

# Role of raltegravir in patients co-infected with HIV and HCV in the era of direct antiviral agents

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## SUMMARY

Integrase strand transfer inhibitors (INSTIs) are the preferred third agent in first-line antiretroviral therapies. Raltegravir (RAL) was the first INSTI to be approved and used in naïve and experienced patients. Due to its good tolerability and low side effects, RAL has been largely used also in hepatitis co-infected patients. Many years of experience in RAL use now allow literature evidence to be gathered on its safety in HIV/HCV-co-infected patients pre, during and post direct acting agents (DAA) treatment, at all possible stages. In both clinical trials and published case series, RAL has been well tolerated in patients harboring HCV co-infection and also in cirrhotic patients with mild hepatic impairment. Literature data show no major interactions or the need for dose adjustments with any of the DAA currently in use for HCV treatment, or with ribavirine. Hence, RAL can be safely administered during HCV treatment with DAA and may be used as a “temporary” regimen in patients who do not present major integrase-inhibitor mutations. Moreover, its characteristics are also favorable in case of orthotopic liver transplantation, both for the evidence of hepatic safety and for possible co-administration with immunosuppressant agents.

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## INTRODUCTION

Integrase strand transfer inhibitors (INSTIs) are currently the preferred first-line antiretroviral therapy in HIV-infected patients (Antinori *et al.*, 2017; Department of Health and Human Services, 2016). Among INSTIs, raltegravir (RAL) was the first-in-class and its efficacy and safety have been proven in multiple settings of patients, clinical trials and case series from real life (Lennox *et al.*, 2009; Eron *et al.*, 2013; Hernandez-Novoa *et al.*, 2014; Macías *et al.*, 2011; Rockstroh *et al.*, 2012; Vispo *et al.*, 2010; Weimer *et al.*, 2013; Hurt *et al.*, 2014; Taramasso *et al.*, 2015; Capetti *et al.*, 2014). Its major advantages are the absence of food restrictions or the need for adjustments in severe renal insufficiency and in moderate hepatic impairment (Brainard *et al.*, 2011), no interactions with cytochrome P450 and a longer post-marketing experience compared to other INSTIs (Günthard *et al.*, 2016). Moreover, it has been demonstrated superior to both ritonavir-boosted atazanavir and darunavir in a comparative clinical trial (Ofotokun *et al.*, 2015). On the other hand, the disadvantages are the lack of co-formulation in a single-tablet regimen and current scheduled twice daily administration (Günthard *et al.*, 2016), even if a once-daily preparation of RAL is now under development (OnceMRK trial, ClinicalTrials.gov identifier NCT02131233).

### Key words:

Raltegravir, DAA, Orthotopic liver transplantation, Hepatic safety, HIV/HCV co-infection.

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RAL has been approved in both naïve and experienced patients for use in combined antiretroviral therapy (cART) and it is now considered a preferred first-line agent by IAS, DHHS, EASL, BHIVA and Italian Guidelines (Günthard *et al.*, 2016; Antinori *et al.*, 2017; Department of Health and Human Services 2016; European AIDS Clinical Society, 2017).

The current recommendation is to use RAL in naïve patients in combination with tenofovir/emtricitabine (TDF/FTC) or tenofovir alafenamide (TAF)/FTC-containing regimens (Department of Health and Human Services, 2016; Günthard *et al.*, 2016; European AIDS Clinical Society, 2017; Antinori *et al.*, 2017). Other options, such as combination with lamivudine/abacavir (3TC/ABC) and dual therapy with ritonavir-boosted darunavir (DRV/r), are considered alternative and limited to particular settings in which other regimens are not feasible (Antinori *et al.*, 2017; Department of Health and Human Services, 2016; Günthard *et al.*, 2016; Raffi *et al.*, 2013; Raffi *et al.*, 2014). However, previous experience showed no difference in efficacy when RAL was administered either with ABC/3TC or TDF/FTC as backbone, even in patients with HIV-RNA superior to 100,000 copies/ml (Raffi *et al.*, 2013). On the other hand, the dual combination with a protease inhibitor (ritonavir-boosted darunavir, DRV/r) showed a risk of virological failure in patients with CD4+ T lymphocyte count <200 cells/ml, and a trend towards failure in patients with basal HIV-RNA higher than 100,000 copies/ml (Raffi *et al.*, 2014; Taiwo *et al.*, 2011). For this reason, this combination might be used in naïve HIV-infected patients (strength of recommendation BIa) (Günthard *et al.*, 2016), but only in the rare situations in which a patient cannot take ABC, TAF, or TDF and only in patients with low level viremia and CD4+ T-cell count higher than 200 cells/ml

(Department of Health and Human Services, 2016). Other combinations are not currently recommended by international guidelines in naive patients (Antinori *et al.*, 2017; Department of Health and Human Services, 2016; Günthard *et al.*, 2016). In the setting of experienced patients, RAL has demonstrated a favorable profile, also in cases of triple-class-resistant (but INSTI-naïve) HIV (Eron *et al.*, 2013) and is now considered an option in patients with failure to other drug classes, but also in optimization strategies (Department of Health and Human Services, 2016). Switching to RAL (or more generally, to an INSTI) may be considered in cases of adverse reaction and in the setting of renal damage, including high creatinine, tubulopathies, or nephrolithiasis attributed to other drug classes (Department of Health and Human Services, 2016).

Moreover, RAL has low metabolic and gastrointestinal impact and good tolerability that confer higher durability compared to efavirenz (Lennox *et al.*, 2009) and protease inhibitors (Lennox *et al.*, 2014). In addition, both TDF and PI-containing cART are associated with a significantly greater loss of BMD than regimens containing other NRTIs and RAL (Duvivier *et al.*, 2009; Brown *et al.*, 2015). Recent data presented in international conferences also suggest a favourable profile of RAL use in the setting of liver steatosis, as in HIV-infected women with central obesity it was found a reduction in adipokine adiponectin as well as in biomarkers of liver steatosis and metabolic syndrome Chi3L1, after the switch from PI- or NNRTI-based

ART to RAL (Reynoso *et al.*, 2017). In the same direction also go the 48 weeks results of the STERAL trial (Macia *et al.*, 2017). In this trial, patients diagnosed with hepatic steatosis, according to controlled attenuation parameter (CAP) values, were randomly assigned to continue an efavirenz (EFV)-containing regimen or to switch from EFV to RAL. After 48 weeks individuals switching to RAL showed a lower proportion of significant hepatic steatosis and decreases in the degree of steatosis (Macia *et al.*, 2017). These metabolic advantages make RAL a commonly used drug and a suitable option in a series of HIV-infected patients with comorbidities. Moreover, RAL has good safety profile in case of co-administration with drugs metabolized through CYP 450 pathways and despite the hepatic metabolism mediated by UDP glucuronosyltransferase enzyme, it has been demonstrated safe also in moderate liver insufficiency (Raltegravir insert package, 2015).

Due to its characteristics, RAL use is appropriate also in “fragile” populations, such as hepatitis co-infected patients, also in view of its lack of interaction with the new direct acting agents (DAAs) used for hepatitis C-virus (HCV) treatment (Günthard *et al.*, 2016).

The newer DAAs have changed the scenario of HCV infection, allowing clearance of the virus in most HIV/HCV-co-infected patients who undergo the treatment and bringing the ideal endpoint of global HCV eradication one step closer (Childs *et al.*, 2016). However, in cases of already advanced fibrosis or hepatic cirrhosis, treatment

**Table 1** - Main studies focused on raltegravir (RAL) use in HIV and HBV or HCV co-infected individuals and number and frequency of liver enzyme elevation (LEE) of high (3-4) grade. ULN: upper level of normality; ALT: alanine aminotransferase; HBsAg hepatitis B surface antigen, Ab: antibody.

Study reference	Type of study	Number of patients included	Definition of hepatitis Co-infection	Number of grade 3-4 LEE, n (%)	Definition grade 3-4 LEE	Number of RAL discontinuations due to LEE
Vispo <i>et al.</i> , 2010	Prospective observational Single centre	92	HCV RNA Positivity	3 (3.2%)	LEE > 5 times the ULN	0
Macías <i>et al.</i> , 2011	Retrospective cohort multicentre	108	HCV RNA Positivity	10 (9.3%)	LEE > 5 times the ULN	0
Rockstroh <i>et al.</i> , 2012; Rockstroh <i>et al.</i> , 2013	Double-blind, randomized, controlled Phase III trial	18	HBsAg positivity and/or HCV-RNA positivity	4 (22.2%)	ALT > 5 times the ULN	0
Rockstroh <i>et al.</i> , 2012; Eron <i>et al.</i> , 2013	Double-blind, randomized, controlled Phase III trial	77	HBsAg positivity or HCV-Ab positivity	10 (13%)	ALT > 5 times the ULN	Not available*
Weimer <i>et al.</i> , 2013	Cohort observational	107	HBsAg positivity or HCV-Ab positivity	3 (2.8%)	LEE > 5 times the ULN	Not available <sup>§</sup>
Hurt <i>et al.</i> , 2014	Cohort observational multi centre	166	HBsAg/HBV-DNA positivity or HCV-Ab/HCV-RNA positivity	12 (7.2%)	LEE > 5 times the ULN	1
Taramasso <i>et al.</i> , 2015	Prospective cohort observational multicentre	140	HCV-RNA positivity	2 (1.4%)	LEE > 5 the ULN	1
Neukam <i>et al.</i> , 2016	Prospective observational multicentre	24	HBsAg or HCV-Ab/HCV-RNA positivity	2 (8.3%)	LEE > 5 times the ULN	0

\* Two discontinuations due to laboratory toxicity reported in the all study population, details on type of toxicity or co-infection with hepatitis virus not available in patients who discontinued treatment.

<sup>§</sup> Two discontinuations due to terminal liver disease and one discontinuation due to an adverse event not further defined in hepatitis co-infected patients.

with DAA may allow clearance of the HCV virus, but not a complete recovery of the hepatic fibrosis (Gentile *et al.*, 2016). As a consequence, to date, the choice of an antiretroviral regimen with low impact on liver function remains a priority in some patients also after HCV eradication. Many years of experience in RAL use allow us to draw conclusions from what has been published so far in this field (Table 1). The aim of this review is to examine the long-term safety and efficacy of RAL use in patients with HIV-1 and hepatitis C virus (HCV) co-infection in the era of DAAs.

*Raltegravir and the liver*

Liver safety is one of the most important elements in the development of an antiretroviral drug and it limits the use of several drugs in clinical practice (Table 2). For instance, nevirapine, the first approved non nucleoside reverse transcriptase inhibitor (NNRTI), is characterized by a good metabolic profile (Shaffer *et al.*, 2014) and a good antiviral action (Bonora *et al.*, 2009), but presents potential liver toxicity, confirmed in real life practice, and which is at least in part responsible for its restricted use (Macias *et al.*, 2012). In the family of NRTIs, zidovudine, didanosine or stavudine have been associated with liver toxicity (Vogel and Rockstroh, 2007). In particular, prolonged exposure to didanosine has been linked to non-cirrhotic portal hypertension and esophageal varices (Gouvêa Ade *et al.*, 2015). Among protease inhibitors, all may induce liver enzyme elevation, with greatest frequency with saquinavir/ritonavir (Sulkowski *et al.*, 2004). Indinavir and atazanavir also determine jaundice due to indirect bilirubin increase (Rotge *et al.*, 2005).

Some of these clinical presentations were first observed in hepatitis C virus (HCV)-negative patients. Indeed the use of these molecules was not recommended in HCV/HIV-co-infected people, mainly due to the risk of faster progression of liver fibrosis (Bani-Sadr *et al.*, 2008). In addition, several non-infectious HIV-related comorbidities, like insulin resistance (Merchadante *et al.*, 2009) and progressive kidney disease (Mocroft *et al.*, 2012), have been linked to the presence of an active HCV infection. Other authors also highlighted the association between HCV and hip fracture (Lo Re *et al.*, 2012) or the development of cognitive impairment (Yarlott *et al.*, 2017). All these elements focus attention on the pivotal role of the liver while planning an antiretroviral regimen. From the first

clinical experiences, RAL has proved to be a safe option for patients with liver diseases (Rockstroh *et al.*, 2012). STARTMRK and BENCHMRK 1 and 2 were developed for the treatment of naïve patients and experienced patients respectively (Lennox *et al.*, 2009; Eron *et al.*, 2013). Hepatitis co-infection (defined as HCV-RNA detectable) was present in 6% of the entire cohort in STARTMRK and in 16% in BENCHMRK. The follow-up period for the three studies was five years for naïve and three years for treatment-experienced patients. Results reported a good safety profile; in fact grade 2-4 alanine aminotransferase (ALT) elevations were seen in 8.9 and 14.3% of naïve and experienced patients in therapy with RAL, while grade 4 in 2.1 and 1.5% of patients, respectively (Rockstroh *et al.*, 2012). Liver enzyme elevations (LEE) were more common in co-infected than in non-HCV-infected (HIV) patients, irrespective of the treatment group (RAL+ TDF/FTC vs. EFC+TDF/FTC or RAL+ optimized backbone vs. non RAL regimen (Lennox *et al.*, 2009; Eron *et al.*, 2013). Very similar findings were reported by Vispo *et al.* (2010) in a prospective observational study on 218 patients who started RAL from January 2006 to January 2009 at a reference HIV clinic in Spain. LEEs were observed only in 10 (7.9%) mono-infected patients and in 23 (25%) co-infected patients. Moreover, severe hepatotoxicity was recorded only in three patients (1.4%), all co-infected with HCV and in all of them other non-drug-related causes explained the LEEs.

In the same study, patients in treatment with PIs or NNRTIs reported higher rates of LEEs: 33%-19% (co-infected/mono-infected) and 29%-18% (co-infected/mono-infected) respectively (Vispo *et al.*, 2010). The most significant data on the use of RAL in co-infected patients derive from the pharmacokinetics study conducted by Hernandez-Navoa *et al.* (2014). They recruited ten patients co-infected with HIV and HCV (five with liver cirrhosis stage CHILD C and five non cirrhotic), clinically stable and with HIV-RNA undetectable for at least six months, for adding RAL to their PI-based regimen for five days. RAL plasma levels were increased in patients with liver cirrhosis (AUC<sub>0-12</sub> 1.72 fold and C<sub>12</sub> 6.58), without presenting any side effects. These results reinforced the previous findings concerning the safety and tolerability of this drug in patients with liver diseases. Moreover, recently published studies not only confirmed the safety of this molecule but also showed an improvement in liver enzymes (Cevik *et al.*, 2014) and liver

**Table 2 - Hepatic Effects of current and most used antiretrovirals. Adapted from DHHS (Department of Health and Human Services, 2016). TDF: tenofovir; XTC: emtricitabine or lamivudine; NVP: nevirapine; ATV: atazanavir; MVC: maraviroc.**

NRTI	NNRTI	Protease inhibitor	INSTI	CCR5 antagonist
Liver enzyme elevation in HIV/HBV-co-infected patients when TDF or XTC are withdrawn or when HBV resistance develops.	NVP > other NNRTIs NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count >250 cells/mm <sup>3</sup> and men with pre-NVP CD4 count >400 cells/mm <sup>3</sup> . NVP should never be used for post-exposure prophylaxis, or in patients with hepatic insufficiency (Child-Pugh B or C).	Liver enzyme elevation with ritonavir. ATV: Jaundice due to indirect hyperbilirubinemia	N/A	MVC: Hepatotoxicity with or without rash or clinically suspected hypersensitivity reactions reported
Principal mechanisms				
Mitochondrial toxicity	Hypersensitivity Host-related	Host-related		Hypersensitivity
Risk of immune reconstitution in patients co-infected with HCV or HBV				

fibrosis, determined by FIB 4 (Taramasso *et al.*, 2015) in co-infected patients with a RAL-based antiretroviral regimen. In particular, the ALT levels were significantly reduced from a median of 254 IU/L to 176 IU/L and 90 IU/L one and six months after the switch to RAL (Cevik *et al.*, 2014), and the median FIB 4 score fell from 2.2 to 1.8 over a two-year period of RAL-therapy (Taramasso *et al.*, 2015). In general, Italian guidelines counsel INSTI as a third agent in the initial cART regimen in co-infected HCV/HIV patients, while it is preferable to avoid nevirapine, tipranavir/ritonavir (especially in cirrhotic patients) and in general the class of protease inhibitors, as their use has been previously associated with metabolic alterations that can potentially increase the grade of hepatic fibrosis or determine an additional liver injury that can persist also after the eradication of HCV (Antinori *et al.* 2017; European AIDS Clinical Society, 2017; Martinez *et al.*, 2015; Iannou *et al.*, 2015). To date, only two other drugs of the INSTI class are already in use, i.e. dolutegravir (DTG) and elvitegravir (EVG).

For DTG, at the time of writing, only one published clinical trial has been conducted specifically in HCV-infected patients (Johnson *et al.*, 2014), while no data have been published to date on EVG use in HCV-co-infected patients. As a consequence, RAL is currently the INSTI with the longest safety record and most experience in the treatment of HCV/HIV-co-infected patients.

### **RALTEGRAVIR AND DIRECT-ACTING ANTIVIRAL AGENTS (DAA)**

Thanks to direct-acting antiviral agents (DAA), a new era where HCV can be cured has begun, with remarkable results also in real-life settings and in special populations such as HCV/HIV-co-infected patients (Milazzo *et al.*, 2016). However, in HIV/HCV-co-infected patients, cART often needs to be changed, to avoid possible drug-drug interactions between DAAs and cART. As already specified, in such cases RAL might constitute an appropriate part of an antiretroviral regimen, as it lacks interactions with any of the DAAs currently in use worldwide (European Association for the Study of the Liver, 2016). In order to specifically manage expected drug interactions, in a case series of 15 patients, pre-emptive cART modification to a RAL-based regimen, before administration of HCV treatment with telaprevir or boceprevir, resulted in maintained virological and immunological functions without adverse effects (Stambough *et al.*, 2016). Although few data have been published on real-life RAL safety during DAA therapy, the RAL-based regimen showed a high profile of safety and tolerability when co-administered with simeprevir (SIM), that targets HCV-NS3/4A protease inhibitor (Ehret *et al.*, 2014), and ombitasvir/paritaprevir/ritonavir + dasabuvir (the three direct-acting antiviral agent - 3D) (Khatri *et al.*, 2016). RAL exposure was increased up to 134% when the drug was co-administered with the 3D regimen, however, due to the wide range of safety of RAL, the increased plasma level is not expected to be clinically relevant (Khatri *et al.*, 2016). In a single case report, a threefold increase in RAL exposure was noted in a co-infected patient, post-liver transplantation, treated with the 3D regimen (Cattaneo *et al.*, 2016a). To date, no dose adjustment of either the RAL or 3D regimen is advised in case of co-administration, but in "special" populations therapeutic drug monitoring (TDM) of RAL concentrations may ameliorate patient manage-

ment (Cattaneo *et al.*, 2016a). Sofosbuvir (SOF), a nucleotide analog that inhibits the HCV-NS5B polymerase ledipasvir (LDV) and daclatasvir (DCV), both targeting HCV-NS5A enzyme, have been administered safely and without dangerous drug-drug interactions in co-infected patients in treatment with RAL (Rodriguet-Torres *et al.*, 2015; Barrail-Tran *et al.*, 2015; Naggie *et al.*, 2015). In a study conducted by Rodriguez-Torres (2015), plasma concentrations of RAL, SOF and its predominant metabolite, GS-331007 (circulating inactive nucleoside SOF metabolite) were evaluated a time 0 and after seven days (Rodriguet-Torres *et al.*, 2015). The modest changes in SOF concentration, even when co-administered with the other cART regimen evaluated in the study, neither preclude the use of SOF in co-infected patients nor suggest dose adjustment during co-administration with RAL (Rodriguet-Torres *et al.*, 2015).

No change in RAL or DAA blood levels were observed with the new NS3 inhibitor asunaprevir (BMS-650032), administered in combination with pegylated-interferon, ribavirin and daclatasvir, even in patients with liver cirrhosis. (Barrail-Tran *et al.*, 2015).

Although nowadays ribavirin has maintained a marginal role in some HCV treatments, it can be safely administered with a RAL-based cART regimen, when needed, without clinical impact in ribavirin antiviral effect and no reported side effects (Ashby *et al.*, 2011).

The new DAA faldaprevir is a NS3/4A protease inhibitor and an inhibitor of UDP-glucuronosyltransferase-1A1 (UGT1A1), also implicated in RAL metabolism, leading to an increased RAL area under the curve (AUC) to 2.7-fold (Joseph *et al.*, 2015). However, a study with 24 healthy volunteer participants reported no serious adverse effects (Joseph *et al.*, 2015) while previous studies found no association between an increase in RAL plasma concentration up to 6.58-fold and any safety issue in HIV/HCV-co-infected patients (Hernández-Novoa *et al.*, 2014). Hence, switching to RAL can be considered to minimize drug interactions in the course of HCV treatment in co-infected patients who do not present major integrase-inhibitor mutations (Malet *et al.*, 2008; Eron *et al.*, 2014, Antinori *et al.*, 2017), also taking into account that, according to current guidelines, an INSTI-based cART is the preferred regimen for HCV/HIV-co-infected patients (Antinori *et al.* 2017). Compared to RAL, fewer data on EVG and DTG use are available in the course of DAA treatment. While possible interactions with many DAAs are expected with EVG, due to its cobicistat-boosted formulation, DTG administration is not expected to interact with any anti-HCV therapy (European Association for the Study of the Liver 2016; Esposito *et al.*, 2015). DTG has been reported to have good efficacy and tolerability in the course of SOF associated with either SIM or LDV (Johnson *et al.*, 2016), and also in cirrhotic patients undergoing treatment with SOF + SIM, without significant changes in the geometric mean concentration of DTG, SIM or SOF during the treatment (Merli *et al.*, 2017). Also, exposures of the 3D regimen were not affected in the course of DTG administration, and the 34% and 28% reported decrease in paritaprevir and ritonavir C<sub>trough</sub> did not involve treatment adjustment during co-administration of DTG and 3D regimen (King and Menon, 2017). On the other hand, no clinical or pharmacokinetics data have yet been published on PubMed on EVG use in course of DAAs.

## RALTEGRAVIR AND ORTHOTOPIC LIVER TRANSPLANTATION

HCV/HIV-co-infected patients may experience end-stage liver disease or hepatocellular carcinoma leading to orthotopic liver transplantation (OLT). In this setting, RAL represents a secure and efficient alternative, for its safety profile, also in patients with HIV and HCV co-infection (Rockstroh *et al.*, 2012), in which a minimal impact on liver function might be vital while in the liver-transplant waiting list. Moreover, RAL showed no interaction with calcineurin inhibitors through cytochrome P450 metabolism (Di Biagio *et al.*, 2009; Tricot *et al.*, 2009), even if a possible interaction between RAL and cyclosporine was recently hypothesized in a study published by Cattaneo and colleagues (Cattaneo *et al.*, 2016b).

In this study, liver-transplanted HIV-infected patients, all with good graft function, who were in treatment with both cyclosporine and RAL were found to have higher RAL concentrations compared to HIV-infected non-transplanted patients with normal liver function (Cattaneo *et al.*, 2016b).

The authors hypothesized that this difference was driven by cyclosporine inhibition of UDP-glucuronosyltransferase, (Liu *et al.*, 2011) and of the drug transporters P-glycoprotein and breast cancer resistance protein (BCRP), two carriers of whom RAL is a substrate (Zembruski *et al.*, 2011; Hashiguchi *et al.*, 2013; Li *et al.*, 2014). Of note, although RAL trough concentrations were largely above the IC95 for wild-type HIV-1 strains, only three out of 17 transplanted patients reported adverse effects in this study (2 liver enzyme elevations, 1 nausea and vomiting). All adverse effects resolved after dose adjustment of RAL guided by TDM (Cattaneo *et al.*, 2016b). Finally, Cirioni *et al.* (2014) discussed, in a unique case report, the effective and safe profile of a RAL-based dual therapy in a HIV-HBV-HDV-HCV-co-infected patient, after liver transplantation, in therapy with tacrolimus and everolimus; no change in plasma concentrations of RAL

or immunosuppressive drugs were observed (Cirioni *et al.*, 2014).

Indeed, in selected cases, RAL-based dual therapy may be used to decrease the risk of adverse effects and drug-drug interactions (Baril *et al.*, 2016).

## FUTURE PERSPECTIVES

The management of HCV/HIV-co-infected patients is rapidly evolving. All published studies suggest that HIV-infected patients treated with DAA regimens have SVR rates similar to those of HCV-mono-infected patients (Milazzo *et al.*, 2017). All HIV-infected people at risk of acquiring hepatitis C should undergo HCV antibody detection once a year (Table 3). Moreover, in the near future a new wave of antiviral drugs and short-term treatment strategies will again change the clinical approach in all patients with HCV infection.

At this time, it is of paramount importance to ensure that all patients with HCV infection receive a DAA-based regimen. In this context all HCV/HIV-co-infected patients that gain SVR should strictly adhere to a prevention program to avoid HCV reinfection. A recent report highlights the rate of re-infections in men who have sex with men in Europe (Ingiliz *et al.*, 2017), so this issue should be carefully evaluated.

Furthermore, it is mandatory to consider that cirrhosis represents an irreversible stage in liver fibrosis development (Ge *et al.*, 2016), and patients need a continuous follow-up. In this paper, we have focused on RAL-based therapies in HCV/HIV-co-infected patients, and more specifically have reviewed the evidence supporting the use of RAL pre, during and post the DAA treatment, at all possible stages.

Our review also highlights potential benefits in terms of hepatic fibrosis preservation. In conclusion, the current evidence suggests a pivotal role for RAL, not only in antiretroviral naïve or experienced patients but also in a more complex setting, where RAL offers a unique option for a total patient care.

**Table 3** - Screening and diagnosis of HCV in HIV/HCV co-infection modified from EACS and EASL (European AIDS Clinical Society 2017, European Association for the Study of the Liver 2017).

All HIV-infected patients should be screened for HCV at time of HIV diagnosis and annually hereafter.		
	Diagnostic procedure	Details
Diagnosis of HCV	HCV-Ab	Turn positive 1-6 months after infection as late seroconversions have been described, may rarely be lost due to immunosuppression Hepatic ultrasound
Status of liver disease	Staging of fibrosis	FibroScan®, liver biopsy >10 Kpa, serum fibrosis markers
	Hepatic synthetic function	Coagulation, albumin, cholinesterase
	Hepatic ultrasound	Every 6 months in individuals with liver cirrhosis to screen for HCC
	Gastroscopy	Upon diagnosis of cirrhosis and every 2-3 years thereafter if negative for oesophageal varices
Before HCV treatment	HCV genotype, HCV-RNA, renal and liver function tests	Re-test for genotype and sub-type should be performed in persons with tests carried out before second-generation tests were available (second generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection'
After SVR (F3-F4)	HCV-RNA every year in risk population and counselling to prevent reinfection	Hepatic ultrasound every 6 months, fibrosis markers; if cirrhosis screening for oesophageal varices (gastroscopy); liver enzyme tests
After HCV treatment (F0-F2)	HCV-RNA every year in risk population and counselling to prevent reinfection	These patients do not need special monitoring or follow-up specifically for hepatitis C or liver care.

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