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Treatment of Hepatitis C Virus in HIV/ HCV Co-Infection

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Abstract

Around 5-10 million people present HIV/ HCV co-infection. The treatment regimen currently recommended in this population is based on pegylated interferon and ribavirin, with a success rate below 30% and multiple side effects.

Various clinical trials have also explored different interferon free regimens in patients with HIV/HCV co-infection, proving that Direct Acting Antivirals (DAAs) can induce a sustained viral response over 95%. Moreover co-infected HIV/ HCV patients receiving HCV treatment could further benefit from HCV clearance as this allows the preservation of liver function, attenuates the harm effect of multiple hepatotoxic therapies and lowers the risk of hepatocellular carcinoma. Nevertheless, the administration of DAAs in HIV patients requires careful monitoring and treatment considerations on various issues such as variable adherence in some categories of patients, insufficient drug interactions or the high cost of therapy.

The current article is an overview of the currently antiviral C hepatitis drugs studied in HIV/ HCV co-infected individuals.

Keywords: Hepatitis C virus; HIV infection; Antiretroviral therapy; Direct acting antivirals

Abbreviations

HAART: Highly Active Antiretroviral Therapy; DAA: Direct Acting Antivirals; ART: Antiretroviral Treatment; ARVs: Antiretrovirals; SVR: Sustained Virologic Response; RBV: Ribavirine; Peg IFN: (Pegylated Interferon); AZT: Zidovudine; ddI: d4T: Didanosine; Stavudine; NRTI: Nucleoside/*Nucleotide Reverse Transcriptase Inhibitors*; ABA: Abacavir; PI: Protease Inhibitors; SMV: Simeprevir; CYP3A: Cytochrome P450 3A; SOF: Sofosbuvir; RTV: Ritonavir; CYP2C8: Cytochrome2C8; IRIS: Immune Reconstitution Inflammatory Syndrome

Introduction

It is estimated that HIV/ HCV co-infection accounts for 5-10 million patients worldwide [1] compared to a total of 130-180 million HCV patients and 33 million HIV patients. In Europe, one in four HIV patients displays a co-infection with HCV. The highest burden of these co-infections is in Eastern and Southern Europe [2] as well as in most regions from Africa and Southeast Asia. Along with the extended use of Highly Active Antiretroviral Therapy (HAART) and the significant reduction of opportunistic infections in HIV patients, chronic hepatitis due to HCV infection has become a major cause of morbidity and mortality in this category of patients [3]. This aspect demands specific strategies for treatment and monitoring of HIV/HCV co-infection and highlights the role of the new antivirals directly targeting HCV viral replication known as Directly Acting Agents (DAA).

Etiopathogenic characteristics in HIV/HCV co-infection

The HIV/HCV co-infection involves the association of 2 RNA viruses independently affecting liver and mononuclear cells [4,5]. HCV displays 6 genotypes with different outcomes and variable therapeutic responses among which genotype 1 is the most aggressive and difficult to treat.

Both HIV and HCV exhibit the following overlapping routes of transmission: infected blood or blood products, unprotected sexual intercourse (anal or vaginal) and sharing of contaminated needles. The two viruses address the same vulnerable groups such as: intravenous drug users, incarcerated patients and some haemophiliac patients who have received clotting factor concentrates before 1987. About 72 to 85% of intravenous drug users are estimated to be HIV/HCV co-infected. To a lower extent, this co-infection affects sex workers and men who have sex with men [6]. The mother-to-child transmission of HCV is usually low (4-7%) although it could increase 4 to 5 times in the case of HIV/ HCV co infection [7]. Of note, the Antiretroviral Treatment (ART) decreases the risk of transmission and improves the overall outcome in HIV/HCV patients [8].

The outcome of HIV/HCV co-infection

1. The impact of HIV infection on the evolution of the HCV patients was approached in numerous studies. HIV infection aggravates the course of HCV through various mechanisms including persistent chronic immune activation, progressive cellular immunodeficiency and liver infiltration [9,10]. As a result, there is a higher risk of fibrosis and hepatocellular carcinoma in these patients [11,12]. ART decreases the hepatic necroinflammatory activity and hepatitis progression [13]. The correct uptake of antiretrovirals should therefore become a priority in the co-infected patients. Nevertheless, Lo Re V. et al have recently published a large study on 10 359 patients presenting with either HCV hepatitis (including 6079 patients) or HIV/HCV co-infection (428 patients) in which the patients displayed a higher overall risk of liver failure independent of ART or HIV evolution [14].

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2. The influence of the HCV infection on the progression of HIV infection is contradictory and less studied. However the treatment of HCV decreases hepatic inflammation and allows for HCV clearance. This could in turn enhance the cellular immunity along with ART and protect against hepatotoxic activity of certain Antiretrovirals (ARVs) [15].

Initiating HCV therapy in HIV/HCV co-infection

HCV treatment has proved beneficial for the overall survival of HIV patients even in cases of liver fibrosis [16]**.** Taking this observation into consideration all HIV/HCV co-infected individuals regardless of fibrosis level should be assessed for the recommendation of HCV treatment. According to the current HIV guidelines the treatment of HCV infection could be: a) started immediately and adapted to the ARV regimens. b) deferred if it cannot be adapted to the ARV regimen; c) not recommended (occasionally) (http://www.hivguidelines.org/clinical-guidelines/adults/hepatitis-c-virus).

a. Treatment recommendations for HIV/HCV co-infection resemble those for HCV mono-infection [17,18]. One should take into account the HCV genotype, the concurrent ARV and non-ARV associated treatments (e.g. antituberculous, antifungal, cholesterol-lowering drugs, etc). Of mention, ART should be prioritized and continued throughout HCV treatment.

b. The HCV treatment could be delayed in some categories of HIV patients:

- in patients with incipient fibrosis who can afford to wait the launch of newer potent DAAs;

- in HIV treated but immunologically unstable patients while expecting their immunologic stabilization;

- in HIV patients on an ARV regimen interacting with HCV treatment but with no other ART alternatives; as a rule ART cannot be changed in severe immunodeficiency patients (CD4 counts below 100 cells/mm^3) or in opportunistic infections undergoing treatment (e.g. tuberculosis) or in experienced patients with multiple resistance mutations and no other options of ART.

c. HCV treatment is not recommended in patients with alcohol addiction or low adherence to ART which also predispose to a low compliance to HCV treatment.

The assessment of HCV therapy in HIV/HCV co-infection

To establish the treatment regimens in patients with HIV/ HCV co-infection, one requires the following assessment:

a) The assessment of the HCV infection; b) The assessment of the available HCV treatment; c) The assessment of the drug interactions between HCV antivirals, ARVs and other concurrent drugs.

a. Assessment of the HCV infection

The HIV infection could be asymptomatic for a long period of time. Approximately 10 to 15% of patients with HCV infection will progress to cirrhosis after 15 to 20 years. In the case of HIV/HCV co-infection, the percentage is even higher and the progression advances with each associated risk factors. The main factors of a severity course are: the high viral load; the HCV genotype (genotype 1 represents the greatest therapeutic challenge and has the fastest evolution compared with other genotypes); the high fibrosis stage; the alcohol and intravenous drug addiction; the co-infections with other hepatitis viruses such as Hepatitis B Virus (HBV) or Hepatitis D Virus (HDV); the masculine gender; the age over 40 years [12,19,20].

Of mention up to 30% of patients with either HCV mono-infection or HIV/HCV co-infection do not present with increased liver enzymes or any abnormal results despite the concurrently increased viral loads. Therefore, patients with HIV infection should be screened for HCV infection even if they asymptomatic and/or have normal liver enzymes. If HCV infection is confirmed further investigations are mandatory to fully assess the impact of the HCV infection namely:

- serum RNA HCV viral load

- liver biopsies or other tests for the evaluation of liver fibrosis (Fibromax, Fibroelastography)

- investigations on carcinogenesis risk: liver tumoral markers (**α-fetoproteins,** carcinoembryonic *antigen***),** ultrasonography and if the risk of hepatocellular carcinoma is present the patient also requires a liver CT scan or MRI.

-investigations on autoimmune HCV complications (cryoglobulinemia, autoimmune glomerulonephritis).

The HCV guidelines recommend the RNA HCV viral load test prior to treatment starting as well as during treatment, based on the observation that RNA HCV kinetics predicts virological response and correlates with treatment outcome. Thus an undetectable HCV viral load at 24 weeks after therapy completion is defined as Sustained Virologic Response (SVR) and represents the best indication of successful therapy for HCV infection. SVR is also a surrogate therapeutic end point, considering that the risk of relapse after SVR at 24 weeks is extremely low, including the case of HIV patients (0% in a study by Soriano) [21]. Nevertheless, HCV replication in peripheral blood mononuclear cells was confirmed as far as 2007 by Laskus et al. in some HIV patients with negative plasma HCV RNA [4]. This finding raises questions on the durability of the HCV cure and could prove of further concern in co-infected patients with undetectable HCV viral loads.

b. Assessment of the HCV treatment

There are several options available for the treatment of HCV but with considerable differences regarding efficiency, side effects and costs. Although the treatment regimens are still changing there are a number of principles that have been established by Infectious Diseases Society of America (http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-hivhcv-coinfection) through an HCV panel designed for the approach of treatment-naive or treatment-experienced HIV/HCV co-infected patients, as follows: monotherapy against the HCV infection is not recommended irrespective of the drug choice, peginterferon Peg IFN), Ribavirine (RBV) or DAAs; dual therapy with IFN/RBV is no longer recommended and neither is the triple therapy with Peg IFN/RBV, telaprevir or boceprevir) [22].

Below are the main anti-HCV drugs that have undergone clinical trials on the treatment of HIV HCV/ co-infection:

Pegylated interferons

Peg IFN exerts an immunomodulatory action. Along with RBV it represents the standard 48-weeks therapy in HCV patients. The dose for weekly Peg IFN is 1.5 μg/kg sc for Peg IFN alfa-2b and 180 μg sc for Peg IFN alfa-2a.

Indications:

Peg IFN remains a salvage option in HIV/HCV co-infection if IFN free regimens cannot be administered (high cost, side effects or contraindications); it could be a preferred alternative in C hepatitis associated with other hepatitis viruses (HCV and HBV/ HDV co-infection).

Disadvantages:

- **Peg IFN** has recorded only 30% cure rates in patients with HIV/ HCV co-infection [23] and ''cured'' patients are still predisposed to relapses. SVR also differs depending on genotype: HCV genotypes 1 and 4 are known to have a poorer response to IFN-based therapy than genotypes 2 and 3.

- **Peg IFN** demands a subcutaneous administration and a prolonged duration (48 weeks) independent of the HCV genotype, an aspect that could further reduce adherence in HIV patients already facing difficulties for adherence to the ARV regimen [24].

- **Peg IFN** exhibits various side effects that should be carefully monitored such as: fever, bone marrow suppression, myalgias, fatigue, depression, anorexia, thyroid dysfunction, polyneuropathy, injection site reactions etc.

- Peg IFN cannot be Associated with Zidovudine (AZT), didanosine (ddI) and stavudine (d4T).

Ribavirine (RBV)

Indications:

RBV is still used in association with Peg IFN or with DAAs due to its ability to improve SVR, shorten the treatment duration and lower the risk of relapse in patients with HIV/ HCV co-infection. RBV is administered orally depending on weight: 1000 mg/day in patients <75kg and 1200 mg/day in the case of patients ≥75 kg.

Taribavirin, an oral RBV pro-drug with significantly lower anemia rates is in phase III trials.

Disadvantages:

-RBV requires a daily administration of 4-5 tablets/day that adds up to a various number of ARV pills; certain side effects could also cumulate with ARV side effects such as: hemolytic anemia (dose-dependent), pancreatitis, lactic acidosis, dyspepsia, rash. The highest risks reside in its association with Nucleoside/*Nucleotide Reverse Transcriptase Inhibitors* (NRTI). Of the latter most frequently cited side effects have involved ddI and AZT. In addition, Abacavir (ABA) as well as RBV is a guanosine analog and exerts a competitive action with RBV when it is administred in the same regimen. The combination of RBV with the above mentioned NRTIs has been correlated with lower SVR according to some authors [25].

DAA agents

The DAA agents in the HCV therapies target different steps of the viral life cycle. Listed below are the main DAAs that have been studied on various groups of patients with HIV/HCV co-infection or are undergoing phase II or phase III trials.

a. NS3/4A Protease Inhibitors (NS3/4A PIs). The NS3/4A PIs bind to a viral protease that cleaves HCV polyprotein into 4 nonstructural proteins.

*Representatives***:**

•Telaprevir and boceprevir were first-generation PIs. They have brought significant benefits to HCV treatment but with the risk of important side effects [26]**.** As a result the sale of telaprevir was discontinued by the producer in October 2014 and boceprevir is expected to be discontinued by the end of 2015.

• Simeprevir (SMV), a new NS3/4A PIs generation has been studied beginning with 2013. SMV exhibits few adverse effects (photosensitivity) and could be administered in usual doses even in the case of mild renal or liver impairment. Positive results have been recorded for a regimen of SMV associated with Peg IFN/RBV in HIV patients [27].

Disadvantages:

SMV presents numerous interactions with drugs metabolized by the cytochrome P450 3A (CYP-P450). These drug interactions involve ARVs belonging to PI and NNRTI class and some antibiotics (claritromycin), antimycobacterials (rifampin, rifabutin, rifapentin), antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole), antiepileptic drugs and corticosteroids. In addition, SMV is also a substrate and mild inhibitor of P-glycoprotein, an efflux pump for various drugs, including PIs and NNRTIs (with the exception of rilpivirine). SMV does not appear to interact with other classes of ARVs.

• Other protease inhibitors undergoing phase III studies are: asunaprevir, vaniprevir, paritaprevir, grazoprevir. Of note, the development of faldaprevir has been discontinued [5]. Asunaprevir (BMS-650032) has been studied in association with other DAAs (DCV-TRIO regimen). Paritaprevir (ABT- 450) is presently used in co-formulations (Viekira pak). Grazoprevir (MK-5172) combined with elbasvir, a NS5A inhibitor has been studied in patients with HIV coinfection and HCV genotype 1, with positive results after 12 weeks: SVR 87% (in a regimen without RBV) and 97% (adding RBV) [28].

b. Nucleoside and Nucleotide NS5B Polymerase Inhibitors. These drugs block the NS5B protein, a RNA-dependent RNA polymerase involved in creating copies of the viral RNA genome.

Representatives:

• Sofosbuvir (SOF) is the most studied NS5B Polymerase inhibitors. Mericitabine (R7128) is currently undergoing a phase III trial. SOF is not metabolized by CYP-P450 and the drug interactions with ARV have been minimal. It can also be administered in patients with mild renal and liver impairment (including compensated cirrhosis). It has been used in the treatment of HCV genotypes 1-4 in association with ledipasvir and SMV, with or without RBV. Some of these combinations are available as once daily Fixed Dose Combinations (FDC) that are easy to administer. SOF is by far the best studied DAA for the treatment of HIV/HCV coinfected

patients and has the broadest indications. It can be associated with all classes of ARVs, including PIs (except for tipranavir). Ritonavir (RTV) boosted ARVs do not interfere with SOF. Nevertheless, SOF cannot be combined with some antimycobacterials (rifampin, rifabutin, rifapentin) and anticonvulsivants. In a recent study, SOF and daclatasvir have lead to a SVR of 97-100% (ALLY-2 study, phase III) [29]. Furthermore, SOF combined with ledipasvir for 12 weeks in patients with HIV and HCV genotypes 1 and 4 has reached a SVR of 99%-100 % [30,31].

In co-infected HIV patients with HCV genotypes 1 and 2, one should also consider the option of SOF+RBV [32,33]. Favorable results were also obtained in patients with genotype 3 undergoing SOF+RBV, according to Molina et al [33].

c. Non-Nucleoside NS5B Polymerase Inhibitors. These drugs bind to allosteric sites of polymerase's active site inducing conformational changes.

Representatives:

• Dasabuvir (ABT-333) or Exviera is the best known representative; it is, used in coformulations (Viekira pak) with a rate of SVR of 91%-96.9% after 24 weeks of treatment (only genotypes 1 and 4) [34,35]. The association of dasabuvir with inhibitors of Cytochrome P4502C8 (CYP2C8) (e.g. gemfibrozil, trimethoprim/sulfamethoxazole) is strongly contraindicated as it increases dasabuvir serum levels and prolongs QT interval. This observation could become a major disadvantage in HIV patients requiring long-term prophylaxis with trimethoprim/sulfamethoxazole for certain opportunistic infections (Toxoplasma gondii, P. jirovecii).

• Beclabuvir (BMS-791325) is another representative with a fixed dose formulation and synergic action with asunaprevir and Daclatasvir. (DCV-TRIO).

d. NS5A Inhibitors. NS5A is an HCV non structural protein, a component of the HCV replicase with multiple functions on the interactions between viral and host cell proteins. NS5A Inhibitors compounds could be used as a part of IFN- and RBV-free regimens.

Representantives:

• Daclatasvir (BMS-7900520) is produced by Bristol-Myers Suibb as a FDC tablet together with asunaprevir and beclabuvir (study of phase III). It can also be used in once daily administration combined with Peg IFN/RBV or just with SOF (SVR 97%) [32]. Daclatasvir needs a dose-adjustment depending on the ARVs that are concomitantly administered: daclatasvir 30 mg with RTV-boosted PIs and 90 mg with NNRTIs (except rilpivirine). Importantly, daclatasavir is not active on HCV genotype 2.

• Ledipasvir (GS-5885) is used as FDC in combination with SOF under the trade name Harvoni. Ledipasvir interferes with some ARVs (e.g. increases the level of tenofovir and the risk of renal failure especially if the ARV regimen includes also RTV).

• Ombitasvir (ABT-267) is administered in FDC (Viekirax si Viekira Pak)

• Elbasvir (MK-8742) is administered in combination with grazoprevir

Importantly, a large number of experimental DAAs are currently tested as multi-class combination drugs, mostly as FDC. The DAAs currently undergoing as FDC in experimental trials are:

• Harvoni (Gilead Sciences): SOF + ledipasvir.

•Viekira Pak (Abbvie): (ombitasvir + paritaprevir + RTV) as a FDC tablet with dasabuvir , for patients with HCV genotype 1. RTV is a potent inhibitor of CYP3A4 enzymes and serves as a pharmacologic booster for paritaprevir when used in this combination. On the other Viekira Pak has several contraindications related to the metabolization of these drugs by CYP3A. Additionaly the patients also receiving RTV boosted PI regimen require the adjustment of RTV doses before using Viekira.

•Viekirax (Abbvie) **:** ombitasvir+paritaprevir+RTV**.**

• DCV-TRIO regimen (Bristol-Myers Squibb): asunaprevir+dacl atasvir+beclabuvir, a FDC for patients infected with HCV genotype 1

•Grazoprevir + elbasvir (Merk)

FDC in HCV treatment of HIV/HCV patients could be a significant advantage through the reduction of pill burden. Still, these studies have not yet published definitive conclusions as to all the indications, contraindications and side effects of these FDC in HIV/HCV populations.

Advantages of the new generation of DAAs are numerous : minimal side effects, improved treatment outcomes with better SVR, shorter treatment duration, and better adverse event rates comparatively with the Peg IFN regimen [36].

Disadvantages: there are few studies on co-infected patients, potential drug interactions in combination with important ARV drug classes such as PIs and NNRTIs, unknown side effects of various combinations and treatment regimens.

c. Assessment of the drug interactions between HCV antivirals, ARVs and other concurrent drugs

ARV therapy improves the clinical outcome in HIV/ HCV co-infected patients and should be immediately administered in contrast with HIV patients without HCV co-infection, in whom a delay in ART based on the CD4 count is accepted by certain guidelines. Should the ART regimen change, HCV therapy is delayed until the patient under the new ARV regimen is stable. If the CD4 count is too low, HCV treatment is also postponed until the CD4 T lymphocytes record an increase over >500/μL [37,38]. To note, occasionally ART is by itself and independent of HCV co-infection responsible for increased hepatocytolysis in some groups of HIV/HCV co-infected patients by developing Immune Reconstitution Inflammatory Syndrome (IRIS) [39]. However IRIS remains an extremely rare complication and some authors dismiss the possibility of a worsening status of HCV patients during ART [40].

ARVs induced hepatotoxicity is a common side effect and has been described in all ARVs. The risk of liver toxicity due to ARVs is increased in HIV patients with other co-infections, risk factors of severity or who are also undergoing other hepatotoxic treatments (statins or antimycobacterials drugs). Therefore each HIV patient should be evaluated independently by taking into account all the

Table: Potential drug interactions between ARVs and DAAs.

ARV drug class	Recommended ARV in HCV patients	Unadvised ARV in HCV patients	Recommended DAAs in HIV patients	Unadvised combinations of DAAs in HIV patients
NRTI	• TDF, 3TC, FTC	• ddI, d4T, ABC (inhibition of mitochondrial DNA and occasionally lactic acidosis) • ddI, risk of non cirotic portal hypertension • ABA, risk of hypersensitivity (rarely, predictible)	• SOF • SMV • SMV + TDF, FTC, 3TC	• RBV should not be combined with AZT, DDI, D4T or ABA • AZT, DDI, D4T or ABA, high risk of liver toxicity with DAAs • ddI, high risk of liver toxicity in any combination
NNRTI	• RIL, ETV	• Nevirapine (risk for acute hypersensitivity reaction especially in women with CD4 counts < 250 cells/mm^3 • EFV	• SOF • Daclatasvir + RIL • SMV+ RIL	• SMV if used with EFV and ETV. • Daclatasvir if combined with NRTIs (except for RIL); it requires dose adjustment when associated with EFV. • Paritaprevir/ritonavir/ombitasvir plus dasabuvir associated with EFV and RIL
PI +/- RTV	• NFV displays a lower liver toxicity compared with other PIs [41]; According to other authors, NFV could also lower the replication of HCV in vitro [42] • DRV (lower risk of dislipidemia, hepatic citolysys and steatosis)	PI drug class exhibits a risk of liver toxicity by direct and indirect effect (insulin resistance, hyperlipidaemia, steatosis); • RTV and tipranavir have the highest risk • Atazanavir (hyperbilirubinemia)	• SOF (but not if combined with tipranavir) • Daclatasvir only in combination with ATZ and with dose adjustment.	• SOF + tipranavir • SMV • Daclatasvir + other PIs • Ledipasvir/SOF with tipranavir • Paritaprevir/RTV/ombitasvir plus dasabuvir with lopinavir/ritonavir or DRV
INSTI +/-cobicistat	No direct liver toxicity	• Cobicistat (high rik of hyperbilirubinaemia) • DTG, risk of IRIS • Hepatocytolisis: RAL> EVG, DTG	• SOF • SMV • Daclatasvir • Ledipasvir/SOF	• SMV should not be associated with cobicistat
HIV Entry Inhibitors	No liver toxicity		• SOF • SMV	

NRTI: Nucleoside/*Nucleotide Reverse Transcriptase Inhibitors*; NNRTI: Non-Nucleoside Revers Transcriptase Inhibitors; PI: Protease Inhibitors; INSTI: Integrase Strand Transfer Inhibitors; AZT: Zidovudine; DDI: Didanosine; D4T: Stavudine; ABA: Abacavir; RTV: Ritonavir; TDF: Tenofovir; FTC: Emtricitabine; 3TC: Lamivudine; SOF: Sofosbuvir; SMV: Simeprevir; RIL: Rilivirine; EFV: Efavirenz; NFV: Nelfinavir; ETV: Etravirine; DRV: Darunavir; DTG: Dolutegravir; RAL: Raltegravir; EVG: Elvitegravir; ATZ: Atazanavir

potential drug interactions, the risk-benefit ratio for the concurrent ART and DAAs and the high costs of the recommended regimens.

The table below displays the risk of hepatotoxicity and potential drug interactions between ARVs and DAAs in HIV/HCV co-infected patients according to current clinical trials (Table). Of note, the tested regimens entailed only a small number of patients with cirrhosis.

Conclusion

Interferon free therapy is a new and important step in the treatment of HCV infection, including patients with HIV/ HCV co-infection. However trials on DAA regimens have yet to be performed in combination with the multiple available ARV regimens and on larger patients groups. For these patients, the greatest challenge appears to be not the DAA regimen by itself, but rather the drugs interactions with ART, adherence difficulties and increased costs. This could play an important role in the future and could ultimately restrict interferon free regimens to certain groups of patients so as to avoid adverse reactions, the risk of ARVs serum levels variations and toxicity issues. Overall, the optimism of new DAA needs to be carefully weighed in each group of patients with HIV/HCV co-infection.

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