LEADING ARTICLE

Drugs 2009; 69 (1): 31-50
0012-6667/09/0001-0031/$55.55/0

Novel Targets for Antiretroviral Therapy
Clinical Progress to Date

Birgitt Dau[1,2] and *Mark Holodniy*[1,2]

1 VA Palo Alto Health Care System, Palo Alto, California, USA
2 Division of Infectious Diseases & Geographic Medicine, Stanford University, Palo Alto, California, USA

Abstract

The advent of HIV-1 resistance to antiretroviral medications, the need for lifelong antiretroviral therapy (ART) for HIV-infected individuals, and the goal of minimizing ART-related adverse effects and toxicity all drive the need for new antiretroviral drugs. Two new classes of antiretroviral medications for HIV treatment, the CCR5 and integrase inhibitors, have recently been approved for use in patients in whom previous HIV treatment regimens have failed. These new agent classes are a welcome addition to other antiretroviral classes, which include nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and fusion inhibitors.

Maraviroc is a CCR5 co-receptor antagonist that blocks HIV binding to the CCR5 receptor, which is a CD4 co-receptor necessary for cell entry. It is approved for use in ART-experienced patients with CCR5-tropic HIV, and was found to significantly reduce HIV viral load and increase CD4+ cell count when combined with an optimized background ART regimen (OBR). Treatment failure with maraviroc has been described and is primarily associated with the presence of CXCR4-tropic virus. Vicriviroc is another CCR5 co-receptor antagonist that is in late clinical trials.

Raltegravir is the first US FDA-approved HIV-1 integrase inhibitor. It is approved for use in ART-experienced patients and was found to significantly reduce HIV viral load and increase CD4+ cell counts compared with placebo in combination with an OBR. Raltegravir has also been studied in treatment-naive patients and was found to be non-inferior to an efavirenz-based regimen. Elvitegravir is another HIV-1 integrase inhibitor in clinical development.

Other new antiretroviral agents in clinical development include PRO140, a monoclonal antibody against CCR5, and bevirimat, a maturation inhibitor that prevents late-stage gag polyprotein processing. A number of other drug targets, such as CCR5 co-receptor agonists, CXCR4 co-receptor antagonists, novel fusion inhibitors, and alternative antiretroviral strategies, such as immune stimulation and gene therapy, are under investigation.

Antiretroviral therapy (ART) has improved life expectancy for HIV-infected patients.[1,2] For most patients, HIV has become a chronic illness, requiring lifelong, uninterrupted ART, and attempts to suspend or stop treatment have resulted in inferior clinical outcomes.[3-5] Although ART

has resulted in virological suppression, improved immune function and improved quality of life, issues such as tolerability, drug-drug interactions and resistance persist.[6-9] Thus, there is a need for antiretroviral agents with new mechanisms of action, and different resistance and toxicity profiles.

The HIV replication cycle is well understood, providing many opportunities for drug targets. Major steps in the HIV life cycle that are targeted by antiretrovirals include attachment, entry, reverse transcription, integration, protein processing and maturation. Viral entry to the host cell begins with attachment of the HIV envelope glycoprotein (gp120) to the CD4 T-cell receptor.[10] This interaction produces a conformational change in gp120, which allows it to bind to the chemokine co-receptor, either CCR5 or CXCR4. CCR5 and CXCR4 bind the V3 region of HIV gp120, which is the site of resistance mutations to CCR5 receptor antagonists (or inhibitors).[11] Further conformational changes in gp120 occur after CCR5 or CXCR4 binding, allowing the HIV envelop gp41 fusion peptide to insert into the cellular membrane, causing the virion to fuse with the viral membrane.[12] Once the HIV virion enters the cell, it is uncoated and the viral RNA genome undergoes reverse transcription into proviral DNA. The proviral DNA becomes part of the pre-integration complex, which enters the nucleus.[13] The proviral DNA is then incorporated into the host-cell genome using the HIV integrase enzyme.[14] HIV viral polyproteins are then expressed using host-cell machinery and the large Gag-Pol polyprotein is cleaved by the HIV protease enzyme. Finally, after the virion buds from the host cell, processing of the HIV viral capsid protein to allow mature viral particles to be produced is accomplished in a process called maturation.[15] Study of HIV cell entry and integration has recently led to the approval of maraviroc, a CCR5 co-receptor antagonist, and raltegravir, an integrase inhibitor. This review discusses the clinical trial results that led to their approval, their role in clinical practice, and drugs for novel targets in clinical and preclinical development.

1. CCR5 Co-Receptor Antagonists

HIV-1 enters and infects cells by interacting with the CD4 receptor and a co-receptor, either CCR5 or CXCR4 (sometimes also simply referred to as R5 and X4). The HIV-1 gp120 envelope protein binds either CCR5 or CXCR4, thereby infecting CCR5- or CXCR4-expressing cells. HIV-1 may also be dual-tropic (i.e. is able to use either receptor). Some patients have mixed HIV populations of CCR5- and CXCR4-tropic viruses. Because current tropism assays cannot distinguish between dual and mixed HIV populations, they are referred to as dual/mixed (D/M) tropic. CCR5-tropic virus predominates in less advanced disease, whereas CXCR4 virus emerges later and is associated with more rapid disease progression (table I).[16,17]

Phenotypic (Trofile™) and genotypic (SensiTrop™) tropism assays that detect CXCR4- and/or CCR5-tropic virus are available to identify patients who are likely to benefit from CCR5 co-receptor antagonists. The original Trofile™ assay detected CXCR4 virus with 100% accuracy when CXCR4 comprised ≥10% of the viral population. Successful detection dropped when viral load was <1000 copies/mL. SensiTrop™ was less sensitive than Trofile™ in detecting D/M or CXCR4 virus. Of 100 samples classified by Trofile™, SensiTrop™ identified a higher proportion as CCR5 (69 vs 52) and a lower proportion as D/M (20 vs 31).[25] An enhanced Trofile™ assay has increased sensitivity for CXCR4 by 10- to 100-fold and identified more patients with D/M virus compared with the original Trofile™ assay.[26,27] This assay is able to detect CXCR4 tropic virus 100% of the time when present at 0.3% of the total viral population.[28] An enhanced genotypic assay (SensiTrop™ II) has been developed, which demonstrated 87% concordance with the original Trofile™ assay and was also able to identify D/M populations in the clade C HIV subtype with significantly more sensitivity than the standard Trofile™ assay.[29] A comparison between the enhanced Trofile™ assay and SensiTrop™ II has not been performed. Finally, genotypic clonal analysis of HIV proviral DNA may be useful in determining tropism in patients with undetectable plasma

Table I. Prevalence of co-receptor tropism[18]

Study cohort	Co-receptor usage (%)			Reference
	CCR5	CCR5/CXCR4	CXCR4	
Treatment-experienced patients				
Chelsea and Westminster cohort (n = 161)	78	22	<1	19
Demarest et al. (n = 117)	67	28	5	20
MOTIVATE 1 and 2 (n = 2560)	56	41.4	2.6	21
TORO 1 and 2 (n = 612)	50	48	2	22
ACTG 5211 (n = 391)	50	46	4	23
Treatment-naive patients				
MERIT cohort (n = 1428)	85	14.7	0.3	21
Homer cohort (n = 979)	82	18	<1	24
Chelsea and Westminster cohort (n = 402)	81	19	<1	19
Demarest et al. (n = 299)	88	12	0	20

ACTG = AIDS Clinical Trials Group; **MERIT** = Maraviroc vs Efavirenz Regimens as Initial Therapy; **MOTIVATE** = Maraviroc Plus Optimized Background Therapy in Viremic, ART-Experienced Patients; **TORO** = T-20 (enfuvirtide) versus Optimised Regimen Only.

viral loads.[30] In CCR5 co-receptor antagonist-naive patients, 7% had baseline HIV envelope gene V3 loop mutations associated with resistance to maraviroc.[31]

Maraviroc is the first approved CCR5 co-receptor antagonist. The trials known as MOTIVATE (Maraviroc Plus Optimized Background Therapy in Viremic, ART-Experienced Patients) 1 and 2 (table II) compared different doses of maraviroc with placebo in the presence of an optimized background regimen (OBR) in patients with CCR5-tropic virus, previous ART experience and antiretroviral resistance.[46,47] Mean CD4+ cell count increases and number of patients who achieved undetectable viral loads (<50 copies/mL) at 48 weeks were significantly greater with maraviroc compared with placebo (table II).[32,48] Virological response was better in those with a baseline viral load <100 000 copies/mL. The most common maraviroc adverse events were diarrhoea, nausea, fatigue and headache. There were similar frequencies of serious adverse events, toxicity-driven discontinuations, laboratory abnormalities, AIDS-defining infections, and AIDS- or non-AIDS-defining malignancies among maraviroc and placebo arms; however, there were higher rates of grade 3 or 4 AST and ALT elevations in hepatitis C virus (HCV) co-infected patients in the maraviroc arm.[49] Virological failure was significantly associated with a switch from CCR5 to D/M or CXCR4 virus (table III). Discontinuation of maraviroc resulted in reversion of D/M or CXCR4 to CCR5 virus in the majority of those who experienced treatment failure.[50] Additional virological failures were explained by changes in tropism (using the original Trofile™ assay) seen between screening and study entry (table III). V3 loop envelope gene mutations that confer genotypic resistance to maraviroc were found in all patients experiencing treatment failure with phenotypic resistance to maraviroc, whether with CCR5- or CXCR4-tropic virus.[11] Another recent analysis using the MOTIVATE 1 and 2 data found that the activity of the OBR was a stronger predictor of virological success in the maraviroc arm than baseline CCR5 tropism, reinforcing the concept that it is important to maximize the number of active drugs in ART regimens.[52]

The MERIT (Maraviroc vs Efavirenz Regimens as Initial Therapy) study (table II) compared maraviroc and efavirenz, in combination with zidovudine/lamivudine, in ART-naive patients.[33] It was a randomized, double-blind, phase III trial of patients with CCR5-tropic HIV-1 and a plasma HIV-1 RNA level ≥2000 copies/mL. The study failed to show maraviroc noninferiority using a noninferiority margin of −10% of maraviroc to efavirenz for the endpoint of viral load <50 copies/mL; however,

Table II. Summary of virological and immunological responses to new antiretroviral agents in representative studies

Study name	Dosage	No. of patients	Mean baseline VL (log_{10} copies/mL)	Mean baseline CD4+ cell count (cells/μL)	Mean VL response (log_{10} copies/mL)	VL <50 copies/mL at study endpoint (%)	Mean CD4+ cell count response (cells/μL)	Timepoint of results (wk)	References
MVC (maraviroc)									
MOTIVATE 1	MVC 150, 300 mg bid + OBR	235	4.86	150	−1.82	46.0	+122	48	32
	MVC 150, 300 mg od + OBR	232	4.85	168	−1.66	42.0	+113		
	PL + OBR	118	4.84	160	−0.80	16.0	+54		
MOTIVATE 2	MVC 150, 300 mg bid + OBR	191	4.84	182	−1.87	45.0	+128	48	32
	MVC 150, 300 mg od + OBR	182	4.87	173	−1.72	45.0	+122		
	PL + OBR	91	4.89	174	−0.76	18.0	+69		
MERIT	MVC 300 mg bid + AZT/3TC	360	4.86	241 (median)	NR	65.3	+170	48	33
	EFV 600 mg od + AZT/3TC	361	4.88	254 (median)	NR	69.3	+144		
MERIT-ES	MVC 300 mg bid + AZT/3TC	361	4.88	236 (median)	NR	68.5	+174	48	34
	EFV 600 mg od + AZT/3TC	303	4.85	254 (median)	NR	68.3	+144		
VCV (vicriviroc)									
ACTG 5211	VCV 5 mg od + OBR	30	4.56[a]	146[a]	[b]	NR	NR	48	35,36
	VCV 10 mg od + OBR	30	4.56[a]	146[a]	−1.92	37	+130		35,36
	VCV 15 mg od + OBR	30	4.56[a]	146[a]	−1.44	27	+96		

Continued next page

Table II. Contd

Study name	Dosage	No. of patients	Mean baseline VL (log_{10} copies/mL)	Mean baseline CD4+cell count (cells/μL)	Mean VL response (log_{10} copies/mL)	VL <50 copies/mL at study endpoint (%)	Mean CD4+ cell count response (cells/μL)	Timepoint of results (wk)	References
	PL+OBT	28	4.56[a]	146[a]	NR	11	NR		
VICTOR-E1	VCV 20 mg od+OBR with boosted PI	116[c]	4.5[d]	200[d]	−2.04	58	+100	48	37
	VCV 30 mg od+OBR with PI	116[c]	4.5[d]	200[d]	−2.04	64	+94		
	OBR	116[c]	4.5[d]	200[d]	−0.96	26	+56		
RAL (raltegravir)									
Protocol 004	RAL 100 mg bid+TDF/FTC	39	4.6–4.8[e]	271–314[e]	At least −2.2	85	+144–221[g]	48	38,39
	RAL 200 mg bid+TDF/FTC	40	4.6–4.8[e]	271–314[e]	At least −2.2	83	+144–221[g]		
	RAL 300 mg bid+TDF/FTC	41	4.6–4.8[e]	271–314[e]	At least −2.2	88	+144–221[g]		
	RAL 400 mg bid+TDF/FTC	40	4.6–4.8[e]	271–314[e]	At least −2.2	88	+144–221[g]		
	EFV 600 mg od+TDF/FTC	38	4.6–4.8[e]	271 to 314[e]	At least −2.2	87	+144–221[g]		
STARTMRK	RAL 100 mg bid+TDF/FTC	281	5.01	219	NR	86	+189	48	40
	EFV 600 mg qhs+TDF/FTC	282	5.02	217	NR	82	+163		
Protocol 005	RAL 100 mg bid+OBR	43	4.6	186	−1.80	65.1	+62.9	24	41
	RAL 400 mg bid+OBR	45	4.8	115	−1.87	55.6	+112.8		

Continued next page

Table II. Contd

Study name	Dosage	No. of patients	Mean baseline VL (log_{10} copies/mL)	Mean baseline CD4+ cell count (cells/μL)	Mean VL response (log_{10} copies/mL)	VL <50 copies/mL at study endpoint (%)	Mean CD4+ cell count response (cells/μL)	Timepoint of results (wk)	References
	RAL 600 mg bid + OBR	45	4.7	161	−1.84	66.7	+94.1		
	PL + OBR	45	4.7	188	−0.35	13.3	+5.4		
BENCHMRK 1	RAL 400 mg bid + OBR	232	4.6	140	−1.7[f]	65	+120	48	42,43
	PL + OBR	118	4.5	105	−0.8[f]	31	+49		
BENCHMRK 2	RAL 400 mg bid + OBR	75	4.7	102	−1.7[f]	60	+98	48	42,44
	PL + OBR	41	4.7	132	−0.8[f]	35	+40		
EVG (elvitegravir)									
GS183-0105	EVG 50 mg od	71	4.59[g]	185[g]	−1.5	38	+52	24	45
	EVG 125 mg od	73	4.59[g]	185[g]	−1.7	40	+61		
	PI	63	4.59[g]	185[g]	−1.2	30	+28		

a For all 118 subjects.

b This arm ended early because of virological failure.

c For all three groups.

d For all 116 subjects.

e For all 198 subjects.

f BENCHMRK 1 and 2 combined.

g For all patients.

ACTG = AIDS Clinical Trials Group; **AZT**/**3TC** = zidovudine/lamivudine; **BENCHMRK** = Blocking Integrase in Treatment-Experienced Patients With a Novel Compound Against HIV; **bid** = twice daily; **EFV** = efavirenz; **FTC** = emtricitabine; **MERIT** = Maraviroc vs Efavirenz Regimens as Initial Therapy; **MOTIVATE** = Maraviroc Plus Optimized Background Therapy in Viremic, ART-Experienced Patients; **NR** = not reported; **OBR** = optimized background regimen; **od** = once daily; **PI** = ritonavir-boosted protease inhibitor; **PL** = placebo; **qhs** = at bedtime; **STARTMRK** = Safety and Efficacy of Raltegravir-Based versus Efavirenz-Based Combination Therapy in Treatment-Naive HIV-1 Infected Patients; **TDF** = tenofovir; **VICTOR-E1** = Vicriviroc in Combination Treatment with an Optimized ART Regimen in HIV-Infected, Treatment-Experienced Subjects; **VL** = viral load; + indicates increase; − indicates decrease.

noninferiority was demonstrated for suppression to <400 copies/mL. When analysed by baseline viral load of less than or greater than 100 000 copies/mL, 71.6% and 69.6%, and 66.6% and 59.6% in the efavirenz and maraviroc arms, respectively, reached a viral load of <50 copies/mL. CD4+ cell count increases were greater in the maraviroc arm (table II). As in the MOTIVATE studies, 25 patients (3.4%) demonstrated a switch from CCR5-tropic virus at screening to D/M virus at study entry and treatment failure was seen in patients with CCR5-, D/M or CXCR4-tropic virus[51] (table III). In the group with D/M virus at study entry, only 54.6% and 7.1% of patients in the efavirenz and maraviroc arms, respectively, achieved a viral load of <50 copies/mL. Of those in whom treatment failed, nucleoside reverse transcriptase inhibitor (NRTI) mutations were more likely to develop with D/M or CXCR4 virus than with CCR5.[51] In the MERIT-ES (enhanced sensitivity) reanalysis of 48-week efficacy and safety data, MERIT study samples were re-tested with the enhanced Trofile™ assay, which was able to detect D/M virus in 55% of the patients who had CCR5-tropic virus at screening but who developed D/M virus during the study.[34] Virological responses with maraviroc and efavirenz were similar: 68.5% and 68.3% of patients, respectively, achieved an HIV-1 RNA <50 copies/mL at week 48. More maraviroc treatment discontinuations resulted from lack of efficacy (9.3% vs 4.0%), whereas more efavirenz discontinuations were for adverse events including CNS adverse effects, rash and aminotransferase elevations (14.2% vs 4.2%).

Vicriviroc is an oral CCR5 co-receptor antagonist with the following characteristics: (i) plasma concentrations are markedly increased by cytochrome P450 (CYP) 3A4 inhibitors (e.g. ritonavir); (ii) a plasma half-life >24 hours; (iii) no food effects; and (iv) durable antiretroviral activity in CCR5-tropic ART-experienced subjects.[35,53,54] The ACTG (AIDS Clinical Trials Group) 5211 study evaluated vicriviroc in ART-experienced adults (table II).[35,36] Following optimization of background ART, vicriviroc (10 or 15 mg once daily) with ritonavir demonstrated sustained antiretroviral activity over 48 weeks in only a minority of patients, although median CD4+ cell count increased by 130 and 96 cells/mm^3 for the 10 and 15 mg groups, respectively. Findings similar to maraviroc of tropism switching and tropism type with virological failure were seen with vicriviroc, and cross-resistance can be expected if treatment failure is due to a change in tropism to CXCR4 (table III). The time to virological failure was quicker in those with D/M than CCR5 virus.[36] ACTG 5211 results were re-analysed with the enhanced Trofile™ assay, and demonstrated greater reductions in HIV-1 viral load at day 14 and week 24 among patients with CCR5- versus D/M-tropic virus at study entry.[55]

The VICTOR-E1 (Vicriviroc in Combination with an Optimized ART Regimen in HIV-Infected Treatment-Experienced Subjects) study compared two higher doses of vicriviroc (20 or 30 mg once daily) with placebo all plus OBR (at least three antiretroviral agents, including a ritonavir-boosted protease inhibitor [PI]) in ART-experienced patients for 48 weeks (table II).[37] HIV-1 viral load was significantly reduced and CD4+ cell counts significantly increased in both vicriviroc arms compared with placebo. Viral tropism changes are described in table III.[56] Once-daily vicriviroc 30 mg was selected for ongoing trials in ART-experienced subjects. Adverse event data from 205 patients in the ACTG 5211 and VICTOR-E1 studies who were followed-up for 96 weeks found few treatment-emergent adverse events including AIDS-associated opportunistic infections and malignancies. A few patients (17 and 14) developed elevated AST and ALT, respectively, but these elevations were judged not to be related to vicriviroc.[57]

1.1 Other CCR5 Co-Receptor Antagonists

Aplaviroc (GSK-873,140) was another CCR5 co-receptor antagonist that showed good antiretroviral activity but clinical development was discontinued because of hepatotoxicity.[58-60] Other small molecule CCR5 co-receptor antagonists in development have included INCB-9471,[61] SCH532706 in combination with low-dose ritonavir,[62] and PF-232798, which has potent

Table III. Tropism and outcome in clinical trials of R5 inhibitors

Trial name (drug)	No. of pts with pretreatment tropism shift (%)	No. of pts with tropism change during study	Virological outcome of D/M at study entry	Tropism at CCR5 inhibitor failure	Time to treatment failure	Reference
MOTIVATE 1 and 2 (MVC)	83 of 1042 (8)	No data	Inferior virological outcome	2 of 3 pts had detectable CXCR4 virus at failure	30 days earlier if D/M or CXCR4	50
MERIT (MVC)	25 of 740 (3.4)	No data	Undetectable VL in 6 of 11 EFV pts and 1 of 14 MVC pts	32 R5 at baseline, 10 of 32 had D/M or CXCR4 at failure.	No data	51
ACTG 5211 (VCV)	12 of 118 (10)	4 of 30 (VCV 10 mg) 3 of 30 (VCV 15 mg) 3 of 28 (placebo) [2 after switch to VCV]	No data	9 of 26 (35%) had CXCR4 virus at failure	Shorter in D/M compared with CCR5	35
VICTOR-E1 (VCV)	6 of 114 (5)	9 of 39 [23% CXCR4] (VCV 30 mg) 7 of 40 [10% CXCR4] (VCV 20 mg)	Not necessarily associated with virological failure	13 of 108 (12%)	No data	37

ACTG = AIDS Clinical Trial Group; **D/M** = dual/mixed tropism; **EFV** = efavirenz; **MERIT** = Maraviroc vs Efavirenz Regimens as Initial Therapy; **MOTIVATE** = Maraviroc Plus Optimized Background Therapy in Viremic, ART-Experienced Patients; **MVC** = maraviroc; **pts** = patients; **VCV** = vicriviroc; **VICTOR-E1** = Vicriviroc in Combination Treatment with Optimized ART Regimen in Experienced Subjects; **VL** = viral load.

activity against CCR5-tropic, maraviroc-resistant HIV-1.[63] Monoclonal antibodies that block the binding of HIV to CCR5 in clinical trials have included HGS004[58,64] and PRO140.[41,64-66] PRO140 was synergistic with maraviroc and vicriviroc, active against maraviroc- and vicriviroc-resistant strains *in vitro*,[67,68] was well tolerated[69] and, in a small number of HIV-infected patients with CCR5-tropic virus, showed a dose-dependent decrease in viral load.[41] One of 30 patients who received PRO140 had a CCR5 to D/M change, but analysis showed that the patient was likely to have had a pre-existing D/M virus rather than developing a mutation following treatment.[70] A randomized, placebo-controlled phase IIA trial compared PRO140 at 5 and 10 mg/kg single infusions, and found a mean 2 $\log_{10}$/mL decrease in viral load in the 10 mg/kg group that was durable for 4 weeks post-injection.[71] Dose administration every 3 weeks may be possible based on these results. Finally, aprepitant, a neurokinin-1 receptor antagonist and approved antiemetic, which downregulates CCR5 expression on macrophages *in vitro*,[72] is currently under investigation in HIV infection.[73]

1.2 Clinical Use of CCR5 Co-Receptor Antagonists

Maraviroc is approved for use in antiretroviral treatment-experienced patients with CCR5-tropic HIV-1, detectable viral loads, and resistance to multiple antiretroviral drugs based on results from the MOTIVATE 1 and 2 studies. Maraviroc is useful in the subset of patients who have some ART experience. However, 50% of patients with low CD4+ cell counts are likely to have D/M- or, less commonly, CXCR4-tropic virus; therefore, tropism testing is required to determine the utility of maraviroc in this population.[23] Furthermore, 5–10% of patients who were found to have CCR5 virus on the original Trofile™ assay will have minority CXCR4 populations capable of causing maraviroc failure. However, with the enhanced sensitivity Trofile™ assay, maraviroc will be used with more confidence because CXCR4 populations will be detected with greater certainty.

Maraviroc should not be used in treatment-naive patients based on MERIT study results, where maraviroc did not meet criteria for noninferiority to efavirenz-based therapy. The MERIT-ES re-analysis of the MERIT data with the enhanced Trofile™ assay did find that maraviroc was noninferior to efavirenz when combined with zidovudine/lamivudine; however, maraviroc is not US FDA approved for use in ART-naive patients, and more information on pairing of maraviroc with other antiretrovirals and longer-term outcomes would be helpful.

If a patient develops virological failure on a maraviroc-containing ART regimen, then standard resistance testing should be performed, and a tropison assay may be useful in determining the cause of treatment failure. Some virological failures on maraviroc regimens are secondary to CCR5 to D/M or CXCR4 tropism changes (57% and 31% of patients with virological failure in the MOTIVATE and MERIT trials).[51,74] However, a small study has shown that it is possible for maravoric treatment to fail in patients with CCR5-tropic but maraviroc-resistant virus secondary to V3 loop mutations.[11] Additional virological failure results from other antiretroviral resistance in the regimen and standard antiretroviral resistance testing should be performed. Tropism testing can be considered at the time of maraviroc-containing regimen failure to prevent inappropriate maraviroc discontinuation; however, no commercially available testing can rule out the presence of CCR5-tropic but phenotypic maraviroc-resistant HIV.

The recommended dose of maraviroc is as follows: (i) 150 mg orally twice daily when used in combination with CYP3A inhibitors, including PIs except the combination of tipranavir plus ritonavir; azoles such as itraconazole and ketoconazole, and clarithromycin; (ii) 300 mg orally twice daily when given in combination with ritonavir boosted tipranavir, NRTIs, enfuvirtide, nevirapine and other drugs without strong CYP3A effects; and (iii) 600 mg orally twice daily with CYP3A inducers, including efavirenz, etravirine and rifampin. Hypericum (St John's wort) should be avoided, whereas hormonal contraceptives can be safely used.[75] Because maraviroc is primarily metabolized by the liver, the FDA recommends caution when giving maraviroc to patients with hepatic impairment, as maraviroc levels may increase.[76] Further caution is indicated in patients with ischaemic heart disease as patients receiving maraviroc had a cardiovascular event rate of 1.34 compared with none in patients receiving placebo.[76]

2. Integrase Inhibitors

Integrase inhibitors are a new class of antiretrovirals that inhibit HIV proviral DNA integration into the host genome. Integration is a multi-step process and currently available integrase inhibitors inhibit the strand transfer step.[77] Raltegravir is a strand transfer inhibitor and was recently approved for use in HIV treatment. It is active against HIV strains with reverse transcriptase (RT) and protease (PR) resistance mutations, different HIV-1 subtypes, and CCR5 or CXCR4 strains. It is metabolized primarily by glucuronidation (UGT1A1) and is not a potent inhibitor or inducer of CYP3A4. Elvitegravir is another potent integrase inhibitor that is also active against antiretroviral (NRTI, non-nucleoside reverse transcriptase inhibitors [NNRTI], PI) resistant strains, different HIV-1 subtypes and HIV-2. Elvitegravir also has additive activity *in vitro* with other antiretrovirals and is a moderate inducer of CYP3A4.[78]

The phase IIa Protocol 004 study evaluated multiple doses of raltegravir compared with efavirenz in treatment-naive patients, all with tenofovir and lamivudine (table II). There was no significant difference in viral load or CD4+ cell count results between the raltegravir and efavirenz arms. Combining all raltegravir doses, there were no dose-related toxicities, and total cholesterol, low-density lipoprotein cholesterol (LDL-C)and triglycerides were not increased by raltegravir.[38,39] The STARTMRK (Safety and Efficacy of Raltegravir-Based versus Efavirenz-Based Combination Therapy in Treatment-Naive HIV-1 Infected Patients) study evaluated raltegravir 400 mg twice a day versus efavirenz 600 mg at bedtime with tenofovir/emtricitabine in treatment-naive patients.[40] There were no significant

differences between raltegravir and efavirenz in the percentage of patients achieving an undetectable HIV viral load, although the increase in absolute CD4+ cell count with raltegravir was greater than with efavirenz. Of 12 patients in the raltegravir arm who did not respond to treatment and had >400 copies/mL of HIV, four had integrase resistance mutations and three did not have the integrase gene amplified. Three of eight patients who did not respond to treatment with efavirenz had efavirenz resistance mutations. Lipid profiles were less affected with raltegravir than with efavirenz; LDL-C increased 6 and 16 mg/dL (0.15 and 0.4 mmol/L) on average and triglycerides decreased 3 and increased 37 mg/dL (0.033 and 0.4 mmol/L) on average, respectively.

The Protocol 005 study compared multiple doses of raltegravir plus OBR versus placebo plus OBR in ART-experienced patients and found that raltegravir resulted in a significantly greater reduction in viral load than placebo after 24 weeks (table II).[79] The BENCHMRK (Blocking Integrase in Treatment-Experienced Patients with a Novel Compound Against HIV) 1 and 2 studies compared raltegravir plus OBR with placebo plus OBR in ART-experienced patients who had antiretroviral resistance (table II). After 48 weeks, patients in the raltegravir arms were significantly more likely to achieve an undetectable viral load compared with those in the placebo arm. The best virological result occurred in those patients who received raltegravir with both darunavir and enfuvirtide in their OBR (89%). Remarkably, 50% of those receiving raltegravir with no other active drugs in the OBR achieved an undetectable viral load compared with only 2% of patients receiving placebo plus OBR. Adverse events were similar between raltegravir and placebo, and no increased risk of malignancy with raltegravir was seen.[42] There was a trend towards decreased AIDS-defining events or death at 48 weeks in the raltegravir arm versus placebo arm relative risk (relative risk [RR] 0.50; 95% CI 0.25, 1.03).[80]

Elvitegravir was evaluated in patients who were ART naive or not receiving their current regimen, at doses of 50, 400 and 800 mg, all with ritonavir, and was shown to reduce viral load by 2.0 $\log_{10}$/mL.[81] The phase II study, GS-US-183-0105, evaluated elvitegravir plus ritonavir plus OBR compared with a comparator ritonavir-boosted PI plus OBR in ART-experienced patients with at least one primary PI mutation (table II). Enfuvirtide, but not NNRTIs, were allowed in the OBR. PIs were not allowed in the elvitegravir arms. After 24 weeks, the mean change in HIV-1 viral load from baseline was 1.7 versus 1.4 $\log_{10}$ copies/mL in the 125 mg elvitegravir and comparator PI arms, respectively. Further analysis found that elvitegravir without active antiretrovirals in the OBR reduced viral load by 0.7 versus 2.1 $\log_{10}$ copies/mL in those with greater than one active NRTI or enfuvirtide in their OBR.[45] Elvitegravir is currently in phase III development.

The integrase gene is highly polymorphic, although, to date, no polymorphisms that have been found are associated with phenotypic integrase inhibitor resistance (table IV). Some polymorphisms are more common in ART-experienced and others in ART-naive patients. Despite integrase polymorphisms, integrase inhibitors are active against HIV-2.[82,87-89] Raltegravir resistance was first described in the Protocol 005 study and later confirmed in other raltegravir studies. Two different pathways of integrase resistance mutations (N155 or Q148) have been described. Additional integrase mutations were frequently observed with both pathways and Q148 mutants were more common than N155. The most common mutation pattern was Q148H/G140S, which resulted in significantly higher raltegravir fold change in the concentration that produces 50% inhibition (IC_{50}) relative to reference than Q148H alone.[43,44,83] At the time of raltegravir failure in BENCHMRK, 53% of patients had a Q148 mutation, 18% had N155 and 10% had a mixture.[90] Q148H in combination with secondary mutations was not associated with a decrease in replication capacity, while N155H was, which helps to explain why Q148H is the more common resistance pathway.[90] Virological failure of elvitegravir regimens also resulted from development of N155H, Q148R/H/K and, additionally, E92Q mutations. Multiple integrase mutations

Table IV. Integrase gene polymorphisms and resistance mutations[42,82-86]

Clinical situation	Polymorphism/mutation
Mutations and combinations associated with virological failure	With raltegravir: Q148R/H/K, Q148/G140S, N155H With elvitegravir: Q148R/H/K, N155H, E92Q
Additional mutations and combinations associated with phenotypic failure and increased fold change *in vitro*	With raltegravir: E92Q, T66I/E92Q, E92Q/N155H, G140S/Q148H, E138K/S147G/Q148R, Q148K/E138A/G140A With elvitegravir: T66I/E92Q, E92Q/N155H, G140S/Q148H, E138K/S147G/Q148R
Polymorphisms and prevalence in antiretroviral-naive patients	80%: V201I 46%: V72I >5%: L74M/I, T97A, T125A/V, V151I, M154I, K156N, V165I, I203M, T206S, S230N
Polymorphisms in antiretroviral-treated patients	M154I, V165I, M185L

(table IV) significantly increased the fold change in IC_{50} relative to reference, resulting in high level phenotypic resistance to both raltegravir and elvitegravir.[84]

Two patients in whom an elvitegravir plus ritonavir regimen failed were switched to a raltegravir-containing regimen, with no virological response after switching. After elvitegravir plus ritonavir virological failure, one patient was found to have a N155H mutation, and the other a Q148H mutation in addition to other INI mutations. One patient achieved an undetectable viral load (<50 copies/mL) after addition of darunavir plus ritonavir to raltegravir, whereas the second patient did not,[91] indicating that cross resistance occurs and virological response is unlikely after failure with one integrase inhibitor. Raltegravir-resistant HIV was recently tested against elvitegravir and found to display even greater resistance to elvitegravir, indicating cross resistance.[85] Two second-generation integrase inhibitors being developed by Merck (MD-0536 and MK-2048) demonstrated much less resistance to these HIV isolates than raltegravir or elvitegravir, and plans are to pursue development of these drugs for treatment of raltegravir- and elvitegravir-resistant HIV-1.

A phenotypic integrase assay (PhenoSense® Integrase Assay) that measures the susceptibility of HIV-1 to integrase inhibitors has been developed.[92] The biological cut-off for raltegravir fold change in IC_{50} in this assay was established as 1.5.

2.1 Clinical Use of Integrase Inhibitors

The BENCHMRK and other trials led to the approval of raltegravir for treatment-experienced HIV-1 infected adults with detectable viral loads and resistance to multiple antiretroviral drugs. Integrase inhibitor-naive patients can be expected to respond to raltegravir; whereas, in the BENCHMRK trials, fewer than 3% of patients receiving raltegravir did not achieve a viral load of ≤400 copies/mL.[42] No clinical trials have addressed which of the antiretroviral agents work best in combination with raltegravir, although in the BENCHMRK studies, the best virological outcomes were seen with patients receiving raltegravir, enfuvirtide and ritonavir boosted darunavir. Thus, the more active the antiretroviral drugs in a regimen, the better the outcome. Raltegravir has a neutral lipid profile and may play a role in patients with poor lipid profiles or in whom lipid-raising regimens should be avoided.[38] Phenotypic assays for measuring integase susceptibility are currently available and genotypic assays are available in some settings. Raltegravir-containing regimens may fail in a patient because of integrase resistance (table IV), resistance to other antiretroviral agents, or reasons such as poor ART adherence or poor

bioavailability. Because there is cross resistance between raltegravir and elvitegravir (table IV), switching agents within the integrase inhibitor class if resistance develops (once elvitegravir becomes available) is not recommended.[85] Studies indicate that raltegravir is likely to be an option for first-line ART.[40] Current dose administration of raltegravir is 400 mg twice daily without dosage adjustment when combined with other ART.

3. Other New HIV Agents in Development

3.1 Attachment Inhibitors

Nonspecific attachment inhibitors, which block binding of HIV to CD4 cells in the initial step of HIV cell entry, such as PC-515 (Carraguard™), cyanovirin-N and molecular umbrella compounds, are being developed as topical microbicides.[93-97] Specific attachment inhibitors include cyclotriazadisulfonamide (CADA), which downregulates expression of CD4,[98-100] and naphthalene sulfonate, which disrupts binding of gp120 to CD4.[101,102] A naphthalene sulfate polymer (PRO 2000)[103,104] is being tested as a vaginal gel.[105] Ibalizumab (TNX-355) is an anti-CD4 monoclonal antibody,[106,107] which has synergy with enfuvirtide,[108] and is in phase II clinical trials.[109]

3.2 HIV Glycoprotein 120 Agents

Agents targeting gp120 are targeting the first step in HIV cell entry by preventing the interaction of CD4 with gp120. SPL7013 binds HIV gp120[102] and is being studied as a microbicide.[110,111] PRO 542 is a CD4 IgG2 that binds to HIV gp120 and was in a phase II open-label study recently completed but is no longer in development.[112] In previous studies, PRO 542 reduced viral load in adults with ART failure and in antiretroviral-naive children.[113-115] Several small molecule CD4 attachment inhibitors have been explored[116-119] and similar compounds are in development.[116]

3.3 CCR5 Co-Receptor Agonists

As discussed in section 1, targeting the chemokine co-receptors for HIV entry, in particular CCR5, has been a successful strategy. Other ways to manipulate the CCR5 receptor are being explored. ESN-196 is a small-molecule CCR5 co-receptor agonist that causes internalization of the receptor and prevents HIV-1 infection *in vitro*.[120] Regulated on Activation, Normal T cell Expressed and Secreted (RANTES), the endogenous CCR5 ligand,[121] is being developed as a topical microbicide, with potent HIV-1 suppressive activity against maraviroc- and vicriviroc-resistant HIV-1 strains *in vitro*.[68,122] An anti-CD40 monoclonal IgG1 that induces RANTES and macrophage inflammatory protein-1α expression is also being developed.[123]

3.4 CXCR4 Co-Receptor Antagonists

The change in HIV-1 tropism to CXCR4 while receiving CCR5 inhibitor therapy has prompted the search for CXCR4 co-receptor antagonists. Several CXCR4 co-receptor antagonists have reached clinical trials, but none have progressed beyond phase II because of problems with toxicity or lack of virological response.[124-126] POL3026 was found to prevent HIV replication and emergence of CXCR4-tropic HIV *in vitro*.[127-129] POL3026 may have the potential for use in combination with CCR5 inhibitors to prevent the on-treatment selection of CXCR4 populations.

3.5 Fusion Inhibitors

Enfuvirtide (T20) is the first-in-class fusion inhibitor to be FDA-approved for clinical use, and it works by binding gp41 and thus preventing fusion of the HIV viral and human cellular membranes. Several fusion inhibitors are in preclinical development, while others are in phase I trials.[130,131] A peptide derived from the gp41 HR2 region, TRI-1144 (TR-029114), is a second-generation fusion inhibitor that has undergone preclinical development,[132] and has now completed a phase I, single-dose, placebo-controlled clinical trial (TRI 1144-101) in 24 healthy volunteers

with results expected later this year. Preliminary results have been announced indicating that TRI-1144 was well tolerated, but, to date, no data has been published. The pharmacokinetics suggest that it can be administered less frequently than enfuvirtide, is stable in solution and therefore does not have to be reconstituted, and has a higher genetic barrier to resistance.[133] Another gp41 inhibitor developed in China, sifuvirtide (FS0101, Fusogen), was able to block fusion of enfuvirtide-resistant HIV strains and was well tolerated in a phase Ia clinical study of healthy volunteers.[134]

3.6 Maturation Inhibitors

Bevirimat (PA103001-4, PA-457) is a gag maturation inhibitor that inhibits the final step in the processing of the HIV-1 gag polyprotein by binding to the HIV-1 capsid precursor CA-SP1 (p25) cleavage site. This prevents conversion to the capsid protein p25, which is required for the formation of infectious viral particles. Both *in vitro* and animals studies indicate that bevirimat impairs SP1-capsid cleavage, delays replication of PI-resistant HIV and reduces viral load in SCID-hu Thy/Liv mice.[135-138] Bevirimat is well tolerated and it significantly decreases viral load.[139,140] None of the mutations associated with bevirimat *in vitro* were found *in vivo*.[136] Bevirimat has activity against ART-resistant and wild-type HIV, and has shown synergy with antiretrovirals from all classes.[141] Results from a phase II clinical trial of bevirimat with OBR in patients with antiretroviral resistance and in whom current ART regimens had failed were recently reported.[142] Bevirimat reduced HIV viral load by a mean of 1.6 $\log_{10}$/mL in patients who achieved trough levels of ≥20 μg/mL and who did not have any of the key baseline gag polymorphisms at Q369, V370 or T371. All responders, defined as those who had a drop in viral load >0.5 $\log_{10}$/mL, had trough levels ≥20 μg/mL, while 60% of nonresponders had troughs levels <20 μg/mL.[143] Trough levels of 20 μg/mL were achieved with a liquid formulation of bevirimat at doses of 250–400 mg/day. Viral load reduction was significantly lower in patients with gag polymorphisms. Adverse advents were not more common in the bevirimat than the placebo arm. Phase III studies are planned.

4. Immunotherapy

Exogenous interleukin (IL)-2 promotes CD4+ T-cell differentiation and proliferation, and has the potential to prevent progression to AIDS. It has increased CD4+ cell counts in clinical trials, but a clear effect on clinical outcome has not been seen.[144-146] In the UK-Vanguard study, IL-2 significantly increased CD4+ cell counts at 24 and 48 weeks, but there was no difference in CD4+ cell counts beyond 48 weeks, and no difference in time to initiation of ART.[144] The ARNS (French Agency for HIV Research) 199 trial found that patients who were given IL-2 were less likely to require ART ($p < 0.0001$).[145] Patients with discordant responses to ART who were given IL-2 therapy and subsequently demonstrated a CD4+ cell count increase actually had a significantly decreased risk of death or AIDS-defining event.[146] IL-2 is being studied further in ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial), an international trial of subcutaneous recombinant IL-2 for patients on combination ART with CD4+ cell counts >300/mm^3 being followed-up for 5 years for disease progression and death.[147] Results are expected at the end of 2008.[148] Finally, in an attempt to improve T-cell memory, maturation and survival, exogenous IL-7 is also under investigation.[149]

5. Gene Therapy

Current gene therapy agents include lexgenleucel-T (VRX496), an antisense HIV envelope gene that has been sequence transduced into CD4+ cells,[150-152] and OZ1 (Johnson & Johnson) an anti-HIV-1 ribozyme that has been transduced into CD34+ cells.[153] A phase I study of VRX496 in five patients found no adverse events and a sustained decrease in viral load was achieved in one of the patients.[154] Three phase II clinical trials are underway.[155-157] A phase II

trial of OZ1 has been completed, but no further development is currently underway.[153]

Other preclinical genetic work has found that HIV is suppressed by small interfering RNAs targeting the RNA helicase DDX3, which exports RNA from the nucleus to the cytoplasm.[158,159] Zinc-finger DNA-binding protein nucleases against CCR5 DNA sequences were found to protect against CCR5-tropic HIV-1 infection in mice.[64,160,161] Finally, fusion inhibitors are being expressed constitutively from viral vectors.[160]

6. Conclusion

Two new classes of antiretroviral drugs (CCR5 co-receptor antagonists and integrase inhibitors), with novel targets, have come into clinical use within the last year and significantly increase drug treatment options for ART-experienced patients. Maraviroc and raltegravir are now approved, and additional agents within these classes are in late clinical development. Maturation inhibitors may be the next class poised to enter clinical usage. Antibody therapy against steps in HIV cell entry is being productively explored, as well as small molecule therapy against new targets of entry, such as CXCR4 receptors and gp120. Gene therapy against many steps in the HIV lifecycle has demonstrated good preclinical results, but clinical effectiveness has yet to be demonstrated. Finally, innovative immunotherapies are being explored, although, to date, results are inconclusive.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008 Jul 26; 372 (9635): 293-9
2. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998 Nov 28; 352 (9142): 1725-30
3. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006 Nov 30; 355 (22): 2283-96
4. Jacobson JM, Turner BJ, Abrutyn E. Trials that matter: CD4+ T-lymphocyte count-guided interruption of antiretroviral therapy in HIV-infected patients. Ann Intern Med 2007 May 1; 146 (9): 682-3
5. Ruiz L, Paredes R, Gomez G, et al. Antiretroviral therapy interruption guided by CD4 cell counts and plasma HIV-1 RNA levels in chronically HIV-1-infected patients. AIDS 2007 Jan 11; 21 (2): 169-78
6. Richman DD, Morton SC, Wrin T, et al. The prevalence of antiretroviral drug resistance in the United States. AIDS 2004 Jul 2; 18 (10): 1393-401
7. Tozzi V, Zaccarelli M, Bonfigli S, et al. Drug-class-wide resistance to antiretrovirals in HIV-infected patients failing therapy: prevalence, risk factors and virological outcome. Antivir Ther 2006; 11 (5): 553-60
8. Truong HM, Grant RM, McFarland W, et al. Routine surveillance for the detection of acute and recent HIV infections and transmission of antiretroviral resistance. AIDS 2006 Nov 14; 20 (17): 2193-7
9. Turner D, Wainberg MA. HIV transmission and primary drug resistance. AIDS Rev 2006 Jan-Mar; 8 (1): 17-23
10. Briz V, Poveda E, Soriano V. HIV entry inhibitors: mechanisms of action and resistance pathways. J Antimicrob Chemother 2006 Apr; 57 (4): 619-27
11. Lewis M, Mori J, Simpson P, et al. Changes in V3 loop sequence associated with failure of maraviroc treatment in patients enrolled in the MOTIVATE 1 and 2 trials [abstract no. 871]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
12. Este JA, Telenti A. HIV entry inhibitors. Lancet 2007 Jul 7; 370 (9581): 81-8
13. Al-Mawsawi LQ, Neamati N. Blocking interactions between HIV-1 integrase and cellular cofactors: an emerging anti-retroviral strategy. Trends Pharmacol Sci 2007 Oct; 28 (10): 526-35
14. Savarino A. A historical sketch of the discovery and development of HIV-1 integrase inhibitors. Expert Opin Investig Drugs 2006 Dec; 15 (12): 1507-22
15. McNicholl IR, McNicholl JJ. On the horizon: promising investigational antiretroviral agents. Curr Pharm Des 2006; 12 (9): 1091-03
16. Daar ES, Kesler KL, Petropoulos CJ, et al. Baseline HIV type 1 coreceptor tropism predicts disease progression. Clin Infect Dis 2007 Sep 1; 45 (5): 643-9
17. Goetz MB, Leduc R, Kostman JR, et al. Predictions of disease progression by HIV co-receptor tropism (CRT) in persons (P) with untreated chronic HIV infection [abstract no. H-1027]. 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 Sep 17-20; Chicago (IL)

18. Daar ES, Eron Jr J, Schapiro JM. Clinical care options HIV. Answering the questions: HIV tropism in clinical practice. 2008 Sep 18 [online]. Available from URL: http://www.clinicaloptions.com/hiv [Accessed 2008 Dec 4]
19. Moyle GJ, Wildfire A, Mandalia S, et al. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. J Infect Dis 2005 Mar 15; 191 (6): 866-72
20. Demarest J, Bonny T, Vavro C, et al. HIV-1 co-receptor tropism in treatment naive and experienced subjects [abstract no. H-1136]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2004 Oct 30-Nov 2; Washington, DC
21. Coakley E, Benhamida J, Chappey C, et al. An evaluation of tropism profiles and other characteristics among 3988 individuals screened from A4001026, A4001027 (MOTIVATE 1) and A4001028 (MOTIVATE 2) studies for maraviroc [abstract no. 8]. Second International Workshop on Targeting HIV Entry; 2006 Oct 20-21; Boston (MA)
22. Melby T, Despirito M, Demasi R, et al. HIV-1 coreceptor use in triple-class treatment-experienced patients: baseline prevalence, correlates, and relationship to enfuvirtide response. J Infect Dis 2006 Jul 15; 194 (2): 238-46
23. Wilkin TJ, Su Z, Kuritzkes DR, et al. HIV type 1 chemokine coreceptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. Clin Infect Dis 2007 Feb 15; 44 (4): 591-5
24. Brumme ZL, Goodrich J, Mayer HB, et al. Molecular and clinical epidemiology of CXCR4-using HIV-1 in a large population of antiretroviral-naive individuals. J Infect Dis 2005 Aug 1; 192 (3): 466-74
25. Tressler R, Valdez H, van der Ryst E, et al. Comparison of results from the SensiTrop™ vs Trofile™ assays on 100 samples from the maraviroc expanded access program [abstract no. 920a]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
26. Reeves J, Han D, Wilkin T, et al. An enhanced version of the Trofile HIV co-receptor tropism assay predicts emergence of cxcr4 use in ACTG5211 vicriviroc trial samples [abstract no. 869]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
27. Reeves JD, Han D, Lui Y, et al. Enhancements to the Trofile HIV coreceiptor tropism assay enable reliable detection of CXCR4-using subpopulations at less than 1% [abstract no. H-1026]. Program and abstracts of the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 Sep 17-20; Chicago (IL)
28. Trinh L, Han D, Huang W, et al. Validation of an enhanced sensitivity Trofile HIV-1 co-receptor tropism assay [abstract no. H-1219]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
29. Li WL, Webb E, Reposar T, et al. Adaptation and validation of the SensiTrop II molecular co-receptor tropism assay on international clades of HIV virus [abstract no. H-1220]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
30. Moores A, Dong W, Wynhoven B, et al. Improved detection of X4 HIV-1 by V3 genotyping: application to plasma RNA and proviral DNA [abstract no. H-1217]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
31. Soulie C, Malet I, Lambert-Niclot S, et al. Primary genotypic resistance of HIV-1 to CCR5 antagonists in CCR5 antagonist treatment-naive patients. AIDS 2008 Oct 18; 22 (16): 2212-4
32. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV infection. N Engl J Med 2008 Oct 2; 359 (14): 1429-41
33. Saag M, Ive P, Heera J, et al. A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc vs efavirenz, both in combination with Combivir (zidovudine [ZDV]/lamivudine [3TC], for the treatment of antiretroviral naive patients infected with R5 HIV 1: week 48 results of the MERIT study [abstract no. WESS104]. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 2007 Jul 22-25; Sydney
34. Saag M, Heera J, Goodrich J, et al. Reanalysis of the MERIT study with the enhanced Trofile assay (MERIT-ES) [abstract no. H1232a]. 48th Annual ICCAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
35. Gulick RM, Su Z, Flexner C, et al. Phase 2 study of the safety and efficacy of vicriviroc, a CCR5 inhibitor, in HIV-1-infected, treatment-experienced patients: AIDS clinical trials group 5211. J Infect Dis 2007 Jul 15; 196 (2): 304-12
36. Gulick R, Su Z, Flexner C, et al. ACTG 5211: phase II study of the safety and efficacy of vicriviroc (VCV) in HIV-infected treatment-experienced subjects: 48 week results [abstract no. TUAB102]. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 2007 Jul 22-25; Sydney
37. Zingman B, Suleiman J, DeJesus E, et al. Vicriviroc, a next generation CCR5 antagonist, exhibits potent, sustained suppression of viral replication in treatment-experienced adults: VICTOR-E1 48-week results [abstract no. 39LB]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
38. Markowitz M, Nguyen BY, Gotuzzo E, et al, for the Protocol 004 Part II Study Team. Rapid onset and durable antiretroviral effect of raltegravir (MK-0518), a novel HIV-1 integrase inhibitor, as part of combination ART in treatment HIV-1 infected patients: 48-week data [abstract no. TUAB104]. 4th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; 2007 Jul 22-25; Sydney
39. Murray JM, Emery S, Kelleher A, et al. The integrase inhibitor raltegravir alters viral decay kinetics of HIV, significantly reducing the second phase and challenging current hypotheses of viral replication [abstract no. TUAB103]. 4th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; 2007 Jul 22-25; Sydney
40. Lennox J, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive HIV-1 infected patients: STARTMRK protocol 021 [abstract no. H-896a]. 48th

Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC

41. Jacobson JM, Thomson M, Saag MS, et al. Antiretroviral activity and pharmacodynamics of PRO 140, a CCR5 monoclonal antibody, in HIV-infected individuals [abstract no. H-716]. 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 Sep 17-20; Chicago (IL)
42. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med 2008 Jul 24; 359 (4): 339-54
43. Cooper D, Gatell J, Rockstroh J, et al, for the BENCHMRK-1 Study Group 48-week results from BENCHMRK-1, a phase III study of raltegravir in patients failing ART with triple-class resistant HIV-1 [abstract no. 788]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
44. Steigbigel R, Kumar P, Eron J, et al., for the BENCHMRK-2 Study Group. 48-Week results from BENCHMRK-2, a phase III study of raltegravir in patients failing ART with triple-class resistant HIV [abstract no. 789]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
45. Zolopa AR, Mullen M, Berger D, et al. The HIV integrase inhibitor GS-9137 demonstrates potent antiretroviral activity in treatment-experienced patients [abstract no. 143LB]. 14th Conference on Retroviruses and Opportunistic Infections; 2007 Feb 25-28; Los Angeles (CA)
46. Lalezari J, Goodrich J, DeJesus E, et al. Efficacy and safety of maraviroc plus optimized background therapy in viremic ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of a phase 2b/3 study in the US and Canada [abstract no. 104bLB]. 14th Conference on Retroviruses and Opportunistic Infections; 2007 Feb 25-28; Los Angeles (CA)
47. Nelson M, Fätkenhever G, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in viremic, ART-experienced patients infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-week results [abstract no. 104aLB]. 14th Conference on Retroviruses and Opportunistic Infections; 2007 Feb 25-28; Los Angeles (CA)
48. Hardy D, Reynes J, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in treatment-experienced patients infected with CCR5-tropic HIV-1: 48-week combined analysis of the MOTIVATE studies [abstract no. 792]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
49. Ayoub A, Goodrich J, van der Ryst E, et al. Adverse event profile of maraviroc in treatment-experienced patients infected wtih R5 HIV-1 [abstract no. H-1264]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
50. van der Ryst E, Westby M. Changes in HIV-1 co-receptor tropism for patients participating in the maraviroc MOTIVATE 1 and 2 clinical trials [abstract no. H-715]. Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 Sep 17-20; Chicago (IL)
51. Heera J, Saag M, Ive P, et al. Virological correlates associated with treatment failure at week 48 in the phase 3 study of maraviroc in treatment-naive patients [abstract no. 40LB]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
52. Valdez H, Lewis M, Delogne C, et al. Weighted OBT susceptibility scor (wOBTSS) is a stronger predictor of virologic response at 48 weeks than baseline tropism result in MOTIVATE 1 and 2 [abstract no. H-1221]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
53. Sansone A, Keung A, Tetteh E, et al. Pharmacokinetics of vicriviroc are not affected in combination with five different protease inhibitors boosted by ritonavir [abstract no. 582]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
54. Sansone A, Seiberling M, Kraan M, et al. Similar increase in SCH 417690 exposure with coadministration of varying doses of ritonavir in healthy volunteers [abstract no. 78]. 6th International Workshop on Clinical Pharmacology of HIV Therapy; 2005 Apr 28-30; Quebec City (QC)
55. Su Z, Reeves JD, Krambrink A, et al. Response to vicriviroc (VCV) in HIV-infected treatment-experienced subjects using an enhanced Trofile HIV co-receptor tropism assay: reanalysis of ACTC 5211 results [abstract no. H-895]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
56. Suleiman J, Sobhie DR, DeJesus E, et al. HIV viral tropism in vicriviroc VICTOR-E1 tials: correlations with clinical variables [abstract no. WEPEA107]. 4th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; 2007 Jul 22-25; Sydney
57. Dunkle LM, Greaves WL, McCarthy MC, et al. Long-term safety of vicriviroc [abstract no. A-954]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
58. Lalezari J, Yadavalli GK, Para M, et al. Safety, pharmacokinetics, and antiviral activity of HGS004, a novel fully human IgG4 monoclonal antibody against CCR5, in HIV-1-infected patients. J Infect Dis 2008 Mar 1; 197 (5): 721-7
59. Currier J, Lazzarin A, Sloan L, et al. Antiviral activity and safety of aplaviroc with lamivudine/zidovudine in HIV-infected, therapy-naive patients: the ASCENT (CCR102881) study. Antivir Ther 2008; 13 (2): 297-306
60. Nichols WG, Steel HM, Bonny T, et al. Hepatotoxicity observed in clinical trials of aplaviroc (GW873140). Antimicrob Agents Chemother 2008 Mar; 52 (3): 858-65
61. Cohen C, DeJesus E, Mills A, et al. Potent antiretroviral activity of the once-daily CCR5 antagonist INCB009471 over 14 days of monotherapy [abstract no TUAB106]. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2007 July 22-25; Sydney
62. Pett S, Emery S, MacRae K, et al. Safety and activity of SCH532706, a Small molecule chemokine receptor 5 antagonist in HIV-1-infected individuals [abstract no. 38]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
63. Dorr P, Westby M, McFadyen L, et al. PF-232798, a second generation oral CCR5 antagonist [abstract no. 738].

15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 3-6; Boston (MA)

64. Biswas P, Tambussi G, Lazzarin A. Access denied? The status of co-receptor inhibition to counter HIV entry. Expert Opin Pharmacother 2007 May; 8 (7): 923-33
65. Antiviral briefs. AIDS Patient Care STDs 2008 Jun; 22 (6): 535-7
66. Progenics Pharmaceuticals. PRO 140 by IV administration in adults with HIV-1 infection [ClinicalTrials.gov identifier NCT00613379]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 19]
67. Murga JD, Franti M, Pevear DC, et al. Potent antiviral synergy between monoclonal antibody and small-molecule CCR5 inhibitors of human immunodeficiency virus type 1. Antimicrob Agents Chemother 2006 Oct; 50 (10): 3289-96
68. Pugach P, Ketas TJ, Michael E, et al. Neutralizing antibody and anti-retroviral drug sensitivities of HIV-1 isolates resistant to small molecule CCR5 inhibitors. Virology 2008 Aug 1; 377 (2): 401-7
69. Olson WC, Doshan H, Zhan C, et al. First-in-humans trial of PRO 140, a humanized CCR5 monoclonal antibody for HIV-1 therapy [abstract no. WePe62C04]. 3rd IAS Conference on HIV Pathogenesis and Treatment; 2005 Jul 24-27; Rio de Janeiro
70. Marozsan AJ, Parsons T, Huang W, et al. Clonal analysis of HIV-1 co-receptor tropism change following treatment with PRO 140, a CCR5 monoclonal antibody [abstract no. H-1218]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
71. Jacobson J, Thompson M, Fischi M. Antiviral activity and tolerability of 5 mg/kg and 10 mg/kg doses of PRO 140, a humanized monoclonal antibody to CCR5 [abstract no. H1269a]. 48th Annual ICCAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
72. Wang X, Douglas SD, Lai JP, et al. Neurokinin-1 receptor antagonist (aprepitant) inhibits drug-resistant HIV-1 infection of macrophages in vitro. J Neuroimmune Pharmacol 2007 Mar; 2 (1): 42-8
73. University of Pennsylvania. Effects of treatment with aprepitant (Emend®) in HIV infected individuals [ClinicalTrials.gov identifier NCT00428519]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 19]
74. Fatkenheuer G, Nelson M, Lazzarin A, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. N Engl J Med 2008 Oct 2; 359 (14): 1442-55
75. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [online]. Available from URL: http://www.aidsinfo.nih.gov/Guidelines [Accessed 2008 Nov 20]
76. Selzentry (maraviroc) tablets [online]. Available from URL: http://www.fda.gov/cder/foi/label/2007/022128lbl.pdf [Accessed 2008 Dec 19]
77. Pommier Y, Johnson AA, Marchand C. Integrase inhibitors to treat HIV/AIDS. Nat Rev Drug Discov 2005 Mar; 4 (3): 236-48
78. Yuji Matsuzaki WW, Yamataka K, Sato1 M, et al. JTK-303/GS 9137, a novel small-molecule inhibitor of HIV-1 integrase: anti-HIV activity profile and pharmacokinetics in animals [abstract no. 508]. 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8; Denver (CO)
79. Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet 2007 Apr 14; 369 (9569): 1261-9
80. Eron JD, Nguyen BY, Steigbigel RT, et al. AIDS defining conditions (ADCs) in the BENCHMRK-1 and -2 trials: 48 week analysis [abstract no. H-1249]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
81. DeJesus E, Berger D, Markowitz M, et al. for the 183-0101 Study Team. The HIV integrase inhibitor GS-9137 (JTK-303) exhibits potent antiviral activity in treatment-naive and experienced patients [abstract no. 160LB]. 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8; Denver (CO)
82. Ceecherini-Silberstein F, Malet I, Perno CF, et al. Specific mutations related to HIV-1 integrase inhibitors are associated with reverse transcriptase mutations in HAART-treated patients [abstract no. 4]. Antivir Ther 2007; 12: S6
83. Hazuda DJ, Miller MD, Nguyen BY, et al. Resistance to the HIV-integrase inhibitor raltegravir: analysis of protocol 005, a phase II study in patients with triple-class resistant HIV-1 infection [abstract no. 8]. Antivir Ther 2007; 12: S10
84. McColl DJ, Fransen S, Gupta S, et al. Resistance analysis of a phase 2 study of the integrase inhibitor elvitegravir (GS-9137) [poster no. P71/03]. 11th European AIDS Conference; 2007 Oct 24-27; Madrid
85. Witmer M, Danovich R, Day A, et al. Cross resistance between HIV-1 integrase strand transfer inhibitors (InSTIs) raltegravir, elvitegravir and second generation InSTIs [abstract no. H-1232]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
86. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. N Engl J Med 2008 Jul 24; 359 (4): 355-65
87. Myers RE, Pillay D. HIV-1 integrase sequence variation and covariation [abstract no. 3]. Antivir Ther 2007; 12: S65
88. Van Baelen K, Clynhens M, Rondelez E et al. Low level of baseline resistance to integrase inhibitors L731,988 and L870,810 in randomly selected subtype B and non-B HIV-1 strains [abstract no. 5]. Antivir Ther 2007; 12: S7
89. Roquebert B, Damond F, Descamps D, et al. Polymorphism of HIV-2 integrase gene and in vitro phenotypic susceptibility of HIV-2 clinical isolates to integrase inhibitors: raltegravir and elvitegravir [abstract no. 83]. Antivir Ther 2007; 12: S92
90. Miller M, Danovich R, Fransen S, et al. Analysis of resistance to the HIV-1 integrase inihibitor raltegravir: results from BENCHMRK 1 and 2 [abstract no. H-898].

48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC

91. DeJesus E, Cohen C, Elion R, et al. First report of raltegravir (RAL, MK-0518) use after virologic rebound on elvitegravir (EVT, GS 9137) [abstract no. TUPEB032]. 4th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; 2007 Jul 22-25; Sydney
92. Fransen S, Gupta W, Huarg W, et al. Preformance characteristics and validation of the phenosense integrase assay [abstract no. H-1214]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC
93. Pearce-Pratt R, Phillips DM. Sulfated polysaccharides inhibit lymphocyte-to-epithelial transmission of human immunodeficiency virus-1. Biol Reprod 1996 Jan; 54 (1): 173-82
94. Perotti ME, Pirovano A, Phillips DM. Carrageenan formulation prevents macrophage trafficking from vagina: implications for microbicide development. Biol Reprod 2003 Sep; 69 (3): 933-9
95. Zappe H, Snell ME, Bossard MJ. PEGylation of cyanovirin-N, an entry inhibitor of HIV. Adv Drug Deliv Rev 2008 Jan 3; 60 (1): 79-87
96. Madan RP, Mesquita PM, Cheshenko N, et al. Molecular umbrellas: a novel class of candidate topical microbicides to prevent human immunodeficiency virus and herpes simplex virus infections. J Virol 2007 Jul; 81 (14): 7636-46
97. McLean C, Jones H, McNicholl J, et al. Evaluation of the safety of carraguard for vaginal use by HIV-infected women: results from a phase I, randomized, placebo-controlled, 3-treatment cross-over study [abstract no. 566]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)
98. Vermeire K, Bell TW, Choi HJ, et al. The anti-HIV potency of cyclotriazadisulfonamide analogs is directly correlated with their ability to down-modulate the CD4 receptor. Mol Pharmacol 2003 Jan; 63 (1): 203-10
99. Vermeire K, Princen K, Hatse S, et al. CADA, a novel CD4-targeted HIV inhibitor, is synergistic with various anti-HIV drugs in vitro. AIDS 2004 Nov 5; 18 (16): 2115-25
100. Vermeire K, Brouwers J, Van Herrewege Y, et al. CADA, a potential anti-HIV microbicide that specifically targets the cellular CD4 receptor. Curr HIV Res 2008 May; 6 (3): 246-56
101. Rusconi S, Moonis M, Merrill DP, et al. Naphthalene sulfonate polymers with CD4-blocking and anti-human immunodeficiency virus type 1 activities. Antimicrob Agents Chemother 1996 Jan; 40 (1): 234-6
102. Cummins Jr JE, Guarner J, Flowers L, et al. Preclinical testing of candidate topical microbicides for anti-human immunodeficiency virus type 1 activity and tissue toxicity in a human cervical explant culture. Antimicrob Agents Chemother 2007 May; 51 (5): 1770-9
103. Mayer KH, Karim SA, Kelly C, et al. Safety and tolerability of vaginal PRO 2000 gel in sexually active HIV-uninfected and abstinent HIV-infected women. AIDS 2003 Feb 14; 17 (3): 321-9
104. Tabet SR, Callahan MM, Mauck CK, et al. Safety and acceptability of penile application of 2 candidate topical microbicides: BufferGel and PRO 2000 Gel: 3 randomized trials in healthy low-risk men and HIV-positive men. J Acquir Immune Defic Syndr 2003 Aug 1; 33 (4): 476-83
105. National Institute of Allergy and Infectious Diseases (NIAID). BufferGel and PRO 2000/5: vaginal gels to prevent HIV infection in women [ClinicalTrials.gov identifier NCT00074425]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]
106. Godofsky E, Zhang X, Sorensen M, et al. In vitro antiretroviral activity of the humanized anti-CD4 monodlonal antibody, TNX-355, against CCR5, CXCR4, and dual-tropic isolates and synergy with enfuvirtide [abstract no. LB-26]. 45th Conference on Antimicrobial Agents and Chemotherapy; 2005 Dec 16-19; Washington, DC
107. Norris D, Morales J, Godofsky E, et al. TNX-355, in combination with optimized background regimen (OBR), achieves statistically significant viral load reduction and CD4 cell count increase when compared with OBR alone in phase II study at 48 weeks [abstract no. THLB0218]. 16th International AIDS Conference; 2006 Aug 13-18; Toronto (ON)
108. Zhang XQ, Sorensen M, Fung M, et al. Synergistic in vitro antiretroviral activity of a humanized monoclonal anti-CD4 antibody (TNX-355) and enfuvirtide (T-20). Antimicrob Agents Chemother 2006 Jun; 50 (6): 2231-3
109. Dimitrov A. Ibalizumab, a CD4-specific mAb to inhibit HIV-1 infection. Curr Opin Investig Drugs 2007 Aug; 8 (8): 653-61
110. Starpharma Pty Ltd. SPL7013 gel: male tolerance study [ClinicalTrials.gov identifier NCT00370357]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]
111. Starpharma Pty Ltd. Safety and acceptability of SPL7013 Gel (VivaGel™) in sexually active women [ClinicalTrials.gov identifier NCT00442910]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]
112. Progenics Pharmaceuticals, Inc. Safety and efficacy of PRO 542 in the treatment of HIV-infected patients [ClinicalTrials.gov identifier NCT00055185]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]
113. Shearer WT, Israel RJ, Starr S, et al. Recombinant CD4-IgG2 in human immunodeficiency virus type 1-infected children: phase 1/2 study. The Pediatric AIDS Clinical Trials Group Protocol 351 Study Team. J Infect Dis 2000 Dec; 182 (6): 1774-9
114. Jacobson JM, Lowy I, Fletcher CV, et al. Single-dose safety, pharmacology and antiviral activity of the human immunodeficiency virus (HIV) type 1 entry inhibitor PRO 542 in HIV-infected adults. J Infect Dis 2000 Jul; 182 (1): 326-329
115. Jacobson JM, Israel RJ, Lowy I, et al. Treatment of advanced human immunodeficiency virus type 1 disease with the viral entry inhibitor PRO 542. Antimicrob Agents Chemother 2004 Feb; 48 (2): 423-9

116. Kadow J, Wang HG, Lin PF. Small-molecule HIV-1 gp120 inhibitors to prevent HIV-1 entry: an emerging opportunity for drug development. Curr Opin Investig Drugs 2006 Aug; 7 (8): 721-6

117. Veazey RS, Klasse PJ, Schader SM, et al. Protection of macaques from vaginal SHIV challenge by vaginally delivered inhibitors of virus-cell fusion. Nature 2005 Nov 3; 438 (7064): 99-102

118. Hanna G, Lalezari J, Hellinger J, et al. Antiviral activity, safety, and tolerability of a novel, oral small-molecule HIV-1 attachment inhibitor, BMS-488043, in HIV-1- infected subjects [abstract no. 141]. 11th Conference on Retroviruses and Opportunistic Infections; 2004 Feb 8-11; San Francisco (CA)

119. Hanna G, Yan J-H, Fiske W, et al. Safety, tolerability, and pharmacokinetics of a novel, small molecule HIV-1 attachment inhibitor, BMS-488043, after single and multiple oral doses in healthy subjects [abstract no. 535]. 11th Conference on Retroviruses and Opportunistic Infections; 2004 Feb 8-11; San Francisco (CA)

120. Ferain O, Schols D, Bernard J, et al. ESN-196, a novel, small-molecule CCR5 agonist inhibits R5 HIV infection [abstract no. 738]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 3-6; Boston (MA)

121. Vangelista L, Secchi M, Lusso P. Rational design of novel HIV-1 entry inhibitors by RANTES engineering. Vaccine 2008 Jun 6; 26 (24): 3008-15

122. Kish-Catalone TM, Lu W, Gallo RC, et al. Preclinical evaluation of synthetic -2 RANTES as a candidate vaginal microbicide to target CCR5. Antimicrob Agents Chemother 2006 Apr; 50 (4): 1497-509

123. Abayneh SA, Ellmark P, Karlsson U, et al. Sensitivity of HIV type 1 primary isolates to human anti-CD40 antibody-mediated suppression is related to coreceptor use. AIDS Res Hum Retroviruses 2008 Mar; 24 (3): 447-52

124. Hendrix CW, Collier AC, Lederman MM, et al. Safety, pharmacokinetics, and antiviral activity of AMD3100, a selective CXCR4 receptor inhibitor, in HIV-1 infection. J Acquir Immune Defic Syndr 2004 Oct 1; 37 (2): 1253-62

125. Saag M, Rosenkranz S, Becker K, et al. Proof of concept of antireetroviral activity of AMD11070 (an orally administered CXCR4 entry inhibitor): results of the first dosing cohort A studied in ACTG protocol A5210 [abstract no. 512]. 14th Conference on Retroviruses and Opportunistic Infections; 2007 Feb 25-28; Los Angeles (CA)

126. Moyle GJ, DeJesus E, Boffito M, et al. CXCR4 antagonism: proof of activity with AMD11070 [abstract no. 511]. 14th Conference on Retroviruses and Opportunistic Infections; 2007 Feb 25-28; Los Angeles (CA)

127. Blanco J, Clotet-Codina I, Bosch B, et al. Multiparametric assay to screen and dissect the mode of action of anti-human immunodeficiency virus envelope drugs. Antimicrob Agents Chemother 2005 Sep; 49 (9): 3926-9

128. Moncunill G, Armand-Ugon M, Clotet-Codina I, et al. Anti-HIV activity and resistance profile of the CXC chemokine receptor 4 antagonist POL3026. Mol Pharmacol 2008 Apr; 73 (4): 1264-73

129. Yi Y, Shaheen F, Collman RG. Preferential use of CXCR4 by R5×4 human immunodeficiency virus type 1 isolates for infection of primary lymphocytes. J Virol 2005 Feb; 79 (3): 1480-6

130. Munch J, Standker L, Adermann K, et al. Discovery and optimization of a natural HIV-1 entry inhibitor targeting the gp41 fusion peptide. Cell 2007 Apr 20; 129 (2): 263-75

131. He Y, Cheng J, Lu H, et al. Potent HIV fusion inhibitors against enfuvirtide-resistant HIV-1 strains. Proc Natl Acad Sci U S A 2008 Oct 21; 105 (42): 16332-7

132. Delmedico M, Bray B, Cammack N, et al. Next generation HIV peptide fusion inhibitor candidates achieve potent, durable suppression of virus replication in vitro and improved pharmacokinetic properties [abstract no. 48]. 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8; Denver (CO)

133. Trimeris. Next generation fusion inhibitor program: TRI-1144 (TR-0291144) [online]. Available from URL: http://www.trimeris.com/300Pipeline.aspx [Accessed 2008 Nov 20]

134. He Y, Xiao Y, Song H, et al. Design and evaluation of sifuvirtide, a novel HIV-1 fusion inhibitor. J Biol Chem 2008 Apr 25; 283 (17): 11126-34

135. Li F, Goila-Gaur R, Salzwedel K, et al. PA-457: a potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing. Proc Natl Acad Sci U S A 2003 Nov 11; 100 (23): 13555-60

136. Adamson C, Salzwedel K, Castillo A, et al. Viral resistance to PA-457, a novel inhibitor of HIV-1 maturation [abstract no. 156]. 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8; Denver (CO)

137. Adamson C, Waki K, Ablan S, et al. Viral resistance to the HIV-1 maturation inhibitor bevirimat in the context of a protease that confers resistance to protease inhibitors [abstract no. 859]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 3-6; Boston (MA)

138. Stoddart CA, Joshi P, Sloan B, et al. Potent activity of the HIV-1 maturation inhibitor bevirimat in SCID-hu Thy/Liv mice. PLoS ONE 2007; 2 (11): e1251

139. Martin D, Ballow C, Doto J, et al. The safety, tolerability, and pharmacokinetics of multiple oral doses of PA-457, the first-in-class hiv maturation inhibitor, in healthy volunteers [abstract no. 551]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25; Boston (MA)

140. Martin D, Jacobson J, Schurmann D, et al. PA-457, the first-in-class maturation inhibitor, exhibits antiviral activity following a single oral dose in HIV-1-infected patients [abstract no. 159]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25; Boston (MA)

141. Kilgore N, Reddick M, Zuiderhof M, et al. The first-in-class maturation inhibitor, PA-457, is a potent inhibitor of HIV-1 drug-resistant isolates and acts synergistically with approved HIV drugs in vitro [abstract no. 509]. 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8; Denver (CO)

142. Lalezari J, McCallister S, Gigliotti M, et al. A phase 2 safety and efficacy study of bevirimat (BVM) in heavily treatment experienced HIV+ patients identifies the target phase 3 study profile [abstract no. H-891]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC

143. Martin DE, Wang-Smith L, Acosta EP, et al. Pharmacokinetics/pharmacodynamics of bevirimat (BVM) in a 14-day functional monotherapy trial in HIV-infected patients [abstract no. A-954]. 48th Annual ICAAC/IDSA Meeting; 2008 Oct 25-28; Washington, DC

144. Herzmann C, Cuthbertson Z, Fosdick L, et al. Long-term clinical and surrogate marker effects of subcutaneous intermittent interleukin-2 without antiretroviral therapy in HIV-infected patients. J Antimicrob Chemother 2008 Sep; 62 (3): 583-6

145. Molina JM, Levy Y, Fournier I, et al, for the ANRS 119-Interstart study team. Predictors of slow disease progression in ART-naive HIV-1-infected patients treated with IL-2: 3 year extended follow-up of the Interstart ANRS 119 trial [abstract no. 702]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)

146. Sanchez-Conde M, Lopez J, Rodriguez C, et al. Response to IL-2 in patients with immunodiscordant response to HAART is associated with long-term clinical benefit [abstract no. 705]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)

147. Copenhagen HIV Program. The ESPRIT trial [online]. Available from URL: http://www.cphiv.dk/ESPRIT/About/tabid/120/Default.aspx [Accessed 2008 Nov 21]

148. ESPRIT. Copenhagen ICC regional newsletter. ESPRIT No 14/SILCAAT No 8. Copenhagen: University of Copenhagen, 2008 Feb 22

149. National Institutes of Health Clinical Center. Interluekin-7 to treat HIV-infected people receiving antiretroviral treatment [ClinicalTrials.gov identifier NCT00105417]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]

150. Dropulic B, MacGregor RR, Humeau L, et al. Phase I clinical trial demonstrates safety and feasibility of autologous cellular therapy with lentiviral vector modified CD4 T cells expressing anti-HIV antisense in patients with HAART-resistant HIV-1 infection [abstract no. 552]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25; Boston (MA)

151. MacGregor RR. Clinical protocol: a phase 1 open-label clinical trial of the safety and tolerability of single escalating doses of autologous CD4 T cells transduced with VRX496 in HIV-positive subjects. Hum Gene Ther 2001 Nov 1; 12 (16): 2028-9

152. Lukashov V, Quinanes-Mateu M, McGarrity G, et al. Lentiviral delivered VRX496 long antisense sequences exerts molecular pressure on HIV-1 in human subjects [abstract no. 753a]. 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 8-11; Boston (MA)

153. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Trial of an anti-HIV-1 gene transfer product [ClinicalTrials.gov identifier NCT00074997]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]

154. Levine BL, Humeau LM, Boyer J, et al. Gene transfer in humans using a conditionally replicating lentiviral vector. Proc Natl Acad Sci U S A 2006 Nov 14; 103 (46): 17372-7

155. VIRxSYS Corporation. A rollover study for subjects who completed participation in the VRX496-USA-05-002 trial [ClinicalTrials.gov identifier NCT00622232]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]

156. University of Pennsylvania. Evaluate the tolerability and therapeutic effects of repeated doses of autologous T cells with VRX496 in HIV [ClinicalTrials.gov identifier NCT00295477]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]

157. VIRxSYS Corporation. Safety and efficacy of T cell genetic immunotherapy for HIV [ClinicalTrials.gov identifier NCT00131560]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 Nov 20]

158. Dayton AI. Within you, without you: HIV-1 Rev and RNA export [letter]. Retrovirology 2004; 1: 35

159. Ishaq M, Hu J, Wu X, et al. Knockdown of cellular RNA helicase DDX3 by short hairpin RNAs suppresses HIV-1 viral replication without inducing apoptosis. Mol Biotechnol 2008 Jul; 39 (3): 231-8

160. Rossi JJ, June CH, Kohn DB. Genetic therapies against HIV. Nat Biotechnol 2007 Dec; 25 (12): 1444-54

161. Perez EE, Wang J, Miller JC, et al. Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases. Nat Biotechnol 2008 Jul; 26 (7): 808-16

Correspondence: Dr *Mark Holodniy*, VA Palo Alto Health-Care System, 3801 Miranda Ave. (132), Palo Alto, CA 94304, USA.
E-mail: holodniy@stanford.edu