EXPERT REVIEWS

Faldaprevir (BI 201335) for the treatment of hepatitis C in patients co-infected with HIV

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Natalia Lorna Laufer*[1,2] and Jürgen Kurt Rockstroh[3]

[1]*Instituto de Investigaciones Biomédicas en Retrovirus y SIDA (INBIRS), Universidad de Buenos Aires - CONICET, Buenos Aires, Argentina*
[2]*Hospital J.A. Fernández, Buenos Aires, Argentina*
[3]*Department of Medicine I, University of Bonn, Bonn, Germany*
**Author for correspondence:*
Tel.: +54 4508 3689
Fax: +54 4508 3705
nlaufer@fmed.uba.ar

Chronic HCV infection affects 130–170 million individuals worldwide and there are currently 34 million people living with HIV/AIDS. The aim of treatment of HCV is the elimination of the virus (sustained virological response). With development of drugs that specifically target HCV replication, direct-acting agents, sustained virological response rates have dramatically changed for genotype 1 infections. Challenges in the use of direct-acting agents in patients with HIV/HCV co-infection include the potential for drug–drug interactions between HIV and HCV drugs, additional drug toxicities and the need for therapy with IFN-α. Faldaprevir (FDV), previously known as BI 201335, is a second-wave HCV NS3/4A protease inhibitor with highly potent *in vitro* activity against HCV GT-1a/1b and improved pharmacokinetics suitable for once-daily dosing. FDV is currently in Phase III development. This article will review the pharmacology and pharmacodynamics of FDV, the efficacy and safety of the drug and explore possible future developments in the management of chronic hepatitis C infection, focusing on HIV/HCV co-infected patients.

Keywords: faldaprevir • hepatitis C • HIV • treatment

Chronic HCV infection affects 130–170 million individuals worldwide [1], whereas currently 34 million people are living with HIV/AIDS [101]. Because of overlapping pathways of transmission, approximately 4–5 million individuals worldwide are estimated to be co-infected with both viruses [2]. Co-infection rates are higher in areas where injection drug use is one of the major transmission pathways for HIV, such as in Eastern Europe where up to 70% of HIV patients are likely to also have HCV co-infection [3].

Genotype (GT)-1 HCV is the most common genotype, which can be found in more than 50% of patients both in HCV mono-infected and HIV co-infected patients [3,4] and, prior to the advent of direct-acting antivirals (DAAs), has been particularly difficult to treat. Like GT-1, GT-4 is challenging to treat and its incidence is increasing in countries in Eastern and Southern Europe and Argentina [5] mainly due to migration. Clearly, this fact emphasizes the need for the development of HCV compounds with pan genotypic activity. HCV GT-3, which is predominantly transmitted through injection drug use, also plays a role in co-infection, whereas GT-2 is present in very few patients [6].

HIV/HCV co-infection accelerates and increases liver fibrosis, particularly in patients with advanced immunodeficiency [7,8]. Since the introduction of HAART, the life expectancy for people living with HIV/AIDS has dramatically improved and hepatitis C co-infection has emerged as an important factor of non-AIDS morbidity [9]. Indeed, in countries with expanded access to HAART, end-stage liver disease has become one of the most common causes of non-AIDS deaths [10].

Since the development of the first protease inhibitor (BILN 2061) to specifically target HCV replication 10 years ago [11], DAAs have been on the horizon for the treatment of chronic HCV infection with numerous agents currently being tested in Phase II and III clinical trials. There are also two HCV NS3/4A protease inhibitors, telaprevir and boceprevir, for the treatment of HCVGT-1 infection,

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Table 1. Direct-acting and host-targeting anti-HCV agents in Phase II or III clinical development.

NS3/4A protease inhibitors	NS5A inhibitors	NS5B nucleos(t)ide polymerase inhibitors	NS5B non-nucleosides polymerase inhibitors	Host targets
Simeprevir	Daclatasvir	Sofosbuvir	Lomibuvir (VX-222)	Alisporivir†
ABT-450	Ledipasvir (GS-5885)	Mericitabine	Deleobuvir (BI-207121)	Miravirsen‡
Faldaprevir	PPI-668	ALS-2200 (VX-135)	ABT-333	
Asunaprevir	ACH-3102		Setrobuvir	
Vaniprevir (MK-7009)	ABT-267		TMC-647055	
Danoprevir	Samatasvir (IDX-719)		BMS-791325	
MK-5172	MK-8742		GS-9669	
Sovaprevir	GSK-2336805			
Vedroprevir (GS-9451) GS-9256	GS-5816			

†Cyclophillin inhibitors.
‡miRNA-122 antagonist.

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which already have been licensed in the USA, Europe and South America and have significantly increased sustained virologic response (SVR) rates in treatment-naïve HCV GT-1 patients to up to 75% [12,13]. Challenges in the use of DAAs in patients with HIV/HCV co-infection include the potential for drug–drug interactions between HIV and HCV drugs, additional drug toxicities and the need for therapy with IFN-α [14].

For that reason, there remains an urgent need for development of further new drugs and ideally IFN-free treatment regimens. Table 1 [15] summarizes the HCV drugs currently in development in Phase II and III. Faldaprevir (FDV), previously known as BI 201335, is a second-wave HCV NS3/4A protease inhibitor with highly potent *in vitro* activity against HCV GT-1a/1b and improved pharmacokinetics suitable for once-daily (q.d.) dosing. BI 201335 is currently in Phase III development. There is an ongoing Phase III study (STARTVerso4) assessing the efficacy and safety of FDV in combination with pegylated interferon and ribavirin (PegIFN/RBV) in HIV/HCV co-infected patients.

Pharmacology

FDV is a peptidomimetic HCV-specific protease inhibitor with *in vitro* activity against GT-1, -2, -4, -5 and -6; but its activity is particularly high for GT-1, subtypes a and b [16,17]. Preclinical and preliminary human pharmacokinetic studies suggested that FDV maintains sufficient plasma concentrations at steady-state allowing q.d. dosing [18]. It is being developed by Boehringer-Ingelheim. FDV works by binding to the active site on the NS3/4A enzyme, which is critical in HCV replication.

Three Phase III trials of FDV and PegIFN/RBV combination therapy have been completed for HIV-seronegative patients infected with HCV GT-1. A further Phase III study of triple therapy in HIV-co-infection (STARTVerso4) is still ongoing as well as studies on IFN-free regimens with other DAA agents including deleobuvir (DBV; BI 207127).

Pharmacodynamics

FDV possesses a C-terminal carboxylic acid that contributes to be a highly optimized non-covalent competitive inhibitor of full-length NS3-NS4A proteases of HCV genotypes 1a and 1b [17]. In preclinical studies, FDV inhibited *in vitro* Huh-7 cells with 50% effective concentration (EC_{50}) of approximately 6.5 and 3.1 nm for genotypes 1a and 1b, respectively [17]. It is a very weak inhibitor of cathepsin B and showed no measurable inhibition of human leukocyte elastase.

Pharmacokinetics & metabolism

The safety and pharmacokinetics of FDV have been characterized in an escalating single-dose study (trial 1220.3) and in a multiple rising dose, 21- to 28-day trial (1220.6) in healthy volunteers. The amino acid side chains and N-terminal capping group of FDV have been optimized for potency in both cellular and biochemical assays to provide good absorption, distribution, metabolism, elimination and pharmacokinetics properties allowing efficient uptake and distribution of the drug to the target organ, the liver [16]. Plasma FDV concentrations peaked at 2–6 h (t_{max}) and increased supra-proportionally with dose as seen for mean C_{max}, C_{min} and area under the curve. Mean elimination half-life of FDV was approximately 20–30 h [18].

Absorption

FDV is rapidly absorbed following oral administration. *In vitro*, a good Caco-II permeability and metabolic stability has been observed. Single-dose PK revealed a clearance of 17, 3.0 and 2.6 ml/min/kg in rat, monkey and dog, respectively, with a corresponding oral bioavailability of 29.1, 25.5 and 35.6% [19].

Distribution

Studies in rats have shown that after oral administration FDV is rapidly distributed to the liver, reaching a mean liver/plasma ratio of 42 within 1 h, and maintaining a similar ratio over the

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Table 2. Phase Ib, II and III clinical trials including faldaprevir.

Study name	Phase	Patients (n)	Prior HCV treatment status	HCV GT	Length of treatment with FDV
SOUND-C1	Ib	32	Naïve	GT-1	28 days[†]
SILEN-C1	IIb	429	Naïve	GT-1	24 weeks
SILEN-C2	IIb	288	Experienced	GT-1	24 weeks
SILEN-C3	IIb	159	Naïve	GT-1	12 or 24 weeks
STARTVerso1/1220.30	III	652	Naïve	GT-1	12 or 24 weeks
STARTVerso2/1220.47	III	657	Naïve	GT-1	12 or 24 weeks
STARTVerso3/1220.7	III	678	Experienced	GT-1	12 or 24 weeks
STARTVerso4/1220.19	III	308	HIV co-infected; naïve + relapser	GT-1	12 or 24 weeks
SOUND-C2	IIb	362	Naïve	GT-1	16–40 weeks[†]

[†]Length of treatment with faldaprevir and deleobuvir.
FDV: Faldaprevir; GT: Genotype.

whole sampling time of 8 h, with comparable mean retention time values in both liver and plasma [20].

Metabolism

The mean half-life of FDV is 20–30 h [18]. It is a substrate and moderate inhibitor of CYP3A4, a mild inhibitor of CYP2C9, and an inhibitor of UGT1A1 from *in vitro* data [21]. It can produce indirect hyperbilirubinemia, especially in patients with Gilbert's syndrome [22].

Elimination

FDV elimination was studied in rats, dogs, monkeys and human volunteers. A very high liver concentration of the drug was observed especially in rats and hepatic-related clearance [19]. The only drug–drug interaction observed in clinical trials suggests that FDV is primarily metabolized by the CYP450 enzyme complex [21,23].

Drug–drug interactions

In vitro studies showed that FDV inactivates the CYP450 enzyme CYP3A4 (K_i = 61.9 μm and k_{inact} = 0.131 min^{-1}). In healthy volunteers receiving FDV 240 mg two-times a day (b.i.d.), increases in plasma concentrations of midazolam were observed following administration of intravenous midazolam, suggesting weak inhibition of hepatic CYP3A4. Greater increases in plasma concentrations of midazolam were observed following the administration of oral midazolam, suggesting moderate inhibition of overall (intestinal and hepatic) CYP3A4. In addition, an increase in S-warfarin exposure was obtained following a weak inhibition of CYP2C9 [21]. A similar increase was seen in the exposure of omeprazole and its metabolite 5-OH omeprazole suggesting that FDV inhibits CYP3A4 metabolism of omeprazole and 5-OH omeprazole but not CYP2C19. FDV had no significant effect on caffeine, efavirenz and dextromethorphan, suggesting that CYP1A2, CYP2B6 and CYP2D6 activities were not significantly affected by FDV [21].

With regard to interactions between FDV and antiretroviral HIV drugs, FDV has been studied in combination with darunavir/ritonavir (DRV/r), efavirenz (EFV) and tenofovir (TFV) in three open-label, Phase I trials in healthy volunteers [23]. When FDV was co-administered with DRV/r or TFV, there were no clinically relevant effects on the PK of DRV or TFV. FDV exposure, however, increased by approximately 130% with DRV/r, but decreased by approximately 22% with TFV, and also decreased by approximately 35% with EFV. The decrease in FDV exposure in combination with EFV is thought to be due to a CYP3A4 induction. As a consequence of the observed drug–drug interactions between FDV and HIV drugs, the following dosing recommendations are provided and have also been studied in the ongoing clinical trial: 240 mg of FDV in combination with EFV and 120 mg in combination with DRV/r or atazanavir/r. No relevant interactions are expected between FDV and raltegravir or maraviroc allowing for the study of different FDV doses in the clinical trial.

In a further Phase IIa study, the interactions between FDV and DBV and their individual and combined effect on CYP-mediated metabolism in patients with chronic GT 1 HCV infection were evaluated. Interestingly, a two-way drug interaction was observed when FDV was combined with DBV, increasing the exposure to both compounds, as well as weakly inducing CYP2C9 and weakly inhibiting CYP3A4 [24].

Clinical efficacy

Table 2 summarizes the clinical trials of the FDV development program.

Phase I studies

Phase Ib studies were conducted in treatment-naïve HCV mono-infected patients with HCV GT-1 infection. During 14-days of monotherapy with FDV a median maximal viral load (VL) reduction of 3.0, 3.6, 3.7 and 4.4 log_{10} for the 20, 48, 120 and 240 mg groups was observed, respectively. VL breakthroughs (increases of 1log_{10} in VL from nadir) were seen in most patients on monotherapy and were caused by NS3/4A variants (R155K, D168V) conferring *in vitro* resistance to

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Table 3. Baseline characteristics of patients enrolled in the STARTVerso4 trial.

Baseline characteristic	HCV treatment-naïve (n = 239)	Previous HCV relapse (n = 69)
Mean age, years	47	47
Male (%)	77	93
Race		
White (%)	75	91
black (%)	16	3
ART		
EFV-based (%)	28	25
ATV/r or DRV/r-based (%)	25	10
Ral-based and other (%)	44	59
No ART (ARV-naïve) (%)	3	6
Mean $CD4^+$ cell count, cells/mm^3	544	549
HCV VL ≥800,000 IU/ml (%)	82	71
Genotype 1a HCV (%)	77	80
Cirrhosis, F4 or transient elastography >13 kPa (%)	17	16

ART: Antiretroviral therapy; ARV: Antiretroviral; ATV/r: Atazanavir/ritonavir; DRV/r: Darunavir/ritonavir; EFV: Efavirenz; F4: Metavir F4; Ral: Raltegravir; VL: Viral load.
Data taken from [32].

FDV [18]. In most of the subjects, the co-administration of PegIFN/RBV at days 15–28 allowed for continuous VL reductions. VL breakthroughs were observed during triple combination in only 16% of patients [18]. FDV was generally well tolerated; overall, mild rash or photosensitivity was reported in 4 of 34 patients. The only dose-dependent laboratory abnormality was a mild unconjugated hyperbilirubinemia (8%).

SOUND-C1 was a Phase Ib study that evaluated FDV in IFN-free regimens. Thirty-two treatment-naïve patients with chronic HCV GT-1 infection were randomized to receive 4 weeks of treatment with DBV [25] (a non-nucleoside NS5B polymerase inhibitor) 400 or 600 mg three-times daily plus FDV 120 mg q.d. and weight-based RBV for 4 weeks. IFN-free therapy was followed by response-guided FDV plus PegIFN/RBV to week 24 or 48. At week 4, 73 and 100% of individuals in the DBV 400 and 600 mg groups reached HCV RNA <25 IU/ml [26]. Two patients exhibited increases in HCV RNA during IFN-free therapy but were successfully treated with IFN-based therapy. After 24 weeks of treatment, the SVR was 73% for DBV 400 mg and 94% for the 600 mg group [26].

Phase II studies

Data from Phase II studies demonstrated potent antiviral activity of FDV against HCV GT-1 both in regimens with PegIFN/RBV and in an IFN-free combination of FDV with DBV and RBV [27–30]. Improved viral cure rates were observed both in patients who had never been previously treated and patients who had not responded to previous treatment, compared with PegIFN/RBV alone. The four Phase II trials were SILEN-C1, SILEN-C2, SILEN-C3 and SOUND-C2.

SILEN-C comprised several multicenter, multinational, randomized, double-blind, placebo-controlled, Phase II studies assessing the efficacy and safety of FDV in combination with PegIFN/RBV in treatment-naïve and treatment-experienced HCV GT-1-infected individuals [28–30]. In the SILEN-C studies, FDV in combination with PegIFN/RBV demonstrated improved SVR rates in both treatment-naïve and treatment-experienced patients. Results also demonstrated that shortening the total treatment duration to 24 weeks was achievable in the majority of treatment-naïve patients.

SILEN-C1 enrolled treatment-naïve HCV GT-1-infected patients who received 120 or 240 mg of FDV q.d. plus PegIFN-α2a/RBV. Participants who received 240 mg of FDV q.d. plus PegIFN/RBV for 24 weeks without any lead-in phase (consisting in 3-day of placebo plus PegIFN/RBV) achieved 84% SVR versus 56% in patients in the control arm receiving dual therapy with PegIFN/RBV. Results from SILEN-C1 demonstrated no benefit in continuing PegIFN/RBV for longer than 24 weeks in patients who achieved a maintained rapid virologic response (mRVR; VL <25 IU/ml at week 4 and undetectable at weeks 8–20) [29].

SILEN-C2 included 290 non-cirrhotic HCV GT-1 patients with prior null or partial-response who were randomized 2:1:1 to receive 48 weeks of PegIFN-α2a/RBV in combination with 24 weeks of FDV 240 mg q.d. with 3 days PegIFN/RBV lead-in (LI); 240 mg q.d. without LI or 240 mg b.i.d. with LI. Patients in the 240 mg q.d./LI group achieving mRVR were re-randomized to cease all treatment at week 24 or continue PegIFN/RBV up to week 48. SVR rates were 32, 50 and 42% in prior partial-responders and 21, 35 and 29% in prior null-responders in the FDV 240 mg q.d./LI, 240 mg q.d. and 240 mg b.i.d./LI groups, respectively. In the 240 mg q.d./LI group, a significantly higher proportion of mRVR patients re-randomized to 48 weeks treatment achieved SVR, compared with those assigned to 24 weeks treatment (72 vs 43%; p = 0.035). Rates of gastrointestinal disorders, jaundice, dry skin and photosensitivity were increased under the 240 mg b.i.d. dose compared with the 240 mg q.d. dose. FDV discontinuations owing to adverse events occurred in 6, 4 and 23% of patients in the 240 mg q.d./LI, 240 mg q.d. and 240 mg b.i.d./LI groups.

SILEN-C3 included 159 treatment-naïve GT-1 HCV patients who were randomized to receive 120 mg q.d. FDV for 12 or 24 weeks, each after 3 days LI with PegIFN-α2a/RBV. In both groups, PegIFN/RBV was administered for 24 weeks. Patients who did not achieve an mRVR (defined in this trial as VL <25 IU/ml at week 4 and undetectable at weeks 8–12) continued PegIFN/RBV to week 48 [30]. A high SVR rate was observed even though 12% of the patients enrolled into the study were cirrhotic at baseline. Both 12- and 24-week arms had similar SVR rates of 67 versus 74% [30].

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The SOUND-C2 trial explored the combination of FDV with the non-nucleoside NS5B inhibitor DBV with and without RBV in HCV-GT-1 treatment-naïve patients [27]. A total of 362 patients, including 33 with liver cirrhosis, were enrolled and randomized into 5 study arms. Patients receiving all three drugs including twice-daily DBV achieved a 69% SVR12, which was higher than the SVR12 rate of 39% observed in those patients receiving the two DAAs without RBV. SVR was higher in patients with HCV GT-1b versus GT-1a (85 vs 43%) and/or IL-28B CC versus non-CC genotype (84 vs 64%) [27].

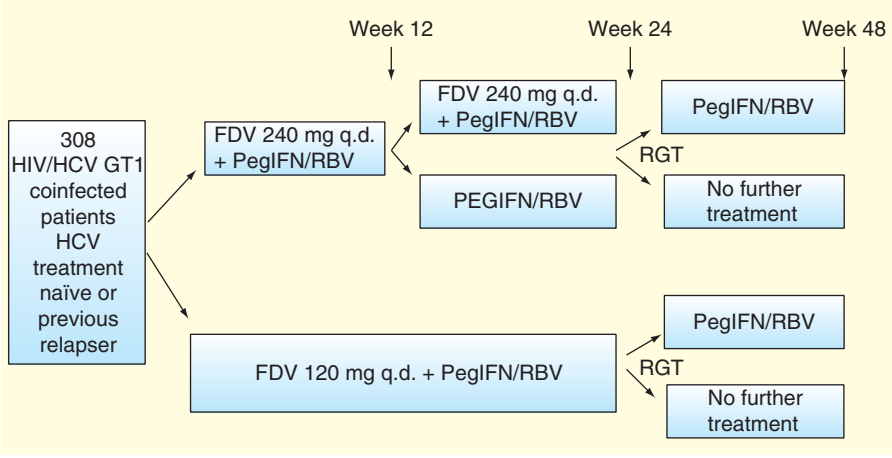

Figure 1. STARTVerso4 study design. Response-guided therapy, patients with HCV RNA below lower limit of quantification, at week 4, and HCV RNA not detected at week 8 (ETS) will be re-randomized 1:1 at week 24 to stop treatment or continue PegIFN/RBV through week 48. Patients who did not achieve ETS will continue PegIFN/RBV through week 48.
ETS: Early treatment success; FDV: Faldaprevir; PegIFN/RBV: Pegylated interferon and ribavirin; RGT: Response-guided therapy.
Data taken from [32].

Phase III studies

Four STARTVerso Phase III trials are currently evaluating FDV combined with PegIFN/RBV. STARTVerso4 includes HIV-HCV co-infected patients.

STARTVerso1 [31] is a double-blind, placebo-controlled Phase III trial of FDV in combination with PegIFN/RBV. The study enrolled and treated 652 treatment-naïve patients from Europe and Japan who were infected with chronic GT-1 HCV infection. Patients were randomized to receive PegIFN/RBV in combination with a q.d. dose of 120 mg FDV, 240 mg FDV or placebo. Treatment duration (total of 24 or 48 weeks) depended on whether patients met criteria for protocol-defined early treatment success (ETS; VL <25 IU/ml at week 4 and undetectable at week 8) [31]. Patients in the FDV arms received this drug during the first 12 weeks of therapy.

ETS was achieved by 87 and 89% of patients treated with the FDV-based regimen (120 or 240 mg), respectively. Patients receiving a shorter treatment of 12 weeks FDV with 24 weeks PegIFN/RBV had an SVR12 rate of 86 and 89% (120 or 240 mg), respectively [31].

Serious adverse events were experienced by 6% of the placebo-treated patients, 7% of patients receiving 120 mg FDV and 7% of patients receiving 240 mg FDV. Rash and gastrointestinal disturbances were the most common adverse events of at least moderate intensity. No rash events were life-threatening. Adverse events led to discontinuation of study medications in 4% (n = 5), 4% (n = 10) and 5% (n = 14) in the placebo, FDV 120 mg and FDV 240 mg arms, respectively [31].

Faldaprevir for HIV/HCV co-infected patients

STARTVerso4 is an open-label, Phase III study assessing the efficacy and safety of FDV in combination with PegIFN/RBV in HIV/HCV co-infected patients. Four hundred and fifty-three patients co-infected with HCV and HIV were screened for the study, and of them 308 individuals were treated.

Inclusion criteria were the presence of HIV-1 and chronic HCV GT-1 infection, patients were naïve of HCV treatment or experienced, only if relapsers; patients were antiretroviral naïve or on stable HAART; HCV viral load was higher than 1000 IU/ml. Exclusion criteria were the presence of mixed HCV genotype infection (1/2, 1/3, 1/4); HBV infection (presence of HBsAg); active malignancy or history of malignancy within the last 5 years; received concomitant systemic antiviral (other than antiretroviral), hematopoietic growth factor or immunomodulatory treatment in 28 days prior enrolment; decompensated liver disease, as evidenced by ascites, hepatic encephalopathy, esophageal variceal bleeding and/or laboratory values that add up to ≥7 points according to the Child–Turcotte–Pugh classification; hemoglobin levels ≤11 g/dl for women and ≤12 g/dl for men; patients with stable cardiac disease and hemoglobin <12 g/dl and known hypersensitivity to any ingredient of the study drugs.

Sixty-nine patients (22%) were relapsers to previous HCV therapy and 239 (88%) were HCV treatment-naïve. Individuals could either be HIV treatment-naïve or currently being treated with antiretroviral therapy. The trial included patients with compensated cirrhosis (17% had F4 cirrhosis or transient hepatic elastography >13 kPa) [32]. Table 3 summarizes the patient's baseline characteristics.

Patients were divided into two groups: group 1 received 12 or 24 weeks of FDV 240 mg q.d. in addition to 24 or 48 weeks of PegIFN/RBV; group 2 received 24 weeks of FDV 120 mg q.d. in addition to 24 or 48 weeks of PegIFN/RBV. Individuals without HAART or with raltegravir or maraviroc were randomized to one of the two study arms [32]. Patients with antiretroviral background therapy shown to impact FDV levels received the following FDV doses: patients with EFV-based regimens were allocated to receive FDV 240 mg q.d. and those on DRV/r or atazanavir/r were allocated to FDV 120 mg q.d. Figure 1 depicts the corresponding study design [32].

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Table 4. Interim safety and tolerability profile reported of STARTVerso4.

Most frequent AEs in >20% of patients	Patients (n; %)
Nausea	113 (37)
Fatigue	102 (33)
Diarrhea	83 (27)
Headache	71 (23)
Asthenia	68 (22)
Other AEs of interest	
Anemia†	55 (18)
Neutropenia†	49 (16)
Rash	55 (18)

†Reported as AEs by the investigator, not as laboratory findings.
AE: Adverse events.
Data taken from [32].

The early treatment response rates were similar to those observed in treatment-naïve HCV-mono-infected patients (SILEN-C1 study) without cirrhosis receiving FDV 240 mg q.d. plus PegIFN/RBV. At week 4, 80 and 91% of treatment-naïve and relapse patients, respectively, had HCV RNA <25 IU/ml. At week 12, 82 and 91% of patients had undetectable HCV RNA. Overall, ETS was observed in 80% of patients: 77% of treatment-naive patients and 88% of relapsed patients. All the individuals maintained HIV suppression (Table 2) [32].

Adverse events are depicted in Table 4. Three deaths were reported due to dyspnea, hemorrhagic cerebrovascular accident and a drug reaction with eosinophilia with systemic symptoms [32]. Overall, 15/239 HCV treatment-naïve patients and 3/69 relapsers discontinued HCV therapy due to adverse events. In the table, discontinuations due to anemia and neutropenia have been reported as an adverse event not as a laboratory event. Hemoglobin <10 or >3.5 g/dl decrease from baseline occurred in 13/306 patients (4%) and neutropenia <750 mm^3 in 44/306 patients (14%). The reason for the difference in the clinical anemia adverse event rate and the number of patients with grade II–IV hemoglobin decline is that many investigators reported the occurrence of anemia in the eCRF based on patients symptoms that were not accompanied by a significant decline in hemoglobin levels.

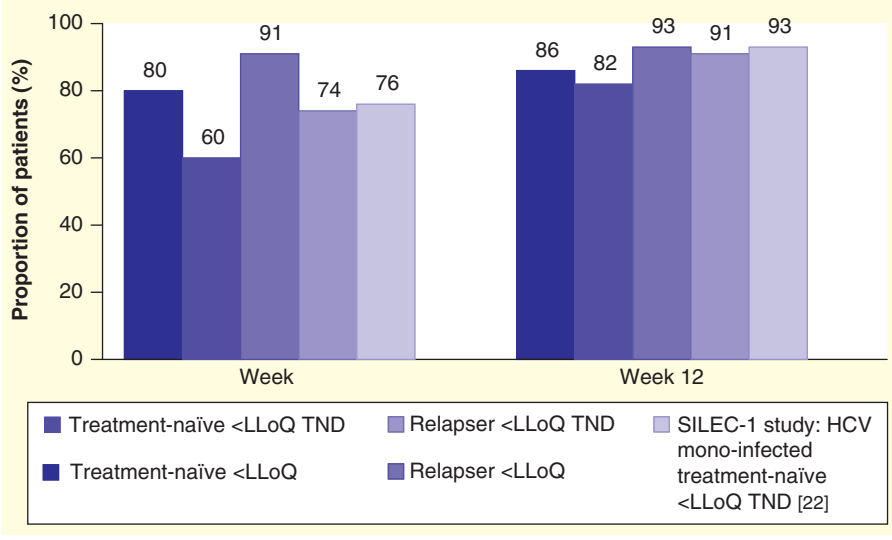

Figure 2. Early virologic response in HIV/HCV co-infected patients: comparison with HCV mono-infected patients.
LLoQ: Lower limit of quantification (25 IU/ml); TND: Target not detected.
Data taken from [32].

Regulatory affairs

In April 2011, the US FDA granted Fast Track designation for the IFN-based development programs for faldaprevir* in combination with PegIFN/RBV for genotype 1 patients and the IFN-free regimen of faldaprevir* and deleobuvir* plus RBV [102]. In November 2013, FDV was accepted for accelerated assessment by the EMA.

Dosage & administration

FDV was studied in healthy volunteers in a multiple dose rising study which found FDV to be safe and well tolerated at doses of 20–240 mg once a day for 21–28 days [18].

FDV has a long elimination half-life with a steady-state achieved after 1 week of dosing. This allows for a q.d. dosing schedule without risk of suboptimal plasma concentrations between doses [18].

Expert commentary

So far, the uptake of DAA-based therapy in HIV/HCV co-infected patients has been very limited even in countries where the drugs have been available for some time, the complexity of HCV treatment in HIV co-infection including drug–drug interactions, limited data available and increased risk for toxicities have prevented more widespread use of these new therapeutic options. The advent of FDV promises some distinct features that may make the use of FDV more appealing in HIV/HCV co-infected individuals. First of all, FDV can be administered q.d. supporting adherence and obviously simplifying HCV therapy quite considerably. In addition, it appears as if FDV, although metabolized by the CYP450 system, has less drug–drug interactions with HIV drugs and can be used in the 120 mg q.d. dose in combination with ritonavir-boosted atazanavir and darunavir. Indeed, the use of DRV/r with telaprevir or boceprevir has been considered contraindicated thus far, in addition simeprevir (the other next wave HCV protease inhibitor expected to be licensed shortly) cannot be combined with ritonavir-boosted protease

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inhibitors due to significant drug–drug interactions. Moreover, the large study of FDV in HIV/HCV co-infected patients is evaluating response-guided therapy with only 24 weeks of triple therapy in patients achieving ETS suggesting that the majority of patients may only need to be treated for 24 weeks. Finally, overall tolerability appears somewhat better than with the first-generation HCV protease inhibitors, thereby further helping to decrease the barriers in uptake of DAA-based HCV therapy.

Five-year view

The introduction of FDV will allow simplified and better-tolerated HCV protease inhibitor-based HCV therapy in combination with Peg-IFN/RBV therapy. The role FDV may play in IFN-free regimens in HIV co-infection still needs to be further explored. However, many Phase III studies in HCV mono-infection are ongoing. So far it looks as if, at least for HCV GT-1b patients, FDV in combination with DBV and RBV can lead to cure rates above 85%. Clearly in 5 years from now the majority of patients (>90%) will be treated with IFN-free combinations.

Financial & competing interests disclosure

JK Rockstroh has received honoraria for consulting or speaking at educational events from Abbvie, Bionor, Boehringer Ingelheim, BMS, Gilead, Janssen, Merck, Novartis, Roche, Tibotec, Vertex and ViiV. NL Laufer has received honoraria for speaking at educational events from Merck. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Faldaprevir (FDV), previously known as BI 201335, is a second-wave HCV NS3/4A protease inhibitor with highly potent *in vitro* activity against HCV GT-1a/1b and improved pharmacokinetics suitable for once-daily dosing. It is currently in Phase III development.
- There is an ongoing Phase III study (STARTVerso4) assessing the efficacy and safety of FDV in combination with pegylated interferon and ribavirin in HIV/HCV co-infected patients.
- In HIV/HCV co-infected patients both in treatment-naïve and treatment-experienced patients, rates of sustained virological response were higher when FDV was added to standard therapy of pegylated interferon and ribavirin.
- The most significant adverse events associated with FDV treatment were nausea, fatigue, diarrhea and headache.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Lavanchy D. The global burden of hepatitis C. *Liver Int.* 29(Suppl. 1), 74–81 (2009).

2 Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J. Hepatol.* 44(1 Suppl.), S6–S9 (2006).

3 Soriano V, Mocroft A, Rockstroh J *et al.* Spontaneous viral clearance, viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. *J. Infect. Dis.* 198(9), 1337–1344 (2008).

4 Laufer N, Quarleri J, Bouzas MB *et al.* Hepatitis B virus, hepatitis C virus and HIV coinfection among people living with HIV/AIDS in Buenos Aires, Argentina. *Sex. Trans. Dis.* 37(5), 342–343 (2010).

5 Bolcic F, Jones LR, Laufer N, Quarleri J. Molecular characterization of hepatitis C virus genotype 4 sequences in HIV-coinfected patients from Argentina. *J. Med. Virol.* 83(6), 935–940 (2011).

6 Soriano V, Vispo E, Labarga P, Medrano J, Barreiro P. Viral hepatitis and HIV co-infection. *Antiviral Res.* 85(1), 303–315 (2010).

7 Benhamou Y, Bochet M, Di Martino V *et al.* Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. *Hepatology* 30(4), 1054–1058 (1999).

8 Poynard T, Mathurin P, Lai CL *et al.* A comparison of fibrosis progression in chronic liver diseases. *J. Hepatol.* 38(3), 257–265 (2003).

9 Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. *Clin. Infect. Dis.* 50(10), 1387–1396 (2010).

10 Smith C, Sabin CA, Lundgren JD *et al.* Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS* 24(10), 1537–1548 (2010).

11 Lamarre D, Anderson PC, Bailey M *et al.* An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature* 426(6963), 186–189 (2003).

12 Poordad F, McCone J Jr, Bacon BR *et al.* Boceprevir for untreated chronic HCV genotype 1 infection. *N. Engl. J. Med.* 364(13), 1195–1206 (2011).

13 Jacobson IM, McHutchison JG, Dusheiko G *et al.* Telaprevir for previously untreated chronic hepatitis C virus infection. *N. Engl. J. Med.* 364(25), 2405–2416 (2011).

14 Sulkowski MS. Current management of hepatitis C virus infection in patients with HIV co-infection. *J. Infect. Dis.* 207(Suppl. 1), S26–S32 (2013).

• **Very comprehensive review on the many issues that need to be addressed to optimize the management of HCV infection in people living with HIV/AIDS.**

15 Pawlotsky JM. Treatment of chronic hepatitis C: current and future. *Curr. Top. Microbiol. Immunol.* 369, 321–342 (2013).

16 Llinas-Brunet M, Bailey MD, Goudreau N *et al.* Discovery of a potent and selective noncovalent linear inhibitor of the hepatitis C virus NS3 protease (BI 201335). *J. Med. Chem.* 53(17), 6466–6476 (2010).

17 White PW, Llinas-Brunet M, Amad M *et al.* Preclinical characterization of BI 201335, a C-terminal carboxylic acid inhibitor of the hepatitis C virus

doi: 10.1586/14787210.2014.868774

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NS3-NS4A protease. *Antimicrob. Agents Chemother*. 54(11), 4611–4618 (2010).

18 Manns MP, Bourliere M, Benhamou Y *et al.* Potency, safety, and pharmacokinetics of the NS3/4A protease inhibitor BI201335 in patients with chronic HCV genotype-1 infection. *J. Hepatol*. 54(6), 1114–1122 (2011).

19 Duan J, Yong CL, Garneau M *et al.* Cross-species absorption, metabolism, distribution and pharmacokinetics of BI 201335, a potent HCV genotype 1 NS3/4A protease inhibitor. *Xenobiotica* 42(2), 164–172 (2012).

20 White PW, Llinas-Brunet M, Amad M *et al.* Preclinical characterization of BI 201335, a C-terminal carboxylic acid inhibitor of the hepatitis C virus NS3-NS4A protease. *Antimicrob. Agents Chemother*. 54(11), 4611–4618 (2010).

21 Sabo J, Kashuba A, Ballow C *et al.* Cytochrome P450 (CYP) Interactions with the HCV Protease Inhibitor Faldaprevir (BI 201335) in Healthy Volunteers. Presented at: *The 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)*. San Francisco, CA, USA, 9–12 September 2012.

22 Sane R, Podila L, Mathur A *et al.* Mechanisms of isolated unconjugated hyperbilirubinaemia induced by the HCV NS3/4A protease inhibitor BI201335. In: abstracts of the 46th EASL Annual Meeting, Berlin, 2011. Abstract 1236. *J. Hepatol*. 54(Suppl. 1), S488 (2011).

23 Sabo J, Kort J, Haschke M *et al.* pharmacokinetic interactions of darunavir/ritonavir, efavirenz, and tenofovir with the hepatitis C virus protease inhibitor faldaprevir in healthy volunteers. Presented at: *20th Conference on Retroviruses and Opportunistic Infections*. Atlanta, GA, USA, 3–6 March 2013 (Abstract 35).

•• **This trial is very important since the posible interactions with antirretroviral drugs are studied wich are very relevant in the management of co-infected patients during HCV treatment.**

24 Poster sessions. *Hepatology* 58(S1), 92A–207A (2013).

25 Kukolj G, McGibbon GA, McKercher G *et al.* Binding site characterization and resistance to a class of non-nucleoside inhibitors of the hepatitis C virus NS5B polymerase. *J. Biol. Chem*. 280(47), 39260–39267 (2005).

26 Zeuzem S, Asselah T, Angus P *et al.* Faldaprevir (BI 201335), BI 207127 and ribavirin oral therapy for treatment-naive HCV genotype 1: SOUND-C1 final results. *Antiviral Ther*. doi:10.3851/IMP2567 (2013) (Epub ahead of print).

• **This review described the results that support the use of faldaprevir (FDV) in IFN-free regimens for the treatment of chronic HCV infection.**

27 Zeuzem S, Soriano V, Asselah T *et al.* Faldaprevir and deleobuvir for HCV genotype 1 infection. *N. Engl. J. Med*. 369(7), 630–639 (2013).

• **This review described the results that support the use of FDV in IFN-free regimens for the treatment of chronic HCV infection.**

28 Sulkowski MS, Bourliere M, Bronowicki JP *et al.* Faldaprevir combined with peginterferon Alfa-2a and ribavirin in chronic HCV genotype-1 patients with prior nonresponse: SILEN-C2 trial. *Hepatology* 57(6), 2155–2163 (2013).

29 Sulkowski MS, Asselah T, Lalezari J *et al.* Faldaprevir combined with peginterferon alfa-2a and ribavirin in treatment-naive patients with chronic genotype-1 HCV: SILEN-C1 trial. *Hepatology* 57(6), 2143–2154 (2013).

• **This review described the improvements and higher rates of sustained virological response (SVR) for HCV treatment with FDV in HCV mono-infected.**

30 Dieterich D, Asselah T, Guyader D *et al.* SILEN-C3: treatment for 12 or 24 weeks with BI201335 combined with peginterferon alfa-2a and ribavirin (P/R) in treatment-naïve patients with chronic genotype-1 HCV infection. Presented at: *62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD 2011)*. San Francisco, CA, USA, 4–8 November 2011 (Abstract 36).

31 Ferenci P, Asselah T, Foster GR *et al.* Faldaprevir plus pegylated interferon alfa-2A and ribavirin in chronic HCV genotype-1 treatment-naive patients: final results from STARTVerso1, a randomised double blind placebo-controlled phase III trial. Presented at: *48th Annual Meeting of the European Association for the Study of the Liver (EASL 2013)*. Amsterdam, the Netherlands, 24–28 April 2013 (Abstract 1416).

32 Dieterich D, Soriano V, Nelson M *et al.* STARTVerso4: high rates of early virologic response in HCV genotype 1/HIV-coinfected patients treated with faldaprevir plus PegIFN and RBV. *CROI 2013*. Atlanta, GA, USA, 3–6 March (2013).

•• **The first and only study that details the efficacy and safety of FDV in the treatment of HCV in HIV co-infected patients.**

Websites

101 WHO. Fact facts on HIV. www.who.int/hiv/data/fast_facts/en/index.html (Accessed 3 August 2012)

102 US FDA. Fast Track Designation. Updated May 2010. www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm (Accessed 16 April 2012)

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