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MEETING REPORT

DEVELOPMENTS IN ANTIRETROVIRAL THERAPY BASED ON DATA PRESENTED AT THE 17TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI) (FEBRUARY 16-19, 2010, SAN FRANCISCO)

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SUMMARY

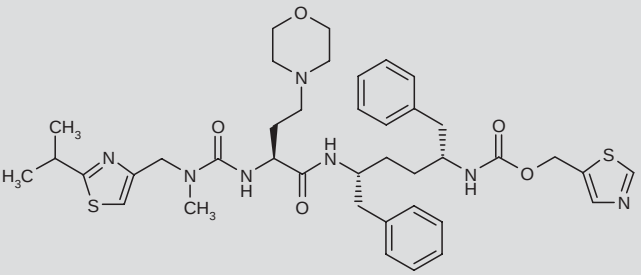
The 17th Conference on Retroviruses and Opportunistic Infections (CROI 2010) took place on February 16-19, 2010 in San Francisco, California. As in previous years, CROI brought together basic scientists and clinicians to discuss the current status and advances in various aspects of HIV medicine. This article focuses on presentations at the conference that directly deal with antiretroviral therapy. The author is solely responsible for the selection of topics and presentations to be included in this report. This report is not an endorsed activity of CROI itself.

NEW DRUGS

Unlike previous years, there were not many presentations on drugs in the antiretroviral development pipeline at CROI 2010. Nevertheless, new drugs in previously identified classes of antiretrovirals, as well as novel drug targets, continue to be investigated and evaluated.

Cobicistat

Cobicistat is a newly developed cytochrome P450 (CYP) 3A inhibitor that has previously demonstrated CYP3A inhibition similar to ritonavir 100 mg, and had no anti-HIV activity at concentrations up to 90 µM (1). Elvitegravir is an investigational integrase inhibitor currently in phase III clinical development (2). A newly developed four-drug, once-a-day, fixed-drug, single tablet containing elvitegravir, cobicistat, tenofovir and emtricitabine was compared to the already licensed three-drug, one-pill, once-a-day tablet Atripla® containing efavirenz, tenofovir and emtricitabine in a double-blind phase II study that randomized 71 antiretroviral therapy (ART)-naïve patients (ClinicalTrials.gov Identifier NCT00869557) (3). Forty-eight patients were randomized to the quad pill arm; 23 were randomized to the Atripla® arm. At 24 weeks, in an intent-to-treat analysis, the fixed-drug cobicistat/elvitegravir/tenofovir/emtricitabine regimen was noninferior to the Atripla® regimen in the proportion of patients who achieved viral suppression below 50 copies/mL. Increases in CD4 counts were similar. Serious adverse events (AEs) were uncommon. As expected, there were more central nervous system (CNS) side effects in the Atripla® arm.



Cobicistat

Another double-blind, randomized phase II study (ClinicalTrials.gov Identifier NCT00892437) compared ritonavir-boosted atazanavir to cobicistat-boosted atazanavir, with a nucleoside backbone of teno-

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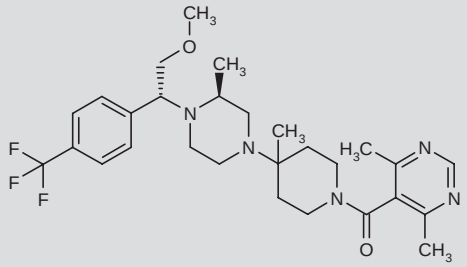


Vicriviroc

fovir/emtricitabine in each arm (3). Randomization was 2:1, with 50 patients in the cobicistat arm and 29 patients in the ritonavir arm. At 24 weeks, in an intent-to-treat analysis the proportion of patients with virological suppression below 50 copies/mL was similar in both arms. Serious AEs were uncommon across arms and the rate of hyperbilirubinemia was also comparable in both arms.

Vicriviroc

Vicriviroc is an investigational chemokine CCR5 receptor antagonist in phase III clinical development. Pooled analysis of 48-week data from two identical double-blind, placebo-controlled trials was presented at CROI 2010 (4). These trials, VICTOR-E3 and VICTOR-E4, compared the safety and efficacy of vicriviroc plus an optimized background regimen (OBR) (n = 486) to that of OBR plus placebo (n = 235) in patients who had documented resistance to at least two antiretroviral classes and had CCR5-tropic virus only. OBR was required to contain a ritonavir-boosted protease inhibitor and at least two fully active drugs. Non-nucleoside reverse transcriptase inhibitors, with the exception of etravirine, were excluded. At 48 weeks, in a modified intent-to-treat analysis, the proportion of patients who achieved viral suppression below 50 copies/mL was similar in both arms (64% vs. 62%; $P = 0.06$). The mean CD4 cell count increases from baseline were also similar between the two arms. The investigators ascribed the lack of superior virological efficacy of vicriviroc plus OBR over OBR alone to the higher proportion (64%) of patients with more than three active agents in the OBR. There were no significant differences in AEs between the two arms, including the incidence of malignancies.

Cenicriviroc mesylate

Cenicriviroc mesylate (TBR-652) is an investigational CCR5 receptor antagonist in early clinical development. The first study of cenicriviroc mesylate in HIV-infected individuals was presented at CROI 2010. The antiviral activity, safety and tolerability of cenicriviroc mesylate were evaluated in a double-blind, placebo-controlled, randomized, dose-escalating study (5, 6). Ten HIV-infected, antiretroviral treatment-experienced patients with CCR5-only virus received 25, 50 or 75 mg cenicriviroc mesylate or placebo for 10 days. HIV-1 RNA was measured from baseline through day 11 and showed a clear dose–response, with all patients receiving 75 mg achieving a viral load reduction of at least 1 $\log_{10}$. The most commonly reported AEs were headache, nausea, constipation, diarrhea and sinusitis. Studies are under way to explore the top of the dose–response curve using doses of 100 and 150 mg once daily of cenicriviroc mesylate.

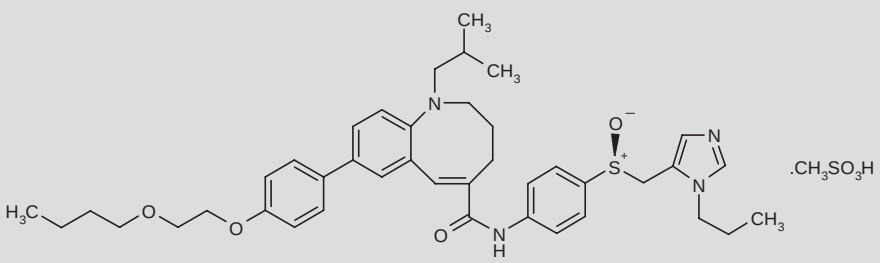
ALREADY APPROVED DRUGS

New data regarding the efficacy and safety of drugs that have already been approved and are in clinical use also continue to be reported and refine our approach to the treatment of HIV infection.

Once-daily darunavir in treatment-experienced patients

The inhibitory effect of protease inhibitors on CYP, and thus on each other's metabolism, has led to the routine use of ritonavir to pharmacokinetically enhance a second protease inhibitor, allowing for reduction in dosing frequency and less pill burden (7). The reduction in dosing frequency has allowed once-a-day dosing for some protease inhibitors, including darunavir, fosamprenavir and lopinavir. However, once-a-day administration of these protease inhibitors had been, to date, limited to the treatment of antiretroviral-naïve patients. This was primarily due to concern that treatment-experienced patients need to achieve higher concentrations of drugs to overcome resistance.

The randomized, open-label phase IIIb ODIN trial compared the efficacy, safety and tolerability of once-daily ritonavir-boosted darunavir, DRV/r 800/100 mg (n = 294), to twice-daily ritonavir-boosted darunavir, DRV/r 600/100 mg (n = 296), in adult HIV-1-infected patients who were treatment-experienced but without darunavir/ritonavir resistance-associated mutations (8). The background regimen was optimized and contained at least two nucleo-



Cenicriviroc mesylate

side/nucleotide reverse transcriptase inhibitors. The two arms were comparable in their baseline characteristics, including age, mean viral load, median CD4 cell count, previous antiretroviral experience, susceptibility to protease inhibitors and nucleoside/nucleotide reverse transcriptase inhibitors. At week 48, in an intent-to-treat/time-to-loss of virological response (ITT-TLOVR) analysis, once-daily DRV/r 800/100 mg was noninferior to twice-daily DRV/r 600/100 mg; the proportion of patients who achieved viral suppression below 50 copies/mL was similar in both arms (72.1% vs. 70.9%). CD4 cell count increases from baseline were also comparable. Lipid abnormalities were significantly higher with twice-daily DRV/r 600/100 mg. The incidence of lipid elevations with once-daily DRV/r was approximately half that of twice-daily DRV/r.

ACTG 5202

A phase IIIb, randomized, four-arm study (ClinicalTrials.gov Identifier NCT00118898) compared the nucleoside backbones abacavir/lamivudine (ABC/3TC) versus tenofovir/emtricitabine (TDF/FTC) in a blinded fashion, with open-label efavirenz (EFV) or atazanavir/ritonavir (ATV/r) as the third drug for each arm. Eligible patients were HIV-infected, ART-naïve men and women with HIV-1 RNA > 1,000 copies/mL. Study participants were also stratified by screening HIV RNA values (< vs. > 100,000 copies/mL). The primary endpoint for efficacy was time to virological failure (confirmed HIV-1 RNA ≥ 1,000 copies/mL at 16-24 weeks or ≥ 200 copies/mL at 24 weeks). The primary endpoint for safety was time to first grade 3/4 AE. The mean baseline CD4 count was 230 cells/mm^3. The median baseline HIV-1 RNA value was 4.7 $\log_{10}$ copies/mL. Approximately 40% of study participants had HIV-1 RNA ≥ 100,000 copies/mL at study entry.

A scheduled interim analysis found a significantly shorter time to virological failure among patients with baseline HIV-1 RNA ≥ 100,000 copies/mL in the ABC/3TC arms compared to the TDF/FTC arms and prompted unblinding of the nucleoside backbones for patients with baseline HIV-1 RNA ≥ 100,000 copies/mL (9). These patients were offered an opportunity to switch therapy. Data from further analysis of these patients indicated that, in patients entering this clinical trial with screening HIV-1 RNA values > 100,000 copies/mL, there was a significantly shorter time to virological failure and grade 3/4 AEs among those randomized to ABC/3TC compared with TDF/FTC (10).

Those patients with baseline HIV-1 RNA values < 100,000 copies/mL continued the study for a median follow-up of 138 weeks. Final data from these participants were presented at CROI 2010 (11). In this study population, ABC/3TC and TDF/FTC with either ATV/r or EFV resulted in similar rates of viral suppression to < 50 copies/mL. There was no significant difference in time to virological failure. CD4 cell increases were also comparable across arms. At virological failure, more treatment-emergent drug resistance mutations were noted with EFV compared to ATV/r, with either ABC/3TC or TDF/FTC. In addition, there were differences noted regarding safety. When combined with EFV as the third drug, there was a significantly shorter time to the first grade 3/4 event with ABC/3TC compared to TDF/FTC. This difference was not observed when the third drug was ATV/r. There was also a significantly shorter time to treatment modification with ABC/3TC compared to TDF/FTC, regardless of whether EFV or ATV/r was the third drug. Total cholesterol, LDL and HDL cholesterol levels were significantly higher with ABC/3TC compared to TDF/FTC, regardless of assignment to EFV or ATV/r. Similarly, total cholesterol, LDL and HDL cholesterol levels were significantly higher with EFV compared to ATV/r, irrespective of the accompanying nucleoside/nucleotide backbone.

Another trial evaluated bone loss and body fat changes in a subset of 269 patients participating in the above-mentioned clinical trial (ClinicalTrials.gov Identifier NCT00118898) (12). The primary endpoints were changes in lumbar spine and hip bone mineral density as measured by dual-energy x-ray absorptiometry (DEXA) and the presence of lipoatrophy at week 96. Lipoatrophy was defined as ≥ 10% loss of limb fat from baseline. All four regimens resulted in an initial bone loss with subsequent stabilization after week 48. TDF/FTC resulted in greater bone mineral density loss in hip and lumbar spine than ABC/3TC. Similarly ATV/r resulted in greater bone mineral density loss than efavirenz in the lumbar spine only. Fractures were similarly distributed among study arms.

As regards lipoatrophy, there was no significant difference in increases of limb and trunk fat among patients randomized to TDF/FTC or ABC/3TC. The proportion of patients with lipoatrophy was not significantly different between TDF/FTC and ABC/3TC or between EFV and ATV/r. However, ATV/r recipients experienced a greater gain in limb fat and trunk fat than those receiving EFV.

TREATMENT INTENSIFICATION STUDIES

Intensification of ART in patients already virologically suppressed is being studied for its potential for reducing HIV RNA in sanctuary sites and reducing immune activation. In the case of maraviroc and enfuvirtide, intensification studies have also investigated the potential use of maraviroc to increase the CD4 cell count in those patients who are virologically suppressed but with a suboptimal CD4 cell count gain following antiretroviral therapy. The general characteristics and results of intensification studies presented at CROI 2010 are detailed in Table I. The studies vary in design and the populations examined. The effects of intensification on reducing viremia or immune activation are at best inconclusive. Intensification of ART with either enfuvirtide or maraviroc did not result in any significant increases in CD4 cell counts.

ANTIRETROVIRAL DRUG LEVELS IN GENITAL SECRETIONS

HIV pre-exposure prophylaxis (PrEP), the concept of administering antiretroviral drugs to individuals not infected with HIV in an attempt to prevent the transmission of HIV, is an area of intense investigation at the present time. Tenofovir disoproxil fumarate has been the leading candidate in current studies exploring the feasibility of PrEP. Other antiretroviral drugs are also being studied for their potential use in this HIV prevention approach. An important component of these studies is determining the concentration of individual antiretroviral drugs. Besides PrEP, determining the concentration of antiretroviral drugs in genital secretions is of interest as part of studies looking into penetration of drugs in various "sanctuary" sites and whether that has additional clinical benefit beyond the virological suppression noted in plasma. Results from studies addressing the penetration of three recently approved antiretroviral drugs were reported at CROI 2010 (Table II).

Table I. *Antiretroviral therapy intensification studies presented at CROI 2010.*

Study (author)	Study objective	Study design	Number of participants	Results
Yukl, S. et al. PLUS study group (13)	Reductions in HIV RNA and in immune activation in the gut	HIV+ men with viral load < 40 copies/mL for 3-12 years and a CD4 count > 200. 12-Week intensification with raltegravir alone (n = 4), raltegravir plus efavirenz (n = 2), or raltegravir plus ritonavir-boosted darunavir	7	Intensification reduced HIV RNA, reduced immune activation and increased $CD4^+$ T cells in the ileum
Wiegand, A. et al. (14)	Reductions in low-level persistent viremia in patients currently virologically suppressed but with a prior history of virological failure	30-Day intensification with raltegravir	8	Raltegravir intensification did not lower the level of persistent viremia
Joly, V. et al. ANRS130 (15)	To analyze the effect of intensification with enfuvirtide on the CD4 cell count response at week 24	Antiretroviral therapy-naïve HIV-infected patients receiving TDF/FTC in combination with lopinavir/ritonavir or enfuvirtide, randomized to enfuvirtide or not	194	The addition of enfuvirtide resulted in a more rapid virological response but did not improve immunological outcome
Evering, T. et al. (16)	To study the effect of intensification with maraviro on immune reconstitution and immune activation	Subjects on antiretroviral therapy for an average of 4 years, randomized to intensification with maraviroc for 24 weeks or intensification with NRTI for 12 weeks, followed by crossover to maraviroc for 12 weeks	6	Intensification with maraviroc did not result in any significant effect on a variety of immunological and virological parameters in the gut-associated lymphoid tissue
Gutiérrez, C. et al. (17)	To study the effect of intensification with maraviroc on latent reservoir and immune activation	Patients virologically suppressed for at least 2 years, CD4 count > 350 cells/mm^3 and demonstrated CCR5-tropism. 12 Weeks of intensification with maraviroc	9	Maraviroc appeared to accelerate the decay of the HIV latent reservoir and decrease the activation of CD4 and CD8 cells
Wilkin, T. et al. ACTG 5256 (18)	To study the effect of intensification with maraviroc on CD4 counts in patients with suboptimal CD4 recovery	Subjects with a CD4 count < 250/μL and undetectable plasma HIV-1 RNA for the 48 weeks preceding study entry. 24-Week intensification with maraviroc	34	Intensification with maraviroc was not associated with an increase in CD4 counts; however, it was associated with decreased immune activation

NRTI, nucleoside reverse transcriptase inhibitor.

Table II. *Studies on concentrations of antiretroviral drugs in genital secretions presented at CROI 2010.*

Study/author	Study drug	Study population	Body fluid sampled	Results
Clavel, C. et al. (19)	Raltegravir	HIV-infected women on a stable raltegravir-containing ART with plasma HIV-RNA < 40 copies/mL for at least 3 months	Cervicovaginal fluid, blood	Concentrations of raltegravir in cervicovaginal fluid were about 2.3-fold those in blood plasma; median concentration was approximately 16-fold higher than the IC_{95} against wild-type HIV-1
Bonora, S. et al. (20)	Raltegravir	8 Healthy male volunteers receiving raltegravir 400 mg twice daily for 4 days plus a single dose on day 5	Seminal fluid, blood	Semen:blood plasma ratio 1.62, 2-4 h after intake; semen:blood plasma ratio 6.45 at the end of dosing interval

Continued

Table II. *Cont. Studies on concentrations of antiretroviral drugs in genital secretions presented at CROI 2010.*

Study/author	Study drug	Study population	Body fluid sampled	Results
Lambert-Niclot, S. et al. (21)	Darunavir	HIV-infected men receiving darunavir/ritonavir (600/100 mg twice daily) either as monotherapy or with two NRTIs after a 10-week run-in period of triple ART	Seminal fluid, blood	Median darunavir concentration in seminal fluid was similar to the free blood plasma fraction of darunavir; median darunavir concentration in seminal fluid was approximately 6-fold higher than the EC_{50} of darunavir corrected for protein binding against wild-type HIV-1 (~55 ng/mL)
Taylor, S. et al. (22)	Darunavir	HIV-infected men on stable darunavir-containing ART	Seminal fluid, blood (time-matched samples)	Darunavir concentrations in seminal fluid 10-20% of the concentrations achieved in blood plasma at the same time point after drug ingestion; darunavir concentrations in seminal fluid above the protein-corrected EC_{50} values for wild-type HIV; one-third of all seminal fluid darunavir concentrations exceeded the protein-corrected EC_{50} values required to inhibit HIV resistant to protease inhibitors
Tiraboschi, J.M. et al. (23)	Maraviroc	Adult HIV-1 antiretroviral-experienced patients receiving maraviroc-containing ART for at least 1 month	Cerebrospinal fluid (CSF), seminal fluid, blood	Median maraviroc CSF:plasma concentration ratio 0.022 (0.004-0.173); median maraviroc seminal fluid:plasma concentration ratio 0.723 (0.244-4.449)

ART, antiretroviral therapy; NRTIs, nucleoside reverse transcriptase inhibitors.

CONCLUSIONS

Incremental knowledge continues to be gained in the field of HIV medicine. Treatment approaches continue to be refined. The first coformulated product containing a non-ritonavir pharmacokinetic enhancer is progressing through clinical evaluation; the relative concentrations of antiretroviral drugs in various body fluids and components and their implications have not yet been fully elucidated. The Conference on Retroviruses and Opportunistic Infections continues to be an important venue for the dissemination of ongoing basic science and clinical research findings and observations regarding HIV infection, its treatment and prevention.

DISCLOSURES

Dr. Temesgen is a member of the scientific advisory board of Merck-Gilead. The author has received research grants from Pfizer and Roche, and education grants from Tibotec and Gilead.

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