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HIV and HCV Therapies in 2016: Optimal Regimens

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Abstract

Approximately 30% of HIV individuals are coinfected with HCV. It is known that HIV accelerates liver fibrosis progression, even with the use of combination antiretroviral therapy, and HCV is now a leading cause of morbidity and mortality in this patient population. Past HCV therapy with pegylated interferon and ribavirin in this setting has demonstrated poor outcomes, which were inferior to those seen in HCV-monoinfected populations, especially in patients with genotype 1 infections. This and the high rate of adverse events with these agents resulted in very limited uptake of these treatment options. The recent advent of direct-acting antiviral therapy for HCV has resulted in vastly improved outcomes in HCV-infected patients. These agents have also demonstrated markedly improved outcomes in HIV/HCV-coinfected settings, with sustained virological response rates now being equivalent to non-HIV patients. The recent introduction of all-oral, interferon-free, and in some instances-ribavirin free, therapies has further improved sustained viral response rates that exceed 95% with minimal adverse events. HIV/HCV-coinfected patients, however, have particular issues with drug-drug interactions with antiretroviral therapy regimens, which need to be carefully evaluated and occasionally require modification. **(AIDS Rev. 2016;18:212-21)**

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Key words

DAA. Drug-drug interaction. Hepatitis C. Coinfection. HIV. Therapy.

Background

Hepatitis C (HCV) is estimated to affect 160 million individuals worldwide[2]. Approximately 80% of infected individuals develop chronic infection and chronically infected individuals are at risk of long-term complications. Approximately 20% of individuals develop liver cirrhosis after 20-30 years of infection, of which 20% develop decompensation over a five-year period and 1-4% develop hepatocellular carcinoma per year. In the absence of liver transplantation, the majority of these individuals will perish[3]. HIV and HCV have shared routes of transmission and as a result approximately 30% of HIV-infected individuals are coinfected with HCV, with the prevalence largely determined by the prevalence of injecting drug use in each jurisdiction[2,4]. Given that an estimated 34 million individuals are currently living with HIV/AIDS, there are an estimated 10 million individuals with HIV/HCV coinfection worldwide[5].

With the advent of combination antiretroviral therapy (cART) in 1996 and the attendant improved outcomes from HIV, other comorbidities such as HCV have assumed an increasing importance in the morbidity and mortality in this patient population[6]. HIV has a significant impact on the natural history of HCV. HIV/HCV-coinfected patients have a lower rate of spontaneous clearance following acute infection[7], higher viral loads

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with increased rates of transmission[8,9], accelerated disease progression, and in particular, accelerated fibrosis compared to HCV-monoinfected individuals[10], which results in increased rates of cirrhosis and hepatic decompensation. Although initial studies were conducted in the pre-cART era[11], more recent studies have demonstrated that, despite cART, rates of fibrosis progression and decompensation remain accelerated for HIV compared to non-HIV individuals, and they have a greater rate of hepatic decompensation and a higher mortality compared to HIV-negative individuals[12,13]. Indeed, with the advent of effective HIV therapy, liver disease is now the equal second most common cause of mortality in HIV patients behind AIDS-related mortality, with most of it driven by chronic HCV[14]. Coinfected patients who achieve a sustained virological response (SVR) and are cured of HCV have been shown to have improved clinical outcomes and survival[15]. This highlights the urgent need for assessment of fibrosis as well as effective HCV therapies in coinfected individuals.

Treatment of HIV/HCV coinfection

Use of antiretroviral therapy to delay fibrosis

Effective ART, especially cART, has been consistently shown to slow the progression of fibrosis in coinfected individuals[16,17]. Accordingly, several guidelines have recommended HIV therapy for HCV-infected individuals, irrespective of CD4 counts, while waiting for HCV clearance[1,18]. This especially applies to individuals who are being warehoused while waiting for new therapies or who are unlikely to have access to them. It is also highly relevant to individuals in resource-limited settings who may not have access to effective HCV therapy in the near future but have access to ART.

Past therapies

Up until recently, the standard of care for HCV therapy in HIV coinfected patients was pegylated interferon and ribavirin (P+R) for between 24 to 48 weeks. Compared to HIV-uninfected individuals, HIV-coinfected patients consistently demonstrated a significantly lower SVR rate, with approximately 60% of genotype (Gt) 3 patients and only 30% of Gt 1 patients achieving SVR[19-24]. The response was particularly poor for Gt 1 patients who had had a prior null response. Another major drawback to P+R was the high rate of adverse events and withdrawal from therapy. Adoption of interferon-based HCV treatments has therefore been low among HIV/HCV-coinfected patients owing to a high adverse-event burden as well as the low rate of SVR[25].

The advent of direct-acting antiviral agents

Over the last few years, a number of different direct-acting antiviral agents (DAA) have been developed. Unlike P+R, these are orally bioavailable small molecules directed against specific HCV targets and many have parallels to agents previously developed for the treatment of HIV. Three major classes of drugs have been developed with differing genotypic activities and barriers to antiviral resistance. The first class to be developed was the protease inhibitors (PI), which inhibited the HCV NS3/NS4 proteases. A second class was the polymerase inhibitors, which inhibited HCV RNA polymerase. These were of two subclasses: nucleoside/tide analogues, which blocked the active site of the polymerase and acted as chain terminators, and non-nucleoside analogues, which acted away from the active site to interfere with the allosteric properties of the enzyme. The third new class is the NS5A inhibitors, a novel class of drug with no parallel in HIV, which blocked the replication complex of HCV[26]. These drugs have been used either in combination with interferon and ribavirin or more recently combined as interferon-free therapies in an attempt to increase the poor response rates cited above.

New drugs and HIV/HCV coinfection

Interferon-based

Early DAAs were shown to have a low barrier to resistance, with rapid development of resistance within days of the onset of therapy, and had to be used in combination with other drugs to prevent resistance[27]. The initial DAAs were first-generation PIs and were initially used in conjunction with P+R. First-generation PIs included telaprevir and boceprevir and only had activity against Gt 1 infection. Telaprevir was studied in a randomized phase II study comparing triple therapy with telaprevir plus P+R to P+R in 60 HCV treatment-naive HIV patients. Thirteen of these were not on ART, but were required to have a CD4 count of > 500 cell/mm^3 and an HIV viral load

of < 100,000 copies/ml, and 47 who were stable on ART with a CD4 count > 300 cell/mm^3 and an HIV viral load < 50 copies/ml. Due to drug-drug interactions (DDI), ART regimens were limited to either efavirenz/tenofovir/emtricitabine or atazanavir/ritonavir (ATV/r) plus tenofovir plus emtricitabine or lamivudine. Telaprevir was given at 750 mg three times a day for 12 weeks while P+R was given for a full 48 weeks. If efavirenz was used, the telaprevir dose was increased to 1,125 mg three times a day. The overall SVR rate at 12 weeks (SVR12) was 74%, which was significantly better than standard of care at 45%, and no patient experienced HIV rebound[28].

A corresponding boceprevir phase II randomized study of 98 patients compared P+R plus boceprevir to P+R alone. All these patients were on ART and had a CD4 count of > 200 cells/mm^3 with an HIV viral load of < 50 copies/ml. Patients were given a total of 48 weeks of therapy and the boceprevir arm received a P+R lead-in for four weeks followed by the addition of boceprevir for 44 weeks. Antiretroviral therapy not permitted included non-nucleoside analogues (NNRTI), zidovudine, and didanosine. The SVR12 rates were 61% for the boceprevir arm, significantly better compared to 27% for P+R. An HIV breakthrough was observed in seven patients, but was equivalent in the two arms with three in the boceprevir arm and four in the standard of care arm[29]. These regimens showed for the first time that the use of a DAA could increase SVR rates to those comparable in HIV-uninfected patients. The regimens, however, were difficult to use due the necessity for a three times a day dosing regimen, a high bill burden (especially when ART dosing was taken into account), the requirement for food restrictions, and a suboptimal adverse event (AE) profile, especially in the case of telaprevir.

Simeprevir is a second-generation once-daily PI with an improved AE profile. Study C 212 evaluated simeprevir for 12 weeks in an open-label study in conjunction with P+R in 108 Gt 1 HCV treatment-naive and experienced HIV-coinfected patients. Of these patients, 88% were on ART and had an HIV viral load < 50 copies/ml. Allowable ARTs were limited, with all PIs being excluded, and the only NNRTI allowable was rilpivirine. Simeprevir was given at 150 mg once daily and treatment-naive patients and prior relapsers to P+R were managed by response-guided therapy, whereby patients whose HCV viral load was undetectable at weeks 4 and 12 had therapy shortened to 24 weeks, while all partial responders and null responders received a full 48 weeks of therapy. The SVR12 rate was again high at 79% in treatment-naive patients and 87, 70, and 57% for relapsers, partial responders, and null responders, respectively. These results were historically similar to HCV-monoinfected patients and the AE profile was also similar[30].

Interferon-free regimens in HIV/HCV coinfection

The holy grail of DAA therapy is to achieve interferon-free therapy and the most recent regimens have finally achieved this. The first regimens to be evaluated included sofosbuvir, a pan-genotypic, once-a-day nucleotide analogue with a high barrier to resistance, in combination with ribavirin. Two similar open-label, non-randomized, large parallel studies, one conducted in the USA and Puerto Rico (Photon 1), which recruited 224 patients, and the other in Europe and Australia (Photon 2), which recruited 275 patients, were conducted. They included HIV-coinfected patients with Gt 1, 2, and 3, although non-Gt 1 patient enrolment was limited to 20% of the study population. Patients were treated with sofosbuvir 400 mg/day and weight-based ribavirin at 1,000-1,200 mg/day. Both studies had three arms: Gt 1 TN (treatment-naive), Gt 2 and 3 TN and TE (treatment-experienced). In both studies, GT 1 TN and GT2/3 TE patients received 24 weeks of therapy. Photon 1 Gt 2/3 TN patients received 12 weeks of therapy. In Photon 2 this was extended to 24 weeks due to emerging data on inadequate efficacy of 12 weeks of therapy in this group. In addition Photon 2 expanded recruitment to include TN Gt 4 patients who received 24 weeks of therapy. Patients were required to have been on stable ART for eight weeks with CD4 > 200 cells/mm^3 or CD4 > 500 cells/mm^3 if not on ART, and up to 20% patients with compensated cirrhosis were permitted with no platelet count cut-off. Antiretroviral regimens permitted were those containing emtricitabine/tenofovir in combination with atazanavir/ritonavir, darunavir/ritonavir, efavirenz, raltegravir, or rilpivirine based on drug-interaction studies with sofosbuvir. The primary endpoint was SVR at 12 weeks. Results for Photon 1 in treatment-naive patients were 76% Gt 1, 88% Gt 2, and 67% Gt 3. In treatment-experienced patients they were 92% Gt 2 and 94% Gt 3. In Photon 2, overall rates of SVR12 were 85% in patients with Gt 1, 88% in patients with Gt 2, 89% in patients with Gt 3, and 84% in patients with Gt 4. Response rates in TN patients with HCV Gt 2 or 3 (89 and 91%,

respectively) were similar to those in TE patients infected with those genotypes (83 and 86%, respectively). The most common adverse events were fatigue, asthenia insomnia, headache, and nausea and were generally mild-to-moderate in severity and no adverse effects on HIV were seen[31,32]. Taken together, these studies demonstrated for the first time that interferon-free regimens in HIV coinfection had equivalent high SVR rates to HCV monoinfection and were very well tolerated.

The next advance in interferon-free therapy was the development of combinations of different DAAs with and without ribavirin and a number of different regimens have emerged. One such combination is the Abbvie 3D twice-daily regimen, which consists of paritaprevir (a protease inhibitor boosted with ritonavir), ombitasvir (an NS5A inhibitor), and dasabuvir (a non-nucleoside polymerase inhibitor) in combination with ribavirin, which was studied in HIV-coinfected patients in the Turquoise 1 study. This was a randomized, open-label study and Part 1a of this pilot study was conducted at 17 sites in the USA and Puerto Rico and included 63 patients who had Gt 1 HCV and were either treatment naive or experienced with prior failure to P+R therapy. Based on extensive drug-drug interaction studies, patients were required to be on a stable ART regimen inclusive of atazanavir or raltegravir plus two nucleos(t)ide analogue reverse transcriptase inhibitors for at least eight weeks before screening, with a plasma HIV-1 RNA of < 40 copies/ml and $CD4^+$ T-cell count ≥ 200/mm^3 or $CD4^+$ T-cell percentage ≥ 14% for at least 24 weeks before and during screening. Patients with cirrhosis were permitted and comprised 19% of the study population. Patients were randomized 1:1 to receive 12 or 24 weeks of therapy. Results from the 63 patients in the pilot (1a) part of the study demonstrated similar SVR rates of 94% in the 12-week arm and 91% in the 24-week arm The most common treatment-emergent adverse events were fatigue (48%), insomnia (19%), nausea (18%), and headache (16%). These were generally mild, with none reported as serious or leading to discontinuation. No patient had a confirmed HIV-1 breakthrough of 200 copies/ml or greater during treatment. Both treatment groups experienced declines in the mean absolute $CD4^+$ T-cell count during treatment, although the mean $CD4^+$ T-cell percentage was unchanged, this being consistent with a RBV effect[33].

Extending the Photon studies, the ION-4 study evaluated the efficacy and safety of sofosbuvir with ledipasvir, an NS5A inhibitor, in the treatment of Gt 1 and 4 HCV in HIV individuals This was given as a fixed-dose combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir, administered orally once daily for 12 weeks. This was a multicenter, open-label study in 335 patients of which 20% had cirrhosis and 36% had received previous DAA drugs, including 13 who had failed prior sofosbuvir plus ribavirin. Patients were required to be receiving a stable, protocol-approved antiretroviral regimen for HIV-1 for at least eight weeks before screening and to have evidence of HIV-1 viral suppression (HIV-1 RNA < 50 copies/ml), with a $CD4^+$ count of > 100 cells/mm^3. Allowable ART included tenofovir and emtricitabine with efavirenz, rilpivirine, or raltegravir and, notably, this was a regimen that was ribavirin-free. The overall SVR12 rate was an impressive 96%, including 96% with HCV Gt 1a, 96% with HCV Gt 1b, and 100% with HCV Gt 4, and there was no difference in patients who were TE versus TN or those with or without cirrhosis. Importantly, all 13 patients who had relapsed to sofosbuvir plus RBV achieved SVR12. No patient had confirmed HIV-1 virologic rebound and the most common AEs were headache (25%), fatigue (21%), and diarrhea (11%), and no patient discontinued treatment because of AEs[34]. It is however important to note that results from phase 1 evaluations showed that concomitant administration of ledipasvir/sofosbuvir and tenofovir disoproxil fumarate as a component of an antiretroviral regimen resulted in modest increases (approximately 40%) in the exposure to tenofovir, as compared with an antiretroviral regimen alone, indicating a need in these patients for increased monitoring of tenofovir toxicity. This effect is further potentially enhanced when used in conjunction with HIV ritonavir-boosted PIs and cobicistat and therefore these combinations are not recommended (Harvoni [ledipasvir-sofosbuvir] tablets: U.S. prescribing information. Foster City, CA: Gilead Sciences, March 2015 (http://www.Gilead.com/ ~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi .pdf).

Another promising regimen is the combination of sofosbuvir with daclatasvir, a pan-genotypic NS5A inhibitor. The advantages of this regimen are that it is once daily and has pan-genotypic activity and, in particular, has good activity against Gt 3 HCV, which has been a gap with many other regimens. In the Ally 2 study, 151 TN HIV-coinfected patients and 52 TE were enrolled with Gt 1-4 HCV, although non-Gt 1 patient enrollment was limited to 20% of the study population.

Cirrhosis was allowed and constituted 14% of the study population. Patients receiving ART were required to have HIV-1 RNA < 50 copies/ml at screening and < 200 copies/ml for at least eight weeks, plus a $CD4^+$ count of at least 100 cells/mm^3. Patients who were not receiving ART were required to have a screening $CD4^+$ count of ≥ 350 cells/mm^3. Patients were permitted to receive a wide range of ART including the following antiretroviral agents: darunavir/ritonavir, atazanavir/ritonavir, lopinavir/ritonavir, efavirenz, nevirapine, rilpivirine, dolutegravir, raltegravir, enfuvirtide, maraviroc, tenofovir, emtricitabine, abacavir, lamivudine, and zidovudine. On the basis of pharmacokinetic data with antiretroviral inducers and inhibitors of cytochrome P-450 3A4, the standard 60 mg dose of daclatasvir was adjusted to 30 mg in patients receiving ritonavir-boosted PIs and to 90 mg in those receiving efavirenz or nevirapine. Patients who had been previously treated for HCV could have received any anti-HCV agents except NS5A inhibitors. Treatment-naive patients were randomized in a 2:1 ratio to receive either 12 or eight weeks of sofosbuvir 400 mg with daclatasvir at 60 mg per day, the latter dose-adjusted according to ART regimen, while treatment-experienced patients all received 12 weeks of therapy. Fourteen percent of patients had cirrhosis and 98% were on ART. The SVR12 rates in Gt 1 were 96.4% for TN patients in the 12-weeks arm, but only 75.6% in the eight-week arm, and 97.7% in the TE arm. For patients with Gt 2, 3, and 4, a SVR12 was reported in all 26 patients (100%) in the 12-week group and in 7/9 patients (78%) in the eight-week group. These data suggest that eight weeks of therapy is inadequate in this patient population. Patients with cirrhosis had comparable response rates to those without cirrhosis. Notably, of the 12 patients who had a relapse, nine were receiving concomitant darunavir/ritonavir[35]. More recent data regarding observed drug-drug interactions showed that darunavir/ritonavir and lopinavir/ritonavir had a reduced effect on daclatasvir exposure that would not require dose adjustment, thereby suggesting that the most effective dose for daclatasvir is 60 mg daily with concomitant administration of darunavir/ritonavir or lopinavir/ritonavir[36]. The most common adverse events were fatigue, nausea, and headache and there were no study-drug discontinuations because of adverse events, while HIV-1 suppression was not compromised.

Another more recent regimen is a two-drug combination of grazoprevir, an NS3/NS4A PI, with elbasvir, an NS5A inhibitor, which have been co-formulated as a once-daily, fixed drug combination. The C-EDGE CO-INFECTION study was a phase III open-label, single-arm study of this combination in HIV coinfection. The study enrolled 218 patients with chronic HCV Gt 1, 4, or 6 infection and HIV coinfection, with or without cirrhosis. Patients were either naive to ART or on stable ART with tenofovir or abacavir, and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine for at least eight weeks before enrolment. The ART-naive patients had to have CD4 T-cell counts > 500 cells/mm^3 and HIV RNA viral load < 50,000 copies/ml. Patients on stable ART had to have CD4 T-cell counts > 200 cells/mm^3 and undetectable HIV RNA (< 20 copies/ml) for at least eight weeks. All patients received grazoprevir 100 mg plus elbasvir 50 mg in a fixed-dose combination tablet once daily for 12 weeks. Notably, this too was a ribavirin-free regimen. The SVR12 was achieved by 96% of patients and all 35 patients with cirrhosis achieved SVR12. The most common adverse events were fatigue (13%), headache (12%), and nausea (9%). No patients discontinued treatment because of an adverse event, and two patients receiving ART had transient HIV viremia[37].

Finally there has been the development of fixed pangenotypic drug combination. In particular velpatasvir, a new generation NS5A inhibitor, has picomolar potency against genotypes 1-6. In the phase III Astral-5 Study, 106 patients received open-label therapy with 12 weeks of sofosbuvir and velpatasvir of 400 and 100 mg/day as a fixed-drug combination. The study included TN and TE patients and 18% were cirrhotic. They were required to be on stable ART for eight weeks with a CD4 count of > 100 cells/mm^3 and an HIV viral load of < 50 copies /ml, and ART was required to consist of a backbone of either tenofovir/emtricitabine or abacavir/lamivudine with either an NNRTI, integrase inhibitor, or protease inhibitor. The overall SVR12 rate was excellent at 95%, with breakdown by genotype being Gt 1a 95%, Gt 1b 92%, Gt 2 100%, Gt 3 92%, and Gt 4 100%. Patients with cirrhosis had 100% SVR12 and TE patients had 97%. As with other studies, the majority of adverse events were mild and there was no HIV rebound observed[38]. A summary of the pivotal studies of interferon-free regimens in HIV/HCV coinfection is shown in table 1.

An important issue is whether these excellent clinical trial results can be replicated in a real world setting, especially given that clinical trial subjects are carefully selected on the basis of high likelihood of success and are intensively monitored. In an Italian real world

Table 1. Summary of sustained viral response rates at 12 weeks with interferon-free regimens in HIV/HCV coinfection

Study	n	Drug combination	Genotypes	SVR
Photon 1	224	SOF + RBV	1, 2, 3	Treatment-naive: – Gt 1: 76% – Gt 2: 88% – Gt 3: 67% Treatment-experienced: – Gt 2: 92% – Gt 3: 94%
Photon 2	275	SOF + RBV	1, 2, 3, 4	Gt 1 Treatment-naive: 85% Gt 2: 88% Gt 3: 89% Gt 4: 84%
Turquoise 1	63	Abbvie 3D + RBV	1	12 weeks: 94% 24 weeks: 91%
Ion-4	335	SOF + LDV	1, 4	Gt 1a: 96% Gt 1b: 96% Gt 4: 100
ALLY-2	151	SOF + DCV	1, 2, 3, 4	Treatment-naive Gt 1: – 12 weeks: 96% – 8 weeks: 76% Treatment-experienced Gt 1: 98% Gt 2, 3, 4 – 12 weeks: 100% – 8 weeks: 78%
C-Edge	218	Graoprevir _ Elbasvir	1, 4, 6	Overall: 96% Cirrhosis: 100%
Astral 5	106	SOF + VEL	1, 2, 4, 13	Overall 95% – Gt 1a: 95% – Gt 1b: 92% – Gt 2: 100% – Gt 3: 92% – Gt 4: 100% Cirrhosis: 100% TE: 97%

DCV: daclatasvir; Gt: genotype, LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained viral response; TE: treatment experienced; VEL velpatasvir.

prospective cohort of 58 HIV/HCV-coinfected individuals, of which 64% had cirrhosis and 45% were prior null responders and were treated with a variety of DAA regimens, 91% of individuals achieved SVR12, suggesting that clinical trial data can be replicated in a real world setting and reflecting real world results in an HCV monoinfection setting[39].

Acute HCV

Since approximately the year 2000, a number of jurisdictions around the world have reported outbreaks of acute HCV in HIV individuals that have been predominantly driven by permucosal rather than parenteral transmission[38]. In particular, these individuals have often been detected in the acute phase of infection as most patients were on cART and were being regularly monitored with liver function tests[40,41]. It has been known for some time that acute HCV offers a window of opportunity for treatment with P+R, with increased SVR rates compared to patients treated in the chronic phase of infections, and SVR rates in HIV patients treated in the acute phase are approximately 60-80%, regardless of genotype[42]. An early uncontrolled pilot study compared P+R plus telaprevir for 12 weeks using response-guided therapy for 24-72 weeks

Table 2. List of significant drug-drug interactions between antiretroviral therapy and direct-acting antivirals and guidelines for management

Selected HIV drugs	HCV DAA drugs				HCV non-DAA drugs	
	NS58 inhibitor	Coformulated NS5A/NS5B inhibitor	Coformulated NS5A/HCV PI plus NS58 inhibitor	HCV protease inhibitor		
	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/paritaprevir/ ritonavir plus dasabuvir	Simeprevir	Ribavirin	Pegylated interferon alpha
NRTIs						
3TC	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓
TDF	✓	✓ Monitor for TDF toxicity	✓	✓	✓	✓
ZDV	✓		✓	✓	×	×
PIs						
ATV (unboosted)	✓	✓	✓ Reduce ATV dose to 300 mg and take it AM at same time as (ombitasvir/paritaprevir/r plus dasabuvir). If RIV cannot be used, choose an alternative HCV regimen	×	✓	✓
ATV/r or ATV/c	✓	✓ If PI/r (or ATV/c, DRV/c) is used with TDF, ↑ TDF concentrations are expected. If coadministration necessary, monitor for TDF-associated toxicities (see footnote)	✓ Take ATV 300 mg in AM at same time as (ombitasvir/ paritaprevir/r plus dasabuvir); discontinue RTV or COBI in HIV regimen until HCV therapy completed	×	✓	✓
DRV/r or DRV/c	✓		×	×	✓	✓
FPV or FPV/r	✓		×	×	✓	✓
LPV/r	✓		×	×	✓	✓
SQV/r	✓		×	×	✓	✓

3TC: lamivudine; ABC: abacavir; ATV: atazanavir; COBI: cobicistat; DAA: direct-acting antivirals; FTC: emtricitabine; LPV: lopinavir; PI: protease inhibitor; RPV: rilpivirine; RTV: ritonavir; SQV: saquinavir, TDF: tenofovir; ZDV: zidovudine.
Adapted from U.S. Department of Health and Human Services[1].

to standard P+R using an historical control. It demonstrated that in the telaprevir group, 84% (16/19) of men achieved SVR12 compared to 63% (30/48) in the control group, suggesting for the first time that the addition of a DAA may increase response rates and decrease duration of therapy, although it needs to be highlighted that the comparator group had poorer baseline response parameters[43]. A more recent all oral study DACRE C-II of sofosbuvir and weight-based ribavirin in 19 patients with recently-acquired HCV, of which 74% were HIV coinfected, attempted a short course of six weeks and demonstrated a suboptimal SVR12 rate

of only 32%[44]. This suggests that future studies of shortened courses of therapy need to utilize agents more potent than ribavirin. More studies of DAAs with more potent all-oral combinations in acute and recently-acquired HCV are needed to determine if they are at least as, if not more, effective than P+R in this setting and whether therapy can be shortened. In addition, given that HIV patients are often at risk of onward transmission of HCV and that spontaneous clearance rates are only 15%, consideration should be given to offering therapy at first diagnosis rather than waiting for spontaneous clearance

Liver transplantation

Liver transplantation has been the only option for many patients who developed liver failure or HCC. Whilst transplantation was offered to HIV patients in the past, it was controversial due to significantly poorer outcomes in HIV-positive patients compared to HIV-negative patients, with a three-year patient survival of only 60% compared to 79%, and graft survival of 74% compared to 53% due to aggressive recurrence of HCV in the graft[45]. More recently, with the advent of DAAs, emerging data has suggested high SVR12 rates treating HIV-coinfected individuals post-transplant (87.5-89.0%)[46,47] and survival has risen 80% in individuals whose HCV is treated post-transplant[48], although drug-drug interactions with antirejection medications have to be considered in addition to ART. While treatment of advanced liver disease pre-transplant will largely transform this landscape, some patients with high MELD scores will not reverse their liver disease and will still require transplantation.

Drug-drug interactions

Although there have been great strides in the management of coinfection, these come at a cost. Many of the new HCV drugs have DDIs, which applies to drugs in general but in particular to ART regimens. This works both ways in that the new HCV agents can affect the pharmacokinetics (PK) of the HIV drugs and conversely the HIV drugs can affect the PK of the HCV drugs. Significant DDIs will push a drug outside its therapeutic window, the consequences of which are that high levels of drug can result in drug toxicity, while low levels can result in decreased efficacy and potentially the development of resistance, especially to components of an ART regimen. The goal of therapy is therefore to safely achieve an SVR for HCV therapy while maintaining HIV suppression. This demonstrates that knowledge of these interactions is critical to the safe use of these drug combinations, and necessitates that each individual on ART be assessed for compatibility of that regimen with whatever HCV regimen is being considered. This may necessitate fashioning an appropriate ART regimen in a treatment-naive patient, a switch of therapy in a treatment-experienced patient, or a dose adjustment of the HCV DAA being considered. This can be particularly challenging in patients with extensive prior ART experience and resistance mutations where treatment options can be very limited. The extent of the problem is illustrated by the limitations of ART regimens permitted in the clinical trials listed above.

There are three mechanisms by which these interactions occur. Usually, drugs either induce or inhibit enzymatic activity, most commonly the cytochrome P450 (CYP450) system, but also glucuronidation, and lead to abnormal drug exposures. In addition, they can induce or inhibit drug transporters such as P-glycoprotein and OATB1B1/3, which are involved in the uptake (influx) and excretion (efflux) of drugs. Finally, they can affect protein binding of drugs and cause displacement of highly protein-bound drugs[49].

Predicting DDIs is based on extrapolation from formal PK evaluation in healthy volunteers. Integrase inhibitors such as raltegravir and dolutegravir have now become the preferred first-line agents for the treatment of HIV[1] and have an excellent DDI profile and are therefore compatible with most HCV DAAs. In addition, of the DAAs, daclatasvir has had the most extensive PK evaluation and is compatible with most FDA-approved ART, including most ritonavir-boosted PIs[36]. It is almost impossible for clinicians to remember all DDIs and therefore physicians should refer to databases that will provide the level of interactions expected. The best known of these are the University of Liverpool HIV and Hepatitis drug interaction websites, known as HIV I Chart and HEP I Chart, respectively[50]. In addition, it is important to remember when using the Abbvie 3D combination in the context of a boosted PI to remove the ritonavir component of the ART for the duration of HCV therapy due it already being present in the HCV regimen. It also needs to be remembered that HIV patients often have significant comorbidities and take multiple other medications, necessitating the evaluation of DDIs of these drugs with DAAs as well as their ART regimens. A comprehensive list of DDIs between ARTs and DAAs is shown in table 2.

The developing world

A major issue with HIV/HCV coinfection is that the majority of infections occur in resource-limited regions. This highlights the issues of access to drugs and our ethical obligation to ensure this, given the extremely high cost of these agents. Added to this is the lack of refrigeration facilities in these regions, which makes the use of older and less expensive interferon-containing regimens impractical, even aside from the poor response rates and adverse event profile of such a regimen. This will necessitate a mechanism whereby DAAs are made affordable to these regions as well as a model of care that will enable roll-out of these drugs to large numbers of people. Part of this is being managed by some pharma companies by selling their drugs at heavily reduced prices in these regions. Whilst this is a start, it will also require the additional engagement of non-government and philanthropic organizations to make this happen effectively, along the lines of what is being achieved in HIV therapy in these regions.

Summary

The landscape for HCV therapy in HIV-coinfected patients has improved with the introduction of combinations of all-oral DAAs. Several late-phase studies have demonstrated very high SVR rates in this patient population with short courses of therapy, which are equivalent to non-HIV populations such that HIV coinfection is no longer considered a special population. They are also safe and associated with minimal adverse events. These characteristics, combined with their widespread rollout, raise the prospect of the potential for eradication of HCV from HIV populations. There are, however, significant DDIs with DAAs and ART, which needs to be carefully considered in the selection of drugs.

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