Direct-acting antivirals for acute hepatitis C in HIV-infected MSM

An epidemic of acute hepatitis C (AHC) has been described amongst HIV-infected MSM [1–8]. Traditionally, treating AHC in this population has had clear advantages over waiting to treat in the chronic phase, with improved sustained virological response (SVR) rates and reduced length of therapy [9–12]. Treatment is offered to those who fail to demonstrate a 2-log decline at week 4 or still have detectable hepatitis C virus (HCV) RNA at week 12 and hence are unlikely to clear spontaneously [13]. The treatment of chronic HCV has been revolutionized by the advent of directly acting antivirals (DAAs) [14]. However, the role of these agents in AHC is unclear, particularly in light of the now-excellent efficacy in chronic infection. Guidelines still recommend therapy with pegylated interferon and ribavirin, and DAAs are not currently licensed for AHC [9,15]. Nonetheless, we have encountered several cases in which we have felt the use of DAAs warranted for AHC. The demographics and essentials of the HIV and AHC history of these patients are presented in Table 1.

Patient 1 was monitored for 4 weeks, failed to reduce his viral load by 2-log and was thus considered for AHC therapy. He had a background of depression and was a healthcare professional in an important role. Two companies were therefore approached to access an all-oral, interferon-free DAA regimen, as DAAs were not licensed at this time, both of whom agreed to provide medication. Patient 1 presented with evidence of hepatic failure, with deranged clotting and low albumin, which failed to resolve after more than 10 days of supportive inpatient therapy. Similarly, although patient 4 had initially normal synthetic function, after a week he developed hepatic failure. Given the clinical severity and, in the case of patient 2, background of depression, we aimed to avoid interferon-based therapy and obtained access to DAAs. Patient 3 was concerned about transmission risk, keen to initiate therapy and had access to DAAs privately.

All patients were commenced on Harvoni, a fixed dose combination of 90 mg of the NS5A inhibitor ledipasvir and 400 mg of the nucleotide analogue NS5B polymerase inhibitor sofosbuvir, once per day. Length of therapy and the addition (or otherwise) of ribavirin was based on current understanding of the length of therapy required for AHC at the time of treatment initiation, HCV RNA viral load and evidence of underlying liver disease; with patient 1 (low viral load, no underlying liver disease and prior to evidence for the possible efficacy of shorter courses [16]) receiving 12 weeks of Harvoni alone, patients 2 and 4 (high viral load and evidence of underlying liver disease on the basis of Fibroscan or liver biopsy) commencing 12 weeks of Harvoni and ribavirin and patient 3 (modest viral load, no underlying liver disease and after publication of evidence for the possible efficacy of shorter courses [16]) receiving only 8 weeks of Harvoni.

Three patients (1, 2 and 4) were receiving protease inhibitor therapy for their HIV infection at the time of the AHC diagnosis. To minimize any potential drug–drug interactions and reduce any liver toxicity, patients 1 and 2 had their HIV therapy switched to integrase inhibitor based therapy (Truvada and Raltegravir in the case of patient 1 and Triumeq, after a 3-week pause to allow liver function test recovery, in the case of patient 4).
Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase?

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References

1. Browne R, Ashoe D, Gilleece Y, Atkins M, Mandalia S, Gazzard B, et al. Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase? Sex Transm Infect 2004; 80:326–327.

Table 1. Demographics, HIV, acute hepatitis C history and therapy for four patients treated with directly acting antivirals for acute hepatitis C.

| Demographics | HIV history | AHC history | Hepatitis C therapy |
|--------------|-------------|-------------|---------------------|
| 1: Man, 37 years, MSM | Diagnosed: unknown Nadir CD4 cell count: unknown | Presentation: Incidental finding of raised ALT Initial blood results: ALT 295 Genotype: 1a HCV RNA: 92 526 IU/ml (log_{10} 4.97) | 12 weeks Harvoni (initiated ~4 weeks postdiagnosis) HCV RNA: Week 4: ND Week 12: ND SVR_{12} |
| 2: Man, 56 years, MSM | Diagnosed: 1988 Nadir CD4 cell count: 25 Current: CD4 cell count 439 (24.1%), viral load <40 Resistance: Nil Current ARVs: Atazanavir/r, Truvada | Presentation: Jaundice and nausea Initial blood results: Bil 187, ALT 1894, ALP 165, Alb 28, PT 15.6 and APTT 36.4 Fibroscan: >70 kPa Transjugular liver biopsy: HVPG = 10 mmHg (normal <5 mmHg), focal bridging fibrosis, severe acute lobular hepatitis and no steatosis Genotype: 1a HCV RNA: 27 537 437 IU/ml (log_{10} 7.44) | 12 weeks Harvoni and ribavirin (initiated ~2 weeks postdiagnosis, ribavirin discontinued after ~2 weeks) HCV RNA: Week 1: 16 544 IU/ml Week 2: 2266 IU/ml Week 8: ND SVR_{12} |
| 3: Man, 52 years, MSM | Diagnosed: 2011 Nadir CD4 cell count: unknown Current: CD4 cell count 689 (37.1%), viral load <40 Resistance: Nil Current ARVs: Eviplerar | Presentation: Investigation of raised ALT Initial blood results: Bil 12, ALT 276, 128 and Alb 36 Genotype: 1a HCV RNA: 2301 877 IU/ml (log_{10} 6.36) | 8 weeks Harvoni (initiated 6 weeks postdiagnosis) HCV RNA: Week 2: 89 IU/ml SVR_{4} |
| 4: Man, 42 years, MSM | Diagnosed: 1998 Nadir CD4 cell count: 497 (38.1%) Current: CD4 cell count 573 (32.8%), viral load <40 Resistance: K103N Current ARVs: Darunavir/r | Presentation: Jaundice, pale stools, dark urine, nausea and fatigue Initial blood results: Bil 411, ALT 2431, ALP 110, Alb 37, PT 12.2 and APTT 27.4 Fibroscan: >70 kPa, improved to 11.8 kPa at week 2 Genotype: 1a HCV RNA: 68 977 554 IU/ml (log_{10} 7.84) | 12 weeks Harvoni and ribavirin (initiated ~10 days postdiagnosis) HCV RNA: Week 1: 11 274 IU/ml Week 2: 10 261 IU/ml Week 4: 163 IU/ml Week 8: ND Week 12: ND SVR_{12} |

AHC, acute hepatitis C; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; APTT, activated partial thromboplastin time; Bil, bilirubin; HVPG, hepatic venous pressure gradient; ND, not detected; PT, prothrombin time; Harvoni; ledipasvir 90 mg/sofosbuvir 400 mg; SVR, sustained virological response.

Patient 2 had extensive previous antiretroviral exposure and current hepatic failure, and hence antiretrovirals were discontinued until complete normalization of liver function tests and completion of DAA therapy, at which point the same antiretrovirals were recommenced. Patient 3 was receiving an non-nucleoside reverse-transcriptase inhibitor-based regimen and had only a modest alanine transaminase (ALT) rise and hence remained on the same antiretrovirals throughout.

Aside from patient 2, who had to discontinue ribavirin after 2 weeks due to nausea, all patients had an uncomplicated follow-up, requiring only three to five short visits. Liver function tests and HCV RNA monitoring were variable and dictated by clinical need, all patients had no detectable HCV RNA and normal ALT by week 8, and those with lower baseline HCV RNA became undetectable sooner. Patients 1, 2 and 4 have achieved an SVR_{12}, and patient 3 has achieved an SVR_{4}.

The optimum regimen and duration of therapy for AHC are unclear, particularly in the light of recent, poorer than expected results, for both 6- and 12-week regimens of sofosbuvir and ribavirin [17,18]. However, our experience offers proof of principle for well tolerated, all-oral DAA therapy with Harvoni (with and without ribavirin) across a range of clinical situations and with minimal follow-up.
A pilot trial of pentoxifylline on endothelial function and inflammation in HIV-infected patients initiating antiretroviral therapy

Systemic and vascular inflammation are thought to be the key mechanisms underlying the increased risk of cardiovascular disease (CVD) in those with HIV infection [1,2]. Antiretroviral therapy (ART) reduces, but does not necessarily normalize, systemic inflammation [3]. As such, adjunctive strategies to further reduce inflammation may be helpful in mitigating the risk of CVD in HIV.

In a single-arm, open-label, 8-week, pilot study, we reported that pentoxifylline (PTX) reduced circulating levels of IFN-γ-induced protein 10 and soluble vascular cell adhesion molecule–1 and improved endothelial function [measured as flow-mediated dilation (FMD)] of the brachial artery in HIV-infected patients not receiving ART [4]. However, in a randomized, placebo-controlled trial of PTX in a similarly untreated population, we did not confirm that PTX reduced inflammation or improved endothelial function [5]. In fact, PTX unexpectedly led to significantly increased circulating soluble tumor necrosis factor–1 (sTNFRI) levels compared with placebo in this trial. However, the potential effects of PTX on FMD and inflammation in a population initiating ART are unknown. Thus, we conducted a randomized, placebo-controlled, single-center pilot trial of PTX 400 mg thrice daily given for 48 weeks in patients concurrently initiating ART (ClinicalTrials.gov NCT00864916).

The eligibility criteria, procedures, and methods in the current study were similar to our previous trial in patients not receiving ART [5]. Participants were instructed to start ART, as chosen by the primary HIV provider, and the study drug together at study entry. Study visits occurred at weeks 0, 8, 24, and 48. No restrictions were made on the ART components or initial CD4+ cell count. The primary endpoint was change in brachial artery FMD, measured using B-mode ultrasound after 5 min of forearm cuff occlusion to a supra-systolic pressure, as previously described [5]. All scans were performed by a certified sonographer and read at the University of Wisconsin, the brachial artery reactivity testing reading center for the NHLBI HIV-CVD collaborative, by a single reader [5]. This trial was approved by the Indiana University Institutional Review Board; all participants provided their written, informed consent. The use of PTX for the purpose of reducing...