Drugs of the Future 2008, 33(6): 551-555

CCC: 0377-8282/2008

Meeting Report

Advances in antiretroviral therapy

Based on data presented at the 15th Conference on Retroviruses and Opportunistic Infections (CROI), February 3-6, 2008

Zelalem Temesgen
Division of Infectious Diseases, Mayo Clinic, Rochester, MN 55905, USA. Correspondence: temesgen.zelalem@mayo.edu

CONTENTS

Abstract 551
Introduction 551
First-line antiretroviral therapy 551
Treatment-experienced patients 552
Investigational agents 554
References 555

Abstract

Advances continue to be made in the field of antiretroviral therapy. New agents are progressing through various stages of preclinical and clinical development. New studies add to our understanding of how best to use the antiretroviral agents that are already available for clinical use. This article reports on antiretroviral therapy-related presentations made at the 15th Conference on Retroviruses and Opportunistic Infections (CROI 2008) which took place on February 3-6, 2008 in Boston, Massachusetts.

Introduction

The Conference on Retroviruses and Opportunistic Infections (CROI) brings together leading HIV scientists and clinicians to present and discuss advances in the prevention and treatment of HIV infection and its complications. The 15th Conference on Retroviruses and Opportunistic Infections (CROI 2008) took place on February 3-6, 2008 in Boston, Massachusetts. This article focuses on presentations at the conference that directly dealt with antiretroviral therapy (ART). The author is solely responsible for the selection of topics and presentations to be included in this report. The report is not an endorsed activity of CROI itself.

First-line antiretroviral therapy

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents currently recommends efavirenz (EFV) or ritonavir-boosted lopinavir (LPV/r), ritonavir-boosted fosamprenavir (FPV/r), or ritonavir-boosted atazanavir (ATV/r) as the preferred "third component" or "anchor drug" in addition to the nucleoside reverse transcriptase inhibitor (NRTI) backbone of either fixed-dose tenofovir/emtricitabine (TDF/FTC) or fixed-dose abacavir/lamivudine (ABC/3TC) as the preferred agents for the treatment of HIV-1 infection in antiretroviral-naïve patients (1). At CROI 2008, two important studies that directly compared components of first-line antiretroviral regimens were presented.

HEAT study

The HEAT study is the first head-to-head comparison of the efficacy and safety of TDF/FTC and ABC/3TC as components of a first-line antiretroviral treatment regimen (2). HEAT was a randomized (1:1), double-blind, placebo-matched, 96-week, multicenter phase IV study that enrolled 688 ART-naïve HIV-infected patients with HIV-1 RNA ≥ 1000 copies/ml and randomized them to TDF/FTC or ABC/3TC groups, each group also receiving open-label once-daily LPV/r. HLA-B*5701 screening was not performed. At 48 weeks, ABC/3TC was noninferior to TDF/FTC when combined with once-daily LPV/r. However, median CD4 cell increases at 48 weeks differed between the two groups and favored the ABC/3TC group. Both regimens were comparable in their rates of drug-related adverse events (Table I).

CASTLE study

CASTLE is the first head-to-head comparison of the efficacy and safety of ATV/r and LPV/r as components of a first-line antiretroviral treatment regimen (3). It is a randomized, open-label, multicenter, 96-week study to assess noninferiority that randomized 883 treatment-naïve patients to either ATV/r 300 mg/100 mg once daily or LPV/r 400 mg/100 mg twice daily, both in combination with fixed-dose TDF/FTC once daily. At 48 weeks, ATV/r demon-

Table I: HEAT: Select baseline data and 48-week results.

	ABC/3TC + LPV/r (n = 343)	TDF/FTC + LPV/r (n = 345)
Median plasma HIV-1 RNA (log_{10} copies/ml)	4.90	4.84
% with HIV-1 RNA ≥ 100,000 copies/ml	45%	41%
Median $CD4^+$ cells/mm^3	214	193
HIV-1 RNA < 50 copies/ml at 48 weeks (ITT)	68%	67%
HIV-1 RNA < 50 copies/ml at 48 weeks (observed)	84%	87%
HIV-1 RNA < 400 copies/ml at 48 weeks (ITT)	75%	71%
HIV-1 RNA < 400 copies/ml at 48 weeks (observed)	94%	92%
Median $CD4^+$ cell increase at 48 weeks from baseline (cells/mm^3)	+201	+173
Drug-related grade 2-4 adverse events	154 (45%)	152 (44%)
Suspected ABC HSR toxicity	14 (4%)	3 (1%)
Proximal renal tubular dysfunction	0	3 (1%)

ABC, abacavir; 3TC, lamivudine; LPV/r, ritonavir-boosted lopinavir; TDF, tenofovir; FTC, emtricitabine; ITT, intent-to-treat population; HSR, hypersensitivity.

strated similar virological and immunological efficacy to LPV/r. Fewer gastrointestinal-related adverse events were seen with ATV/r. Patients receiving ATV/r also had a significantly better lipid profile compared to LPV/r (Table II).

Treatment-experienced patients

Three new antiretroviral drugs (maraviroc, etravirine, raltegravir) have been approved in recent months for the treatment of patients who have failed multiple previous antiretroviral regimens and have developed multiclass-resistant HIV virus. The pivotal studies that led to the approval of these drugs have been either previously published or presented. However, additional efficacy and safety analyses were presented at CROI 2008.

MOTIVATE studies

The MOTIVATE (**M**araviroc plus **O**ptimized background **T**herapy **i**n **V**iremic, **A**R**T**-**E**xperienced patients) 1 and 2 studies are two parallel double-blind, placebo-controlled phase IIb/III studies of maraviroc (MVC) in antiretroviral treatment-experienced HIV-infected adults. A combined analysis of final 48-week data from MOTIVATE 1 and 2 was presented at CROI 2008 (4).

One thousand forty-nine patients with triple-class experience or triple-class resistance, R5 virus and HIV-1 RNA ≥ 5000 copies/ml were randomized 2:2:1 to MVC once or twice daily + optimized background therapy (OBT), or placebo + OBT. Patients whose OBT contained a PI (except tipranavir) or delavirdine received a dose of 150 mg of MVC; all other patients received a dose of 300 mg. At 48 weeks, the MVC + OBT groups had superior virological and immunological efficacy compared to the placebo + OBT group. Discontinuations due to adverse events, serious adverse events and laboratory abnormalities were comparable among treatment groups (Table III).

BENCHMRK studies

Raltegravir (RAL) is the first in a novel class of antiretroviral drugs known as integrase inhibitors. It was approved by the U.S. Food and Drug Administration (FDA) in October 2007 for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. BENCHMRK-1 and -2 are two identical double-blind, placebo-controlled, parallel, pivotal phase III studies that evaluated the efficacy and safety of RAL plus an OBT in patients with triple-class-resistant HIV-1 virus. Sixteen-week results for the individual studies, as well as combined 24-week data, have previously been reported (5-7). Follow-up results presented at CROI 2008 confirmed that the superior virological and immunological responses noted with RAL + OBT compared to OBT alone were sustained out to 48 weeks (8, 9) (Table IV).

DUET studies

Etravirine (ETR) is a newly approved non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent activity against HIV resistant to first-generation NNRTIs. DUET-1 and -2 are two randomized, double-blind, placebo-controlled, parallel, multinational phase III trials that assessed the long-term efficacy and safety of ETR in treatment-experienced HIV-1-infected patients. Patients were randomized to receive ETR 200 mg twice daily or

Table II: CASTLE: Select baseline data and 48-week results.

	ATV/r + TDF/FTC (n = 440)	LPV/r + TDF/FTC (n = 443)
Median baseline plasma HIV-1 RNA (log_{10} copies/ml)	5.01	4.96
Median baseline $CD4^+$ cells/mm^3	205	204
HIV-1 RNA < 50 copies/ml at 48 weeks (ITT)	78%	76%
HIV-1 RNA < 400 copies/ml at 48 weeks (ITT)	86%	82%
Median $CD4^+$ cell increase at 48 weeks from baseline (cells/mm^3)	+203	+219
Drug-related grade 2-4 diarrhea	2%	11%
Grade 3-4 aminotransferase elevations	2%	2%
% with TC:HDL > 5	12	20
Mean change from baseline in fasting TC	12%	24%
Mean change from baseline in fasting LDL cholesterol	12%	15%
Mean change from baseline in fasting HDL cholesterol	27%	32%
Mean change from baseline in fasting total non-HDL cholesterol	7%	21%
Mean change from baseline in fasting TG	13%	51%

ATV/r, ritonavir-boosted atazanavir; TDF, tenofovir; FTC, emtricitabine; LPV/r, ritonavir-boosed lopinavir; ITT, intent-to-treat population; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

Table III: MOTIVATE 1 and 2: Select 48-week results.

	MVC once daily + OBT (n = 414)	MVC twice daily + OBT (n = 426)	Placebo + OBT (n = 209)
Mean change in HIV-1 RNA from baseline (log_{10} copies/ml)	–1.68	–1.84	–0.78
% with HIV-1 RNA < 50 copies/ml	43.2%*	45.5%*	16.7%
% with HIV-1 RNA < 400 copies/ml	51.7%*	56.1%*	22.5%
Mean change in $CD4^+$ from baseline (cells/mm^3)	+116*	+124*	+61
Discontinuations due to adverse events	24 (5.8%)	21 (4.9%)	11 (5.3%)
Deaths	6 (1.4%)	9 (2.1%)	2 (1.0%)

MVC, maraviroc; OBT, optimized background therapy; *P < 0.0001 *vs.* placebo.

Table IV: BENCHMRK-1 and -2: 48-Week results.

	BENCHMRK-1		BENCHMRK-2	
	RAL + OBT (n = 232)	Placebo + OBT (n = 118)	RAL + OBT (n = 230)	Placebo + OBT (n = 119)
Proportion of patients with HIV-1 RNA < 50 copies/ml	65%	31%	60%	34%
Proportion of patients with HIV-1 RNA < 400 copies/ml	74%	36%	71%	38%
Mean change in HIV-1 RNA (log_{10} copies/ml) from baseline	–1.7	–0.7	–1.8	–0.9
Mean change in $CD4^+$ count (cells/mm^3) from baseline	+120	+49	+98	+40
Deaths	1.3%	2.5%	3%	2.5%
All-cause adverse events	90.9%	84.7%	89.6%	91.6%

RAL, raltegravir; OBT, optimized background therapy.

placebo. All patients also received ritonavir-boosted darunavir and investigator-selected NRTIs. Enfuvirtide use was at the discretion of the individual investigator. Twenty-four-week results have previously been published and demonstrated that ETR led to better virological suppression than did placebo in treatment-experienced patients with NNRTI resistance (10, 11). Forty-eight-week results were reported at CROI 2008 and confirmed the sustained superior virological and immunological responses with ETR compared to placebo in this treatment-experienced population (12) (Table V).

Investigational agents

Vicriviroc

Vicriviroc (VCV) is a CCR5 chemokine receptor antagonist currently in clinical development. In a previous phase IIb study (ACTG 5211), at doses of 10 and 15 mg once daily in combination with OBT, VCV was associated with sustained efficacy in treatment-experienced patients (13).

VICTOR E-1 is a double-blind, placebo-controlled phase II trial that compared VCV at doses of 20 and 30 mg once daily to placebo in CCR5-tropic HIV-infected patients experienced with at least three classes of ART (14). Each arm of the trial also had an OBT that contained at least three drugs, including a new ritonavir-boosted protease inhibitor. At 48 weeks, VCV at 20 and 30 mg once daily demonstrated superior antiviral efficacy over OBT alone (Table VI). The most stringent criteria for efficacy, *i.e.*, efficacy in those that had HIV-1 RNA > 100,000 copies/ml and no active drugs in OBT, favored VCV 30 mg once daily (Table VII). No clinically significant differences in the safety profile between the VCV and placebo groups were noted, including hepatotoxicity, opportunistic infections, malignancies or other conditions. Thus, the dose of 30 mg once daily was chosen as the dose that will be used in phase III clinical trials of VCV.

Table V: DUET-1 and -2: 48-Week results.

	DUET-1		DUET-2	
	ETR + OBT (n = 304)	Placebo + OBT (n = 308)	ETR + OBT (n = 230)	Placebo + OBT (n = 119)
Proportion of patients with HIV-1 RNA < 50 copies/ml	60%	39%	61%	41%
Proportion of patients with HIV-1 RNA < 400 copies/ml	71%	47%	72%	48%
Mean change in HIV-1 RNA (log_{10} copies/ml) from baseline	–2.29	–1.52	–2.2	–1.5
Mean change in $CD4^+$ count (cells/mm^3) from baseline	+103	+74	+94	+72

ETR, etravirine; OBT, optimized background therapy.

Table VI: VICTOR E-1: Select baseline data and 48-week results.

	VCV 30 mg + OBT (n = 39)	VCV 20 mg + OBT (n = 40)	Placebo + OBT (n = 35)
Mean baseline plasma HIV-1 RNA (log_{10} copies/ml)	4.5	4.5	4.6
Mean baseline $CD4^+$ cells/mm^3	202.2	202.1	226.1
% with baseline HIV RNA > 100,000 copies/ml	31%	30%	27%
Prior AIDS-defining event	46%	50%	35%
HIV-1 RNA < 50 copies/ml at 48 weeks (ITT)	56%	52%	14%
HIV-1 RNA < 400 copies/ml at 48 weeks (ITT)	67%	60%	26%
Median $CD4^+$ cell increase at 48 weeks from baseline (cells/mm^3)	+102	+136	+63
Mean change from baseline in HIV-1 RNA (log_{10} copies/ml)	–1.77	–1.75	–0.80
Drug-related grade 3-4 adverse events	21%	20%	20%

VCR, vicriviroc; OBT, optimized background therapy; ITT, intent-to-treat population.

Table VII: VICTOR E-1: Subgroup analysis of study participants with HIV-1 RNA < 50 copies/ml at week 48.

	VCV 30 mg + OBT (n = 39)	VCV 20 mg + OBT (n = 40)	Placebo + OBT (n = 35)
Baseline HIV-1 RNA ≥ 100,000 copies/ml	4/12 (33%)	2/12 (17%)	1/10 (10%)
Baseline HIV-1 RNA < 100,000 copies/ml	18/27 (67%)	19/28 (68%)	4/25 (16%)
≥ 3 active drugs in OBT	5/7 (71%)	5/6 (83%)	0/6
1-2 active drugs in OBT	14/22 (64%)	15/26 (58%)	5/22 (23%)
0 active drugs in OBT	2/7 (29%)	1/8 (12%)	0/7

VCV, vicriviroc; OBT, optimized background therapy.

References

1. Department of Health and Human Services (DHHS) Panel on Clinical Practices for Treatment of HIV Infection: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. January 29, 2008. http:\\www.aidsinfo.nih.org. Accessed 05/15/2008.

2. Smith, K., Fine, D., Patel, P. et al. *Efficacy and safety of abacavir/lamivudine compared to tenofovir/emtricitabine in combination with once-daily lopinavir/ritonavir through 48 weeks in the HEAT study*. 15th Conf Retroviruses Opportunistic Infect (CROI) (Feb 3-6, Boston) 2008, Abst 774.

3. Molina, J.M., Andrade-Villanueva, J., Echevarria, J. et al. *Efficacy and safety of once-daily atazanavir/ritonavir compared to twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine in ARV-naive HIV-1-infected subjects: The CASTLE study, 48-week results*. 15th Conf Retroviruses Opportunistic Infect (CROI) (Feb 3-6, Boston) 2008, Abst 37.

4. 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.* 15th Conf Retroviruses Opportunistic Infect (CROI) (Feb 3-6, Boston) 2008, Abst 792.

5. Cooper, D., Gatell, J., Rockstroh, J. et al. *Results of BENCHMRK-1, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus.* 14th Conf Retroviruses Opportunistic Infect (CROI) (Feb 25-28, Los Angeles) 2007, Abst 105aLB.

6. Steigbigel, R., Kumar, P., Eron, J. et al. *Results of BENCHMRK-2, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus.* 14th Conf Retroviruses Opportunistic Infect (CROI) (Feb 25-28, Los Angeles) 2007, Abst 105bLB.

7. Kumar, P., Cooper, D., Steigbigel, R. et al. *Efficacy of raltegravir, an HIV integrase inhibitor, in combination with regimens containing enfuvirtide, darunavir, or tipranavir in patients with triple-class resistant virus: Combined results from Benchmrk-1 and Benchmrk-2.* Eur AIDS Conf (Oct 24-27, Madrid) 2007, Abst P7.2/06.

8. Cooper, D.A., Gatell, J., Rockstroh, J. et al. *48-Week results from BENCHMRK-1, a phase III study of raltegravir in patients failing ART with triple-class resistant HIV-1*. 15th Conf Retroviruses Opportunistic Infect (CROI) (Feb 3-6, Boston) 2008, Abst 788.

9. Steigbigel, R., Kumar, P., Eron, J. et al. *48-Week results from BENCHMRK-2, a phase III study of raltegravir in patients failing ART with triple-class resistant HIV.* 15th Conf Retroviruses Opportunistic Infect (CROI) (Feb 3-6, Boston) 2008, Abst 789.

10. Madruga, J.V., Cahn, P., Grinsztejn, B. et al. *Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-Week results from a randomised, double-blind, placebo-controlled trial*. Lancet 2007, 370(9581): 29-38.

11. Lazzarin, A., Campbell, T., Clotet, B. et al. *Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-Week results from a randomised, double-blind, placebo-controlled trial.* Lancet 2007, 370(9581): 39-48.

12. Haubrich, R., Cahn, P., Grinsztejn, B. et al. *DUET-1: Week 48 results of a phase III randomized double-blind trial to evaluate the efficacy and safety of etravirine (ETR; TMC125) versus placebo in 612 treatment-experienced HIV-1-infected patients.* 15th Conf Retroviruses Opportunistic Infect (CROI) (Feb 3-6, Boston) 2008, Abst 790.

13. 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*. 4th IAS Conf HIV Pathog Treat Prevent (July 22-25, Sydney) 2007, Abst TUAB102.

14. 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*. 15th Conf Retroviruses Opportunistic Infect (CROI) (Feb 3-6, Boston) 2008, Abst 39LB.