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MEETING REPORT

PROGRESS IN THE TREATMENT OF HIV INFECTION

BASED ON DATA PRESENTED AT THE XVIII INTERNATIONAL AIDS CONFERENCE (JULY 18-23, 2010, VIENNA)

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SUMMARY

The International AIDS Conference continues to be a forum for the dissemination of important and relevant scientific information on the treatment and management of HIV infection. The most important information from AIDS 2010 was the results of the microbicide CAPRISA 004 trial. After years of negative results, we finally have the proof that impacting the transmission of HIV through a woman-controlled, biomedical intervention is possible. This is huge progress and further developments in microbicides, as well as preexposure prophylaxis, are eagerly awaited. The antiretroviral development pipeline does not appear to be as robust as in recent years. However, it seems very likely that clinicians will have available another one-pill, once-daily treatment option in the near future with continued development of rilpivirine. Several reports from this conference highlight our continued attempts to refine HIV treatment strategies. While the results are mostly preliminary, mixed and not ready for immediate clinical application, treatment options for those who could not tolerate a certain class of antiretroviral drugs have certainly expanded and one can expect further paradigm shifts in the future in the composition of antiretroviral treatment regimens.

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INTRODUCTION

The XVIII International AIDS Conference (AIDS 2010), convened by the International AIDS Society (IAS), took place on July 18-23, 2010, in Vienna, Austria. AIDS 2010 was attended by approximately 20,000 participants from 193 countries. As in previous years, its agenda was broad, featuring 248 sessions that included policy and programmatic topics, as well as scientific research. This report focuses on findings presented at the conference that directly deal with novel antiretroviral drugs, as well as novel strategies and mechanisms of action. The author is solely responsible for the selection of topics and presentations to be included in this report.

MICROBICIDES

The results of CAPRISA 004, a randomized, placebo-controlled, double-blind study evaluating the efficacy and safety of tenofovir gel as a microbicide, were arguably the most important news that came out of AIDS 2010. The study was conducted in Kwa Zulu Natal, South Africa, in 18- to 40-year-old, sexually active, nonpregnant women without HIV infection (N = 889), who were randomized to receive tenofovir gel or placebo gel. These gels appeared identical and were also dispensed in identical packaging. Participating women were instructed to insert 1 dose of gel within 12 h before sex and a second dose of gel as soon as possible within 12 h after sex and no more than 2 doses of gel in a 24-h period. There were no significant differences at enrollment in the demographics or sexual behavior of women in the two study arms. Participants were provided with risk reduction counseling, condoms, reproductive health services and treatment of sexually transmitted infections at enrollment and at monthly follow-up visits. HIV status, safety and sexual behavior, as well as gel and condom use, were also assessed at these visits. A total of 889 women were enrolled and followed up for 30 months (total of 1,341 women-years, mean follow-up of 18 months). Thirty-eight women in the tenofovir gel arm and 60 women in the placebo gel arm acquired HIV infection during the study. The HIV incidence

rate in the tenofovir gel arm was 5.6 per 100 women-years compared with 9.1 per 100 women-years in the placebo gel arm (incidence rate ratio = 0.61; confidence interval [CI]: 0.40-0.94; *P* = 0.017). Thus, tenofovir gel reduced HIV infection by an estimated 39% (1, 2). Adherence estimates were based on applicator returns and did not significantly differ between the two arms. However, the protective effective of tenofovir was higher (54%) in those with high adherence (defined as > 80% gel adherence). In those women who acquired HIV infection while receiving tenofovir gel, there were no tenofovir-related or thymidine analogue resistance mutations detected. There were no significant differences in the frequency of adverse events or pregnancy outcomes between the two arms.

NEW ANTIRETROVIRAL DRUGS

Data on only a limited number of investigational antiretroviral drugs were presented at AIDS 2010.

Cenicriviroc mesylate (TBR-652)

Cenicriviroc mesylate is an investigational chemokine receptor CCR5 antagonist that also has activity against CCR2. CCR2 is a chemokine receptor found on the cell surface of monocytes, dendritic cells and memory T cells. It is believed to play an important role in inflammation and is being studied in a variety of inflammation-associated diseases, including the metabolic syndrome and atherosclerosis. Monocyte chemoattractant protein 1 (MCP-1) is the primary ligand for CCR2. Cenicriviroc has a favorable pharmacokinetic profile, with a plasma $t_{1/2}$ of 35-40 h that supports once-daily dosing. In HIV infection, previous studies have reported good antiviral activity at doses ranging from 25 to 75 mg daily (3, 4).

The results of study TBR-652-2-201, a randomized, double-blind, placebo-controlled, dose-escalating study to assess the antiviral activity, safety and tolerability of cenicriviroc monotherapy were reported at AIDS 2010 (5). Study participants (N = 54) were HIV-infected individuals who were antiretroviral therapy-experienced but had not had treatment for at least 6 weeks before entering the study. Additional inclusion criteria included CCR5-tropic virus by Trofile-ES assay, a CD4 cell count ≥ 250 cells/mm^3 and HIV-1 RNA ≥ 5,000 copies/mL. Study participants received 25, 50, 75, 100 or 150 mg of cenicriviroc or placebo orally once daily for 10 days. Antiviral activity was monitored by changes in HIV-1 RNA, and CCR2 activity was measured by changes in the levels of MCP-1, high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) levels from baseline. The most commonly reported adverse events were headache, nausea, fatigue and diarrhea. There were no study drug-related serious adverse events, discontinuations or deaths. All cenicriviroc dose levels had a statistically significantly larger effect on HIV-1 RNA compared to placebo. The largest median change in HIV-1 RNA from baseline was noted in those participants receiving 75 mg of cenicriviroc daily. There was also a dose-dependent effect on MCP-1 (Table I).

S/GSK-1349572

S/GSK-1349572 is an investigational integrase inhibitor in early clinical development. Similar to raltegravir and elvitegravir, it blocks the strand transfer step of integration of the HIV genome into the host cell DNA. Previous studies have documented its potent short-term antiviral activity in HIV-1-infected individuals (6), as well as in vitro activity against known raltegravir-resistant clinical isolates from patients experiencing virological failure while being treated with raltegravir (7). Results from two phase IIb clinical trials of S/GSK-1349572, one in antiretroviral treatment-naive and the other in those with raltegravir-resistant virus, were reported at AIDS 2010.

SPRING-1 is a randomized, dose-ranging phase IIb study of S/GSK-1349572 in antiretroviral therapy-naive HIV-infected adults. Two hundred and five study participants with screening plasma HIV-1 RNA ≥ 1,000 copies/mL were randomized 1:1:1:1 to once-daily S/GSK-1349572 10, 25 or 50 mg or efavirenz 600 mg with either coformulated tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC). The 16-week results were reported at AIDS 2010 (8). Time to HIV RNA < 50 copies/mL was shorter for those receiving S/GSK-13249572 than for those in the efavirenz arm (*P* < 0.001 for each S/GSK-13249572 arm vs. efavirenz). This rapid antiviral effect is consistent with what has been observed with raltegravir and elvitegravir. More adverse events were reported in patients in the efavirenz arm (Table II). Additionally, the mean change from baseline in low-density lipoprotein (LDL) cholesterol was lower among S/GSK-1349572-treated subjects than efavirenz-treated subjects (+0.066 mmol/L vs. +0.436 mmol/L, respectively).

Table I. *TBR-652-2-201: selected baseline characteristics and study results.*

	TBR-652 25 mg (n = 9)	TBR-652 50 mg (n = 7)	TBR-652 75 mg (n = 9)	TBR-652 100 mg (n = 10)	TBR-652 150 mg (n = 9)	Placebo (n = 10)
Median baseline HIV-1 RNA (log_{10} copies/mL)	4.2	4.5	4.6	4.4	4.0	4.2
Median baseline CD4 cell count (cells/mm^3)	415	456	442	449	503	495
Median HIV-1 RNA change from baseline (log_{10} copies/mL)	–0.7 (*P* = 0.002 vs. placebo)	–1.7 (*P* < 0.001 vs. placebo)	–1.8 (*P* < 0.001 vs. placebo)	–1.4 (*P* < 0.001 vs. placebo)	–1.7 (*P* < 0.001 vs. placebo)	–0.3
Median MCP-1 change from baseline (pg/mL)	25	56 (*P* < 0.02 vs. placebo)	36	74 (*P* < 0.02 vs. placebo)	322 (*P* < 0.02 vs. placebo)	0
Any adverse events	4	3	0	5	8	3

Table II. *SPRING-1: selected baseline characteristics and 16-week study results.*

	S/GSK-1349572 10 mg (n = 53)	S/GSK-1349572 25 mg (n = 51)	S/GSK-1349572 50 mg (n = 51)	Efavirenz (n = 50)
Mean baseline HIV-1 RNA (log_{10} copies/mL)	4.42	4.38	4.58	4.46
Mean baseline CD4 cell count (cells/mm^3)	309	334	327	328
Proportion of HIV-1 RNA < 50 copies/mL (%)	96	92	90	60
Median increase in CD4 cell count from baseline (cells/mm^3)	153	176	160	116
Discontinuations for adverse events	0	2	0	8

The VIKING study (ING112961) is a phase IIb study that explored the activity of S/GSK-1349572 in HIV-infected individuals with raltegravir-resistant HIV (9). Study participants (N = 27) were antiretroviral therapy-experienced (median of 17 antiretroviral drugs in the past) adult subjects with screening plasma HIV-1 RNA ≥ 1,000 copies/mL and with documented genotypic resistance to raltegravir, as well as resistance to at least two other antiretroviral therapy classes. The median fold changes in susceptibility compared to wild-type at baseline were 161 (0.57- > 166) for raltegravir and 1.46 (0.55-35) for S/GSK-1349572. Study participants received S/GSK-1349572 at a dose of 50 mg once daily in addition to their failing regimen (but without raltegravir) for 11 days. On day 11, the background regimen was optimized and S/GSK-1349572 continued. In general, S/GSK-1349572 was well tolerated, with diarrhea and insomnia being the most frequent adverse events. By days 11, 21 and 27 study participants achieved the primary endpoint of decline in plasma HIV-1 RNA < 400 copies/mL or ≥ 0.7 log_{10} copies/mL from baseline. This effect on plasma HIV-1 RNA was dependent on the type of raltegravir-associated mutations present at baseline. None of the participants who had the signature Q148 mutation plus 2 or more additional mutations responded to treatment (0 of 5), while all the participants with single N155H, Y143H or Q148 mutations (16 of 16), as well as 3 of the 4 participants who had the Q148 mutation plus only 1 additional mutation responded to treatment with S/GSK-1349572. Similarly, the fold change for S/GSK-1349572 at baseline was a predictor of subsequent response to S/GSK-1349572. Only 2 patients experienced an increase in fold change for S/GSK-1349572 from baseline to day 11: 1 from 6.49 to 38 and the other from 21 to 40 (10).

Rilpivirine

Rilpivirine, previously known as TMC-278, is an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI) in advanced clinical development. Pooled 48-week results from two pivotal phase III studies of rilpivirine were presented at AIDS 2010.

TMC278-C209 (ECHO) was a randomized phase III study comparing the safety and efficacy of rilpivirine 25 mg once daily to efavirenz 600 mg once daily, both in combination with tenofovir and emtricitabine. Study participants were 690 HIV-infected, antiretroviral treatment-naive individuals with baseline HIV-1 RNA ≥ 5,000 copies/mL, with virus susceptible to nucleoside analogue reverse transcriptase inhibitors (NRTIs) and no NNRTI resistance-associated mutations at baseline. Study participants were also stratified by baseline HIV-1 RNA above or below 100,000 copies/mL. TMC278-C215 (THRIVE) had an identical design to the ECHO study, with the primary difference being that investigators were allowed to select the nucleoside backbone themselves from tenofovir/emtricitabine, abacavir/lamivudine and zidovudine/lamivudine. Participants of the THRIVE study were then stratified according to the selected nucleoside backbone.

At 48 weeks, the combination of rilpinavir and NRTIs was noninferior to the combination of efavirenz and NRTIs in the proportion of patients with HIV-1 RNA < 50 copies/mL (11). This noninferiority was not affected by baseline HIV-1 RNA values above or below 100,000 copies/mL. However, virological failure was more common in the rilpivirine arms. Analysis of resistance data in those who failed treatment showed that treatment-emergent NNRTI resistance-associated mutations were noted in 63% of the rilpivirine and 54% of the efavirenz arms. Furthermore, 90% of patients who developed resistance to rilpivirine were also resistant to etravirine. Rilpivirine was better tolerated and had a more favorable effect on lipid parameters than efavirenz. There were significantly fewer adverse events in the rilpivirine arms, including rash and neuropsychiatric adverse events. The rate of grade 3/4 abnormalities in total and LDL cholesterol, as well as triglycerides, was higher in the efavirenz arms (Table III).

Rilpivirine is also being developed as part of a fixed-dose product coformulated with tenofovir and emtricitabine. Results of a study evaluating the bioequivalence of the three-drug fixed-dose product to the coadministration of the individual components were reported at AIDS 2010. In this randomized, single-dose, open-label phase I study, pharmacokinetic parameters were calculated from serial blood samples from 36 healthy adults under fed conditions. All pharmacokinetic parameters met the criteria for bioequivalence (12).

CLASS-SPARING STRATEGIES

Attempts to further fine-tune antiretroviral treatment with the goal of lessening the pill burden, as well as toxicity, continue to be of interest to the HIV-treating community. These attempts have employed a variety of approaches, including initiating a regimen in treatment-naive patients without the inclusion of the traditional nucleoside backbone; an induction/maintenance, simplification strategy in patients virologically suppressed on a conventional three-drug, two-class regimen; as well as a monotherapy approach with ritonavir-boosted protease inhibitors. A number of clinical trials exploring such strategies were presented at AIDS 2010 and will be briefly reviewed below.

Table III. *ECHO and THRIVE studies: select baseline characteristics and 48-week outcomes.*

	Rilpivirine arms (n = 686)	Efavirenz arm (n = 682)
Median baseline HIV-1 RNA (log_{10} copies/mL)	5.0	5.0
Median baseline CD4 cell count (cells/mm^3)	249	260
Proportion of HIV-1 RNA < 50 copies/mL (%)	84.3	82.3
Mean increase in CD4 cell count from baseline (cells/mm^3)	192	176
Treatment failure (%)	9.0	4.8
Rash (%)	3.1 ($P < 0.0001$)	13.6
Psychiatric adverse events (%)	14.9 ($P = 0.0002$)	22.7
Neurological adverse events (%)	17.1 ($P < 0.0001$)	37.8
Grade 3/4 total cholesterol (%)	0.1	2.5
Grade 3/4 LDL cholesterol (%)	0.7	4.1
Grade 3/4 triglycerides (%)	0.3	2.2

Nucleoside-sparing strategy

Three studies that explored the utility of an NRTI-sparing strategy are discussed below. Two of the studies used raltegravir instead of the conventional NRTI backbone, and the third used maraviroc.

PROGRESS (PROtease/InteGRasE Simplification Study) was an open-label study that evaluated the efficacy and safety of a nucleoside-sparing regimen consisting of ritonavir-boosted lopinavir and raltegravir (13). Two hundred and six antiretroviral therapy-naive, HIV-infected patients were randomized to receive either lopinavir/ritonavir 400/100 mg twice daily plus raltegravir 400 mg twice daily (raltegravir arm) or a conventional combination antiretroviral regimen of lopinavir/ritonavir (400/100 mg twice daily) plus tenofovir and emtricitabine (NRTI arm). There were no significant differences at baseline between the two arms in demographics, HIV-1 RNA (mean HIV-1 RNA = 4.25 log_{10} copies/mL) or CD4 cell count (mean = 293.5 cells/mm^3). The primary efficacy endpoint was the proportion of patients with plasma HIV-1 RNA < 40 copies/mL at week 48, by intent-to-treat, time to loss of virological response analysis; the predefined criteria for noninferiority was an estimated difference between the raltegravir and NRTI arms within a 20% margin. At 48 weeks, the raltegravir arm was found to be noninferior to the NRTI arm; the proportion of patients with plasma HIV-1 RNA < 40 copies/mL was 83.2% in the raltegravir arm compared to 84.8% in the NRTI arm (difference: –1.6%; 95% CI: –12.0% to +8.8%). The mean increases in CD4 cell count were similar: 215 cells/mm^3 for the raltegravir arm compared to 245 cells/mm^3 for the NRTI arm. The most common adverse event was diarrhea, but there were no significant differences in the overall risk of moderate to severe adverse events between the two arms. Rates of premature discontinuation were also similar. However, the mean increases from baseline in total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were significantly greater in the raltegravir arm.

The SPARTAN study was a pilot study conducted to evaluate the safety and efficacy of atazanavir in combination with raltegravir. It randomized, in a 2:1 ratio, 94 HIV-infected, antiretroviral treatment-naive patients with baseline HIV-1 RNA > 5,000 copies/mL to receive atazanavir 300 mg twice daily plus raltegravir 400 mg twice daily (raltegravir arm) or ritonavir-boosted atazanavir (ATV/r, 100/300 mg) once daily plus tenofovir and emtricitabine (NRTI arm). Thus, SPARTAN explored the utility of not only nucleoside sparing, but also ritonavir sparing. Study participants were additionally stratified according to their baseline HIV-1 RNA values (above or below 100,000 copies/mL). Twenty-four-week data were presented at AIDS 2010 (14). At week 24, the virological efficacy of the two arms was similar: 74.6% of patients with HIV-1 RNA < 50 copies/mL in the raltegravir arm compared to 63.3% of patients in the NRTI arm. Notably, virological failure, defined as HIV-1 RNA > 50 copies/mL at week 24, was more frequent in the raltegravir arm: 11 patients in the raltegravir arm compared to 8 patients in the NRTI arm. However, these numbers do not tell the whole story; of the 11 patients with virological failure in the raltegravir arm, 6 had HIV-1 RNA > 400 copies/mL compared to only 1 of 8 patients in the NRTI arm. Raltegravir resistance mutations were noted in four of the patients in the raltegravir arm. No atazanavir resistance was noted in either arm. Discontinuation for toxicity was more frequent in the twice-daily ATV/r arm; grade 3/4 adverse events, including hyperbilirubinemia, were also more common in this arm. Interestingly, no significant differences in fasting lipids were noted between the two arms. The differences in virological failure noted above raised concerns of the vulnerability of raltegravir when used in this combination and led to the discontinuation of the SPARTAN study.

Study A4001078 was an open-label pilot clinical trial that evaluated the safety and efficacy of a once-daily nucleoside-sparing regimen of maraviroc in combination with ATV/r. Results of a planned 24-week analysis were presented at AIDS 2010 (15). One hundred and twenty-one antiretroviral therapy-naive, HIV-infected patients with R5 virus and CD4 cell counts > 100 cells/mm^3 were randomized to receive ATV/r (300/100 mg) with either maraviroc 150 mg once daily (n = 60) or tenofovir/emtricitabine once daily (n = 61). Baseline characteristics were comparable. At week 24, on an intent-to-treat, discontinuation-equals-failure analysis, a greater proportion of patients in the NRTI arm achieved suppression of HIV-1 RNA to < 50 copies/mL: 54 of 61 (88%) versus 48 of 60 (80%) patients in the maraviroc arm. The mean change in CD4 cell count from baseline was 190 for the maraviroc arm versus 159 for the comparator arm. Discontinuations and grade 3/4 adverse events were more common in the maraviroc arm (3.3% vs. 0% and 33.3% vs. 21.3%, respectively).

Protease inhibitor-sparing strategy

Two studies, ODIS and SPIRAL, evaluated the safety and efficacy of a switch from protease inhibitors to raltegravir.

The ODIS trial was a randomized clinical trial that compared the safety and efficacy of replacing protease inhibitors with either 800 mg once daily or 400 mg twice daily raltegravir in 222 HIV-infected individuals on stable protease inhibitor-based antiretroviral therapy with plasma HIV-RNA < 50 copies/mL for at least 24 weeks (16). One hundred and forty-nine patients were randomized to the once-daily raltegravir arm and 35 patients were randomized to the twice-daily raltegravir arm. Thirty-eight additional patients were randomized to the twice-daily raltegravir regimen for the first 3 months and then switched to receive raltegravir once daily. Either abacavir/lamivudine (31%) or tenofovir/emtricitabine (68%) was used as the NRTI backbone. Virological failure was noted in 13 (5.9%) of patients by week 24, with more virological failure reported in the once-daily raltegravir arm: 12 (6.4%) in the once-daily raltegravir arm and 1 (2.9%) in the twice-daily raltegravir arm. This difference did not reach statistical significance ($P = 0.18$). On further analysis, the major determinant of virological failure appeared to be prior NRTI experience rather than assignment to once-daily versus twice-daily raltegravir. The virological failure rate in patients with prior NRTI resistance was 16.2% (12 of 74) compared to only 0.7% (1 of 148) in those without NRTI resistance ($P < 0.001$).

The SPIRAL trial was an open-label study that randomized 273 HIV-infected patients on stable ritonavir-boosted protease inhibitor-based therapy with plasma HIV-1 RNA < 50 copies/mL for at least 6 months to either continue the same regimen (n = 134) or switch from the current ritonavir-boosted protease inhibitor to raltegravir (n = 139) (17). At 48 weeks, on an intent-to-treat, non-completion-equals-failure analysis (the primary endpoint), the raltegravir arm was noninferior to the protease inhibitor-based arm (89.2% vs. 86.6% patients free of treatment failure; difference: 2.6%; 95% CI: −5.2% to +10.6%). Noninferiority was also confirmed for virological failure, defined as two consecutive plasma HIV-1 RNA measurements ≥ 50 copies/mL; 96.9% of patients on raltegravir-based therapy had plasma HIV-1 RNA < 50 copies/mL at week 48 compared to 95.1% of patients on ritonavir-boosted protease inhibitor-based therapy (difference: 1.8%; 95% CI: −3.5% to +7.5%). There were no significant differences between the two arms in CD4 cell count changes from baseline. The overall incidence of adverse events was similar between the two arms. However, fasting plasma lipid values decreased in the raltegravir arm over the course of the study, while they continued to increase in the protease inhibitor arm.

Protease inhibitor monotherapy

Another attempt at simplification of antiretroviral therapy is the use of ritonavir-boosted protease inhibitor monotherapy.

The MONET trial randomized darunavir-naive HIV-infected patients receiving stable antiretroviral therapy with plasma HIV-1 RNA < 50 copies/mL for at least the previous 6 months and without previous virological failure to either darunavir/ritonavir (800/100 mg once daily) plus two NRTIs (n = 129) or darunavir/ritonavir monotherapy (n = 127). At week 48, switching to darunavir/ritonavir monotherapy had met the noninferiority criteria (18). Ninety-six-week data were presented at AIDS 2010 (19). On the primary, intent-to-treat, switch-equals-failure efficacy analysis, the proportion of patients with plasma HIV-1 RNA < 50 copies/mL was 77.9% in the darunavir monotherapy arm compared to 82.1% in the comparator arm (difference: −5.2%; 95% CI: −14.3% to +5.8%). Thus, for this primary efficacy analysis, the darunavir monotherapy arm did not meet the predefined criteria for noninferiority. However, on secondary switch-included, observed-failure analysis, ritonavir-boosted darunavir monotherapy was noninferior to the comparator arm; the proportion of patients with plasma HIV RNA < 50 copies/mL on darunavir monotherapy was 94.2% versus 91.8% in the comparator arm (difference: +2.4%; 95% CI: −4.0 to +8.8%). Protease inhibitor resistance was found in one patient in each arm. On multivariate analysis, hepatitis C coinfection was found to be a significant predictor of failure. At baseline, 22 of 127 (17%) patients on the monotherapy arm versus 12 of 129 (9%) patients in the comparator arm were coinfected with hepatitis C. Additionally, four acute hepatitis C infections (all in the monotherapy arm) occurred during the trial (20).

DISCLOSURES

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