifically recognizes and binds the chemokine CCR5 receptor. It is currently in early clinical trials at Human Genome Sciences for the treatment of HIV-1 infection. Preclinical studies showed that it binds specifically and with high affinity to human CCR5, prevents HIV-1 entry, demonstrates no agonist activity or effector functions, and has a prolonged serum half-life. The compound was generated by HGS using Abgenix's XenoMouse® technology.

Cytolin®

Cytolin® is a murine monoclonal antibody in early clinical trials at CytoDyn for the treatment of HIV infection. The MAb specifically binds to the α-subunit of leukocyte function-associated antigen-1 (LFA-1), and may reduce HIV viral load by inhibiting the killing of CD4-positive T-cells by cytotoxic T-cells. Cytolin® was originally developed at Amerimmune, and rights to the compound were later acquired by CytoDyn.

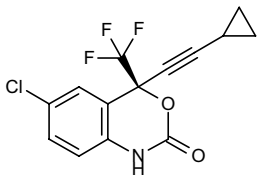
Darunavir



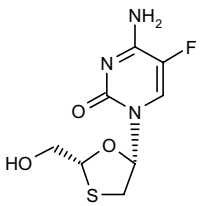
Darunavir (TMC-114), an HIV protease inhibitor, was launched in the U.S. in 2006 as Prezista™ for the oral treatment of HIV infection in antiretroviral treatment-experienced adult patients, in combination with ritonavir and other antiretroviral agents. The compound is also approved in Canada and has been filed for approval in the E.U. Discovered and developed at Tibotec, the compound is highly active *in vitro* against protease inhibitor-resistant clinical isolates of HIV. Upon approval, darunavir will be marketed outside the U.S. by Tibotec's parent company Johnson & Johnson.

Original monograph – Drugs Fut 2005, 30(5): 441.

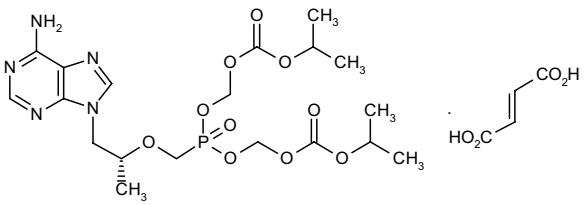
Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate



Efavirenz



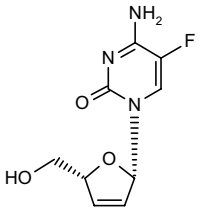
Emtricitabine



Tenofovir Disoproxil Fumarate

Atripla™ is a combination of Bristol-Myers Squibb's NNRTI Sustiva® (efavirenz) and Gilead's Truvada™, itself a combination of two NRTIs: emtricitabine (Emtriva®) and tenofovir disoproxil fumarate (Viread®). The product is a once-daily, single-tablet regimen that was approved in July 2006 under the FDA's fast track program for the treatment of HIV infection in adults and launched in the U.S. the same month. Atripla™ was developed under a collaboration agreement between Gilead and Bristol-Myers Squibb signed in December 2004. The drug was approved just 3 months after receiving fast track designation from the FDA.

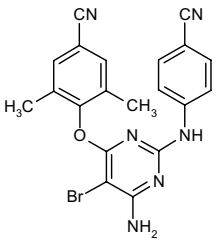
Elvucitabine



The L-cytosine nucleoside analogue elvucitabine (ACH-126443) is in phase II clinical development at Achillion for the oral treatment of HIV infection. Originated at Yale University, elvucitabine has shown potent *in vitro* activity against wild-type strains of HIV, as well as strains of HIV that are resistant to certain currently used therapies. The mechanism of action of the compound appears to be inhibition of the HIV reverse transcriptase enzyme. Clinical and preclinical data collected to date indicate that elvucitabine can be administered once daily and may be used in combination therapy. The company had been evaluating elvucitabine for the treatment of chronic hepatitis B, although no new development for this indication has been reported. In 2000, Vion licensed elvucitabine to Achillion. Vion was incorporated in 1992 to commercialize several discoveries made at Yale University, including elvucitabine.

Original monograph – Drugs Fut 2002, 27(12): 1131.

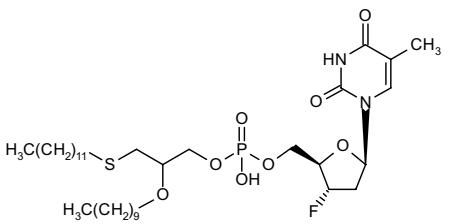
Etravirine



Etravirine (TMC-125), a next-generation NNRTI, is currently undergoing phase III clinical trials at Tibotec, a division of Johnson & Johnson, for the treatment of HIV infection. The compound has demonstrated high activity against strains of HIV that are resistant to current NNRTIs.

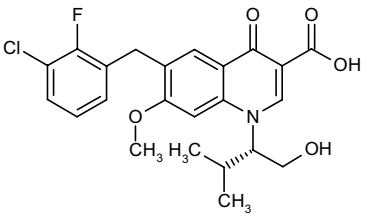
Original monograph – Drugs Fut 2005, 30(5): 462.

Fosalvudine Tidoxil



The alovudine (FLT) prodrug fosalvudine tidoxil (HDP-990003) is a reverse transcriptase inhibitor that recently entered phase II clinical trials at Heidelberg Pharma for the oral treatment of HIV infection. The compound was originally developed at Roche. The drug candidate has the potential to be highly active in patients who are resistant to standard anti-HIV therapy.

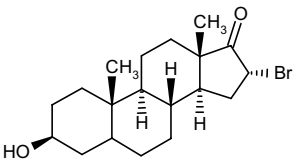
GS-9137 (JTK-303)



GS-9137 (JTK-303) is an oral HIV integrase inhibitor in early clinical development for the treatment of HIV. Originally developed by Japan Tobacco, the compound was licensed to Gilead in March 2005. Gilead has exclusive rights to develop and commercialize GS-9137 in all countries of the world, excluding Japan where Japan Tobacco retains rights.

Original monograph – Drugs Fut 2006, 31(4): 310.

HE-2000



HE-2000 (Immunitin™) belongs to Hollis-Eden's proprietary class of adrenal hormones that have been shown in preclinical and clinical studies to regulate immune responses and metabolic functions. The compound demonstrated antioxidant and antiinflammatory properties and the company is conducting phase II clinical trials in South Africa for the treatment of HIV infection. HE-2000 is also in phase I trials as an agent for cystic fibrosis. Furthermore, Hollis-Eden is evaluating the potential of the product for the treatment of biowarfare pathogens in preclinical studies. The company had been evaluating the drug for the treatment of malaria and tuberculosis, but recent progress reports for these indications are not available at present. HE-2000, licensed from the Irish company Colthurst, has been shown to upregulate antioxidant response genes and downregulate inflammatory mediators, thereby controlling oxidative stress and inflammation.

INCB-9471

Incyte is conducting early clinical trials with INCB-9471, a chemokine CCR5 receptor antagonist for the oral

treatment of HIV infection. CCR5 antagonists block entry of the HIV virus into the cell and are active against strains of the virus that are resistant to currently used HIV treatments.

ISIS-5320

ISIS-5320, a G-quartet-forming phosphorothioate oligonucleotide, is in development at ImQuest BioSciences as a topical microbicide to prevent the sexual transmission of HIV infection. The safety of the oligonucleotide as a systemic treatment was demonstrated in human clinical trials conducted by Isis Pharmaceuticals, prior to its licensing to ImQuest, and the company therefore believes that the time to development of the agent as a topical microbicide will be significantly shortened, with submission of an IND planned for later this year. ISIS-5320 specifically and potently inhibits the attachment of HIV to target cells by interfering with the interaction of the HIV receptor gp120 with CD4 on target cells. Pursuant to a license agreement signed with originator Isis Pharmaceuticals in April 2006, ImQuest has sole responsibility for the clinical development and commercialization of the drug.

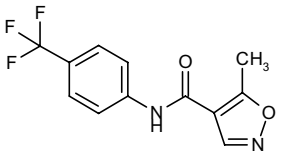
KD-247

KD-247 is an anti-V3 monoclonal antibody in phase I clinical trials at the Chemo-Sero Therapeutic Research Institute for the treatment of HIV infection. The third variable loop (V3) of the HIV-1 surface envelope glycoprotein gp120 is the binding site for the gp120 co-receptors on T-cells (CXCR4) and macrophages (CCR5). It is therefore a major neutralizing determinant of HIV-1 and a target for antibody therapy to abolish infectivity. Earlier trials demonstrated synergistic interactions between KD-247 and CCR5 inhibitors. The compound was co-developed at the Chemo-Sero Therapeutic Research Institute and Kumamoto University.

KP-1461

Early clinical trials for the treatment of HIV infection are under way at Koronis Pharmaceuticals with KP-1461, an oral prodrug of KP-1212, a nucleoside proven active in cell culture against both HIV-1 and HIV-2. KP-1461 is metabolized to KP-1212 triphosphate, the active metabolite and substrate for viral reverse transcriptase. In preclinical cell culture studies, KP-1212 demonstrated an efficacy-dependent increase in random transitional mutations in the HIV genome, without host cell toxicity. This phenomenon is a therapeutic approach known as Selective Viral Mutagenesis™, which works to eliminate a targeted virus by increasing the natural rate of mutation.

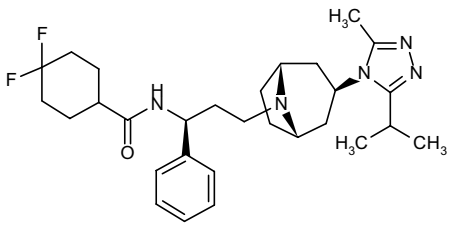
Leflunomide



Leflunomide is a dihydroorotate dehydrogenase and platelet-derived growth factor receptor (PDGFR) inhibitor first introduced in 1998 by Aventis Pharma (now sanofi-aventis) as Arava® once-daily tablets for the treatment of adult patients with active rheumatoid arthritis. The agent, a disease-modifying antirheumatic drug (DMARD), is now available for this indication in over 70 countries, including the E.U., Asia and parts of Latin America. In 2004, leflunomide was approved in the E.U. for the treatment of adult patients with active psoriatic arthritis and is available for this new indication in the U.K. and France. Leflunomide has also been approved by the FDA for the improvement in physical function in patients with rheumatoid arthritis. The NIAID is studying leflunomide in early clinical trials for the treatment of HIV infection.

Original monograph – Drugs Fut 1998, 23(8): 827.

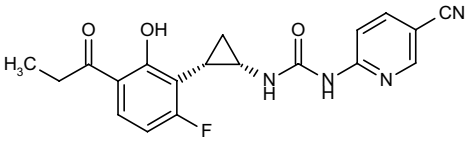
Maraviroc



The chemokine CCR5 antagonist maraviroc (UK-427857) is in phase III clinical trials at Pfizer for the treatment of HIV infection. HIV enters the host cell by a sequential process that requires engagement with CD4, followed by binding to a co-receptor: the chemokine CCR5 (R5 strains) or CXCR4 (RX strains) receptor. Most HIV strains use CCR5 at the time of initial infection and CCR5 antagonism by maraviroc prevents viral entry into white blood cells. Due to its novel mechanism of action, the compound has been shown to be active against HIV strains that are resistant to current classes of antiretroviral agents. The FDA has granted fast track designation for the clinical development program of maraviroc based on the drug's potential to satisfy an unmet medical need in HIV patients who have exhausted currently available options.

Original monograph - Drugs Fut 2005, 30(5): 469.

MIV-150

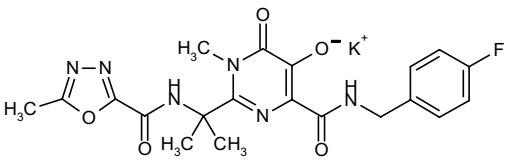


MIV-150 is an NNRTI in early clinical trials in combination with Carraguard™ as a microbicide intended to prevent HIV transmission. Originally developed at Medivir, MIV-150 was licensed to the nonprofit Population Council in August 2003 and rights for topical use of the drug candidate as a vaginal microbicide in developing countries were later voluntarily donated to the Population Council. Medivir retained sales rights in other countries, as well as an option on exclusive rights in the Nordic countries. The compound was also previously outlicensed to Chiron, but rights were returned to Medivir after it was discovered that formulating MIV-150 in order to achieve good oral bioavailability would take considerable effort.

MIV-210

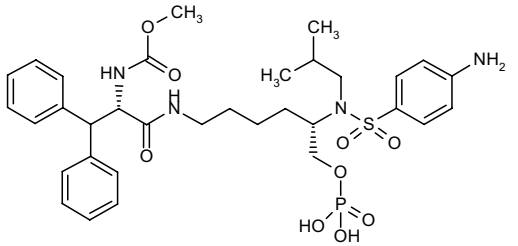
The NRTI MIV-210 is in phase I and phase IIa clinical development for the oral treatment of hepatitis B and HIV infection, respectively. In 2006, Medivir licensed MIV-210 to Tibotec, while retaining rights to MIV-210 in the Nordic market.

MK-518



MK-518 is an HIV integrase inhibitor in phase III clinical trials at Merck & Co. for the oral treatment of HIV infection. Phase II trials are also under way to evaluate MK-518 for the treatment of treatment-naïve, HIV-infected patients in combination with tenofovir and lamivudine.

PPL-100



The protease inhibitor PPL-100 is in phase Ib clinical development at Ambrilia Biopharma, a company formed by the merger of Procyon Biopharma and Cellpep, for the treatment of HIV infection. By inhibiting the action of the HIV protease enzyme, PPL-100 blocks the cleavage of HIV polyproteins, rendering the virus incapable of infecting new cells. PPL-100 is a phosphorylated prodrug of the company's PL-100 protease inhibitor.

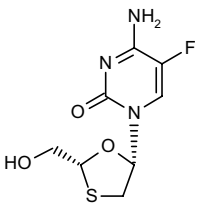
PRO-140

Progenics is conducting early clinical trials with an i.v. infusion formulation of PRO-140, a humanized monoclonal antibody, for the treatment of HIV infection. The drug candidate acts as a viral entry inhibitor by attaching to a specific segment of the chemokine CCR5 receptor, which the HIV virus uses as a co-receptor to enter its target cells. PRO-140 achieves its effects without interfering with the normal function of CCR5. In May 1999, Progenics entered into a collaboration agreement with Protein Design Labs to humanize the monoclonal antibody. In February 2006, PRO-140 received fast track designation in the U.S.

PRO-542

PRO-542 is a recombinant fusion protein incorporating human IgG_2 and the HIV-binding region of the human cell-surface receptor CD4. It is currently under early clinical investigation at the NIAID and the National Institute of Child Health and Human Development (NICHD) for the treatment of HIV infection in children. PRO-542 is a viral entry inhibitor that binds directly to the HIV envelope glycoprotein gp120, which resides on the surface of the virus and mediates its attachment to target cells. PRO-542 was discovered to possess a remarkably extended and flexible structure that enables it to bind four molecules of gp120 at once. Based on molecular modeling in combination with experimental findings, researchers concluded that PRO-542 possesses a unique ability to cross-link multiple gp120 spikes. Developed at Progenics, PRO-542 was the subject of a collaboration with GTC Biotherapeutics (formerly Genzyme Transgenics, a subsidiary of Genzyme) to prepare a transgenic source, which was terminated in 2005.

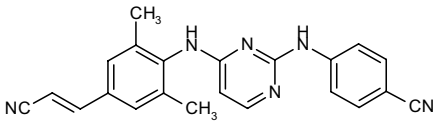
PSI-5004



PSI-5004 ([±]-FTC, Racivir®) is an oral, once-daily cytidine nucleoside analogue in phase II clinical trials at

Pharmasset as a first-line HIV therapy in treatment-naïve patients for use in combination with other approved HIV drugs. In preclinical studies, a prevalent viral mutation named M184V, which typically confers resistance to L-cytidine analogues, took longer to emerge with PSI-5004 than other L-cytidine analogues. These results suggested that an initial HIV combination therapy regimen containing PSI-5004 may prolong the benefit of therapies for treatment-naïve HIV patients. In addition, in certain preclinical studies, PSI-5004 retained more activity against those HIV strains containing the M184V viral mutation than another L-cytidine analogue. Based on these observations, a phase II trial in patients with HIV containing the M184V viral mutation is under way. PSI-5004 has also been studied at Pharmasset for the treatment of hepatitis B infection.

Rilpivirine

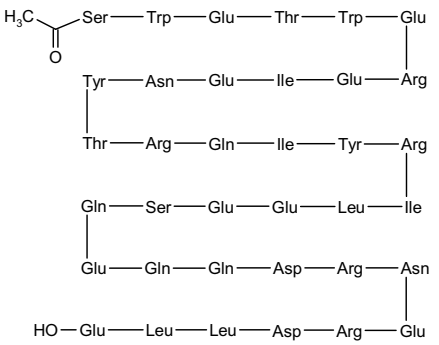


A diarylpyrimidine (DAPY) derivative and NNRTI, rilpivirine (TMC-278, R-278474) is in phase II clinical trials at Janssen and Tibotec (both members of the Johnson & Johnson group of companies) for the treatment of HIV infection. Rilpivirine exhibits potent *in vitro* anti-HIV activity and shows little or no loss of activity against HIV-1 variants having key NNRTI resistance mutations. A possible explanation for this is the internal conformational flexibility of the drug candidate, which allows it to bind in different modes and adjust in case of reverse transcriptase mutations.

S-364735

S-364735 (364735) is an HIV integrase inhibitor undergoing early clinical evaluation for the treatment of HIV infection under a joint venture between Shionogi and GlaxoSmithKline.

Sifuvirtide

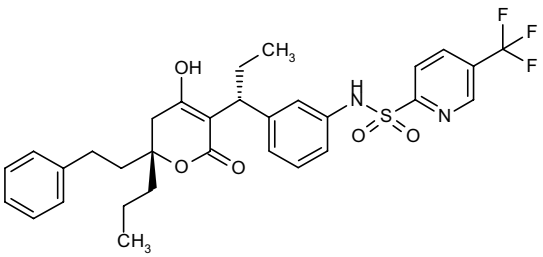


The HIV fusion inhibitor sifuvirtide is in phase II clinical trials at FusoGen Pharmaceuticals for the treatment of HIV infection. The drug candidate works by targeting the membrane fusion protein gp41, the critical protein for membrane fusion of the HIV virus to host cells.

SP-01A

SP-01A (Anticort™) is a viral entry inhibitor in phase II clinical trials at Samaritan Pharmaceuticals for the oral treatment of HIV infection in treatment-experienced patients. Through inhibition of the expression of HMG-CoA reductase mRNA, the compound inhibits actin cytoskeletal filament re-organization and removes membrane cholesterol, preventing viral fusion and entry, respectively. SP-01A was originally developed at Georgetown University and was later licensed to Samaritan and Quest PharmaTech; the latter company recently sold its licensing rights back to Samaritan.

Tipranavir



Tipranavir (Aptivus®) is a nonpeptide HIV protease inhibitor that was launched in 2005 by Boehringer Ingelheim for use in combination with ritonavir for the oral treatment of HIV-1 infection resistant to multiple protease inhibitors. Resistance to tipranavir itself appears to require multiple mutations. Tipranavir works by inhibiting the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1-infected cells, thus preventing the formation of mature virions. Originally developed at Pfizer, exclusive worldwide marketing rights were acquired by Boehringer Ingelheim pursuant to an agreement signed in January 2000.

Original monograph – Drugs Fut 1998, 23(2): 146.

TNX-355

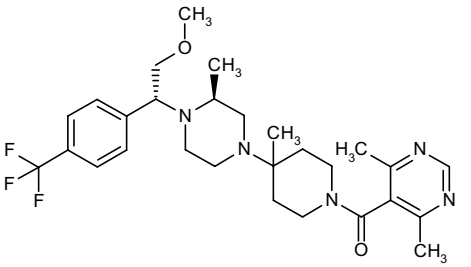
Tanox is evaluating the monoclonal antibody TNX-355 in phase II clinical trials for the intravenous treatment of HIV-1 infection resistant to antiretroviral therapy. The MAb binds to the CD4 receptor on the cell surface, an entry gate for infection, preventing viral entry and thereby

blocking infection. Preclinical studies demonstrated that TNX-355 does not suppress immune function and does not deplete CD4 cells. Originally developed at Biogen Idec, Tanox obtained exclusive rights to the drug candidate in an agreement signed in 1998.

VGV-1

Viral Genetics' immune-based therapy VGV-1 is a thymus nuclear protein suspension extracted from bovine thymus gland which is in phase III clinical trials for the treatment of HIV infection as an intramuscular injection. Further studies are needed to determine the precise mechanism of action of the protein, which may be totally different from that of existing antiretrovirals.

Vicriviroc



Vicriviroc (SCH-D, Sch-417690) is a chemokine CCR5 receptor antagonist undergoing phase II clinical trials at Schering-Plough for the treatment of HIV infection in treatment-experienced patients in combination with an optimized ritonavir-boosted protease inhibitor-containing antiretroviral regimen.

Vaccines and Other Products Under Development for the Treatment of HIV Infection

825780

PowderMed's DNA HIV vaccine is currently undergoing early clinical trials at GlaxoSmithKline (825780) for the treatment of HIV infection. The immunotherapeutic encodes a fusion protein incorporating epitopes from the HIV proteins reverse transcriptase, Gag and Nef and is administered via PowderMed's proprietary Particle Mediated Epidermal Delivery (PMED™) technology, formerly known as PowderJect®. DNA immunotherapeutics administered using PMED™ have the potential to induce both humoral and cell-mediated immunity. Using the needle-free injector device, DNA encoding an antigen and precipitated onto microscopic gold particles is propelled by pressurized helium gas at near supersonic speeds into the epidermis. The microscopic gold particles are used as the carrier because they have the appropriate size and density needed to deliver the DNA directly into the immunologically active antigen-presenting cells (APCs) of the epidermal layer. PowderMed was created in May 2004 as a spin-off of Chiron, which acquired the technology through its acquisition of PowderJect. PowderMed acquired rights to the PowderJect technology and also inherited an ongoing collaboration with GlaxoSmithKline.

ADMVA

ADMVA is an HIV vaccine based on a recombinant modified vaccinia Ankara (MVA) vector containing HIV-1 *env/gag-pol* and *nef-tat* fusion genes from an HIV-1 clade C isolate that is prevalent in China, India and sub-Saharan Africa. Originally developed at Impfstoffwerk Dessau-Tornau, it is currently undergoing early clinical trials at the Aaron Diamond AIDS Research Center, the University of Rochester and the International AIDS Vaccine Initiative (IAVI) for the prophylaxis of HIV infection.

AGS-004

AGS-004 is an autologous HIV immunotherapeutic in early clinical trials at McGill University for the treatment of HIV infection in infected adults on stable antiretroviral therapy (ART) with durable viral suppression.

Aldesleukin

Aldesleukin (recombinant IL-2, Proleukin®) was launched in 1989 by Chiron for the treatment of metastatic renal cell carcinoma and again in 1998 for the treatment of metastatic melanoma. The drug is currently in phase II trials at the National Institute of Allergy & Infectious Diseases (NIAID) for the treatment of HIV infection with or without anti-HIV therapy, and in phase II trials at Chiron for the subcutaneous treatment of low-grade non-Hodgkin's lymphoma (NHL) in combination with rituximab.

ALVAC vCP1452

ALVAC vCP1452 is a vaccine that consists of a recombinant canarypox vector that expresses genes from HIV-1 subtype B: envelope gp120 (MN) linked to the transmembrane portion of gp41 (LAI), *pol*/protease, *gag* and a synthetic polynucleotide sequence that encodes multiple epitopes from *nef* and *pol*, as well as two vaccinia virus-coding sequences, E3L and K3L. It is currently in phase II clinical development at the NIAID and the Agence Nationale de Recherches sur le SIDA (ANRS) for the prevention of HIV infection. It has also been evaluated in combination with LIPO-5 (see below), aldesleukin (IL-2) and AIDSVAX® B/B, and in HIV-infected patients. ALVAC vCP1452 was originally developed under a collaboration between sanofi pasteur and Virogenetics.

ALVAC vCP1521

ALVAC vCP1521 is a similar AIDS vaccine consisting of a recombinant canarypox vector expressing HIV-1 subtype E envelope gp120-TM (from a primary isolate) and *gag* and *pol* genes from HIV-1 subtype B (LAI). It is currently undergoing phase III clinical development in combination with the AIDSVAX® B/E vaccine as a booster at sanofi pasteur and the Walter Reed Army Institute of Research (WRAIR) for the prevention of HIV infection, and it is also being studied in phase I trials at the NIAID, the National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH) for the treatment of infants born to HIV-1-infected mothers. Like the above vaccine, it was originally developed under a collaboration between Virogenetics and sanofi pasteur.

AMZ-0026

AMZ-0026, a natural whole-plant pharmaceutical product consisting of 11 plants, is under development by Amazon Biotech. In June 2006, the FDA approved an IND allowing the company to begin phase I/II clinical evaluation of the product candidate to treat nonsymptomatic HIV-infected patients who have not yet been treated with highly active antiretroviral therapy (HAART). Although its mechanism of action is not fully understood, AMZ-0026 appears to act as an immunomodulator. Amazon intends to develop AMZ-0026 through phase II, at which point the company will seek a joint venture partner for phase III development.

AVX-101

AlphaVax's AVX-101 is an HIV vaccine consisting of the *gag* gene from HIV-1 subtype C, the most prevalent variant found in South Africa, in an alphavirus (Venezuelan equine encephalitis virus) replicon, which is currently in phase I clinical trials. The vaccine candidate utilizes the ArV™ technology, which incorporates a nonpropagating form of an alphavirus vector that has been engineered to express genes from disease-causing pathogens or cancers. The technology appears to be able to target the immune system and elicit broad-based immune responses, including significant cellular immunity. Developed at AlphaVax, AVX-101 research was originally supported by the IAVI and is now being pursued in collaboration with the National Institutes of Health (NIH) and the South African Medical Research Council. Other institutions, including Johns Hopkins, the University of North Carolina at Chapel Hill, the University of Cape Town and Duke University, provide further support.

DermaVir™

DermaVir™ (LC002) is a plasmid DNA encoding the majority of HIV proteins, formulated in a mannosylated particle. It is currently in early clinical trials under a collaboration between originator Genetic Immunity, the NIAID and the Research Institute for Genetic and Human Therapy as a topical formulation for the treatment of HIV-1 infection in patients undergoing HAART. DermaVir™ is applied to the skin, where it is taken up by Langerhans cells, which then migrate to the lymph nodes and mature to HIV antigen-expressing dendritic cells that elicit potent HIV-specific immunity and eliminate HIV-infected cells. The vaccine is hypothesized to mimic, in chronically infected patients, the T-cell-mediated immunity induced in early infection using HAART together with structured treatment interruptions (STI-HAART).

DNA-HIV-C

DNA-HIV-C, originally developed at the University of Regensburg, is currently undergoing early clinical trials sponsored by the EuroVacc Foundation for the prevention of HIV infection, alone and as a prime-boost regimen with NYVAC-HIV-C. The vaccine is based on HIV subtype C, which is prevalent in China, India and sub-Saharan Africa.

DNA/PLG Microparticles/ gp140/MF59

A phase I trial is under way at the NIAID in HIV-uninfected adults examining the safety and immune response generated by a prime-boost combination of two experimental HIV vaccines. DNA/PLG microparticles is a DNA plasmid vaccine carrying HIV-1 clade B *env* and *gag* genes and incorporating polylactide *co*-glycolide (PLG) microparticles to help it enter the body. The second vaccine –gp140/MF59– is a recombinant oligomeric gp140 protein vaccine that includes the MF59 adjuvant. The vaccines were developed by Chiron, now part of Novartis.

DP6-001

CytRx's HIV vaccine DP6-001 is in early clinical trials for the prophylaxis of HIV infection. The vaccine is comprised of a polyvalent DNA primer followed by a multivalent gp120 protein boost. The HIV vaccine formulation is based on multiple strains of HIV collected from infected people living in different parts of the world, representing 5 different strains of the virus. The vaccine initially primes the subject's immune system through the injection of DNA that causes the subject's own cells to produce the HIV envelope and Gag proteins, followed by protein

boosts from an injection that contains the corresponding HIV envelope proteins. DP6-001 was developed by researchers at the University of Massachusetts Medical School (UMMS) and Advanced BioScience Laboratories (ABL) and was subsequently licensed exclusively to CytRx.

E1M184V Peptide Vaccine

E1M184V peptide vaccine is an immunomodulator in phase II clinical trials at the National Cancer Institute (NCI) for the treatment of HIV infection in combination with sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF).

EnvDNA

A recombinant multienvelope DNA plasmid vaccine, EnvDNA, is undergoing early clinical trials at St. Jude Children's Research Hospital and the NIH for the prevention of HIV infection.

EP1043

EP1043 is a recombinant protein vaccine designed to induce HIV-1-specific helper T-lymphocyte responses. Developed by IDM Pharma (formerly Epimmune) and subsequently licensed to Pharmexa, the vaccine is in phase I clinical trials sponsored by the NIAID alone or in combination with EP1090 (see below) for the prevention of HIV infection. EP1043 consists of a string of 18 HIV-associated helper cell epitopes, each separated by a spacer designed to optimize potency. The epitopes included in the vaccine were selected using Epimmune's proprietary Epitope Identification System (EIS) and each of them is predicted to be recognized in the majority of the prospective patient populations. The vaccine protein is adsorbed onto Alhydrogel adjuvant and has been shown to effectively stimulate helper T-lymphocyte responses against multiple epitopes in a mouse model.

EP1090

An epitope-based DNA vaccine that activates cytotoxic T-lymphocytes (CTLs), EP1090 has been evaluated in a phase I clinical trial sponsored by the NIAID for the treatment of HIV infection, and is also being tested in phase I trials alone and in combination with EP1043 for the prevention of HIV infection. It is a DNA-based vaccine stabilized in polyvinylpyrrolidone that encodes 21 HIV-1-derived CTL epitopes for *gag, pol, env, nef, rev* and *vpr*, which are highly conserved among viral subtypes. Like EP1043, EP1090 was originally developed at IDM Pharma (formerly Epimmune), but was subsequently licensed to Pharmexa.

gp120/NefTat/AS02A

GlaxoSmithKline is developing a vaccine in early clinical trials for the treatment and prevention of HIV infection. The vaccine, referred to as gp120/NefTat/AS02A, consists of three recombinant HIV clade B viral antigens: the envelope glycoprotein gp120 and the two regulatory proteins Nef and Tat. The antigens are formulated in a proprietary adjuvant, AS02A, comprised of two immunostimulants in an oil-in-water emulsion.

GTU®-MultiHIV

FIT Biotech's GTU®-MultiHIV is a DNA-based HIV vaccine based on a novel gene transport vehicle, known as Gene Transport Unit (GTU®), which is a naked DNA plasmid. It is currently undergoing phase II clinical trials in South Africa for the treatment of HIV infection. The vaccine is comprised of gene products of up to 6 HIV genes and gene fragments.

HGTV43

HGTV43 is a gene medicine in early clinical trials at Enzo Biochem for the treatment of HIV infection. The drug candidate, also known as Stealth Vector™, carries anti-HIV-1 antisense RNA genes, which are incorporated into the DNA of the subjects' blood stem cells. Subsequent production of the anti-HIV-1 antisense RNA is designed to prevent replication of the virus.

HIV CTL Multiepitope Peptide Vaccine

Wyeth's HIV CTL multiepitope peptide (HIV CTL MEP) vaccine is in early clinical trials under a collaboration with the NIAID for the prevention of HIV infection alone or co-administered with GM-CSF and for the treatment of HIV infection when adjuvanted with both RC529-SE and GM-CSF, and a phase I trial is also under way testing the vaccine's potential as a boost with an HIV-1 *gag* DNA vaccine (see below) in uninfected adults. This vaccine consists of a mixture of 4 synthetic peptides, each containing 1 of 3 different HIV CTL epitopes derived from *env* or *gag*, with the RC529-SE adjuvant.

HIV-1 *gag* DNA Vaccine

An HIV-1 *gag* DNA vaccine is currently being studied in early clinical trials at the NIAID and Wyeth for the prevention and treatment of HIV infection. The DNA vaccine candidate encodes the HIV-1 clade B *gag* gene and is being tested alone, with DNA plasmid cytokine (IL-12 or IL-15) adjuvants and boosted with Wyeth's HIV CTL

multiepitope vaccine plus RC529-SE and GM-CSF adjuvants.

HIV gp140/LTK63/ HIV gp140/MF59

A phase I trial is under way in healthy adults at St. George's University of London to evaluate the safety and immunogenicity of nasal immunization with HIV gp140 V2 loop-deleted protein adjuvanted with LTK63, followed by boosting with HIV gp140 V2 loop-deleted protein adjuvanted with MF59. The HIV gp140 subunit vaccine and the labile toxin mutant adjuvant were developed by Chiron, now part of Novartis.

Interferon Alfa-n3 (Human Leukocyte-Derived)

Interferon alfa-n3 derived from human leukocytes was initially launched as an injectable formulation in 1989 by HemispheRx as Alferon N Injection® for the intralesional treatment of refractory or recurring external genital and perianal warts caused by human papillomavirus (HPV) in patients 18 years of age or older. Phase II trials are under way with the low-dose oral formulation (Alferon® LDO) for the treatment of HIV infection and severe acute respiratory syndrome (SARS). In November 2005, HemispheRx established an agreement with Defence R&D Canada - Suffield (DRDC), an agency of the Canadian Department of National Defence, to evaluate the antiviral efficacy of Alferon N®, as well as atvogen (Ampligen®), another HemispheRx drug candidate, for protection against human respiratory influenza virus infection in well-validated animal models. HemispheRx has a partnership with Guangdong for the compound's clinical development, sales and distribution in China for infectious disease indications. Alferon N® is a highly purified, natural-source, glycosylated, multispecies interferon alfa product comprised of 8 forms of highly purified interferon alfa. The product does not induce antibody formation, a problem associated with recombinant forms of nonglycosylated interferon alfa. Alferon N® is the only natural-source, multispecies interferon alfa currently sold in the U.S. for the treatment of refractory HPV and is also approved in several other countries, including Singapore and Hong Kong.

IR-103

IR-103 is an immune-based therapy in phase II clinical trials at Immune Response as a first-line treatment for drug-naïve HIV-infected individuals not yet recommended for antiretroviral therapy. The drug candidate is comprised of the gp120-depleted HIV-1 immunogen Remune® (see below) and the second-generation immunostimulatory oligonucleotide adjuvant Amplivax™, developed by Idera Pharmaceuticals. Preclinical studies have demonstrated potent HIV-1-specific immunogenicity, and Immune Response believes that the immune-based therapy could stabilize CD4+ counts and delay initiation of antiretroviral therapy.

LIPO-5

LIPO-5 is an AIDS vaccine that contains 5 lipopeptides representing CTL epitopes contained in Gag, Nef and Pol proteins. The vaccine candidate is currently undergoing phase II clinical trials sponsored by the ANRS to evaluate the safety and immune response in healthy volunteers. LIPO-5 was also previously evaluated by the ANRS and the NIAID alone and in combination with ALVAC vCP1452 (see above). Each peptide in LIPO-5 is modified in the *C*-terminal position by the addition of a palmitoyl-lysylamide group to form the lipopeptide. This lipid chain produces internalization of the lipopeptide into the cytoplasm of APCs. The epitopes were selected on the basis of their strong affinity for HLA class I molecules, on their ability to form a stable complex with these molecules, and on the capacity of these epitopes to be recognized by T-cells. LIPO-5 was originally developed under a collaboration between the Institut National de la Santé et de la Recherche Médicale (INSERM) and sanofi pasteur.

MRKAd5gag

MRKAd5gag is an AIDS vaccine comprised of an optimized HIV-1 *gag* gene under the control of a cytomegalovirus (CMV) promoter without intron A, delivered via a replication-defective adenovirus Ad5 vector with an E1 deletion. The vaccine candidate, developed at Merck & Co., is being evaluated in a phase II trial sponsored by the NIAID for the treatment of HIV infection followed by treatment interruption.

MRKAd5gag/pol/nef

Merck & Co.'s MRKAd5gag/pol/nef is a trivalent adenovirus Ad5 vector that expresses the HIV-1 *gag, pol* and *nef* genes. The vaccine candidate is currently undergoing phase II clinical trials at the NIAID to determine its efficacy when followed by treatment interruption in adults with acute or recent HIV infection who have started taking anti-HIV drugs.

MVA-BN® Polytope

MVA-BN® polytope (MVA-mBN32) is a recombinant MVA vaccine under development at Bavarian Nordic for both the treatment and prevention of HIV. The vaccine candidate, based on an MVA-BN® virus expressing 21

epitopes from killer T-cells and 18 epitopes from helper T-cells, is expected to enter clinical trials soon in both healthy volunteers and HIV-infected patients in the U.S. and Europe. Under a grant from the NIAID, Bavarian Nordic is also collaborating with Pharmexa on the pre-clinical development of a preventive combination vaccine comprising MVA-BN® polytope (MVA-mBN32) and EP1233, an epitope-based DNA vaccine that activates both killer T-cells and helper T-cells. Pharmexa obtained rights to these vaccines from IDM Pharma (formerly Epimmune) in late 2005.

MVA-CMDR

Early clinical trials are under way with MVA-CMDR, a vaccine which consists of an MVA viral vector expressing the three HIV-1 genes CM235 *env*, CM240 *gag* and CM240 *pol*. The vaccine candidate is being developed by the WRAIR for the intramuscular or intradermal prophylaxis of HIV infection.

MVA HIV *nef*

Bavarian Nordic's MVA HIV *nef* vaccine is based on a recombinant MVA vaccine expressing the HIV-1 Nef protein. It is currently in phase II clinical trials for the treatment of HIV infection in patients previously taking HAART.

Palifermin

Palifermin, a recombinant keratocyte growth factor (KGF), was initially launched by Amgen in the U.S. in 2005 for the treatment of chemotherapy/radiotherapy-induced mucositis. The product is also now available in the E.U for this indication and approval is pending in Canada. Phase II clinical trials are under way at the NIAID to evaluate its potential to increase CD4 cell counts in patients undergoing potent antiretroviral therapy for the treatment of HIV infection.

PEHRG214

PEHRG214 is a polyclonal antibody therapy in early clinical trials at Virionyx for the prophylaxis of HIV infection. PEHRG214 targets multiple epitopes on HIV that are not recognized by the human immune system, are highly conserved and functionally important. The antibodies are extracted and purified from plasma from goats immunized with a combination of HIV viral lysate and selected peptides and recombinants. *In vitro* and *in vivo*, these antibodies are responsible for the lysis and/or neutralization of multiple laboratory and wild strains of HIV and the discriminative lysis of infected CD4 cells. Virionyx expects that PEHRG214 will need to be taken on a repeated basis, possibly for many weeks. A phase II trial in HIV-infected patients is scheduled to begin soon.

pGA2/JS7/MVA-HIV62

The NIAID and HIV Vaccine Trials Network are conducting a phase I clinical study to evaluate the safety and immunogenicity of the pGA2/JS7 DNA vaccine followed by an MVA-based vaccine (MVA-HIV62) in healthy adults. The DNA vaccine consists of a DNA plasmid coding for HIV-1 clade B Gag, Pol, Env, Tat, Rev and Vpu proteins, and the MVA vaccine contains the clade B genes *gag, pol* and *env.* The vaccines were originally developed at Emory University.

pHIS-HIV-AE/rFPV-HIV-AE

The University of New South Wales is conducting a phase I clinical study of a candidate prophylactic pHIS-HIV-AE prime and rFPV-HIV-AE boost vaccination strategy in healthy adult Thai volunteers. The pHIS-HIV-AE vaccine is a DNA plasmid encoding modified AE clade HIV-1 antigens Gag, Pol, Tat/Rev and Env, and the rFPV-HIV-AE boost is a nonreplicating recombinant fowlpox virus encoding the same antigens.

PolyEnv1

The PolyEnv1 vaccine is being tested in phase I clinical trials at the NIAID and St. Jude Children's Research Hospital for the prevention of HIV infection. The vaccine is prepared by inserting a portion of the HIV-1 viral envelope into a recombinant vaccinia virus based on the NYCDH vaccinia isolate.

Recombinant IL-7

Cytheris' lead compound, recombinant interleukin-7 (rIL-7), is a growth factor in phase I/II clinical trials for the treatment of immunological disorders in patients with myeloid malignancies who have undergone a T-cell-depleted allogeneic hematopoietic cell transplant (HCT). Phase I trials are also in progress at the NCI for the enhancement of immune reconstitution in cancer patients, and at the NIAID for the enhancement of immune reconstitution in HIV-1-infected subjects who are receiving antiretroviral treatment. rIL-7 has been designed with unique features for rebuilding the immune system and enhancing global and specific immune responses. IL-7 is a nonredundant and pleiotropic growth factor for T-cell homeostasis. It plays an important role at various stages of T-cell development, from T-cell precursors in the bone marrow to mature T-cells in the periphery. The homeostatic effect of IL-7 is characterized by the expansion of T-cells (CD4 and CD8) through thy-

mopoiesis stimulation and peripheral T-cell expansion. IL-7 is also known to enhance antigen-specific T-cell responses, and to assist in the activation and proliferation of effector T-cells. According to recent medical literature, this antigen-specific effect is bolstered by the generation and maintenance of memory T-cells, which are critical to the development of an efficient and sustained immune response.

Remune®

Remune® is an HIV vaccine candidate in phase II clinical trials at Immune Response for the treatment of drug-naïve HIV-infected patients. Remune® is manufactured by culturing HIV-infected human cells using the HIV-1 viral strain HHZ-321 from Zaire, one of the earliest identified strains. The virus is purified from the cell culture, inactivated with β-propiolactone and irradiated. During processing and purification, the outer envelope protein gp120 is depleted from the inactivated HIV. The inactivated virus is then emulsified in incomplete Freund's adjuvant and filled into syringes. It appears to boost HIV-specific immune responses and may slow the progression of HIV infection when used alone or in combination with antiretroviral therapy.

SCBaL/M9

SCBaL/M9 is a recombinant *Salmonella typhi* HIV-1 gp120 vaccine in early clinical trials at the NIAID for the oral prophylaxis of HIV infection. The body produces an HIV protein from the gene, which stimulates an anti-HIV immune response. In this vaccine, a conformationally constrained *gp120* gene is delivered orally via a live attenuated *S. typhi*.

Tat Toxoid Vaccine

Neovacs' Tat toxoid vaccine, which consists of chemically inactivated Tat toxoid protein, is currently in early clinical trials for the treatment of HIV-1 infection. The company has a development and licensing agreement with sanofi pasteur for the development of this vaccine candidate.

TBC-M4

TBC-M4, a preventive HIV-1 multigenic (*env, gag, tat-rev, nef*-RT) subtype C vaccine delivered via an MVA poxvirus vector is undergoing phase I clinical trials in India under a collaboration between Therion Biologics and the IAVI.

tgAAC09

The recombinant adeno-associated virus (AAV)-based prophylactic HIV vaccine candidate tgAAC09 based on HIV subtype C, the most prevalent subtype in China, India and sub-Saharan Africa, is designed to protect against HIV infection in HIV-negative individuals and/or prevent progression to AIDS in HIV-infected subjects, and to elicit both antibody- and cell-mediated immune responses. The vaccine candidate is currently in phase II clinical trials in healthy uninfected subjects pursuant to a collaboration between Targeted Genetics and the IAVI.

Vacc-4x

Vacc-4x is an HIV-1 immunotherapeutic agent composed of 4 water-soluble synthetic peptides (Vac-10, -11, -12 and -13), each corresponding to conserved domains on the HIV-1 p24 capsid protein and modified to improve immunogenicity. It is currently undergoing phase II clinical trials at Bionor Immuno for the treatment of HIV infection.

Vacc-5q

Vacc-5q is another AIDS vaccine in early clinical trials at Bionor Immuno for the treatment of HIV infection.

VICHREPOL

VICHREPOL is an HIV vaccine consisting of the recombinant protein rec(24-41) that comprises HIV-1 *gag*- and *env*-coded proteins (p24 and fragment of gp41) conjugated with the adjuvant polyoxidonium. It is currently in early clinical trials at the Ivanovsky Institute of Virology for the treatment of HIV infection.

VIR201

VIR201 is a recombinant fowlpox virus vector based on Virax's Co-X-Gene™ technology and designed to co-express the *gag* and *pol* genes of the HIV-1 virus together with the human interferon gamma cytokine, under development for the treatment of early-stage HIV infection. The company has conducted a phase I/II clinical trial in Australia and has filed INDs in South Africa to conduct another phase I/II trial and in the U.S. to conduct a phase II trial.

VRC-HIVADV014-00-VP

VRC-HIVADV014-00-VP is a vaccine candidate being evaluated under a collaboration between GenVec and the NIAID for the prevention and treatment of HIV infection.

The vaccine is a multiclade recombinant AVV vaccine comprised of 4 adenovirus vectors encoding HIV-1 Gag/Pol proteins from clade B and the HIV-1 Env protein from clades A, B and C. It is being tested in phase I trials alone, in phase I and II trials as a booster to VRC-HIVDNA016-00-VP and in phase I trials as a booster to VRC-HIVDNA009-00-VP (see below).

VRC-HIVDNA009-00-VP

VRC-HIVDNA009-00-VP is a multiclade HIV DNA vaccine composed of 4 DNA plasmids encoding HIV-1 Gag, Pol and Nef proteins from clade B and the HIV-1 Env protein from clades A, B and C, currently in phase I/II trials at the NIAID for both the treatment and prevention of HIV infection, alone and together with an adenoviral vector booster (VRC-HIVADV014-00-VP) or an adjuvant.

VRC-HIVDNA016-00-VP

VRC-HIVDNA016-00-VP is a multiclade HIV DNA vaccine comprised of 6 closed circular DNA plasmids encoding HIV-1 Gag, Pol and Nef proteins from clade B and the HIV-1 Env protein from clades A, B and C. It is undergoing clinical trials at the NIAID for the prevention of HIV infection, both alone (phase I) and in combination with VRC-HIVADV014-00-VP (phase II), as well as phase I clinical trials for the treatment of HIV-infected individuals in combination with VRC-HIVADV014-00-VP as booster.

VRX-496

VRX-496 is a lentiviral vector expressing an antisense sequence targeted to the HIV-1 envelope (*env*) gene. It is currently in phase II clinical trials under a collaboration between the University of Pennsylvania, the NIAID and originator VIRxSYS as an intravenous infusion for the treatment of HIV infection. VRX-496 has an antisense sequence over 900 nucleotides long. The length of the sequence weakens the ability of HIV to resist treatment in comparison to short antisense treatments such as ribozymes or RNAi. The sequence is delivered to T-cells, which are later infected by HIV. Replication of HIV triggers vector replication and the association of the vector and HIV RNA. The HIV RNA is then destroyed, preventing HIV proliferation. The lentiviral vector is capable of delivering therapeutic payloads into human cells with greater than 90% efficiency without toxicity. The payload is located upstream of a major splice acceptor site and is thus dependent on the expression of Tat and Rev proteins that are provided by HIV, ensuring that the antisense sequence is only expressed in HIV-infected cells. The lentiviral vector is also able to transfer genetic material into dividing and quiescent cells, and demonstrates a reduced risk of immunogenicity and insertional oncogenesis.