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Rebecca Cope
Touro College of Pharmacy, rebecca.cope@touro.edu

Aaron Pickering

Thomas Glowa

Samantha Faulds

Peter Veldkamp

See next page for additional authors

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Majority of HIV/HCV Patients Need to Switch Antiretroviral Therapy to Accommodate Direct Acting Antivirals

Rebecca Cope, PharmD,[1*] Aaron Pickering, PharmD,[2*] Thomas Glowa, PharmD,[3] Samantha Faulds, BA,[3] Peter Veldkamp, MD, MSc,[3] and Ramakrishna Prasad, MD, MPH[3]

Abstract

The impact of drug–drug interactions (DDIs) between interferon-free direct acting antiviral (DAA) regimens and antiretrovirals (ART) among HIV/HCV co-infected individuals in clinical practice settings is unknown. A single-center, retrospective chart review of co-infected patients was conducted from June 2014 to February 2015. Significant interactions between simeprevir (SMV), ledipasvir (LDV), and paritaprevir/ritonavir/ombitasvir plus dasabuvir (3D regimen) with ART were identified based on available literature. SMV had the largest number of DDIs and was further investigated to determine the feasibility of ART switch to allow for DAA use. Of 127 subjects, 23% had advanced liver disease; 86% of those with known HCV genotype were HCV genotype 1. An ART switch allowing use of SMV, LDV, and 3D regimen was recommended in 97/127 (76%), 81/127 (64%), and 91/127 (72%) patients, respectively. Subjects on PI/r regimens had limited options for ART switch, with 40% of these patients unable to be switched to an ART regimen that avoided the use of a PI. In conclusion, the majority of HIV/HCV co-infected patients will be recommended to switch ART prior to use of interferon-free, DAA regimens, and an ART switch may not be feasible for more than a third of patients on a boosted PI. DDIs between ART and DAAs represent an additional barrier to treatment efficacy in clinical practice settings that are unaccounted for in clinical trials.

Introduction

Although effective antiretroviral therapy (ART) for the human immunodeficiency virus (HIV) has significantly improved survival,[1–4] liver disease continues to be a substantial source of morbidity and mortality among HIV-infected individuals. In the US, much of the burden for end-stage liver disease, hepatocellular carcinoma, and liver transplantation is due to hepatitis C virus (HCV) infection.[5–8] End-stage liver disease is currently a leading cause of death in this population.[9]

Approximately one-third of those infected with HIV are concomitantly infected with HCV.[6] Compared to HIV-uninfected individuals, untreated HCV infection in an HIV/HCV co-infected population results in accelerated liver disease progression, higher rates of end-stage liver disease, and more reduced life expectancy.[10] Successful HCV therapy is defined as achieving an undetectable HCV RNA 12 weeks after the completion of treatment (SVR12). This is associated with a reduction in morbidity and mortality due to liver failure and hepatocellular carcinoma.[11] Historically, older regimens containing pegylated interferon alfa and ribavirin had low efficacy (SVR12 14–38%) and were poorly tolerated by HIV/HCV co-infected individuals.[12–14] Consequently, less than 15% of co-infected patients had received treatment for HCV as of 2011.[15]

The landscape of hepatitis C treatment was transformed with the approval of sofosbuvir (SOF), an NS5B inhibitor, and simeprevir (SMV), an NS3/4A protease inhibitor, in 2013. For the first time, an all oral, interferon-free HCV treatment option became available. In October 2014, a single tablet combination pill of sofosbuvir and ledipasvir (SOF/LDV), an NS5A inhibitor, was approved. This regimen has rapidly emerged as the preferred option for HCV genotype 1 due to ease of use, high SVR rates, and tolerability.[18–20] More recently, dasabuvir (NS5B inhibitor taken twice a day) in addition to the once-daily combination pill of ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor),

[1]University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania.
[2]Baltimore Washington Medical Center, University of Maryland, Glen Burnie, Maryland.
[3]Division of Infectious Diseases, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.
*Drs. Cope and Pickering contributed equally to the development of the study.

and ritonavir (utilized as a boosting agent for paritaprevir) became available in December 2014 (3D regimen). The American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and the International Antiviral Society-USA (AALSD/IDSA/IAS-USA) released a joint guideline in 2013 which has been updated to recommend all three of these regimens as viable options with similar efficacy for treatment-naïve and experienced individuals with HCV Genotype 1 or 4.[16]

Clinical decision making regarding the most appropriate DAA therapy is left largely to individual HCV treatment providers. One significant factor that should influence this decision is the presence of drug–drug interactions (DDIs). This is particularly important among HIV/HCV co-infected individuals receiving antiretroviral therapy. Sofosbuvir, ombitasvir, and dasabuvir have few DDIs. In contrast, simeprevir and paritaprevir have DDIs with several antiretrovirals as they undergo oxidative metabolism by the cytochrome P450 (CYP) 3A enzyme subfamily. Simeprevir and paritaprevir levels will be altered by inducers or inhibitors of CYP3A4, and both inhibit enzymes such as organic anion transporters (OAT).[21,22] This has resulted in a recommendation to avoid simeprevir and paritaprevir co-administration with HIV protease inhibitors (PI), cobicistat-containing regimens, or certain non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz (EFV), nevirapine, and etravirine because these agents increase or decrease the levels of these DAAs beyond what is considered safe and efficacious.[21–23]

SOF/LDV was anticipated to have much less drug–drug interactions than SOF/SMV as LDV is not metabolized by the CYP enzyme family.[23] However, LDV may increase levels of tenofovir disoproxil fumarate when used in conjunction with efavirenz, a ritonavir-boosted HIV protease inhibitor, or elvitegravir boosted by cobicistat. The safety of increased tenofovir levels in this situation is not yet established, but it is currently recommended to avoid tenofovir in combination with these specified ART during treatment with SOF/LDV.[22,23] The 3D regimen contains the CYP3A4 inhibitor ritonavir as a boosting agent for paritaprevir. The study protocol for TUROQUOISE I, which evaluated the efficacy of this treatment in co-infected patients, allowed only raltegravir or atazanavir (without additional ritonavir) based regimens.[24.] Other ARTs are not recommended for concomitant use due to concerns of altered drug levels or additive QTc prolongation[22,25]

Providers face many challenges if an ART switch is recommended to avoid DDIs with DAAs The first challenge is the risk of inappropriate ART to accommodate anti-HCV therapy, which may put patients at risk for: (a) HIV virologic failure; (b) development of resistance in both HIV and hepatitis C viruses; and (c) a potential for increased adverse effects leading to discontinuation and non-adherence with therapy. Additionally, both patients and providers may be reluctant to switch ART regimens.

The intent of this study was to determine the need for antiretroviral therapy switch prior to initiation of HCV DAAs, and the feasibility of ART switch to allow for DAA use. It was hypothesized that the majority of HIV/HCV co-infected patients considered for such treatment will be recommended to switch ART. We additionally hypothesized that the majority of patients on a PI-based ART regimen would be difficult to switch due to HIV drug resistance.

Methods

A retrospective chart review was conducted at the University of Pittsburgh Medical Center's HIV Adult Primary Care Center. The study received exempt IRB approval from the Review Board of the University of Pittsburgh. All patients with HIV and active HCV >18 years old and seen at the center at least one time between January 2013 and August 2014 were included in the study. Exclusion criteria included spontaneous clearing of HCV as demonstrated by an undetectable HCV RNA following a positive HCV antibody, SVR12 previously achieved through use of peg-interferon, ribavirin, boceprevir, or telaprevir, and current enrollment in another clinical trial for HCV treatment. Demographic data and information regarding the patient's ART regimen was collected. Patients not currently on ART were included in the study. Liver staging was done with the APRI (AST to Platelet Ratio) index. Advanced liver disease was defined as APRI index ≥1 and/or radiographic findings of cirrhosis.[29,30]

Three pharmacists with infectious disease experience (AP, RC, and TG) reviewed the medication list of all patients to identify interactions between SMV, LDV, 3D regimen, and ART. To aid this review, the DAA package insert,[21,22,24] University of Liverpool HIV-Interaction Drug Charts,[31] and AASLD/IDSA/IAS-USA Hepatitis C Treatment Guidelines[23] were used. If sources conflicted, AASLD/IDSA/IAS-USA recommendations were considered to be the most relevant to clinical practice. If a patient's current ART was incompatible with DAA use due to a DDI, this individual was recommended for ART switch (Table 1).

SMV had the largest number of DDIs and was further investigated to determine the feasibility of ART switch to allow for DAA use. If DDIs limiting co-administration of SMV and the patient's ART regimen were noted, previous HIV genotype reports and medication history were reviewed by a team consisting of previously mentioned pharmacists (AP, RC, and TG) and two HIV specialist physicians (RP and PV) to determine if switching to an alternative but effective ART regimen would be feasible. Feasibility was defined as the ability to safely change ART to a regimen expected to effectively suppress HIV viral load based on treatment history and viral resistance patterns. The scope of our investigation was limited to treatment history and drug resistance and did not incorporate renal function, patient preference, financial constraints, or other factors typically considered

Table 1. Antiretroviral Therapy (ART) Regimens Without Clinically Significant Interactions with Direct-Acting Antivirals (DAAs)[a]

DAA	*Safe ART*
Simeprevir	RAL, RPV, T20, MVC, TDF, FTC, 3TC, ABC
Ledipasvir	All regimens except: • EVG/cobi + TDF • EFV + TDF • PI/r + TDF
Paritaprevir/r	RAL, TDF, FTC, 3TC, ATV, T20

[a]As per drug package inserts and AASLD/IDSA/IAS/USA HCV Treatment Guidelines.

when changing ART. Cases in which a switch was not deemed feasible were reviewed a second time by both HIV specialist physicians to assure all possible ART regimens were considered.

Results

In total, 161 patients were reviewed for inclusion. Of these, 34 had characteristics that excluded them from the study. The most common reason for exclusion was lack of follow-up at the clinic within the specified time period. An additional six patients were deemed ineligible due to treatment with boceprevir as part of a clinical trial. Ultimately, 127 were found to have a current HCV infection while actively receiving care from the clinic. Baseline patient characteristics and distribution of ART regimens are shown in Table 2. An ART switch allowing use of SMV was recommended in 97/127 (76%) patients. For LDV and 3D regimen, an ART switch was recommended in 81/127 (64%) and 91/127 (72%), respectively (Table 3).

In terms of ART substitutions, individuals with viral susceptibility to efavirenz may be assumed to also have sensitivity to rilpivirine, and a one-to-one switch between these agents was deemed safe. A straightforward substitution in this manner could be made in 47/97 (48%) of patients. For the remaining patients (mostly on a PI), a switch following HIV expert opinion was deemed safe in 32/97 (33%), while safe switch was not possible in 18/97 (19%) due to archived HIV drug resistance mutations.

Notably, for 40% of patients on a PI, an ART switch was not feasible. This was primarily due to use of salvage regimens where the PI/r had become indispensable. All patients deemed unable to switch ART were known or predicted to have high levels of HIV drug resistance in which a safe switch could not be made to a regimen which would avoided the use of a boosted PI. Among patients who were unable to switch, 28% had evidence of advanced liver disease.

Table 2. Baseline Characteristics of HIV/HCV Co-infected Adults at a Single-Center HIV Primary Care Clinic in 2013–2014

Clinical characteristic	*All patients* N *(%)* $N=127$	*Recommended switch—feasible* N *(%)* $N=79$	*Recommended switch—not feasible* N *(%)* $N=18$
Age, median years	54	56	55
Sex, male	90 (71%)	54 (68%)	15 (83%)
Race, African American	69 (54%)	47 (59%)	11 (61%)
Known HCV genotype 1[a]	81 (86%)	48 (83%)	15 (100%)
CD4 < 200 cells/mm^3	14 (11%)	10 (13%)	3 (17%)
HIV viral load > 200	22 (17%)	15 (19%)	3 (17%)
Advanced liver disease	29 (23%)	19 (24%)	5 (28%)
Not on ART	8 (6%)	–	–
2 NRTI + additional agent			
Efavirenz	45 (35%)	45 (57%)	–
Rilpivirine	8 (6%)	–	–
Raltegravir	14 (11%)	–	–
Elvitegravir	2 (2%)	2 (3%)	–
Boosted PI	44 (35%)	26 (33%)	18 (100%)
Other	6 (5%)	6 (8%)	–

[a]An HCV genotype was available in only 94 patients.

All percentages have been calculated using the *N* stated in the second row of each column.

Table 3. Need for Antiretroviral Therapy (ART) Switch Prior to Direct Acting Antiviral Use in HIV/HCV Co-Infected Adults Based on Potential for Drug–Drug Interactions

	ART switch recommended N *(%)*	*ART switch not recommended* N *(%)*
Simeprevir	97 (76%)	30 (24%)
Ledipasvir	81 (64%)	46 (36%)
Paritaprevir/r	91 (72%)	36 (28%)

Discussion

Managing DDIs for HCV treatment in HIV co-infected patients on ART can be complex and challenging. This study found that the majority of HIV/HCV co-infected patients at our center will be recommended to switch ART prior to use of any interferon-free DAA regimen. Additionally, for over a third of patients on a PI, an ART switch to accommodate use of DAAs did not prove feasible. Our study also highlights that 28% of individuals unable to switch ART had evidence of advanced liver disease and would meet high priority treatment criteria per the AASLD/IDSA/IAS-USA HCV guidelines.[16]

Implications on choice of HCV therapy among HIV-infected individuals

These findings highlight the complexity of treating HCV, even with the new DAA's, and are highly significant to real world HIV clinical practice settings. To make this research as relevant as possible, only sources that would commonly be available, such as the AASLD/IDSA/IAS-USA guidelines and drug package inserts, were consulted when identifying DDIs. As the AASLD/IDSA/IAS-USA guidelines do not indicate a preference as to which DAA regimen should be used for the treatment of HCV, choosing the most appropriate DAA therapy in the face of DDIs becomes a clinical decision that should consider several elements. First, the level of urgency for HCV treatment must be balanced with the severity of the DDI. This evaluation should incorporate the degree of liver fibrosis, other extrahepatic comorbidities, and the duration of HCV treatment indicated.

The use of ledipasvir is not recommended in combination with tenofovir and efavirenz, a ritonavir-boosted HIV protease inhibitor, or elvitegravir boosted by cobicistat due to an increase in tenofovir levels. However, the predicted increases in tenofovir may not be clinically significant as tenofovir levels do not correlate well with intracellular toxicity,[32] particularly over a short treatment course of 8–12 weeks. For the purposes of this study, individuals on tenofovir in combination with efavirenz, protease inhibitors, or cobicistat containing agents were recommended for ART switch prior to use with SOF/LDV. Preliminary data from the ION-4 study suggests use of regimens containing tenofovir and efavirenz is actually well tolerated in co-infected patients.[33] Further experience with the

concomitant use of these medications in the clinical practice setting will reveal the true significance of this interaction.

For individuals who do not require immediate treatment, a potential solution in the FDA review pipeline includes the NS5A inhibitor, daclatasvir, in combination with sofosbuvir for HCV genotypes 1–4.[34] Daclatasvir is similar to SMV in that it undergoes metabolism by the CYP3A4 enzyme subfamily. However, daclatasvir may be dose-adjusted to accommodate concomitant antiretrovirals: 30 mg with ritonavir or cobicistat-boosted agents, 90 mg with NNRTIs except rilpivirine.[35,36] No dose adjustment is required with raltegravir, dolutegravir, rilpivirine, or NRTIs including tenofovir. Data from the Phase III, ALLY-2 study in HIV-HCV co-infected patients showed SVR12 rates of 97% in treatment-naïve and experienced patients following 12 weeks of therapy.[37]

Future relevance of simeprevir

In the various phase III ION trials for approval of SOF/LDV, baseline NS5A resistance was detected in 11–18% of participants.[18–20] This group tended to have a lower SVR12 rate of 89–90% (as compared to rates as high as 98% overall). Resistance not present at baseline was also seen to develop during the course of treatment for a small proportion of virologic failures. With widespread use of this regimen in patients of varying complexity, it is possible that treatment failure will occur in practice more often than predicted in the clinical trials. Cross-resistance to all NS5A inhibitors is likely to occur if mutations develop,[38,39] leaving SOF/SMV as a second-line option for those who have previously failed this type of therapy. As a result, SMV is likely to remain relevant in the future. However, previous treatment failure on a NS3/4A protease inhibitor regimen and the inability to safely change ART to accommodate SMV would represent a significant barrier to its use.

Limitations of this study

As this is a single-center study, results may be limited to the patient population at our specific HIV Primary Care Clinic. This study was additionally limited by the consideration of only HIV drug resistance and treatment history when evaluating for safety and efficacy of ART switch. In practice, patient preference, need for ART dose adjustment, and other DDIs such as those between atazanavir or rilpivirine and acid-suppressing agents would also need to be weighed when making such a decision. Another limitation is our inclusion of patients with an unknown HCV genotype in our analysis. While the reviewed interferon-free DAA treatments would not necessarily be applicable to all HCV genotypes, given that genotype 1 accounted for 86% of patients whose genotype was known, we felt it was valuable to include these patients in our analysis. Additionally, these findings will be of relevance with the emergence of future therapies with extended or pangenotypic activity.

Conclusions

This study shows that DDIs between ART and DAAs continue to represent an additional barrier to reducing the gap between efficacy and effectiveness which should not be overlooked. Although HIV/HCV co-infected patients now achieve SVR12 rates comparable to those of mono-infected patients in clinical trials, these anti-HCV therapies may be less effective in practice for co-infected patients due to the obstacle posed by DDIs. Our results illustrate a strong need for treatment providers with expertise in both HIV and HCV to diminish the possibility for loss of HIV virologic suppression and HCV treatment failure. As only 59% of HIV clinicians report actively managing HIV/HCV co-infection,[41] the use of a team approach including both a clinical pharmacist and physician is an effective way to address the barriers described by this article. Models for capacity building to expand access to this expertise are of urgent need.

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Address correspondence to:
Ramakrishna Prasad, MD, MPH
Keystone Building
520 Fifth Avenue Suite 510
Pittsburgh, PA 15213

E-mail: dr.rk.prasad@gmail.com

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