Recommendations for the use of Hepatitis C virus protease inhibitors for the treatment of chronic Hepatitis C in HIV-infected persons.
A position paper of the Italian Association for the Study of Infectious and Tropical Diseases

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―――――――――― SUMMARY ――――――――――

The efficacy data obtained with boceprevir and telaprevir for persons with hepatitis C virus (HCV) genotype 1 infection raise the question of whether HCV protease inhibitors should be used in human immunodeficiency virus (HIV)/HCV co-infected persons. The Italian Association for the Study of Infectious and Tropical Diseases has made these recommendations to provide the rationale and practical indications for the use of triple anti-HCV therapy in persons living with HIV (PLWHIV).

A Writing Committee of experts indicated by the President of the Association and a Consulting Committee contributed to the document. The final draft was submitted to the evaluation of external experts and the text modified according to their suggestions and comments.

Treatment of HCV co-infection should be considered for all HCV RNA positive PLWHIV. Response-guided therapy with pegylated interferon and ribavirin is the standard treatment of PLWHIV with infection by HCV genotype 2, 3, 4, 5 and 6. Boceprevir and telaprevir should be used to treat HCV genotype 1 infection in HIV/HCV co-infected patients for 48 weeks on an individual basis, with close monitoring of their efficacy and tolerability with concurrent antiretroviral therapy, taking into account potential drug-drug interactions. The decision to treat a patient or to wait for better treatment options, or to discontinue treatment should be made on an individual basis taking into account pre-treatment variables and the on-treatment HCV RNA kinetics.

KEY WORDS: HIV, HCV, Antiretroviral therapy, Boceprevir, Telaprevir, PEG-IFN, RBV.

INTRODUCTION

The efficacy data obtained with boceprevir (BCV) and telaprevir (TPV) in persons with genotype 1 hepatitis C virus (HCV) infection together with current and future drug availability raise the question of whether HCV protease inhibitors (PIs) should be used in human immunodeficiency virus (HIV)/HCV co-infected persons. Only the data from two phase II pilot studies are available (Sulkowski and Pol, *et al.,* 2013; Sulkowski and Sherman KE *et al.,* 2013). Due to the absence of large studies on HIV/HCV co-infected persons, the clinical and policy decisions must be based largely on the data obtained from HIV-uninfected persons, but they should be adjusted according to the unique biological and clinical characteristics of HCV co-infection in persons living with HIV (PLWHIV). For these reasons the Italian Association for the Study of Infectious and Tropical Diseases has put forward the present *"Recommendations for the use of Hepatitis C virus protease inhibitors for the treatment of Hepatitis C in HIV-infected persons"*. These recommendations are intended to provide the rationale and practical indications for the use of triple anti-HCV therapy for PLWHIV.

The recommendations are graded in three levels according to the GRADE system based on the evidence available: A (high), B (medium) and C (low, based only on expert opinion), with 3 degrees of strength of the recommendation: 1 (strong), 2 (medium), 3 (weak) reported in brackets for each statement. It should be noted that most of the recommendations are based on expert opinion because of the lack of conclusive evidence on the use of telaprevir and boceprevir for PLWHIV. A Writing Commission of experts indicated by the President of the Association and a Consulting Committee contributed to the document. The final draft was then submitted to the evaluation of external experts (Reviewing Committee) and the text modified according to their suggestions and comments.

RATIONALE FOR THE TREATMENT OF HEPATITIS C IN PLWHIV

HCV prevalence and mortality in PLWHIV

HIV and HCV share common transmission

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pathways, but HCV is more efficiently transmitted through blood and blood products and less efficiently transmitted through sexual intercourse (Puoti and Moioli *et al.*, 2012).

For these reasons, in Italy, where the HIV epidemics in the 1980s and 1990s were mainly driven by intravenous drug use (IDU), 20-40% of PLWHIV are co-infected with HCV. In particular, in the ICONA cohort (an Italian cohort that enrolled more than 10,000 HIV-positive HCV-therapy-naïve patients from different centers in Italy), the prevalence of anti-HCV antibodies (HCV-Ab) was 32.6%, with 2.6% also co-infected with the hepatitis B virus (HBV). HCV infection is highly prevalent among intravenous drug users (87.4%), while it is less frequent among individuals infected through heterosexual or homosexual intercourse (11.4% and 6.1%, respectively) (d'Arminio Monforte A for the ICONA cohort. Personal communication).

Thus, the prevalence of HCV co-infection is related to risk factors for HIV. In another large Italian cohort (MASTER), 5688/10206 (55.4%) patients followed up in 2012 had positive HCV RNA: 46% reported IDU as a risk factor, while 29% were males having sex with males (MSM) [Torti C. for the MASTER cohort. Personal communication].

After the introduction of combination antiretroviral therapy (cART) in 1996, the HIV-related mortality declined in PLWHIV, while liver-related causes of death (liver decompensation and hepatocellular carcinoma) still remain among the primary causes of death in PLWHIV (Ioannou *et al.*, 2013). In the ICONA cohort, liver-related death accounted for 19.4% of all deaths (n=624) [d'Arminio Monforte A for the ICONA cohort. Personal communication]. HCV is not the only liver-related cause of death since other factors contributing to this are: HBV co-infection, alcohol abuse, HIV-induced CD4 depletion and diabetes (Ioannou *et al.*, 2013).

As a consequence, a multi-target clinical strategy has been proposed to decrease liver-related morbidity and mortality in PLWHIV. This strategy should include: hepatitis B vaccination and the optimization of dual anti-HIV and anti-HBV therapy, screening for and proactive treatment of alcohol abuse, optimization of cART, management of insulin resistance and

a prompt diagnosis and treatment of glucose intolerance and diabetes (Puoti *et al.*, 2013). As HCV co-infection is the leading cause of liver disease in PLWHIV, a "screen and treat" strategy for HCV co-infection is, at least in theory, the most effective measure to decrease liver-related mortality in PLWHIV (Puoti *et al.*, 2013). The impact of HIV co-infection on the natural history of hepatitis C is strong, as HIV increases the rate of chronicization of acute HCV infection and accelerates the progression to cirrhosis, liver decompensation and hepatocellular carcinoma (Orsetti *et al.*, 2013; Soriano *et al.*, 2007). It has recently been observed that in HIV/HCV co-infected subjects advanced fibrosis, defined by a liver stiffness measurement >14.6 kPa, is associated with a risk of 17% of liver decompensation at 2 years (95% confidence interval [CI] 13-23%) (Macías *et al.*, 2013). Despite excellent results of orthotopic liver transplantation in HIV-infected patients with non-HCV-related liver disease, the results are poorer for HIV/HCV co-infected recipients. The worse outcome is mainly related to the severity of HCV recurrence, with a more frequent occurrence of fibrosing cholestatic hepatitis and a more rapid progression of fibrosis (Miro *et al.*, 2012; Antonini *et al.*, 2011). Given the fundamental role of HCV reinfection in this setting, a dramatic impact can be expected once new and more potent anti-HCV drugs are available for use in the pre- and post-transplant phase.

Recommendations

1. *Liver diseases are important causes of death in PLWHIV in Italy. Hepatitis C is the most frequent cause of liver disease in PLWHIV. HIV accelerates the progression of hepatitis C to cirrhosis, liver decompensation and death. All anti-HCV-negative PLWHIV should be screened for HCV co-infection at least once a year (A1).*
2. *Treatment of HCV co-infection should be considered for all HCV RNA-positive patients (A1). Because of the rapid progression of liver disease, the priority for PLWHIV for anti-HCV treatment is always very high (B1), but it is highest among those with advanced fibrosis, due to the high mortality of these patients in the short term (B1).*
3. *Survival after liver transplant is suboptimal in HCV RNA-positive PLWHIV. A specific study*

protocol set up for the centers participating in the HIV transplant program is strongly needed (C2); this protocol should also evaluate the implementation of new anti-HCV drugs, including compassionate and off-label use whenever appropriate (C1).

Benefits of HCV clearance in PLWHIV

HCV co-infection in PLWHIV has been independently associated with an increased incidence of diabetes, neurocognitive impairment and kidney failure and of pathological hip fractures (Slama et al., 2009; Peters et al., 2012; Lo Re et al., 2012; Ciccarelli et al., 2013).

The severity of the liver disease only partly explains the HIV/HCV-associated increased risk of these conditions (Maalouf et al., 2013). There are also controversial data regarding an unfavorable impact of HCV co-infection on the progression of HIV infection to AIDS and on CD4 recovery after cART initiation.

Several cohort studies, including those performed within the ICONA cohort, showed an accelerated progression to AIDS, and two Italian cohort studies and a meta-analysis of combined data of four AIDS clinical trial group studies showed reduced immune recovery with ART (Pulido et al., 2012; Hua et al., 2013), while other cohort studies did not confirm an influence of HCV on the natural history of HIV or on its evolution after ART (Pulido et al., 2012).

These discordant results could be due to confounders associated with HCV co-infection: history of injection drug use, low socioeconomic status, African American ethnicity and, finally, discordance between the CD4 counts and the percentage of patients with severe liver fibrosis (Pulido et al., 2012).

However, there is clear evidence that HCV co-infection increases the liver toxicity of all antiretrovirals, including those of the newer generations (Borghi et al., 2013), thereby limiting the potential benefits of cART.

This risk declines once the patient has achieved a sustained virological response (SVR) after anti-HCV therapy (Uberti-Foppa et al., 2003).

Achieving SVR to anti-HCV treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) is associated with an increased overall survival due to a decrease in liver-related mor-

tality and also to a decrease in AIDS-related and even in AIDS- and liver-unrelated mortalities (Berenguer et al., 2012; Cenderello et al., 2013].

Thus, SVR to anti-HCV treatment is an important outcome that can improve the life expectancy and quality of life for PLWHIV.

Recommendation

4. *SVR to anti-HCV treatment is an important endpoint in the management of HIV/HCV coinfected patients because it is associated not only with a decrease in liver-related morbidity and mortality (A1), but also a better efficacy and tolerability of cART (B2) and, presumably, a reduced incidence and severity of HIV-related comorbidities such as bone and renal disease, neurocognitive impairment and diabetes (C3).*

RESULTS OF ANTI-HCV TREATMENT WITH PEGYLATED INTERFERON AND RIBAVIRIN IN PLWHIV

Unfortunately, only a small proportion of HIV/HCV co-infected persons are treated with PEG-IFN + RBV. This is because of the low propensity of HIV-treating physicians to prescribe interferon, or treatment refusal due to the fear of the well-known treatment side-effects, or because of contraindications and comorbidities (Kramer et al., 2012). In the Italian MASTER cohort, of the 5688 HIV/HCV co-infected patients followed up, only 926 (16.3%) had received interferon with or without RBV [Torti C for the MASTER cohort. Personal communication].

Several studies assessed the SVR rate to PEG-IFN+RBV in HIV/HCV co-infected patients (Soriano et al., 2007), which overall was lower than 60% in all the studies and substantially less than 50% in PLWHIV infected by HCV genotype 1 or 4 (Soriano et al., 2007).

Several national and international guidelines indicate response-guided therapy as the best way to optimize treatment with PEG-IFN and RBV (Figure 1) and this indication should still be followed for patients infected by HCV genotypes 2, 3 or 4 for whom direct-acting antivirals (DAAs) are still not available in clinical practice (Soriano et al., 2007).
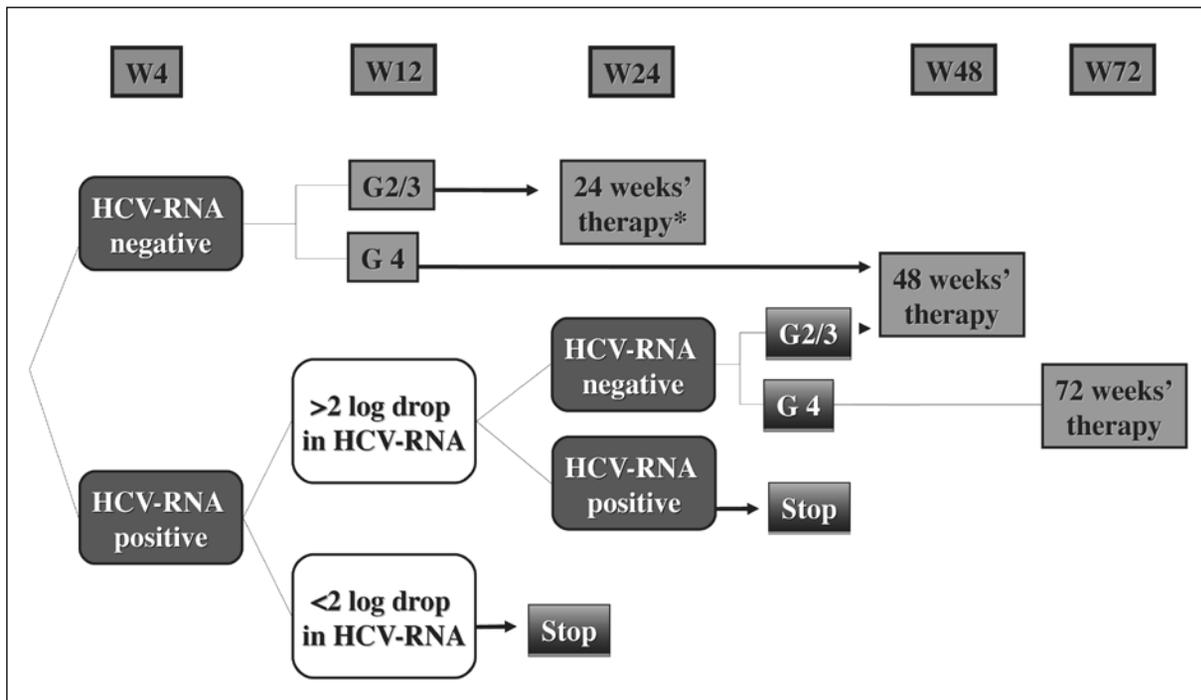
FIGURE 1 - *Response-guided therapy in PLWHIV with HCV non-1 genotypes.*

Recommendation

5. *Response-guided therapy with PEG-INF and RBV is the standard treatment for PLWHIV infected by HCV genotypes 2, 3, 4, 5 or 6 (B1).*

ANTI-HCV THERAPY WITH PROTEASE INHIBITORS IN PLWHIV

The treatment of HCV genotype 1 infection in PLWHIV is evolving rapidly following the availability of the first HCV PIs. TPV and BOC were approved by the US Food and Drug Administration in May 2011 for the treatment of chronic hepatitis C both for therapy-naïve and PEG-IFN+RBV-experienced patients. They are currently used in combination with PEG-IFN+RBV in patients infected with HCV genotype 1.

Anti-HCV treatment of therapy-naïve PLWHIV

Phase III clinical trials evaluating the safety and efficacy of HCV PIs are underway for therapy naïve HIV/HCV co-infected patients. The first data from two phase-2 pilot studies on the efficacy and tolerability of BOC- and TPV-based triple therapy were released in 2013 (Sulkowski and Pol, *et al.,* 2013; Sulkowski and Sherman KE *et al.,* 2013). The two studies have a major limitation: they enrolled a small number of patients with a high rate of screening failure (50% of those screened) with a small proportion of patients with advanced fibrosis (F3 and F4 according to the METAVIR classification) lower than that included in previous studies with PEG-IFN + RBV (Soriano *et al.,* 2007).

Nevertheless, in both studies the SVR rate was significantly higher with triple therapy than with double therapy. Adverse events (AE) were similar and even arithmetically better than those observed in HCV mono-infection. Some data from ongoing real-life studies confirmed that the efficacy and tolerability of TPV and BOC in PLWHIV are similar to those observed in HIV uninfected persons (Kostman *et al.,* 2013; Benito *et al.,* 2013; Martel-Laferriere *et al.,* 2013). There is also some evidence of a lower incidence of rash and anal discomfort in PLWHIV (Kostman *et al.,* 2013; Benito *et al.,* 2013; Martel-Laferriere *et al.,* 2013). However, in an unselected patient population treated in a real-life setting in the USA, a 50% incidence

of severe adverse events (SAE) was reported (Cachay *et al.,* 2013). In HIV negative cirrhotic patients enrolled in a large French study, a high rate of SAE and liver decompensation with related and unrelated death was reported, with the highest incidence in patients with low platelet counts and albumin levels (Fontaine *et al.,* 2013). Although these preliminary data are encouraging, these two drugs carry the same challenges for PLWHIV as for the HCV mono-infected:

a) complex treatment schedules;
b) high drug costs;
c) heavy pill burden;
d) t.i.d. administration (although a b.i.d. schedule has since been registered for TPV [GU Serie Generale n.105 del 7-5-2013]);
e) potential generation, selection and persistence of viral quasispecies associated with resistance to the drug used;
f) marked cross-resistance to the same class and potential for cross-resistance to newer generation drugs of the same class;
g) a higher incidence of side-effects compared with double therapy.

In the two pilot studies, treatment was given for a fixed duration of 48 weeks. Studies to assess the feasibility of response-guided anti-HCV triple therapy in PLWHIV are ongoing.

Recommendations

6. *BOC and TPV should be used ideally in prospective controlled studies in HIV/HCV co-infected patients (A2). However, in the absence of these studies patients should be treated on an individual basis with close monitoring of the efficacy*

Telaprevir (TPV) in combination with Pegylated Interferon and Ribavirin (PEG-INF + RBV): suggested treatment schedule in PLWHIV

750 mg (two 375-mg tablets) q8hr or 1125 (three 375 mg tablets) q12h with food (not low fat; standard fat meal is 21 g)

If on efavirenz based ART:1125 (three 375-mg tablets) q8hr with food (not low fat; standard fat meal is 21g). If TPV adiministered with drugs having potential clinically signif cant interactions t.i.d. schedule should be preferred.

TEL + PEG-INF + RBV	PEG-INF + RBV

0   4   12   24   48

eRVR: HCVRNA undetectable at 4 and 12 weeks: 24 weeks treatment duration could be considered in naives non cirrhotics with poor tolerability

Time Point	Criterion	Stopping Rule
Wk 4 or 12	HCV RNA > 1000 IU/mL (> 100 if TPV started after lead in with PEG-INF + RBV)	Discontinue all therapy
Wk 24	Detectable HCV RNA	Discontinue PEG-INF + RBV
Any	Discontinuation of PEG-INF + RBV for any reason	Discontinue TVP

Modif ed from Telaprevir [package insert]. May 2011 and EMA. Telaprevir [package insert] 2011.

FIGURE 2 - *PEG-IFN + RBV + telaprevir triple therapy. Treatment schedule in PLWHIV.*

and safety of anti-HCV treatment and of concurrent antiretroviral therapy (C2).

The treatment risk/benefit ratio is related to the incidence and severity of the side-effects, which, in HIV-uninfected patients are more severe in patients with advanced fibrosis or cirrhosis (A1). Treatment should generally be avoided in patients with a history of ascites or with albumin <3.5 g/dL or platelets <100,000 µL. (B1) and may be considered only for selected patients with hepatocellular carcinoma who are candidates for liver transplantation (C3).

7. *Patients should be adequately counseled regarding the side-effects, treatment schedule, predicted treatment efficacy and the measures to improve the cost effectiveness of treatment (i.e. futility rules, rash management plan) (B1). Treating physicians should see the patient frequently*

and be available for any emergency (B1). Treating centers should organize a treating team involving specialists in infectious diseases, nurses and other specialists (hepatologists, dermatologists, pharmacologists, psychiatrists) with adequate human resources and time for the management of scheduled and unscheduled visits. (B2).

8. *The recommended schedule of triple therapy in PLWHIV is:* (Figures 3 and 4).

- 12-week triple therapy followed by 36 weeks with PEG-IFN + RBV for patients treated with TPV (Figure 2) *(B2).*

- 4-week "lead in" double therapy with PEG-IFN + RBV followed by 44-week triple therapy with BOC (Figure 3) *(B2).*

The HCVRNA levels should be monitored at least with the same frequency indicated for HIV uninfected patients (B1). HCV sequencing to iden-

Boceprevir (BOC) treatment schedule in PLWHIV

800 mg (four 200-mg capsules) q8hr with meal or light snack.

PEG-INF + RBV	BOC + PEG-INF + RBV

Time Point	Criterion	Stopping Rule
Wk 12	HCV RNA 100 IU/mL	Discontinue all therapy
Wk 24	Detectable HCV RNA	Discontinue all therapy
Any	Discontinuation of PR for any reason	Discontinue BOC

Modif ed from Boceprevir [package insert]. May 2011. EMA. Boceprevir [package insert] 2011.

FIGURE 3 - *PEG-IFN + RBV + boceprevir triple therapy. Treatment schedule in PLWHIV.*
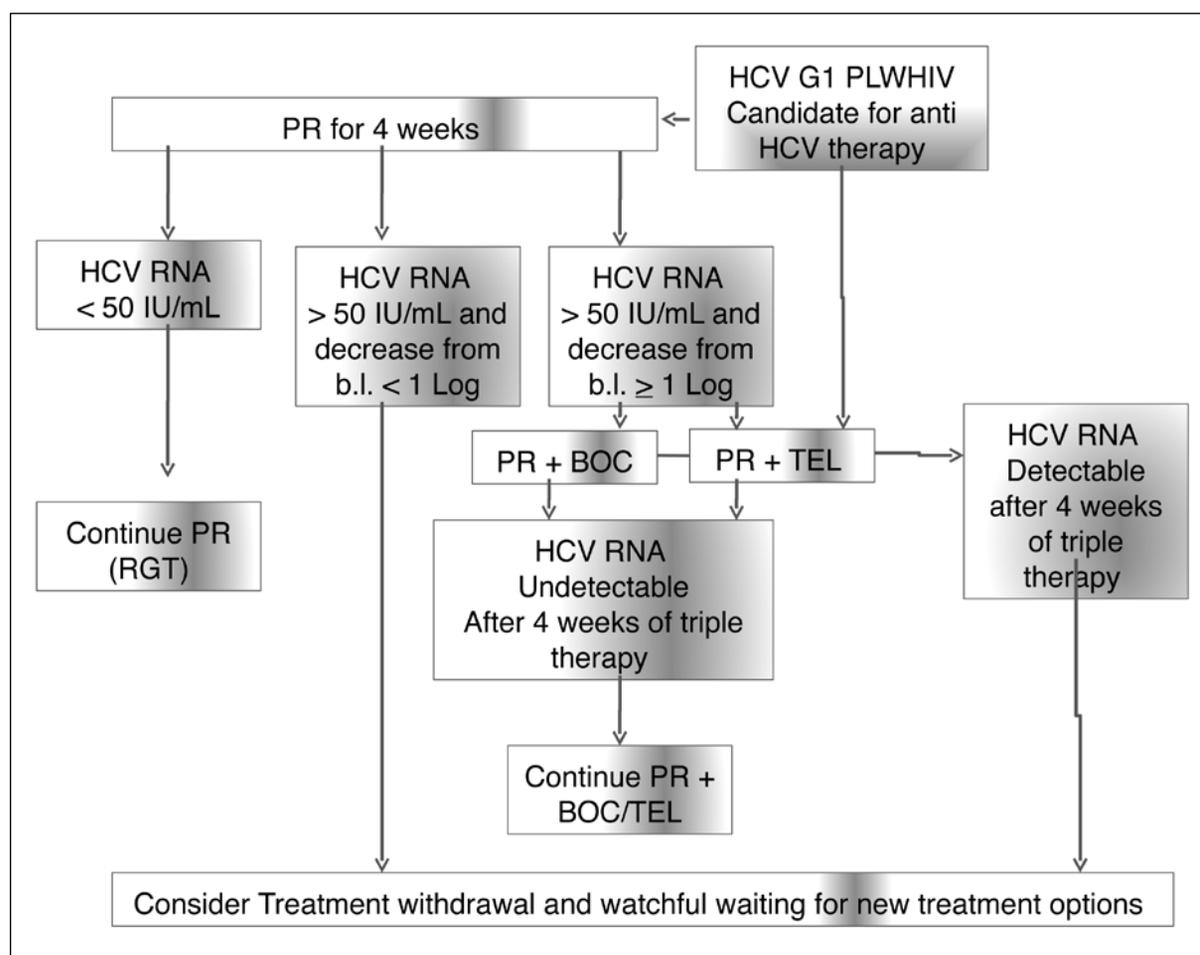
FIGURE 4 - *Suggested algorithm for HCV genotype1 treatment in 2013 CE.*

tify resistance-associated variants is useful only for research purposes both for therapy-naive and DAA-experienced subjects (C3). The management of side-effects should follow the same indications given for HIV-uninfected patients (A2).

9. *Shorter treatment durations (i.e., 12 week-triple therapy with TPV followed by 12-week double therapy or 4-week "lead in" with double therapy followed by 24 weeks of triple therapy with BOC) could be considered for patients without cirrhosis with very poor tolerability and with undetectable HCV RNA at weeks 4 and 12 for patients treated with TPV or at weeks 8 and 24 with BOC (C2).*

10. *The same futility rules indicated in the product characteristics of TPV and BOC should be applied for PLWHIV (Figures 2 and 3) (B2). However, for all the patients showing a virologi-*

cal breakthrough during triple therapy (i.e., a confirmed increase in HCV RNA of at least 1 log above the nadir) immediate withdrawal of TPV and BOC is mandatory (B1). Intensive HCV RNA on-treatment monitoring is strongly recommended.

11. *The 4-week "lead in" phase has been considered by many authors as a sensitivity and tolerability test to PEG-INF and RBV. It could also be applied for TPV, but TPV should be stopped if HCV RNA is >100 IU/mL after 4 or 12 weeks of triple therapy, as defined in the REALIZE study (Zeuzem et al., 2011) (C2).*

In patients with HCV RNA <50 IU/mL after the lead-in phase, treatment with PEG-INF and RBV should be continued if the patient is therapy-naïve and without cirrhosis (C2).

TPV 1125 mg b.i.d. after a meal with 21g of fat could also be considered for PLWHIV (C2).

12. *In the presence of risk factors for SAE, cirrhotic patients should be treated in centers with extensive expertise in the administration of antiviral therapy (B2). Patients for whom anti-HCV treatment has been deferred must be monitored periodically according to their disease stage to detect any progression of the liver disease and possibly be reconsidered for treatment (A1).*

Treatment of PEG-IFN + RBV-experienced PLWHIV

There are currently no conclusive data on the efficacy and safety of triple therapy with BOC or TPV for PLWHIV without SVR to a previous cycle of PEG-IFN and RBV. Recently the preliminary data from two French investigator-driven studies on PEG-IFN and RBV-experienced PLWHIV have been reported (Cotte *et al.*, 2013; Poizot-Martin *et al.*, 2013). The studies used a lead-in phase with either anti-HCV protease inhibitor, and the rate of HCV RNA undetectability proved to be unaffected by the previous treatment response, fibrosis stage and concurrent cART and was similar to that reported in HIV-uninfected patients.

However, in HIV-negative subjects the SVR was clearly related to the response to the previous treatment as it was higher in relapsers and lower in null responders.

Recommendations
13. *Treatment with BOC and TPV may be considered for patients who have failed to respond to a previous course of PEG-INF and RBV, ideally in prospective controlled studies (B2). For null responders, triple therapy must be carefully assessed considering the risk/benefit ratio (A2). The tolerability and efficacy of the previous treatment cycle must be taken into consideration (B1). The best candidates are relapsers with good tolerability, while the worst are null responders with poor tolerability (C2).*
14. *In PEG-IFN+RBV-experienced patients the same schedules, precautions and futility rules indicated for the therapy-naïve should be followed (C2).*

Treatment of acute Hepatitis C in PLWHIV
In the last 10 years an ongoing epidemic of acute HCV infection has been observed in HIV-infected MSM worldwide (European AIDS Treatment Network, 2013). In the ICONA cohort, the incidence rate of HCV infection was 1.2 per 100 persons per year of follow-up (PYFU) (95% CI 1.0-1.4), and decreased from 2.7 per 100 PYFU in 1997-2000 (95% CI 2.1-3.3) to 0.8 (95% CI 0.6-1.2) in 2009-2012. The highest incidence was observed in IDU (8.8 per 100 PYFU; 95% CI 6.5-11.9), followed by MSM (1.4 per 100 PYFU; 95% CI 1.1-1.7) (Puoti *et al.*, *Submitted*). Recommendations for the treatment of acute HCV infection in PLWHIV have been published and are currently included in the guidelines of The European AIDS Clinical Society (European AIDS Treatment Network, 2013). Preliminary data on the successful use of TPV-based triple therapy for the treatment of acute HCV infection in PLWHIV have recently been reported (Fierer , 2013).

Recommendation
15. *Acute HCV infection in PLWHIV should be treated according to the EACS guidelines. TPV or BOC should be used for the treatment of acute HCV mainly in the setting of clinical studies.*
The use of TPV-based triple therapy should be evaluated on an individual basis for selected cases (i.e., reinfection in patients with advanced fibrosis and compensated liver disease or treatment of patients with very poor predictors of SVR).

DRUG-DRUG INTERATIONS OF BOCEPREVIR AND TELAPREVIR WITH ANTIRETROVIRALS

Several drug-drug interaction studies between TPV, BOC and antiretrovirals have been published as full papers or presented at International Conferences and their results are summarized in Table 1, where clinically significant interactions are shown for healthy volunteers (Burger *et al.*, 2013; Wilby *et al.*, 2013; Puoti and Rossotti *et al.*, 2012; Rhee *et al.*, 2013).
However, there are several "caveats" for the interpretation of these indications:
- It is difficult to interpret results from drug–drug interaction studies without detailed insight into the concentration–response relationships, which for an antiretroviral are also dependent on the susceptibility of HIV

Table 1A - *Drug-drug interactions between antiretrovirals and Telaprevir (TPV).*

HIV drug	Effect on ART AUC	Effect on TPV AUC	Can it be used?
FTC, 3TC	No data	No data	Yes, no potential interactions
ABC	No data	No data	Yes, although interactions cannnot be excluded
TDF	+30%	0%	Yes
EFV	-7%	-18% TPV dose 1125 mg q8h	Yes
ETR	-6%	-16%	Yes
NVP	No data	No data	No (potential interactions)
RPV	+79%	-8%	Yes
ATV/r	+17%	-20%	Yes
DRV/r	-40%	-35%	No
FPV/r	-47%	-32%	No
LPV/r	+6%	-54%	No
RAL	+31%	+7%	Yes
DOLU	+25%	Unknown	Yes
MAR	+949%	Similar to monotherapy	Yes, dose: 150 mg bid

Table 1B - *Drug-drug interactions between antiretrovirals and Boceprevir (BOC).*

HIV drug	Effect on ART AUC	Effect on BOC AUC	Can it be used?
FTC, 3TC	No data	No data	Yes (no potential interactions)
ABC	No data	No data	Yes (even if interactions cannot be excluded)
TDF	+5%	+8%	Yes
EFV	+20%	-19%	No
NVP	No data	No data	No (potential interactions)
ETR	-23%	+10%	Yes
RPV	+39%	-6%	Yes
ATV/r	-35%	-5%	No
LPV/r	-34%	-34%	No
DRV/r	-44%	-32%	No
RAL	+1%	+7%	Yes
DOLU	+8%	Unknown	Yes
ELVI/COBI	-16.2%/+2%	+13%	Yes
MAR	+302%	Similar to monotherapy	Yes, dose: 150 mg bid

FTC: emtricitabine; ABC: abacavir; 3TC: lamivudine; TDF tenofovir; EFV: efavirenz; NVP: nevirapine; ETR: etravirine; RPV: rilipivirine; ATV/r atazanavir boosted with ritonavir; DRV/r darunavir boosted with ritonavir; LPV/r: lopinavir boosted with ritonavir; FPV/r: fosamprenavir boosted with ritonavir; RAL: raltegravir; DOLU dolutegravir; ELVI: elvitegravir; COBI: cobicistat; MAR: maraviroc; TPV: telaprevir; BOC: boceprevir; ART: antiretroviral therapy; AUC: area under the curve.

to the relative antiretroviral in the individual patient.

- Pharmacokinetics studies assess plasma (or serum) pharmacokinetic parameters, while it is known that anti-HCV agents are primarily active inside the hepatocyte and not in plasma.

Despite expected reductions in the levels of plasma drug levels due to drug-drug interactions, the above-mentioned pilot study including 55 patients treated with BOC in combination with anti-HIV PIs did not show an increased incidence of virological rebound of HIV during BOC exposure or any decrease in SVR to anti-HCV therapy related to the exposure to the anti-HIV PI (Sulkowski and Pol *et al.*, 2013).

CONCURRENT ANTIRETROVIRAL THERAPY

Patients not taking antiretrovirals

TPV-based triple therapy has been administered in 7 patients not taking antiretrovirals, with SVR in 5/7. The most important finding for these 7 subjects was the absence of resistance mutations in HIV after exposure to TPV (Sulkowski and Sherman *et al.*, 2013). Thus, for patients with CD4 counts greater than 500 cells/mL and not receiving antiretrovirals, HCV treatment could be considered without starting antiretroviral therapy.

However, many guidelines support anti-HIV treatment in all HCV co-infected patients independently of the CD4 count.

Recommendation

16. *Patients with CD4 >500 cells/mL and a stable HIV disease not under antiretrovirals can start anti-HCV triple therapy directly. However, starting stable ART could also be considered before starting anti-HCV treatment as an alternative measure for these patients (C2). The time interval between starting ART and the start of anti-HCV treatment should be at least 8 weeks (C2).*

Patients taking antiretrovirals without a clinically significant interaction with telaprevir and boceprevir

For patients taking effective and tolerated antiretrovirals without a clinically significant

drug-drug interaction with TPV or BOC, some issues should be taken into account: exposure to tenofovir is increased by concurrent TPV administration, so close monitoring of the renal and tubular functions is mandatory during the co-administration of these 2 drugs (Wilby *et al.*, 2013). For patients taking efavirenz, TPV should be given at 1125 mg t.i.d. (Sulkowski and Sherman *et al.*, 2013; Wilby *et al.*, 2012), which results in a 50% increase in TPV costs.

Atazanavir C through is increased by the concurrent administration of TPV, so patients should be advised of a possible increase in or onset of jaundice during the co-administration of these drugs (Sulkowski and Sherman *et al.*, 2013; Wilby *et al.*, 2012), Finally, treatment with abacavir has been associated in some studies with a reduced efficacy of double therapy based on low doses of RBV. Although the data on this issue are controversial, this should be taken into account when decreasing the RBV dose for patients taking abacavir (Puoti and Rossotti *et al.*, 201).

Rilpivirine exposure is increased by 79% by concurrent TPV administration. This increase does not seem to be associated with an increased incidence of QT interval prolongation, but ECG monitoring is advisable for patients taking other drugs with the potential to increase the QT interval (Wilby *et al.*, 2013).

Raltegravir and dolutegravir can be co-administered safely with BOC and TPV, though the pharmacokinetics of raltegravir in HIV-infected subjects are characterized by both high intra- and inter-patient variability, a condition that limits the application of Therapeutic Drug Monitoring (TDM) for raltegravir (Cattaneo *et al.*, 2012; Johnson *et al.*, 2013). The preliminary data did not show any significant interaction between TPV and elvitegravir/cobicistat (Custodio *et al.*, 2013).

Recommendation

17. *For patients receiving an antiretroviral regimen without significant interaction with TPV or BOC, cART should be maintained without modifications (B1), but the renal and tubular functions should be closely monitored in those receiving TPV and tenofovir without efavirenz (B2). The efficacy of anti-HCV therapy should be assessed more frequently in those taking abacavir*

and receiving a reduced RBV dose because of anemia (C2).

The increased cost of TPV should be taken into account for those receiving efavirenz (B1) and the increased severity of jaundice for those taking atazanavir (C2).

Drug-drug interaction between antiretrovirals, anti-HCV drugs and additional drugs or substances taken by the patient should be carefully evaluated and patients should be advised of potential interactions (B1).

Patients receiving antiretrovirals with significant interaction with telaprevir and boceprevir

Some authors suggest suspending all antiretrovirals for the three months of TPV co-administration when the clinical history of the patient (CD4 nadir, current CD4 counts, treatment history) does not indicate a contraindication to interrupting ART. However, this option does not seem to be feasible for most patients and may induce a loss of HIV disease control, which is the highest priority for HIV-infected patients. For patients with a complex ART history or resistance to multiple classes of ART, consultation with experts regarding the optimal strategy to minimize the risk of HIV breakthrough is advised. For these patients, TPV may be the preferable HCV NS3 PI because of its shorter treatment duration (12 weeks) than BOC (24 to 44 weeks).

Recommendations

18. *For HCV genotype 1 patients taking antiretrovirals with significant interaction with BOC or TPV who cannot wait for new anti-HCV combinations and who show good predictors of response to double therapy, there are 2 possible solutions:*
- Switching the current regimen to another without significant interaction if there are no issues regarding the potential efficacy and tolerability of the new regimen. The efficacy and tolerability of the new regimen should be evaluated for at least 8 weeks before starting anti-HCV treatment (C2);
- Maintaining the current regimen if the decreased or increased exposure to anti-HCV and anti-HIV drugs does not seem to be related to a loss of efficacy or to increased toxicity based on the individual patient's treatment history and HIV resist-

ance profile. In this case intense monitoring of HIV RNA and HCV RNA is mandatory and when the TDM of the antiretrovirals is available (C2).

FUTURE PERSPECTIVES FOR ANTI-HCV TREATMENT IN PLWHIV

The advent of TPV and BOC heralded a new era of more effective HCV treatment. There are currently more than 50 agents under investigation in human studies for HCV infection, with 7 different mechanisms of action directed toward the virus and the host (Wilby *et al.*, 2012). Clinical trials with these agents are ongoing in HIV co-infected patients and preliminary data on drug-drug interactions with antiretrovirals and on their efficacy and safety in HIV co-infected patients have already been presented for two protease inhibitors simeprevir (Dieterich and Rockstroh *et al.*, 2013) and faldaprevir (Dieterich and Soriano *et al.*, 2013) and a polymerase inhibitor sofosbuvir (Rodriguez-Torres *et al.*, 2012). There are also ongoing trials with quadruple anti-HCV therapy including asunaprevir + daclatasvir + PEG-IFN + RBV (Pilot Study to Assess the Efficacy of and Tolerance to a Quadruple, 2013). This drug development pipeline could lead in the future to new anti-HCV treatment schedules, even interferon-free, with a single daily dose, fewer adverse effects, potency across all HCV genotypes, and reduced selection of resistant viral strains, either through the use of combinations of agents with different mechanisms of action or resistance profiles or the use of agents with high individual barriers to resistance. Most importantly, these combinations of DAAs might eradicate HCV without the need for PEG-IFN. For this reason, the decision to treat or not an HIV/HCV co-infected patient with the currently available anti-HCV DAAs needs to be made taking into account the advantages and disadvantages of early versus delayed treatment.

TREATMENT OF HIV/HCV CO-INFECTED PATIENTS IN 2013 CE: WAIT OR TREAT?

The first decision regarding an HIV/HCV co-infected patient who is a candidate for anti-HCV treatment is: should we wait for upcoming and

promising new drugs or should we treat now? This decision should be based on 6 points:

1) The urgency of treatment, which is essentially related to the stage of the liver disease, taking into account that 20-24% of HIV/HCV co-infected patients could progress by 2 Ishak stages of fibrosis (or more) in less than 3 years and that the vast majority of HIV/HCV co-infected patients contracted HCV more than 20 years ago.

2) The probability of SVR, which is related to: mild fibrosis, low HCV RNA levels (<400,000 IU/mL), favorable IL28 genetic profile in HCV genotypes 1 and 4 and subtype 1b, gender and ethnicity. An index is available that allows the probability of SVR to PEG-IFN plus RBV to be calculated for a single patient. The HCV genotype is the strongest predictor of SVR, with the lowest probability for genotypes 1 and 4, but if the results obtained with BOC and TPV in pilot studies on genotype 1 are reproducible in real life, only HCV genotype 4 will remain a strong predictor of non-response to anti-HCV treatment. A rapid virological response (negativization of HCV RNA) after 4 weeks of PEG-IFN and RBV is associated with an SVR rate higher than 85%. Thus, patients with RVR to double therapy could be treated without the addition of TPV or BOC. In HCV genotype-1 patients without HIV co-infection, a decrease of 1 log after 4 weeks of PEG-IFN and RBV treatment identifies patients with the highest probability of SVR to triple therapy with BOC, as well as previous null responders with a significantly higher probability of SVR to triple therapy with TPV. There are no data on the predictability for HIV-infected patients.

3) The presence of relative contraindications, and the predicted patient tolerability of the side-effects of treatment and treatment compliance with a complex daily schedule with a heavy pill burden.

4) The patient's motivations, which are influenced by social and working conditions, the perception of HCV liver disease and propensity to treatment.

5) The interactions between anti-HCV drugs and concurrent antiretroviral therapy and the possibility of switching to antiretrovirals without significant drug-drug interaction without changing the efficacy of stable antiretroviral treatment based on drugs that may exert clinically significant interaction with BOC or TPV.

6) The sustainability of the costs of treatment by the patient or other party.

The patients should be involved in this decision and should receive full information on these issues. If controlled trials are available the patient should also be informed of the same.

Recommendation

19. *The decision to treat a patient now or to wait for better treatment options should be taken with the patient on the basis of (B2):*
1. The urgency of treatment.
2. The probability of SVR.
3. The presence of relative contraindications and the patient's predicted tolerability of the side-effects of treatment and treatment compliance with a complex daily schedule with a heavy pill burden.
4. The patient's motivations.
5. The interactions between anti-HCV drugs and concurrent antiretroviral therapy.
6. The sustainability of current treatment options and the predicted sustainability of future treatment options.

A practical algorithm for a moving target

Recent phase III data on the efficacy and tolerability of sofosbuvir in combination with PEG-INF and RBV in HCV monoinfection showed an overall SVR rate of 90% with an 80% rate in HCV therapy-naïve cirrhotics infected by HCV genotype 1 (Wilby *et al.*, 2012). The same response rate was obtained in registration trials in some categories of HIV-uninfected patients (Wilby *et al.*, 2012):
- Patients with undetectable HCV RNA after the lead-in phase who continued treatment with PEG-INF and RBV.
- Patients with undetectable HCV RNA after 4 weeks of triple therapy treated with PEG-INF and RBV plus TPV or BOC.

Recommendations

20. *A pragmatic algorithm (Figure 4) could be considered in 2013 CE for genotype 1 HCV-HIV co-infected patients.*
- Treatment could be initiated with PEG-INF and RBV for 4 weeks in order to assess the efficacy and tolerability of this "backbone" of therapy.
- For those with undetectable HCV RNA and ac-

ceptable tolerability, continuation of treatment with PEG-INF and RBV could be considered following the classic treatment schedule for co-infected patients (C2).

- For those with detectable HCV RNA but with a decrease in HCV RNA of at least 1 log and acceptable tolerability, BOC or TPV could be added (C2).
21. *For those without a decrease in HCV RNA of at least 1 log and/or with poor tolerability, treatment withdrawal and waiting for a new treatment option could be discussed with the patient (C2). For patients with greater urgency of treatment and more advanced fibrosis, the addition of BOC or TPV should always be considered (C3).*
22. *Four weeks after starting treatment with PEG-INF + RBV and BOC or TPV:*
a. For those with undetectable HCV RNA and acceptable tolerability, triple therapy could be continued according to the above-mentioned schedule (C2).
b. For those with detectable HCV RNA and/or without acceptable tolerability, treatment withdrawal should be considered and a watchful waiting strategy for newer treatment options could be discussed with the patient (C2).
23. *For patients with confirmed HCV RNA breakthrough (i.e., a one-log increase in the nadir level on treatment) or severe side-effects during triple therapy, treatment withdrawal and watchful waiting for new treatment options is mandatory (C2).*

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