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Update in HIV/HCV Co-Infection in the Direct Acting Antiviral Era

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Abstract

Purpose of Review—Availability of direct acting antivirals (DAAs) that demonstrate remarkable clinical efficacy and safety has revolutionized the ability to treat chronic infection with hepatitis C virus (HCV). An equal measure of clinical success has now been achieved in persons co-infected with HCV and the human immunodeficiency virus (HIV), a historically harder to cure cohort with interferon-based therapy. Global goals include identifying all HIV/HCV-infected persons, gaining access to DAA-therapy, preventing de novo and re-infection, and managing the sequelae of chronic infection. This review will discuss advances in the field of HIV/HCV co-infection reported during the last 18 months, and will suggest areas for future investigation.

Recent Findings—An expanding body of literature has enhanced our understanding of the clinical and epidemiologic issues surrounding HIV/HCV co-infection. DAA therapy for HCV is highly efficacious in HIV/HCV co-infected persons if drug-drug interactions are appropriately considered.

Summary—Eradicating HCV infection in persons with HIV co-infection can be achieved safely and effectively with available DAAs. Economic and social approaches to enable access and delivery of curative HCV therapy to HIV-infected persons require continued research and resource allocation.

Keywords

HIV/HCV co-infection; direct acting antivirals; global health; hepatic fibrogenesis

Introduction

HIV/HCV co-infection is common due to shared routes or risk factors for acquisition, and has been associated with more rapid HCV-induced fibrosis progression and lower odds of successful treatment outcome with interferon-based therapy. With the development of interferon-free DAA therapy, efficacy in HIV/HCV co-infected persons has received significant recent attention. Eradicating HCV in HIV co-infected persons is now medically achievable in most cases, when access to medication is possible. Here we review recent findings in the field.

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Efficacy of DAAs in Co-infection

Historically, persons with HIV/HCV coinfection achieved lower rates of sustained virologic response (SVR) after interferon-based HCV treatment compared to persons with HCV mono-infection. Multiple recently published clinical trials highlight comparably high rates of SVR with DAA therapy in HIV/HCV co-infection, reviewed in detail by Wyles et al [1–3] (3**) and summarized in Table 1. High SVR rates (>90%) in co-infection were reported with sofosbuvir and ledipasvir (ERADICATE, ION-4) [4, 5], daclatasvir and sofosbuvir (ALLY-2)[6, 7], grazoprevir and elbasvir (C-EDGE, C-WORTHY) [8, 9], and the combination of ombitasvir, paritaprevir/ritonavir, dasubavir, and ribavirin (TURQUISE-1) [10]. Practically speaking, the choice of regimen for clinical use in co-infection is often dictated less by relative efficacy, and more by medication access, insurance formulary preferences, and drug-drug compatibility, discussed below.

Although there has been concern that SVR results obtained in clinical trials may not be generalizable, since persons with co-morbid conditions are often excluded [11], a number of recent “real-world” studies have reported encouragingly high rates of both adherence and SVR in HIV/HCV co-infected cohorts that included patients with active substance use, prior HCV treatment experience, and advanced liver disease [12–18]. (18*).

Interestingly, recent results from a large real-world multi-center study (German Hepatitis C Cohort) suggested shortening therapy with ledipasvir/sofosbuvir to 8 weeks in HIV/HCV-infected persons with GT-1 infection, early liver disease, and low viral load may be as effective as in HCV-monoinfected cohorts [19], results that require further validation. Finally, while virologic relapse occurs in a minority of treated patients, preliminary studies have demonstrated efficacy of re-treatment strategies [20], and use of HCV resistance testing and alternate regimens in the setting of relapse is anticipated, as is currently recommended in HCV mono-infection (www.hcvguidelines.org).

Drug Interactions

Potential drug-drug interactions between HCV and HIV medications, as well as other commonly prescribed medications including statins and acid-suppressing agents, require consideration [9, 21–23]. In most cases, drug interactions can be managed and are not a barrier to achieving HCV cure with DAA therapy. Several cases of suspected drug-induced liver injury associated with DAA therapy in HIV/HCV infected persons have been recently reported, notably in HIV-patients with advanced liver disease receiving lopinavir/ritonavir as part of their ARV regimen [24–26]. The reader is directed to several recent reviews, including the IDSA-AASLD treatment guidelines (www.hcvguidelines.org), for detailed recommendations for how to manage and consider potential ARV-DAA drug interactions [27, 28] (*28) and an online resource (www.hep-druginteractions.org) allows physicians to perform interaction checks in real time. As an example of pertinent drug-drug interaction considerations, HCV regimens that include NS3/4A protease inhibitors may be incompatible with HIV regimens that also contain a protease inhibitor, and the potential inclusion of ritonavir in both HCV and HIV regimens requires reconciliation.

Improved Patient-Reported Outcomes

Several studies examined patient reported outcomes (PROs), including measures of energy and activity levels, in HCV/HIV relative to HCV mono-infected persons, during and after DAA treatment. While both HIV/HCV and HIV mono-infected patients experienced moderate declines in PRO scores during treatment with a ribavirin containing regimen (sofosbuvir and ribavirin), both groups manifested improvement in PRO scores when SVR was achieved [29]. In HIV/HCV co-infected persons treated with a ribavirin-free regimen (sofosbuvir and ledipasvir), in which 20% of participants had advanced liver disease, improved PROs were observed both during and after treatment [30].

Prevalence and Morbidity Associated with Co-infection

With increased availability of DAA-therapy, attention to the prevalence of HCV and HIV/HCV has continued world-wide. A global evaluation examining 783 distinct studies estimated there are ~2.27 million persons living with chronic HIV/HCV infection [31]. HIV-infected persons had an HCV infection rate 6 times higher than the general population, and the rate of HCV co-infection in HIV-infected people who inject drugs (PWID) was 82% [31]**.

A number of regional epidemiology studies were also recently reported, and highlight the need for increased access to care and treatment uptake. Analysis of non-AIDS events in a Spanish cohort of 320 HIV controllers implicated HCV co-infection as the predominant factor contributing to hepatic and extra-hepatic non-AIDS defining clinical events [32]. Similarly, HCV infection significantly contributed to excess mortality observed in a large Spanish HIV-infected cohort (10,340 persons) between 2004–14 [33], and 22.1% of HIV-infected persons in Spain were estimated to have HCV co-infection in 2015 [34].

A systematic review of 37 studies from Latin America and the Caribbean showed marked heterogeneity in the prevalence of HCV infection in HIV-infected persons (0.8–58.5%), data limited in part by differences in data collection practices and sample size [35], while a prospective HIV/HCV co-infected cohort in Vietnam found that 25% of patients had evidence of advanced liver disease indicating urgent need for HCV treatment [36].

Several African epidemiology studies showed a surprising discordance between estimated HCV prevalence in HIV-infected persons based on antibody screening alone, without confirmatory immunoblot or RNA testing, relative to prevalence assessed by HCV RNA testing, suggested previous estimates may have overestimated population prevalence [37, 38]. Results from 159 studies including 108,180 persons with HIV infection showed an HCV antibody prevalence of 3.3% in Southern Africa and 42.3% in Northern Africa, although data from studies with confirmatory testing suggested a 4 times greater rate of positive antibody than replicating virus [39]. In a small Malawian cohort, 5 of 227 HIV-infected patients had anti-HCV IgG but none had positive HCV RNA [40], while an additional study in Mozambique and Zambia found no HCV cases in 1812 HIV-infected persons [41].

In a large modeling study of the global burden of HBV, HCV, and HIV due to IVDU, a collective 4-fold increase in disability-adjusted life years was observed between 1990 and 2013, with the highest attributable HIV burden in low-to-middle-income countries, and the highest attributable HCV burden in high-income countries [42]*. A substantial number of incident and prevalent HIV and HCV cases were associated with IVDU and mass incarceration globally, including in Eastern Europe and Central Asia [43, 44](*43)

In the United States, between 2008–14 new HIV diagnoses in people who inject drugs decreased in the setting of reduced syringe sharing, but this decrease levelled off in recent years in PWID [45]. Motivated by a recent outbreak of HIV in PWID in rural Scott County, Indiana, a tool was developed based on 6 community level indicators to predict the county-level risk of acute HCV infection in PWID, an approach that can be utilized to target resources to at-risk communities [46]**.

In addition to IVDU, re-emergence of an HCV epidemic between 2011–14 in a cohort of MSM in Baltimore, MD, was associated with favorable socioeconomic status, high-risk sexual behavior, and polysubstance use [47]. Sexual behavior as well as biologic factors, appear to contribute to the ongoing epidemic of HCV in HIV-infected MSM, including re-infection after DAA therapy [48, 49]. In a multi-cohort of 7229 HIV/HCV co-infected persons examined between 2001–14, HCC incidence increased and other liver related events declined, with cirrhosis and low CD4 count associating with higher risk for events [50].

Together these data highlight ongoing efforts and challenges to tracking and understanding the epidemics and intersection of HIV and HCV world-wide, the context in which DAA therapy will need to be considered.

Staging Liver Disease

HIV co-infection has previously been associated with faster HCV-induced fibrosis progression, but a recent review highlights findings suggesting optimal HIV management likely attenuates this phenotype [2]. While all patients with HIV co-infection warrant curative HCV treatment, staging liver disease retains importance to determine the need to screen for sequelae of advanced liver disease both before treatment and after SVR, choosing the most appropriate DAA composition and duration, and to frame the importance and urgency of treatment. While no test to stage liver disease has perfect sensitivity and specificity, liver biopsy is typically avoidable in most patients, transient elastography (TE) offers excellent diagnostic information when available, and multiple non-invasive blood tests can provide meaningful information, with the appreciation that most non-invasive tests have better performance in the setting of advanced liver disease than in intermediate stages of fibrosis [51, 52].

While the predictive validity of staging approaches in HIV/HCV co-infection has historically been less studied than in HCV mono-infection, a number of recent studies have helped close this gap. A systematic review and meta-analysis in HIV/HCV co-infected persons, encompassing 6 studies, concluded TE had similar pooled sensitivity and specificity for prediction of liver-related events as in HCV mono-infection, with better

performance in cirrhotics than those with intermediate stages of fibrosis, and with no impact of CD4 count on diagnostic accuracy [53]. A retrospective study of 957 HIV/HCV co-infected patients with compensated cirrhosis found that liver stiffness <12 kPa, measured by TE, had excellent negative predictive value for liver related events after a median follow up of 6 years, with a proportional increase in events for pressures above this cutoff [54]. In a cohort of 275 HIV/HCV co-infected patients with cirrhosis, a significant increase in liver stiffness measured by TE over a median follow-up time of 32 months was associated with a higher risk of hepatic decompensation and HCC [55]. In another study of 105 HIV/HCV coinfecting persons followed for 3 years, TE outperformed six blood tests in terms of correlation with histopathologic fibrosis, while APRI and FIB-4 performed as well as other as commercially available blood tests [56].

An observational, retrospective study in 646 HIV/HCV co-infected patients examining the accuracy of liver staging with blood biomarkers (APRI, FIB-4, Forns) relative to TE found that for patients with cirrhosis suggested by a TE score > 13 kPa, most (80%+) would have been staged correctly with non-invasive blood markers [57]. Most misclassified cases were due to false attribution of cirrhosis, and this study suggested an APRI score < 0.87, a FIB-4 score < 2.02, or a Forns score < 0.78 have accuracy for predicting the absence of cirrhosis [57].

After multivariate adjustment including control for TE-measured liver stiffness, a cross-sectional analysis in 297 women showed that HIV/HCV co-infected women had higher ELF (enhanced liver fibrosis) scores than women with HIV infection alone, with relation of ELF score to age and nadir CD4 count, suggesting the score could be modulated in part by extrahepatic fibrosis associated with HIV infection [58]. The ELF score had better predictive accuracy for all-cause mortality than the APRI or FIB-4 scores in 381 HIV/HCV co-infected women enrolled in the prospective, multicenter Women's Interagency HIV Study over a mean follow-up of 8.3 years [59]. Finally, a retrospective analysis of 6016 HIV/HCV co-infected persons followed at the Veterans Healthy Administration between 1997–2010 found that race and elevated FIB-4 score (>3.25) had predictive value for predicting end-stage liver disease [60].

In sum, available staging tests perform well in HIV/HCV co-infected persons, although for individual patients a risk of false attribution of liver fibrosis for any of the available tests remains, issues also germane in HCV mono-infection.

Non-viral Causes of Fibrosis Progression

In addition to the direct influence of HIV and HCV, recent studies have examined, and in some cases re-examined, the impact of comorbid conditions and medications on fibrosis progression.

In the Women's Interagency HIV Study (WHIS), alcohol use, but not long-term cannabis use, was associated with fibrosis progression in a cohort of 575 co-infected women [61]*. A separate analysis in the WHIS cohort failed to reveal an impact of isolated hepatitis B core antibody status on fibrosis progression in HIV/HCV co-infected women, over a median of

9.5 years, based on serial ELF measurements analyzed from stored samples [62], while a larger cross-sectional study of 44,180 in HIV and HIV/HCV infected persons in the Veterans Aging Cohort Study found an association of isolated anti-HBc with advanced fibrosis in HIV/HCV co-infected, but not HIV-infected persons [63]. While previous cross-sectional analyses suggested tobacco use may hasten fibrosis progression, a longitudinal prospective study of 1,072 co-infected persons failed to support this association [64]. Interestingly, host interferon lambda genotype, previously associated with odds of spontaneous HCV clearance and response to IFN-based therapy, was shown to correlate with fibrosis progression in an HIV/HCV cohort, suggesting a role for host genetics [65]. Finally, analysis of 936 longitudinally collected biopsies from a cohort of HCV and HIV/HCV infected patients suggested non-linear fibrosis progression between stages and an association of hepatic inflammation flares with more rapid fibrosis progression [66]*.

With respect to medications and fibrosis progression, a retrospective study of 5,985 HIV/HCV co-infected veterans suggested statin use may be associated with slower fibrosis progression, although this finding was only significant in a sub-cohort of patients with low ALT [67]. An exploratory study in co-infected patients with concomitant non-alcoholic steatohepatitis showed 48 weeks of pioglitazone therapy resulted in reduced hepatic fat measured by magnetic resonance spectroscopy [68].

Immuno-pathogenesis

A comprehensive look at the continually evolving field of HIV and HCV immuno-pathogenesis is well described in recent reviews, including a growing appreciation for the impact of HIV infection on fibrogenesis and increased cardiovascular risk in co-infection [69–73]. The reader is also directed to number of intriguing *in vitro* and patient sample-based studies have examined the molecular mechanisms by which HIV infection could accelerate HCV-induced fibrogenesis [74–78].

Diagnosis, Cost, and Access

As medical barriers to eliminate HCV in HIV-infected persons have diminished, increased attention has focused on cost and value with respect to DAA access for populations.

In terms of opportunities to diagnosis and prevent new cases, a 2013 study of community health centers in the US indicated that most providers did not follow guidelines for screening for HIV and HCV, and suggested the time required for counselling was a potential barrier to increased screening uptake [79]. Applying lessons learned from annual syphilis screening efforts in HIV when considering annual HCV testing in HIV-infected MSM, could improve opportunities to identify and cure incident cases in HIV-infected persons [80]. Because most persons with HCV and HBV infection and 15–30% of those with HIV-infection in the US and Europe remain undiagnosed, increased uptake of simultaneous point-of-care testing for HIV, HCV, and HBV in high-risk populations merits consideration [81]. While emergency rooms represent an opportunity to increase HCV and HIV diagnoses through opt-out testing [82], barriers to linkage to care persist and require dedicated resources [83].

A transmission model based on existing prevalence data of HIV/HCV co-infection in MSM suggested a combination of increased DAA uptake combined with behavioral intervention will be required to address the epidemic, as part of a treatment as prevention strategy [84]. A similar modeling study using the HIV Swiss cohort suggested behavioral interventions alone, independent of increased DAA-uptake, could impact the growing HCV epidemic in HIV-infected MSM [85].

While preventing hepatic decompensation and HCC are the most recognized advantages of treating HCV, a retrospective analysis of HIV/HCV patients with early liver disease between 2004–2013 indicated patients achieving SVR with IFN-based therapy had lower health-care utilization during the following 5 years, suggesting health systems value of treatment aside from prevention of hepatic complications [86]. A modelling study examining liver fibrosis progression in HCV/HIV co-infected MSM, who often have other co-morbid factors modulating fibrosis progression, suggested deferring treatment in persons who had F0–F1 disease until fibrosis had progressed to F2 or beyond would result in an increase in overall liver-related morbidity and mortality [87].

Evaluation of a national strategy to promote access to HCV treatment in HIV/HCV co-infected persons in Spain indicated that over a 6-month period, 23.5% of 3474 persons had initiated therapy with DAAs, nearly half of whom had cirrhosis [88]. Analysis of a large French HIV cohort between 2000–12 indicated that 5,562 of 34,308 had HCV infection, but that HCV prevalence had decreased and treatment initiation increased with availability of DAAs, suggesting that HCV prevalence will continue to decline in coming years [89]. A prospective cohort from one specialty pharmacy serving patients in Delaware, Maryland, New Jersey, and Pennsylvania between November 2014 and April 2015 found significant disparities in DAA access based on insurance, with nearly half of Medicaid patients having declined applications [90]. Much effort will continue to be appropriately focused on the question of DAA access and affordability.

Conclusion and Unresolved Issues

In the setting of the remarkable clinical success achieved (and to be achieved) with DAA therapy in HIV/HCV co-infected persons, a number of questions will benefit from further research efforts in coming years. What is the best modality to follow liver stiffness and the risk of HCC post-SVR in HIV/HCV infected persons, and how does this risk change with time [51]? What is the best way for health care systems to tackle the overlapping epidemics of opiate use, mass incarceration, and HIV/HCV infections from the perspective of testing, treating, and cost [91]*?. How can we apply lessons learned from the HIV epidemic to HCV, including treatment as prevention, treatment of high risk populations, medication affordability/delivery/financing, and patient/community participation [92]? Will there be cases of HBV reactivation in HIV/HCV/HBV infected persons as has been observed in the setting of HBV/HCV co-infection [93]? Finally, how high will re-infection rates be after SVR for HCV is achieved, how will this be managed by providers and payers, and what strategies will most effectively mitigate this risk [3]?

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Key points

HCV infection is a significant cause of morbidity and mortality in HIV-infected persons.

Clinical efficacy of DAA therapy in HIV/HCV co-infected persons is high in clinical trials and real-world settings.

Non-invasive approaches to staging liver disease in HIV/HCV co-infected persons have reasonable predictive accuracy.

Continued efforts are required to understand the epidemiology and impact access to care for HIV/HCV co-infected persons in the DAA era.

Table 1

Recent Pivotal Clinical Trials in HIV/HCV Co-Infection

Trial	# of HIV/H CV Patients	HCV Regimen	Treatment Duration	% with Cirrhosis	HCV Genotypes	HIV Medications Allowed	Overall/Combined SVR Rate
ION-4	335	sofosbuvir/ledipasvir	12 weeks	20%	1,4	TDF, FTC, EFV, RPV, RAL	96%
C-EDGE	218	grazoprevir/elbasvir	12 weeks	16%	1,4,6	TDF, FTC, ABC, LAM, RPV, RAL, DTG	96%
ALLY-2	203	sofosbuvir/daclatasvir	8–12 weeks	14%	1,2,3,4	DRV/r, ATZ/r, LPV/r, EFV, NVP, RPV, RAL, DTG, INN, maraviroc, TDF, FTC, ABC, LAM, AZT	97% (12 week arms) 76% (8 week arm)
TURQUOISE-I	63	ombitasvir, paritaprevir/ritonavir, dasubavir, and ribavirin	12–24 weeks	19%	1	NRTIs, ATZ/r, RAL	92%
C-WORTHY	59	grazoprevir/elbasvir +/- ribavirin	12 weeks	0%	1	TDF, FTD, ABC, LAM, RAL	92%
ERADICATE	50	sofosbuvir/ledipasvir	12 weeks	0%	1	TDF, FTC, EFV, RPV, RAL	98%

TDF: tenofovir-DF, FTC: emtricitabine, EFV: efavirenz, RPV: rilpivirine, RAL: raltegravir, ABC: abacavir, LAM: lamivudine, AZT: zidovudine, DVR/r: darunavir–ritonavir, ATZ/r: atazanavir–ritonavir, LPV/r: lopinavir–ritonavir, INN: enfuvirtide, NRTIs: nucleos(t)ide analogue reverse transcriptase inhibitors, PIs: protease inhibitors