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Congress Report

Update on antiretroviral therapy

based on data presented at the 14th Conference on Retroviruses and Opportunistic Infections (CROI 2007)

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Abstract

The 14th Conference on Retroviruses and Opportunistic Infections (CROI 2007) took place in Los Angeles, California, on February 25-28, 2007. This scientifically focused meeting covered a variety of HIV-related topics, including molecular epidemiology, immunology, virology, pathogenesis and the treatment and prevention of HIV infection. This article summarizes important presentations related to antiretroviral therapy that were made at the meeting. Highlights included efavirenz-associated lipoatrophy, the anti-HIV activity of entecavir and phase III results for two novel first-in-class antiretroviral agents: maraviroc and raltegravir.

Introduction

The Conference on Retroviruses and Opportunistic Infections (CROI) is an important annual scientific meeting that brings together leading scientists and clinicians to present and discuss advances in the prevention and treatment of HIV infection and its complications. The 14th Conference on Retroviruses and Opportunistic Infections (CROI 2007) took place on February 25-28, 2007, in Los Angeles, California. This article focuses on presentations at the conference that deal directly with antiretroviral therapy. The author is solely responsible for the selection of topics and presentations included in this report. The report is not an endorsed activity of CROI 2007 itself.

FDA-approved antiretroviral drugs

ACTG 5142: metabolic outcome

ACTG 5142 was a randomized, open-label, prospective study that compared efavirenz (EFV)-based regimens to lopinavir/ritonavir (LPV/r)-based regimens, as well as to a nucleoside-sparing regimen of LPV/r plus EFV as first-line therapy (1). The nucleoside reverse transcriptase inhibitor (NRTI) backbone consisted of lamivudine (3TC) with zidovudine (ZDV), extended-release stavudine (d4T) or tenofovir disoproxil fumarate (TDF). The efficacy results from this study have previously been reported. Differences in metabolic outcome were reported at CROI 2007 (2).

The metabolic objectives were changes from baseline in fat (as measured by dual-energy X-ray absorbitometry, or DEXA) and changes in fasting lipids. These were measured at baseline, 48 weeks and 96 weeks. The analyses were intent to treat. The combination of EFV with LPV/r increased lipids significantly more than EFV or LPV/r alone with a nucleoside backbone. There were no significant differences between the EFV and LPV/r arms regarding changes in total cholesterol (TC), HDL and non-HDL lipids. However, the LPV/r arm had significantly larger increases in triglycerides (TG) than the EFV arm. A surprising finding was that the EFV arm had more lipoatrophy than the LPV/r or the LPV/r plus EFV arms. The explanation for this was not clear. The frequency of lipoatrophy was lowest in the NRTI-sparing arm of LPV/r plus EFV. As expected, the d4T arm was associated with larger increases in TG and a higher frequency of lipoatrophy compared to ZDV or TDF (Tables I and II).

Table I: 96-Week results of the metabolic outcome of ACTG 5142. Adopted from CROI 2007.

Week 96 results	n	Primary randomized arm		
		EFV	LPV	LPV/EFV
		Median value or %		
%Δ extremity fat	498	0.3	9.9	18
%Δ trunk fat	498	12	19	17
Lipoatrophy	498	32%	18%	8%
Δ TC (mg/dl)	517	33	33	57
Δ HDL (mg/dl)	508	9	8	16
Δ non-HDL (mg/dl)	506	21	26	43
Δ TG (mg/dl)	518	14	47	63

Table II: 96-Week results of the metabolic outcome of ACTG 5142. Adopted from CROI 2007.

Week 96 results	n	NRTI (LPV and EFV arms)		
		d4T	TDF	ZDV
		Median value or %		
%Δ extremity fat	329	–11	17	2.0
%Δ trunk fat	329	11	23	16
Lipoatrophy	329	43%	10%	27%
Δ TC (mg/dl)	343	41	21	33
Δ HDL (mg/dl)	334	8	8	9
Δ non-HDL (mg/dl)	333	26	17	26
Δ TG (mg/dl)	344	47	21	24

ACTG 5160

Initial viral clearance, also referred to as phase-1 decay half-life, is one way of comparing the potency of different regimens. ACTG 5160 was a substudy of ACTG 5142 that compared the initial viral clearance of the three ACTG 5142 regimens in 68 participants (50% female) to evaluate gender differences and to determine the relationship of initial viral clearance to longer term virological responses (3). Initial viral clearance was significantly shorter for EFV than for LPV (1.1 days *vs.* 1.3 days; $p = 0.03$). Overall, initial viral clearance was not different by gender ($p = 0.14$); however, within the LPV arm, women had slower clearance than men (1.7 days *vs.* 1.1 days; $p = 0.03$). Viral clearance at day 7 (VLC7) was greater for EFV than the other 2 arms and predicted week 48 virological outcome.

DAUFIN study

Current HIV treatment guidelines recommend EFV or boosted protease inhibitor (PI)-based regimens with a nucleoside backbone as preferred first-line regimens (4). Nevirapine (NVP) is an alternative to EFV in these guidelines. The DAUFIN study, a randomized, open-label, multicenter, noninferiority trial, compared two regimens; group 1 (n=35) received ZDV/3TC 300/150 mg and NVP 200 mg twice daily, and group 2 (n=36) received 3TC 300 mg, TDF 245 mg and NVP 400 mg once daily (5). Participants were antiretroviral-naïve HIV-infected patients with CD4 cell counts below 350 mm^3 (men) or 250 mm^3 (women).

Viral rebound occurred in 10 patients, 9 of them in group 2. Six of these patients had K65R. Non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations were also noted: 5 patients had 2 or 3 mutations and 7 patients had Y181C/A. Failing patients had higher HIV RNA and lower CD4 cell counts at baseline. Virological failures could not be explained by lower trough plasma NVP concentrations.

Although the once-a-day 3TC/TDF/NVP combination in naïve HIV-infected patients is associated with a high rate of virological failure (9/36 = 25%), the combination of 3TC/TDF/EFV once daily in treatment-naïve patients has been highly effective. The 903 study, a prospective, randomized, double-blind trial, compared the regimens of TDF (n=299) or d4T (n=303) in combination with 3TC and EFV (6). Forty-seven (16%) of 299 patients in the TDF group failed treatment. The K65R mutation emerged in 8 patients on the TDF arm through 144 weeks and was always accompanied by resistance to EFV or EFV plus 3TC. The rapidity and the magnitude of failure in the DAUFIN study appear to be greater than those observed in study 903. Could this be a reflection of differences in potency between NVP and EFV?

Entecavir

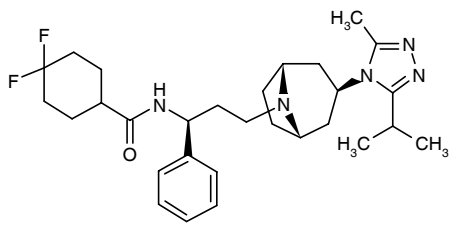
Entecavir is a nucleoside analogue anti-hepatitis B virus (HBV) drug that was previously thought not to have activity against HIV. Based on this assumption, current HBV/HIV co-infection treatment guidelines recommend entecavir for the treatment of HBV in those HIV-infected patients who do not require treatment of their HIV infection (4). New and surprising information was provided at CROI that should change these recommendations. McMahon and colleagues from Johns Hopkins University observed a 1 $\log_{10}$ decline in HIV-1 RNA in 2 HIV/HBV co-infected patients receiving entecavir monotherapy (7). Subsequent investigations using *in vitro* infective assays

showed that entecavir inhibited HIV replication with an IC_{50} of 0.1-1 nM. Additional analysis demonstrated accumulation of the M184V mutation in 96% of the clones from patient samples at 6 months after entecavir monotherapy. Real-time PCR showed that entecavir inhibits HIV replication at or before the reverse transcription step. Entecavir has *in vitro* and *in vivo* activity against HIV. Thus, its use as monotherapy in HIV/HBV-co-infected patients can no longer be recommended.

New antiretroviral agents

Results from a number of important clinical trials of new antiretroviral drugs were presented at CROI 2007. We report on several of these new antiretroviral agents that are relatively advanced in their clinical development and thus may be of more immediate interest.

Maraviroc



Maraviroc (MVC) is a CCR5 antagonist with *in vitro* activity against R5- but not XR4- or dual-tropic HIV-1 strains. Planned interim 24-week analyses of two ongoing, double-blind, placebo-controlled, parallel phase IIb/III studies of MVC in antiretroviral treatment-experienced HIV-infected adults were presented at CROI 2007 (8, 9). These studies were designated MOTIVATE (**M**araviroc Plus **O**ptimized Background **T**herapy **i**n **V**iremic, **A**RT-**E**xperienced Patients) 1 and 2 and were conducted in North America (MOTIVATE 1), as well as Europe and Australia (MOTIVATE 2). Eligible participants were triple antiretroviral class-experienced with detectable viremia of > 5000 copies/ml, had only R5 virus based on baseline screening using the Trofile assay, and were randomized 1:2:2 to receive placebo, once-daily MVC 300 mg or twice-daily MVC 300 mg. An optimized background therapy (OBT) was selected by the treating physician. The dose of MVC was reduced to 150 mg if the OBT contained PIs (except tipranavir) or delavirdine. Participants were further stratified by enfuvirtide use or by an HIV-1 RNA value > or < 100,000 copies/ml.

Results are shown in Tables III and IV. Overall, similar results were noted for once- and twice-daily MVC arms. However, in a combined analysis, a larger proportion of patients with no active drug in OBT achieved HIV-1 RNA of < 50 copies/ml in the b.i.d. MVC arms compared to once-daily MVC or placebo arms (29% *vs.* 18% *vs.* 3%). No differences in reductions in HIV-1 RNA were noted with analyses of stratification whether patients did or did not receive enfuvirtide or with baseline high *vs.* low HIV-1 RNA values. Adverse events were similar in all arms. Specifically, no increased risk of lymphoma or other malignancies was observed.

Maraviroc was recently recommended for accelerated approval by an FDA advisory committee. It represents a welcome addition to the antiretroviral armamentarium, although its optimal role in antiretroviral therapy remains to be defined. Chemokine receptor inhibitors are the first antiretroviral drugs that target host proteins rather than viral targets. While the apparent absence of any significant sequelae among individuals with congenital deficits in chemokine receptors (*e.g.*, CCR5Δ32 homozygotes) provides some reassurance that the therapeutic use of

Table III: Results from the MOTIVATE 1 trial.

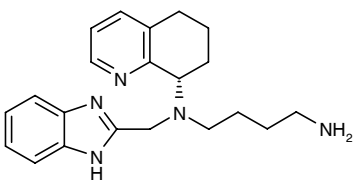
	Placebo	MVC (once daily)	MVC (twice daily)	Comments
n	118	232	235	
Baseline CD4 count (median)	163	168	150	
Baseline HIV-1 RNA (mean; log_{10} copies/ml)	4.84	4.85	4.86	
Proportion of patients with enfuvirtide in OBT	42%	43%	46%	
Proportion of patients with 2 or less active drugs in OBT	66.1%	68.5%	75.7%	
Mean change in HIV-1 RNA (log_{10} copies/ml) from baseline to 24 weeks	–1.03	–1.82	–1.95	
Mean change in CD4 count (cells/mm^3) from baseline to 24 weeks	+52	+107	+111	$p < 0.0001$ *vs.* placebo for each MVC arm
Proportion of patients with HIV-1 RNA < 400 copies/ml	31.4%	54.7%	60.4%	$p < 0.0001$ *vs.* placebo for each MVC arm
Proportion of patients with HIV-1 RNA < 50 copies/ml	24.6%	42.2%	48.5%	$p < 0.0006$ for once-daily MVC *vs.* placebo; $p < 0.0001$ for b.i.d. MVC *vs.* placebo

Table IV: Results from the MOTIVATE 2 trial.

	Placebo	MVC (once daily)	MVC (twice daily)	Comments
n	91	182	191	
Baseline CD4 count (median)	174	174	182	
Baseline HIV-1 RNA (mean; log_{10} copies/ml)	4.89	4.87	4.84	
Proportion of patients with enfuvirtide in OBT	45%	37%	39%	
Proportion of patients with 2 or less active drugs in OBT	66.0%	62.6%	62.3%	
Mean change in HIV-1 RNA (log_{10} copies/ml) from baseline to 24 weeks	–0.93	–1.95	–1.97	
Mean change in CD4 count (cells/mm^3) from baseline to 24 weeks	+64	+112	+102	$p < 0.0001$ *vs.* placebo for each MVC arm
Proportion of patients with HIV-1 RNA < 400 copies/ml	23.1%	55.5%	61.3%	$p < 0.0001$ *vs.* placebo for each MVC arm
Proportion of patients with HIV-1 RNA < 50 copies/ml	20.9%	45.6%	40.8%	$p < 0.0001$ *vs.* placebo for each MVC arm

chemokine receptor inhibitors will similarly be benign, the long-term safety of CCR5 inhibition has yet to be proven. Recent reports that homozygous CCR5Δ32 is a strong host genetic risk factor for symptomatic laboratory-confirmed West Nile virus infection further fuels safety concerns (10). Similarly, while initial concerns regarding the emergence of X4 virus during treatment with an R5 antagonist have been somewhat allayed by experience to date, widespread use may resurrect these fears. Additionally, the clinical use of MVC, in particular in treatment-experienced patients, appears to require pretreatment screening with a tropism assay. This may strain already stretched financial resources. Finally, resistance to R5 antagonists is incompletely understood.

AMD-11070



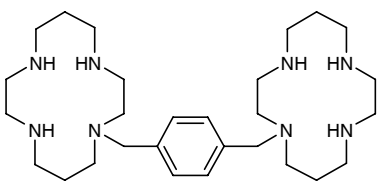
AMD-11070 is a first-in-class, orally bioavailable small-molecule antagonist of the HIV co-receptor CXCR4. It is a substrate of cytochrome P-450 (CYP) 3A4. In healthy volunteers, the concentrations of both CYP3A4 and CYP2DE probe drugs were increased, suggesting that it inhibits these metabolic pathways (11).

The X4 Antagonist Concept Trial (XACT) investigated the safety and efficacy of AMD-11070 monotherapy for 10 days in 10 patients who were treatment-naïve or had gone at least 14 days without antiretroviral therapy (13). Study entry criteria also included HIV-1 RNA > 5000 copies/ml and evidence of X4 virus. Nine of the 10 patients had dual R5 and X4 virus. AMD-11070 was dosed as monotherapy twice daily for 10 days. Four patients met the primary endpoint of > 1 log_{10} reduction in X4.

The activity of AMD-11070 was also investigated in ACTG A5210, a dose-escalating, open-label study in patients with HIV-1 RNA > 5000 copies/ml who had been off antiretroviral therapy for at least 14 days at study entry and had evidence of X4 virus (13). Six patients were administered 200 mg orally twice daily for 10 days. Reductions of 1 log_{10} or more in X4 virus were seen in 3 of the 6 subjects.

Both XACT and ACTG A5210 provide proof of concept for the activity of AMD-11070 against X4 virus. However, the drug's development has been placed on clinical hold by the FDA due to liver histology changes observed in preclinical toxicity experiments.

AMD-3100 (plerixafor)



.8HCl

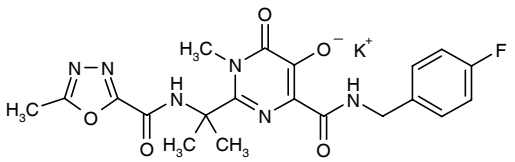
.2H_2O

AMD-3100 is another X4 inhibitor that was previously shown in a phase I/II study to reduce X4 virus only in patients with a pure X4 virus population (14). Fransen and colleagues evaluated 15 patients with dual- or mixed-tropic virus from the phase I/II study to further characterize the response to AMD-3100 in these virus populations (15). They identified two groups of virus populations: one group (designated suppressor; n=11) showed a lower level of luciferase activity on X4 cells and a higher proportion of R5-tropic variants than the second group (non-suppressor group; n=4) at baseline. At day 11, most subjects in the suppressor group experienced > 5-fold reductions in CXCR4 infectivity and 8 of the 11 subjects

became R5-tropic. In contrast, no changes in CXCR4 infectivity were observed in the nonsuppressor group. However, no significant viral load reductions were observed in any subject from either group. The authors concluded that dual-tropic viruses exhibit considerable variation in their efficiency of co-receptor use and that AMD-3100 has the ability to inhibit certain dual-tropic variants *in vivo.*

CXCR4 inhibitors lag far behind CCR5 inhibitors in their progress through the development process, although proof of concept for the activity of such drugs has been obtained. While investigations are under way on the safety of AMD-11070 and the efficacy of AMD-3100 against dual-tropic viruses is still in question, the development of additional candidate X4 inhibitor drugs would be welcome. The susceptibility of dual-tropic viruses to CXCR4 and CCR5 inhibitors also requires more comprehensive study.

Raltegravir

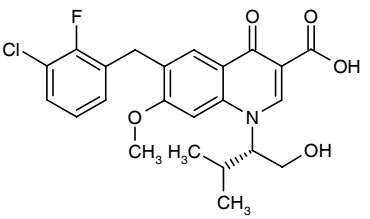


Raltegravir, formerly known as MK-0518, is an integrase inhibitor that was previously shown to confer significant virological benefit to antiretroviral-naïve HIV-infected patients, as well as heavily treatment-experienced patients with triple class-resistant HIV (16). Sixteen-week data from two ongoing double-blind, placebo-controlled, parallel phase III studies, designated BENCHMRK-1 and -2, were presented at CROI 2007 (17, 18) (Table V). BENCHMRK-1 was conducted in Europe, Asia and the Pacific, and Peru, while BENCHMRK-2 was conducted in North, Central and South America. Eligible participants were those failing antiretroviral therapy with triple antiretroviral class resistance and were randomized 2:1 to raltegravir 400 mg twice daily or placebo. An OBT was selected by the treating physicians. Select investigational drugs (*e.g.*, darunavir) were permitted as part of OBT.

Superior efficacy for the raltegravir arms over placebo was maintained regardless of baseline CD4 count, HIV-1 RNA values, as well as genotypic and phenotypic scores in the OBT. Adverse events were similar between groups.

Raltegravir has shown impressive efficacy in both antiretroviral-naïve and treatment-experienced patients. While its approval by the FDA is eagerly anticipated, its optimal role in the sequencing of antiretroviral therapy remains to be well defined.

Elvitegravir



Elvitegravir, formerly known as GS-9137, is an investigational integrase inhibitor that previously demonstrated significant HIV-1 RNA reductions in a phase I monotherapy study (19). Twenty-four-week data from an ongoing phase II noninferiority study in heavily treatment-experienced patients were presented at CROI 2007 (20) (Table VI). Eligibility criteria for the study were HIV-1 RNA > 1000 copies/ml and at least one PI mutation. Participants were further stratified by baseline enfuvirtide use and randomized 1:1:1:1 to one of four groups: elvitegravir 20 mg, elvitegravir 50 mg, elvitegravir 125 mg or comparator ritonavir-boosted PI (CPI/r). Elvitegravir was always dosed once daily with 100 mg of ritonavir. Interim analysis at week 8 showed poor virological response for the elvitegravir 20 mg group, which was then terminated. Darunavir and tipranavir were allowed in the elvitegravir arms after week 8 once studies were completed demonstrating a lack of significant drug-drug interactions. Fewer patients discontinued therapy because of adverse events in the elvitegravir arms *vs.* the comparator arm. No dose relationship was observed for treatment-emergent grade 3 or 4 adverse events or laboratory abnormalities in the elvitegravir arms.

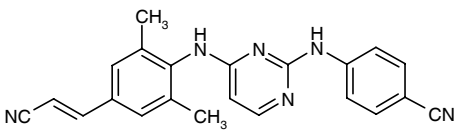
Table V: Results from the BENCHMRK 1 and 2 trials.

	BENCHMARK1		BENCHMRK2	
	Placebo	Raltegravir	Placebo	Raltegravir
n	118	232	119	230
Baseline CD4 count (mean)	153	156	163	146
Baseline HIV-1 RNA (mean; $\log_{10}$ copies/ml)	4.5	4.6	4.7	4.7
Mean change in CD4 count (cells/mm^3) from baseline to 16 weeks	+31	+83	+40	+86
Proportion of patients with HIV-1 RNA < 400 copies/ml	41%	77%	43%	77%
Proportion of patients with HIV-1 RNA < 50 copies/ml	33%	61%	36%	62%

Table VI: 24-Week results from a phase II noninferiority trial of elvitegravir and comparator ritonavir-boosted protease inhibitor (CPI/r).

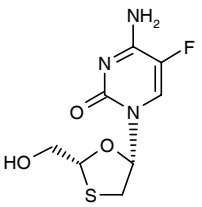
	CPI/r	Elvitegravir 50 mg	Elvitegravir 125 mg
n	63	71	73
Baseline CD4 count (mean)	158	243	157
Baseline HIV-1 RNA (mean; $\log_{10}$ copies/ml)	4.54	4.47	4.71
Median PI mutations	11	10	11
Proportion of patients with first-time enfuvirtide use in OBT	19%	24%	26%
Proportion of patients with no active drugs in OBT	51.0%	49%	48%
Mean change in HIV-1 RNA ($\log_{10}$ copies/ml) from baseline to 24 weeks	–1.2	–1.4	–1.7 (p = 0.01 *vs.* CPI/r)
Mean change in CD4 count (cells/mm^3) from baseline to 16 weeks	+28	+52	+61
Proportion of patients with at least 1 log HIV-1 RNA decrease at week 24	61%	91% (p < 0.0001 *vs.* CPI/r)	92% (p < 0.0001 *vs.* CPI/r)
Proportion of patients with at least 2 log HIV-1 RNA decrease at week 24	51%	69% (p < 0.06 *vs.* CPI/r)	76% (p < 0.005 *vs.* CPI/r)
Proportion of patients with HIV-1 RNA < 50 copies/ml at 16 weeks	30%	38%	40%

Rilpivirine



Rilpivirine (TMC-278) is an investigational NNRTI with activity against both wild-type and resistant HIV isolates. A previous randomized, double-blind, placebo-controlled phase IIa monotherapy study demonstrated a significant reduction in HIV-1 RNA in antiretroviral-naïve patients (21). Forty-eight-week data from a partially blinded phase IIb dose-ranging study were presented at CROI 2007 (22). Antiretroviral treatment-naïve patients with HIV-1 RNA values > 5000 copies/ml and without NNRTI resistance mutations were randomized to receive EFV or three doses of rilpivirine (25, 75 or 150 mg) once daily. The NRTI backbone for all four arms consisted of either ZDV/3TC or TDF/emtricitabine and was assigned by the treating physicians. Baseline median CD4 counts were similar for all arms: 200 for rilpivirine and 207 for the EFV group. Baseline median HIV-1 RNA values were also comparable: 4.84 $\log_{10}$ copies/ml for the rilpivirine arms and 4.88 $\log_{10}$ copies/ml for the EFV arm. 48-Week results are shown in Table VII. The 75-mg dose has been selected for further development.

Racivir



Racivir (RCV) is a cytosine nucleoside analogue with activity against HIV and HBV. A previous phase I study had provided preliminary antiviral activity data for RCV in combination with d4T and EFV for 2 weeks (23). Results of a study conducted to determine the activity of RCV in patients infected with HIV containing the M184V mutation were reported at CROI (24). Forty-two such patients were randomized to receive either RCV (n=26) in place of 3TC or to continue with 3TC (n=16) in a double-blind manner for 28 days of blinded treatment. After 28 days, the change in mean HIV-1 RNA was 0.13 $\log_{10}$ in the 3TC group and –0.4 $\log_{10}$ in the RCV group (p = 0.0004). Those patients who had < 3 thymidine analogue mutations in addition to the M184V mutation appeared to have an even better virological response, with a mean HIV-1 RNA change of –0.7 $\log_{10}$ (p = 0.0002) and 28% achieving < 400 copies/ml.

If these results hold true and no significant safety concerns emerge, racivir may have an important role to play

Table VII: 48-Week results from a phase IIb dose-ranging trial of rilpivirine and efavirenz (EFV).

	Rilpivirine 25 mg	Rilpivirine 75 mg	Rilpivirine 150 mg	EFV
n	93	95	91	89
Proportion of patients with HIV-1 RNA < 50 copies/ml (ITT)	81%	80%	77%	81%
Proportion of patients with HIV-1 RNA < 50 copies/ml (observed)	92%	89%	96%	93%
Virological failure	9%	5%	7%	6%
Mean increase in CD4 cell count (cells/mm^3)	125	145	143	127

as part of a nucleoside backbone in second-line antiretroviral regimens.

Summary

CROI continues to be an important venue for the presentation and dissemination of cutting-edge HIV-related clinical and basic science data. At CROI 2007, the greatest excitement was generated by presentations on maraviroc and raltegravir. These two drugs represent two novel antiretroviral classes and have the potential to change the prevailing treatment paradigm of combining two nucleoside analogue reverse transcriptase inhibitors with a PI or an NNRTI as the cornerstone of highly active antiretroviral therapy (HAART).

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