Drugs of the Future 2012, 37(5): 369-374

CCC: 0377-8282/2012
DOI: 10.1358/dof.2012.37.5.1799889

MEETING REPORT

ADVANCES IN ANTIRETROVIRAL AND ANTI-HEPATITIS C VIRUS INFECTION THERAPY

A REPORT FROM CROI 2012 – MARCH 5-8, SEATTLE, OREGON, USA

Z. Temesgen

Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota, USA

CONTENTS

SUMMARY

The Conference on Retroviruses and Opportunistic Infections (CROI) remains a venue for important exchanges of information and dissemination of knowledge. New anti-hepatitis C virus (HCV) therapies remain a focus of interest at CROI 2012. Telaprevir and boceprevir, two recently approved, direct-acting anti-HCV drugs, have now been associated with improved virological responses in patients co-infected with HIV and hepatitis C. However, overlapping toxicities and substantial drug–drug interactions will severely limit their clinical utility. Yet another single-pill, once-daily antiretroviral regimen is on the horizon, and the proof of concept for purging HIV from latent CD4⁺ cells may have been provided at CROI 2012.

Key words: Hepatitis – HIV – Telaprevir – Boceprevir – Elvitegravir – Dolutegravir

INTRODUCTION

The 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012) convened over 4,000 scientists and clinicians from more than 80 countries to discuss a wide range of research in HIV medicine. Given the scope of the journal in which it is intended to be published, this article focuses on presentations at the conference that address the development of new therapies. 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.

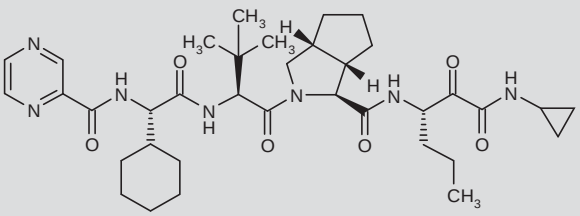
Correspondence: Zelalem Temesgen, MD, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA. E-mail: temesgen.zelalem@mayo.edu.

NEW ANTI-HEPATITIS C VIRUS DRUGS

Telaprevir and boceprevir, two new direct-acting anti-hepatitis C virus (HCV) drugs, were approved by the U.S. Food and Drug Administration (FDA) for the treatment of genotype 1 chronic HCV infection in combination with pegylated interferon (pegIFN) and ribavirin (RBV) (1, 2). Data on the efficacy and safety of these agents in patients co-infected with HIV had not been available until CROI 2012.

Telaprevir

Interim, week 24 analysis of Study 110, a randomized, double-blind, placebo-controlled, parallel-group phase II trial of telaprevir in combination with pegIFN-alfa-2a plus RBV in previously untreated genotype 1 HCV treatment-naive, HIV-infected patients was presented (3). Sixty-two HIV/HCV co-infected patients were randomized into 2 groups: telaprevir 750 mg every 8 hours + pegIFN 180



Telaprevir

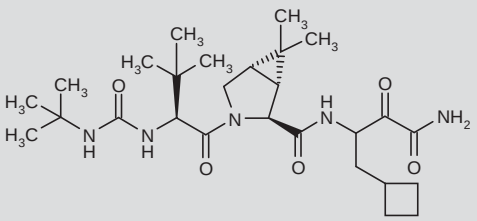
µg/week + RBV 800 mg/day for 12 weeks followed by 36 weeks of pegIFN + RBV (T/PR group) and placebo + pegIFN + RBV for 48 weeks (PR group). The study was conducted in two parallel parts. In part A, 13 patients with CD4 cell count ≥ 500 cells/mm^3 and plasma HIV-1 RNA ≤ 100,000 copies/mL received no concurrent antiretroviral therapy (ART). In phase B, 47 patients with CD4 cell count < 300 cells/mm^3 and plasma HIV-1 RNA ≤ 50 copies/mL on either efavirenz/tenofovir/emtricitabine or ritonavir-boosted atazanavir plus tenofovir plus emtricitabine or lamivudine were randomized into the 2 treatment groups. The telaprevir dose was increased to 1125 mg every 8 hours when the ART regimen included efavirenz. Baseline characteristics were as follows: mean age 46 years; 88% male; 27% African-American; 68% subtype 1a; 3.3% with cirrhosis. At baseline, 92% and 81%, respectively, of part A and B patients had HCV RNA ≥ 800,000 IU/mL, and mean CD4 counts were 690 and 562 cells/mm^3, respectively.

The primary endpoint of the study was undetectable HCV RNA at week 12 of telaprevir plus pegIFN/RBV. On intent-to-treat analysis, substantially more patients in the T/PR group achieved undetectable HCV RNA at weeks 4 and 12 compared to patients in the PR group (63% vs. 4.5%). Secondary endpoints included additional measures of efficacy, as well as safety analysis. Sustained virological response rates 12 and 24 weeks following end of therapy (SVR12 and SVR24, respectively) were higher for the T/PR group. These higher response rates were noted for all subgroups, i.e., patients in part A, as well as patients on either of the two ART regimens in part B. Relapse and virological failure rates were also lower for the T/PR groups (3% vs. 15% and 8% vs. 36%, respectively). Absolute CD4 counts declined from baseline in both groups, although CD4 percentage remained unchanged. Abdominal pain, vomiting, nausea, pyrexia, dizziness, depression, pruritus and anemia were noted more frequently in the T/PR groups. As would be expected, those patients receiving atazanavir containing ART experienced elevated bilirubin levels more frequently.

In a separate study, the anti-HIV activity of several HIV protease inhibitors (amprenavir, atazanavir, darunavir and lopinavir) when combined with telaprevir, was evaluated using an anti-HIV-1 cytoprotection assay in CEM-SS cells acutely infected with HIV-1_{IIIB}. There was no antagonism demonstrated. Telaprevir itself exhibited no anti-HIV activity in this assay (4).

Boceprevir

The efficacy and safety of boceprevir in combination with pegIFN and RBV in HCV/HIV co-infected patients was investigated in a multicenter, double-blind phase II trial. One-hundred HIV/HCV co-infected patients with untreated HCV genotype 1 infection, CD4$^+$ cell count ≥ 200 cells/mm^3 and on effective antiretroviral therapy (HIV RNA < 50 copies/mL) were randomized in a 2:1 ratio to receive boceprevir + pegIFN + RBV or placebo + pegIFN + RBV for 44 weeks. This was preceeded by a 4-week lead-in of pegIFN + RBV in all patients (total 48 weeks). Patients were stratified by: cirrhosis/fibrosis (yes vs. no; 95% had no cirrhosis) and baseline HCV RNA (< 800,000 IU/mL vs. ≥ 800,000 IU/mL; 88% had high baseline HCV RNA). The median age was 43, 82% were white and 69% were male. The primary efficacy endpoint was SVR24; interim SVR12 results were reported at CROI 2012 (5). Sixty-three percent of



Boceprevir

patients in the boceprevir arm and 35% of patients in the placebo arm completed the 48-week treatment period. SVR12 was 60.7% in the boceprevir arm compared to 26.5% in the placebo arm. On analysis of secondary endpoints, better virological response rates were noted for the boceprevir arm at treatment weeks 8, 12 and 24. Patients in the placebo arm had more HCV treatment failures (53% vs. 9%); HIV RNA breakthroughs were noted in three and four patients, respectively, in the boceprevir and placebo arms. There were more discontinuations because of adverse events in the boceprevir arm compared to the placebo arm (20% vs. 9%). Patients in the boceprevir arm experienced more pyrexia, dysgeusia, vomiting, asthenia, anemia and neutropenia than patients in the placebo arm.

The pharmacokinetic interaction of boceprevir with the ritonavir-boosted protease inhibitors atazanavir, darunavir and lopinavir was evaluated in a 3-part, open-label study in 39 healthy adult subjects who received boceprevir on days 1-6 and then the protease inhibitors on days 10-31 following a 4-day washout (6). Subjects received both boceprevir and protease inhibitors on days 25-31. The exposure of all three protease inhibitors, as well as ritonavir, was substantially decreased when coadministered with boceprevir. Coadministration with ritonavir-boosted atazanavir did not alter the boceprevir exposure. However, the exposure of boceprevir was substantially decreased when coadministered with ritonavir-boosted lopinavir or darunavir.

OTHER ANTI-HCV DRUGS IN DEVELOPMENT

A summary of presentations at CROI 2012 on other candidate anti-HCV drugs is provided in Table I.

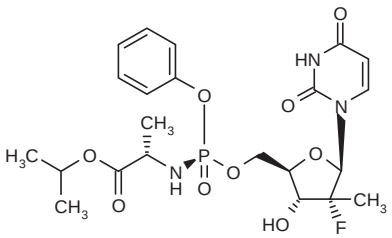
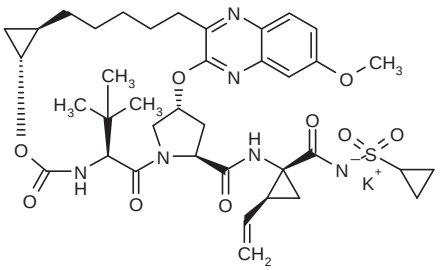
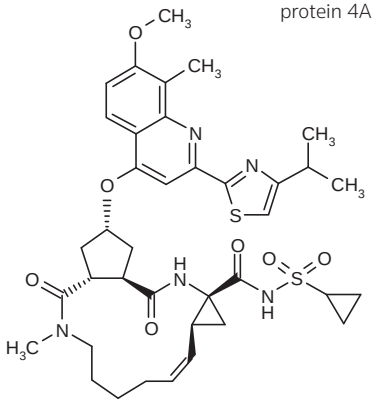
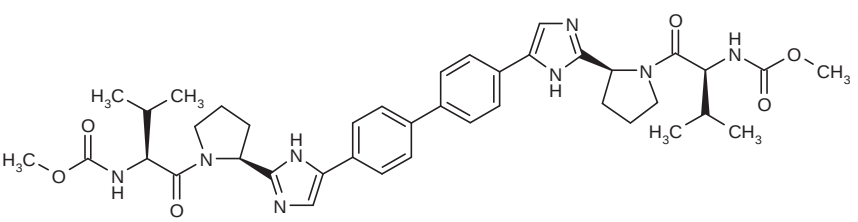
NEW ANTI-HIV DRUGS

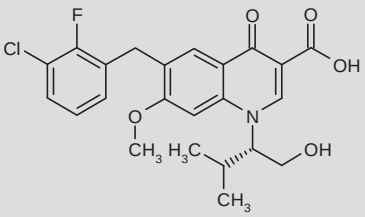
The antiretroviral development pipeline is somewhat less robust than a few years ago. However, there are a number of new drugs and drug formulations that will likely be available in the near future. Several presentations at CROI 2012 addressed these drugs.

Elvitegravir

Elvitegravir is an investigational integrase inhibitor that specifically inhibits the strand transfer step in the integration of proviral DNA into the host genome. Previous studies had shown that coadminis-

Table I. *Candidate anti-HCV drugs presented at CROI 2012.*

Drug	Mechanism of action	Development phase	Study	Results
PSI-7977 (7) 	Uridine nucleotide analogue	Phase III	HCV genotype 1-monoinfected patients, 10 null responders and 25 treatment-naive, received 400 mg PSI-7977/ribavirin for 12 weeks	At week 4, all subjects had HCV RNA below the limit of detection
MK-5172 (8) 	HCV protease inhibitor	Phase I	HCV genotype 1-monoinfected treatment-naive patients received MK-5172 at doses ranging from 50 to 800 mg daily in a 7-day monotherapy study	No virological breakthrough; viral suppression continued 1-3 weeks after the last dose; NS3 amino acid variants remained detectable at day 56
TMC-435 (9) 	Serine protease NS3/non-structural protein 4A inhibitor	Phase I	Two open-label, randomized, two-panel, three-way crossover pharmacokinetic interactions between TMC-435 and rilpivirine or tenofovir, efavirenz (EFV) or raltregavir in 48 healthy subjects	EFV decreases TMC-435 exposure by 70% and coadministering these two drugs should be avoided; dose adjustments are not required when rilpivirine, tenofovir or raltegravir are coadministered with TMC-435
Daclatasvir dihydrochloride (BMS-790052) (10) 	Non-structural protein NS5A replication complex inhibitor	Phase I	Three open-label studies in healthy subjects evaluating steady-state pharmacokinetic interactions between BMS-790052 and tenofovir, efavirenz or ritonavir-boosted atazanavir .2HCl	No clinically relevant drug–drug interactions with tenofovir; dose adjustment for BMS-790052 may be necessary when given with efavirenz or ritonavir-boosted atazanavir. No dose adjustment necessary for efavirenz or ritonavir-boosted atazanavir when coadministered with BMS-790052



Elvitegravir

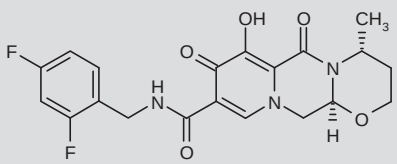
tration of elvitegravir with low-dose ritonavir improved the relative oral bioavailability and exposure of elvitegravir and allowed once-daily dosing (11). More recently, elvitegravir has been undergoing clinical development as a component of a once-daily, single-tablet regimen containing tenofovir, emtricitabine and cobicistat (a cytochrome P450 3A inhibitor, and thus a pharmacological booster for elvitegravir with no direct anti-HIV effect).

This investigational once-daily, single-tablet regimen (dubbed "Quad") was compared to the once-daily, single-tablet regimen already in clinical practice, tenofovir/emtricitabine/efavirenz, in a randomized, double-blind phase III study (12). Seven hundred HIV-infected, treatment-naive patients with HIV RNA > 5,000 copies/mL and creatinine clearance ≥ 70 mL/min were randomized 1:1 to either Quad or TDF/FTC/EFV once daily plus matching placebos. Randomization was further stratified by HIV-1 RNA below or above 100,000 copies/mL (a third had viral load > 100,000 copies/mL). The primary endpoint was the proportion of subjects with HIV RNA < 50 copies/mL at week 48 per the FDA snapshot algorithm (intent-to-treat), with a prespecified non-inferiority margin of 12%. At 48 weeks, the Quad regimen was non-inferior to TDF/FTC/EFV, with viral suppression in 88% and 84%, respectively (difference: +3.6%; 95% CI: –1.6 to +8.8). Virological failure rates at week 48 were also similar at 7% in both arms. Response rates were also similar for those with baseline HIV RNA ≥ 100,000 copies/mL. A greater increase in mean $CD4^+$ cell count from baseline was observed for the Quad arm (239 vs. 206 cells/mm^3; $P = 0.009$). While discontinuation rates due to toxicity were comparable between the two groups (3% vs. 5%), there were differences in the type of adverse events observed. Nausea was significantly more frequent in Quad, while dizziness, abnormal dreams, insomnia and rash were significantly more common in TDF/FTC/EFV. The decrease in creatinine clearance from baseline was significantly greater in the Quad arm. Increases in total cholesterol and LDL from baseline were lower in the Quad arm.

The efficacy and safety of Quad in treatment-naive HIV-infected subjects was also compared to that of a regimen containing ritonavir-boosted atazanavir (ATV/r) plus fixed-dose TDF/FTC (three pills once daily) in a randomized, blinded phase III study (13), similarly designed to the above study (eligibility criteria, stratification, endpoints, non-inferiority margin). Seven hundred and eight subjects were randomized 1:1 to receive Quad or ATV/r + TDF/FTC. Secondary objectives included pharmacokinetics/pharmacodynamics (PK/PD) and bone mineral density (BMD) analyses. At 48 weeks, Quad was non-inferior to ATV/r + TDF/FTC, with viral suppression in 90% and 87%, respectively (difference: +3.0%; 95% CI: –1.9 to +7.8); virological failure was 5% in both arms. Median CD4 increases were similar (207 vs. 211 cells/mm^3). Significantly greater elevations in bilirubin and median triglyceride increases were noted in the atazanavir arm, while the decrease in creatinine clearance from baseline was significantly greater in the Quad arm. Discontinuation rates for adverse events were comparable (4% vs. 5%).

Dolutegravir

Dolutegravir is another investigational strand transfer step integrase inhibitor in advanced clinical development. It is also a once-daily drug, but unlike elvitegravir, it does not require pharmacological boosting. Results from a 48-week interim analysis of SPRING-1, a phase IIb study, have been published and virological response rates comparable to the efavirenz-based regimen have been reported (14). The durability of response and safety profiles across the 4 doses employed in SPRING-1 were assessed by extension through 96 weeks (15). At week 96, there were comparable rates of viral suppression between the efavirenz arm and each dolutegravir dose arm. Protocol-defined virological failure was observed in one patient receiving efavirenz and three patients receiving dolutegravir. However, none of the failures in the dolutegravir arms were from the dolutegravir 50-mg arm. The median change in CD4 cell count from baseline was also comparable across treatment arms. Safety issues were similar to what was noted in the earlier stages of the study, i.e., more psychiatric adverse events and rash and more discontinuations due to adverse events in the efavirenz arm.

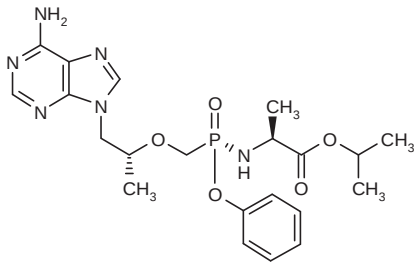
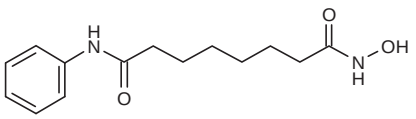


Dolutegravir

OTHER ANTI-HIV DRUGS IN DEVELOPMENT

Table II provides a summary of presentations at CROI 2012 on other candidate anti-HIV drugs.

Table II. *Candidate anti-HIV drugs presented at CROI 2012.*

Drug	Mechanism of action	Development phase	Study	Results
GS-7340 (16) 	Nucleotide analogue, tenofovir prodrug	Phase I	Randomized, dose-finding, 10-day monotherapy study comparing 3 different doses of GS-7340 (8, 25 and 40 mg once daily) to open-label tenofovir (300 mg once daily) and placebo in 38 HIV-1-infected subjects with HIV-1 RNA ≥ 2000 copies/mL, no genotypic resistance to tenofovir and CD4 cell count ≥ 200 cells/mm^3	Time-weighted average HIV-1 RNA change from baseline after 10 days of treatment was greater in the GS-7340 than in the tenofovir group; plasma tenofovir exposures across the GS-7340 groups were about 80-97% lower
Vorinostat (17) 	Histone deacetylase (HD) inhibitor	Proof of concept; disrupting HIV-1 latency	Six HIV-positive men with HIV RNA < 50 copies/mL and CD4 cell counts > 500 cells/mm^3 received a single dose of 400 mg vorinostat after baseline virus levels in latent cells established	A single dose of vorinostat increased biomarkers of cellular acetylation and induced expression of HIV RNA (1.5- to 10-fold) within latently infected resting CD4 T cells in all 6 patients

CONCLUSION

Valuable and clinically relevant data were presented at CROI 2012. It was encouraging to see that the improved virological responses noted in HCV-monoinfected patients were duplicated in patients co-infected with HIV. However, overlapping toxicities and drug–drug interactions between HIV and HCV therapy present a formidable challenge. Both boceprevir and telaprevir are substrates and inhibitors of cytochrome P450 3A4 and P-glycoprotein; boceprevir is also metabolized by aldo-ketoreductase. Therefore, the coadministration of boceprevir with ritonavir-boosted protease inhibitors or efavirenz is not recommended. Similarly, the coadministration of telaprevir with ritonavir-boosted fosamprenavir, darunavir or lopinavir is contraindicated. Telaprevir can be coadministered with ritonavir-boosted atazanavir or raltegravir at the standard doses; however, the dose of telaprevir needs to be increased if coadministered with efavirenz. Boceprevir can be administered with raltegravir without dose adjustment. The availability of additional drugs for the treatment of chronic HCV infection with less toxicity and less potential for drug interactions is eagerly anticipated.

The armamentarium of antiretroviral drugs for clinical use continues to expand, albeit at a slower pace than in previous years. However, the era of drug development for the treatment of HIV infection has entered an exciting new phase, focused on curing HIV infection rather than just durable suppression.

DISCLOSURES

The author states no conflicts of interest.

REFERENCES

1. Poordad, F., McCone, J. Jr., Bacon, B.R. et al. *Boceprevir for untreated chronic HCV genotype 1 infection*. N Engl J Med 2011, 364(13): 1195-206.
2. Jacobson, I.M., McHutchison, J.G., Dusheiko, G. et al. *Telaprevir for previously untreated chronic hepatitis C virus infection.* N Engl J Med 2011, 364(25): 2405-16.
3. Dieterich, D., Soriano, V., Sherman, K. et al. *Telaprevir in combination with peginterferion α 2a + ribavirin in HCV/HIV-co-infected patients: A 24-week treatment interim analysis*. 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 46.
4. Dierynck, I., De Meyer, S., Kieffer, T., Picchio, G. *Evaluation of telaprevir and HIV-1 protease inhibitors in 2-drug combination studies against HIV-1 activity*. 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 756.
5. Sulkowski, M., Pol, S., Cooper, C. et al. *Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV-co-infected patients: end of treatment (week-48) interim results*. 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 47.
6. Hulskotte, E., Feng, H.-P., Xuan, F. et al. *Pharmacokinetic interaction between the HCV protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, lopinavir, and darunavir.* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2011, Abst 771LB.
7. Gane, E., Stedman, C., Anderson, J. et al. *100% rapid virologic response for PSI-7977 + ribavirin in genotype 1 null responders (ELECTRON): Early viral decline similar to that observed in genotype 1 and genotype 2/3 treatment-naïve patients.* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 54LB.
8. Barnard, R., Strizki, J., McHale, C. et al. *Evaluation of NS3 amino acid variants in a phase 1b study of GT1 infection with the HCV protease inhibitor,*

MK-5172. 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 48.

9. Ouwerkerk-Mahadevan, S., Peeters, M., Beumont-Mauviel, M. *The pharmacokinetic interactions of HCV protease inhibitor TMC435 with RPV, TDF, EFV, or RAL in healthy volunteers.* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 49.
10. Bifano, M., Hwang, C., Oosterhuis, B. et al. *Assessment of HIV ARV drug interactions with the HCV NS5A replication complex inhibitor BMS-790052 demonstrates a pharmacokinetic profile which supports co-administration with tenofovir disoproxil fumarate, efavirenz, and atazanavir/ritonavir*. 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 618.
11. Kearney, B.P., Mathias, A., Zhong, L. et al. *Pharmacokinetics/pharmacodynamics of GS-9137 an HIV integrase inhibitor in treatment-naïve and experienced patients.* 7th Int Workshop Clin Pharmacol HIV Ther (April 20-22, Lisbon) 2006, Abst 73.
12. Sax, P., DeJesus, E., Mills, A. et al. *Ivitegravir/cobicistat/emtricitabine/tenofovir (Quad) has non-inferior efficacy and favorable safety compared to efavirenz/emtricitabine/tenofovir in treatment-naive HIV-1+ subjects.* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 101.
13. DeJesus, E., Rockstroh, J., Henry, K. et al. *Week 48 results of an ongoing global phase 3 study comparing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate with atazanavir/ritonavir-boosted plus emtricitabine/tenofovir disoproxil fumarate in treatment naive HIV-1+ subjects showing efficacy, safety, and pharmacokinetics.* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 627.
14. van Lunzen, J., Maggiolo, F., Arribas, J.R. et al. *Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial.* Lancet Infect Dis 2012, 12: 111-8.
15. Stellbrink, H., Reynes, J., Lazzarin, A. et al. *Dolutegravir in combination therapy exhibits rapid and sustained antiviral response in ARV-naive adults: 96-Week results from SPRING-1 (ING112276).* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, 1., Seattle) 2012, Abst 102LB.
16. Ruane, P., DeJesus, E., Berger, D. et al. *GS-7340 25 mg and 40 mg demonstrate superior efficacy to tenofovir 300 mg in a 10-day monotherapy study of HIV-1+ patients.* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 103.
17. Archin, N., Liberty, A., Kashuba, A. et al. *Administration of vorinostat disrupts HIV-1 latency in patients on ART.* 19th Conf Retroviruses Opportunistic Infect (CROI) (March 5-8, Seattle) 2012, Abst 157LB.