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Sustained Virologic Suppression After 4 Weeks of Ledipasvir/Sofosbuvir in Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Co-Infection

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 28-year-old
Final Diagnosis: HCV infection
Symptoms: Not applicable
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual or unexpected effect of treatment

Background: Short-course hepatitis C (HCV) treatment with direct-acting antivirals (DAA) under 8 weeks in duration has resulted in variable efficacy rates in HCV mono-infection. Further, DAA courses under 8 weeks in duration have not been studied in HIV/HCV co-infection. We present a case report of 12-week sustained virologic suppression after treatment interruption of ledipasvir/sofosbuvir at 4 weeks in a patient with HIV/HCV co-infection.

Case Report: A 28-year-old male patient diagnosed with well-controlled HIV infection and HCV co-infection (treatment-naïve, genotype 1a, unknown hepatic fibrosis) started a 12-week course of ledipasvir/sofosbuvir (LDV/SOF) for HCV treatment. The patient completed only 4 weeks of LDV/SOF before returning for follow-up 7 weeks after initiation. Ledipasvir/sofosbuvir treatment was discontinued. Sustained virologic suppression at 12 weeks was observed after completion of a short, 4-week course of LDV/SOF.

Conclusions: Compared to currently recommended treatment durations, clinical trials of short-course DAA treatments of less than 8 weeks have not demonstrated successful rates of SVR12. However, in cases of DAA interruption or incomplete treatment, clinicians may choose to assess for SVR12 prior to continuing or restarting the full treatment course.

MeSH Keywords: Antiviral Agents • Hepatitis C • HIV Infections

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Background

Approximately 25% of people living with human immunodeficiency virus (HIV) in the United States are co-infected with HCV [1]. Expert guidelines recommend prioritization of HCV treatment in patients with HCV/HIV co-infection due to higher rates of advanced liver fibrosis, cirrhosis, and hepatocellular carcinoma compared to patients with HCV mono-infection [2–4]. Reports of HCV and HIV transmission within sexual and illicit drug use networks further support the use of expedited treatment to reduce community viral loads for both HCV and HIV [5,6].

Treatment of hepatitis C virus (HCV) is more efficacious with the advent of direct-acting antiviral (DAA) agents. Direct-acting antiretroviral therapy has led to high rates of sustained virologic response 12 weeks after completion of treatment (SVR12). Selection of DAA therapy is dependent upon previous treatment experience, HCV genotype, and cirrhosis status. Adherence to DAA treatment for the full duration of therapy is fundamental to HCV treatment success. Higher rates of marginalized housing, stigmatization, and ongoing substance use and mental health disorders are observed in HCV/HIV co-infection [7,8]. Thus, adherence to prescribed treatments among patients with HCV/HIV co-infection is often challenging.

Current American Association for the Study of Liver Diseases-Infectious Diseases Society of America (AASLD-IDSA) HCV treatment guidelines for patients with HCV/HIV co-infection recommend treatment durations of 8–24 weeks. The duration of DAA therapy is based on the selected treatment regimen and certain demographic and clinical characteristics [4]. Several small clinical trials have evaluated the efficacy of DAA treatment courses of less than 8 weeks in duration in HCV mono-infected patients, with variable results [9–12]. However, the AASLD-IDSA do not recommend DAA treatment courses shorter than 8 weeks [4].

We are not aware of any clinical trials or case reports demonstrating successful SVR12 after DAA treatment of less than 8 weeks in duration among patients with HCV/HIV co-infection. Here, we present a single case of successful HCV treatment after an unplanned 4-week course of ledipasvir/sofosbuvir in a patient with HIV co-infection. Informed consent was provided by the patient.

Case Report

A 28-year-old white man presented for evaluation and management of newly diagnosed HIV in June of 2018. He was diagnosed with HIV 2 months prior during routine HIV/sexually transmitted infection (STI) screening. Past medical history was notable for treated chlamydia, gonorrhea, and syphilis, and untreated HCV, diagnosed 1 year prior. Baseline laboratory test results (reference range in brackets) revealed mild thrombocytopenia (platelet count – 126×10^3/uL, [150-400]), transaminitis (aspartate aminotransferase [AST] – 50 U/L, [15–41], alanine transaminase [ALT] – 84 U/L, [7–52]), hepatitis A and hepatitis B virus immunity, HCV RNA 151,551 IU/mL [<15], HIV RNA 31,941 copies/mL [<20], and CD4 372 cells/cmm [233–2,555]. He was started on dolutegravir 50 mg/abacavir 600mg/lamivudine 300mg for antiretroviral therapy (ART), attaining viral suppression (HIV RNA <20 copies/mL) 11 weeks later.

Six months after starting ART, the patient returned to our clinic for routine HIV follow-up. A thorough HCV work-up was performed. Hepatitis C clinical factors included: HCV genotype (GT) 1a, had cannabinoids present on urine drug screen, and an AST-to-Platelet Ratio Index (APRI) was calculated at 0.9. The patient was referred for transient elastography to evaluate for hepatic fibrosis, but he failed to complete the testing prior to initiation of DAA treatment. A 12-week course of ledipasvir 90 mg/sofosbuvir 400 mg (LDV/SOF) was prescribed. The patient's prescription insurance carrier mandated use of a specialty mail-order pharmacy instead of the local pharmacy he utilized for his ART prescription. The patient was notified of the treatment approval via telephone and an electronic health record messaging portal. However, he was unresponsive to clinic inquiries until 3 months later. At that time, the 12-week treatment course was re-approved by the insurance provider. He started LDV/SOF coordinated by clinical staff and the specialty mail-order pharmacy.

The patient missed the 4-week HCV follow-up visit due to a schedule conflict. He returned for follow-up 7 weeks after LDV/SOF initiation. At that time, he had completed only 4 weeks of LDV/SOF treatment and had not taken LDV/SOF for approximately 3 weeks. The patient had misunderstood the plan for 12 weeks of LDV/SOF treatment. Clinicians chose to discontinue LDV/SOF at this time. Follow-up laboratory tests were performed, including an HCV RNA and HCV NS5a resistance panel. Laboratory tests revealed a normalization of transaminases, undetectable HIV RNA, undetectable HCV RNA (<15 IU/mL), and stable CD4 counts. HCV RNA was again collected 6 weeks later, approximately 12 weeks after the end of the 4-week LDV/SOF course. Demonstration of successful SVR12 was observed with undetectable HCV RNA. Longitudinal laboratory testing over the patient's clinical course is described in Table 1.

Discussion

This case report demonstrates successful HCV treatment with SVR12 after only 4 weeks of LDV/SOF in a 28-year-old male with HCV/HIV co-infection. To the best of our knowledge, this

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Table 1. Case report longitudinal laboratory tests.

Laboratory test	Treatment timeline*				
	Week 0	Week 11	Week 29	Week 44	Week 50**
AST	50	–	43	15	–
ALT	84	–	92	8	–
HIV RNA (copies/mL)	31,491	<20	<20	<20	–
CD4 (cells/ccm)	372	–	593	–	–
HCV RNA# (IU/mL)	151,551	–	–	<15	<15
Platelet Count (cells×10^3/uL)	126	–	196	–	204
APRI	0.97	–	0.54	0.18	–

* Dolutegravir/abacavir/lamivudine started at Week 3 and ledipasvir/sofosbuvir started at Week 35 through week 39; ** week 50 represented 11 weeks post ledipasvir/sofosbuvir 4-week course; # patient was naïve to treatment, presumed non-cirrhotic, and infected with HCV genotype 1a. Dashes denote no value for laboratory test within respective time points. AST – aspartate aminotransaminase; ALT – alanine aminotransaminase; APRI – AST-to-platelet ratio index.

is the only case report of SVR12 after 4 weeks of DAA therapy in a patient with HCV/HIV co-infection. Synergism between HCV and HIV treatments has been suggested between nelfinavir and interferon-alpha [13], but we are unaware of any synergism between the DAA and ART agents described in this case report.

Currently, 2 combination DAA regimens have indications for as little as 8 weeks of treatment: glazeprovir/pibrentasvir (naïve, non-cirrhotic patients, regardless of HIV co-infection) and ledipasvir/sofosbuvir (non-cirrhotic, HCV mono-infection, GT 1a or 1b, HCV RNA <6 million IU/mL). The use of short-course (<8 weeks) HCV DAA combination treatments has been evaluated in several small clinical trials exploring DAA treatment efficacy after 4- and 6-week treatment durations. Low rates of SVR12 were observed in nearly all of these studies with the 4-week treatment duration in non-cirrhotic, naïve, GT 1-infected patients (LEPTON [velpatasvir/SOF/voxilepravir]: 27%; SYNERGY [LDV/SOF+vedroprevir]: 40%; SYNERGY2 [LDV/SOF+vedroprevir+radalbuvir]: 20%; C-SWIFT [elbasvir/grazeprovir+SOF]: 32%; FOURward [daclatasvir/asunaprevir/beclabuvir + SOF]: 29%). More favorable rates of SVR12 were observed with 6-week courses (LEPTON: non-cirrhotic – 93%, cirrhotic – 87%; SYNERGY [F3-F4 fibrosis]: naïve – 55%, interferon-experienced – 56%; C-SWIFT: non-cirrhotic – 87%, cirrhotic – 80%; FOURward [non-cirrhotic]: 57%) [9–12]. Very little DAA resistance was observed in the patients with HCV relapse. High rates of SVR12 were observed in the SYNERGY and FOURward trials with repeat treatment of study agents for 12 weeks in patients experiencing treatment relapse [9,14].

Younger age, lower baseline HCV RNA, and HCV GT 1b infection were identified as predictors of SVR 12 in exploratory analyses of shorter-course DAA treatments [9,12]. Our case report demonstrates a patient with similar positively-associated clinical factors (young age, treatment-naïve, low baseline HCV RNA, and taking an ART regimen without drug–drug interaction potential). A thorough examination of hepatic fibrosis was not performed. Cirrhosis status is indeterminate in our patient based on the baseline APRI score. Thus, the impact of cirrhosis is unclear in our case report.

Shorter-course DAA treatment may still be a viable option in key at-risk populations if efficacy is justified in future clinical trials. Shorter-course DAA treatments allow for faster treatment completion, potentially leading to lower community HCV burden. A resultant theoretical reduction in incident HCV infections and/or re-infections may occur. This would be of particular benefit to marginalized populations exhibiting risks for medication non-adherence and lack of persistence in medical care (e.g., people with injection drug use, ongoing mental and/or substance use disorders, and housing instability).

This case report possibly informs providers on the clinical management of HCV treatment during instances of DAA interruption and supports the use of repeat HCV RNA for assessment of virologic response before restarting the full DAA treatment course in cases of treatment interruption or non-completion.

Further, this case highlights some of the pitfalls of prescription procurement in the United States. Pharmacy mail-order mandates for specialty drugs, such as LDV/SOF, are increasingly common across insurance providers. Despite the advertised adherence and education benefits of these pharmacies, challenges for medication access exist for patients without consistent telephonic and/or technological access. Our case report illustrates a patient who was mostly unresponsive to telephonic and electronic communications. While he only

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received a 4-week supply of LDV/SOF, he was still filling his ART prescription monthly without difficulty. He might have completed the original 12-week course if he could have received the LDV/SOF prescription at his local pharmacy along with his ART prescription.

Conclusions

In summary, this case report demonstrates SVR12 after 4 weeks of ledipasvir/sofosbuvir in a patient with HCV/HIV co-infection. Clinical trials of short-course DAA treatments of less than 8 weeks have not demonstrated successful rates of SVR12. Still, in cases of DAA interruption or incomplete treatment such as the case described herein, clinicians may choose to assess for SVR12 from the shorter course of treatment as opposed to continuing or restarting the full treatment course.

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Cocflict of interests

Joshua P. Havens and Sara H. Bares report grants from Gilead Sciences, Inc., outside of the submitted work. Nichole N. Regan reports no conflicts.

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