Within Europe and recently in the USA and Australia an ongoing epidemic of acute hepatitis C virus (HCV) infections among HIV-positive individuals, mainly men who have sex with men, has been observed. Other concomitant sexually transmitted diseases and sexual practices with a high risk of mucosal trauma and damage have been established as risk factors for sexual transmission. In HIV-positive patients the diagnosis of acute HCV infection may be obscured by delayed anti-HCV antibody seroconversion, and HCV RNA testing may be warranted. It is estimated that up to 85% of HIV-positive patients take a chronic course after acute HCV infection, and early treatment of acute HCV infection within 12 weeks after the presumed date of infection is recommended unless spontaneous clearance of HCV has occurred. A watch and wait strategy for 4–8 weeks after the date of diagnosis with 4 weekly HCV RNA controls may help to distinguish patients who will spontaneously clear acute HCV infection from those who will not. Treatment of acute HCV infection with interferon-based therapy has been shown to be highly efficacious, with sustained virological response rates in between 60% and 70% of HIV-positive individuals. Though data are sparse, controlling treatment response at weeks 4 and 12 may further help to individualize therapy, and patients who have not reached a negative HCV RNA by week 12 may benefit from prolonged treatment beyond 24 weeks.

Keywords: interferon, ribavirin, infection transmission, sexual behaviour

Introduction
Since the original report of an increased incidence of acute hepatitis C virus (HCV) infections among HIV-positive men who have sex with men (MSM) in London at the beginning of 2000 several groups have observed similar epidemics, and worldwide ~1,000 cases have been reported to date (Figure 1). The epidemic appears to be ongoing and its impact has been visible within existing large HIV cohorts such as the Amsterdam, French PRIMO and Swiss HIV cohorts, all of which noted an increase in sexually transmitted acute HCV infections after the year 2000.

Sexual transmission
The present epidemic is mainly characterized by sexually transmitted HCV infections, and the majority of cases presenting to infectious disease clinics are HIV-positive MSM, though in eastern Europe the transmission route remains mainly intravenous drug abuse. In a recent epidemiological survey among genitourinary medicine (GUM) and HIV clinics in London and the Brighton area on acute HCV infections among MSM, of 395 acute HCV infections between 2002 and 2006, 389 had occurred in HIV-positive patients. Similarly Urbanus et al. investigated the prevalence of HCV infection among MSM attending the sexually transmitted disease clinic in Amsterdam. They found a significantly higher HCV prevalence among those co-infected with HIV (28/157, 18%), and a history of intravenous drug use, fisting and the use of gamma-hydroxybutyrate (GHB) were all significantly associated with an increased risk for HCV infection. Only 2 of 532 HIV-negative MSM were found to be HCV positive, and one of these reported previous intravenous drug abuse. Sexual transmission of HCV has not been reported at increased rates for HIV-positive women. Within a French study, 402 HIV-positive individuals were followed for a median time of 36 months. Among women, two HCV infections occurred during follow-up; however, these were related to body piercing in one and intravenous drug abuse in the other. In contrast, all four men in this study with acute HCV infection during follow-up only reported unsafe sex as a possible transmission risk. Within the German cohort, only 1 of 157 HIV-positive patients with acute HCV infection was female, and a steady sexual relationship with her HIV/HCV-positive male partner was the only transmission risk factor for HCV (data on file). Sexual transmission of HCV has been reported previously; however, amongst heterosexual couples it is regarded as an uncommon event with a lifetime risk of <1%. Current studies on the epidemic of acute HCV among HIV-positive MSM have identified high rates of concomitant sexually transmitted infections and high risk sexual behaviour, both of which are associated with an enhanced risk for mucosal damage and thus blood-to-blood transmission, as risk factors for acquisition of acute HCV. Phylogenetic analysis revealed a high degree of relatedness among sexually transmitted HCV strains and a recent
international study demonstrated MSM-specific clusters of HCV infections.\textsuperscript{20} These findings support HCV transmission among MSM separate from intravenous drug-related transmission. Moreover, almost 75\% of all HCV strains were highly related to a strain in another country, suggesting a spread of HCV via a European sexual network. This network hypothesis is further supported by an anonymous questionnaire which showed that cases with acute HCV infection were more likely to meet men using the internet (a median of 50 times versus 7 times for controls, $P=0.003$).\textsuperscript{18} Spread of HCV within the HIV-positive MSM community via sexual networks could also explain why the epidemic is not observed everywhere. For instance, whereas numerous countries in Europe have observed increased rates of sexually transmitted acute HCV infections among HIV-positive MSM, in Spain no increase was observed despite a retrospective cohort analysis being conducted to determine whether this was the case.\textsuperscript{21}

### Delayed anti-HCV seroconversion

HCV infection is considered acute if the time between the suspected date of transmission and diagnosis is $\leq$6 months, whereas a chronic infection is established if the infection has been ongoing for 6 months or longer. The diagnosis of acute HCV infection is often hampered by the fact that acute HCV infection is usually asymptomatic, with an acute rise in alanine transaminase (ALT) which goes unnoticed unless regular liver function tests are being performed. This may be true in particular for HIV-positive patients. In a recent cross-trial comparison HIV-positive patients presented less often with clinical signs or symptoms of hepatitis and had less pronounced elevations of serum ALT compared with HIV-negative patients.\textsuperscript{6}

In the routine clinical setting a careful transmission risk history in conjunction with a review of the patient’s liver transaminases within the past year is probably the best way to assess the timepoint of infection. Of note, in HIV-positive patients a rise of liver transaminases proved to be more sensitive in the detection of acute HCV infection than repeated testing of anti-HCV.\textsuperscript{22} Of 43 patients with acute HCV infection, 76\% showed an abnormal ALT $>40$ U/L at the time of first positive HCV RNA and 88\% of patients had a raised ALT either at the time of first positive HCV RNA or 3 months later. At the same time the anti-HCV antibody test was found to be positive in only 25\% of patients at the time of the first positive HCV RNA and in 63\% of patients 3 months thereafter, which is markedly delayed compared with HIV-negative patients.

### Treatment of acute hepatitis C infection

#### When to start therapy

Recent studies on the diagnostics and natural course of acute HCV infection in HIV-positive individuals have reported rates of spontaneous clearance in between 13\% and 16\% of patients,\textsuperscript{2,2,3} the values being much reduced compared with HCV-mono-infected individuals, where rates between 20\% and 50\% have been reported.

Acute HCV infection most probably resolves within the first 12 weeks, though this timepoint may not be so clear-cut. Within a pooled analysis of untreated HIV-positive patients in UK, German and French cohorts,\textsuperscript{24} a negative HCV RNA 12 weeks after diagnosis was observed in 14/39 (36\%) of the untreated patients. During further follow-up, three patients who had been HCV-RNA negative at week 12 were positive at week 24, and another five who were negative at week 24 were HCV positive at week 48. In contrast, four patients and one patient who had been HCV RNA positive at week 12 and 24 were negative at week 24 and 48, respectively, so that overall 11/39 patients (28\%) had cleared acute HCV infection at week 48. Whereas undoubtedly late viral clearance may occur in individual cases, the high rate of viral ‘relapse’ after week 12 may
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also be explained in part by re-infection. In a recent analysis of the UK cohort, most cases of ‘late viral relapse’ after sustained virological response (SVR) in HIV-positive patients with successfully treated acute HCV infection were indeed re-infections after new exposure.25

Whereas ideally only individuals who will not go on to spontaneously clear HCV should receive treatment, delaying the start of treatment for too long may eradicate the benefit of early treatment (increased rates of SVR) and treatment outcomes become similar to response rates observed in the setting of chronic HCV infection. For instance, a Japanese study found that delaying treatment for 1 year compared with 8 weeks after acute HCV infection in HIV-negative individuals reduced SVR rates from 86% to 40%.26 On the other hand, a recent analysis of the German HEPNET III cohort of 108 HIV-negative patients with acute HCV showed that—comparing adherent patients with complete follow-up—a delay of treatment in patients with symptomatic hepatitis for 12 weeks did not cause a deterioration in treatment outcomes compared with patients who had received treatment immediately.27 In the light of the present data the updated recommendations from the European AIDS Clinical Society (EACS) therefore recommend early therapeutic intervention in acute hepatitis C infection for HIV-positive individuals.28 Waiting for up to 12 weeks from the estimated date of exposure is recommended to allow spontaneous clearance. However, any further delay to treatment is discouraged in order to prevent reduced treatment response.

In most cases the exact date of HCV infection cannot be determined definitely. In HIV-negative patients, a pilot study on 12 patients with acute HCV showed that determination of HCV RNA after 4 weeks of diagnosis may help to discriminate those who take a chronic course from those who spontaneously clear HCV infection.29 Gerlach et al.30 had previously shown in a larger cohort of HIV-negative patients that acute HCV infection usually resolves by week 12 after onset of symptoms. Unfortunately, for HIV-infected patients, clinical trials on proceeding in this way are lacking. If the level of serum HCV RNA has dropped significantly (>2 logs) within 4 weeks of diagnosis, a further watch and wait strategy may be reasonable. However, if a 2 log drop has not occurred treatment should be recommended at this timepoint. For those who have shown a significant decrease in HCV RNA at week 4, further HCV RNA tests should be undertaken at weeks 8 and 12. If there is no further decrease or even an increase in HCV RNA at week 8 or the patient is still HCV RNA positive at week 12 treatment should be advised.

How to treat

Most data available on the treatment of acute HCV infection in HIV-co-infected individuals show SVR rates of 60%–70% in individuals who have been treated with pegylated interferon and ribavirin combination therapy for a duration of 24 weeks (Table 1). However, due to the non-comparative design of the studies, there are some unanswered questions.

Is ribavirin necessary in the treatment of acute HCV infection? Studies in HCV-mono-infected patients showed that the use of ribavirin in the setting of acute HCV infection is not necessary considering the very high rates of SVR reached with non-pegylated or pegylated interferon monotherapy.30–32 This may differ in HIV-infected patients as viral breakthrough or non-response has been reported on a case basis in individuals undergoing pegylated interferon monotherapy.12,33 Preliminary results from a recent prospective pilot study on the use of pegylated interferon monotherapy substantiates this observation. In that study HIV-positive patients with acute HCV infection were monitored for 12 weeks to determine whether a spontaneous clearance occurred. Twelve patients who had not cleared infection received pegylated interferon alfa-2a. All subjects had acquired difficulty to treat HCV genotype 1 (n = 8) or 4 (n = 4) infections. Patients were allowed to add-on ribavirin at week 4 if no rapid virological response (RVR, negative HCV RNA at week 4) had been achieved. Though only week 12 data were presented, the findings are disappointing compared with results from other trials, with 6 of the 12 patients (50%) stopping therapy at week 12 because of lack of response.34 On the other hand in the analysis of the German cohort, patients treated with pegylated interferon alone achieved higher SVR rates and developed anaemia less often than patients on pegylated interferon and ribavirin combination therapy, though the difference in SVR was not statistically different and the study was limited by design and number of patients recruited.35 Taken together, current data do not allow us to draw definite conclusions on the use of ribavirin, though caution may be warranted using pegylated interferon alone in HIV-positive patients with difficult to treat HCV genotypes 1 or 4.

What duration of therapy is necessary to achieve an SVR in the majority of individuals? In HCV-mono-infected patients most trials have used a treatment course of 24 weeks and have achieved high rates of response in up to 98% of patients.31 Compared with HIV-negative patients, in HIV-co-infected patients with acute HCV infection reduced SVR rates of 60%–70% are reached after a 24 week treatment course and the question arises of whether a longer duration of therapy may improve treatment response rates. Within an analysis of the German cohort, patients who were treated for 48 weeks achieved higher SVR rates compared with those treated for 24 weeks only, though the data are limited because of the observational nature of the data and small patient groups.35 Only one pilot trial has investigated the possibility of a shorter treatment duration in HIV-co-infected individuals. They trialled 12 weeks of pegylated interferon monotherapy.36 However, even though the infection resolved following treatment in 3/4 patients, 2 patients carried genotype 2 infections and the overall group is too small to generalize these results.

Until further data are available most experts recommend a combination therapy of pegylated interferon with ribavirin over a 24 week course. Response to treatment may help to individualize therapy, though the first data regarding this come from an observational database and should be confirmed in a prospective randomized controlled trial. In a recent analysis of the European Collaborative, 39 of the 42 patients (93%) who had achieved an RVR (in this case due to the observational database an HCV RNA <600 IU/mL was considered negative) achieved an SVR.37 In contrast, only 3/33 patients (9%) who did not reach a negative HCV RNA at week 12 achieved an SVR. In individual cases without an RVR and persistently detectable HCV RNA up to week 12 (but at least a 2 log drop in HCV RNA), a prolongation of therapy beyond 24 weeks may thus be reasonable to improve the odds for an SVR.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Demographics</th>
<th>Treatment</th>
<th>SVR outcome and predictors (factors marked with * were statistically significant)</th>
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<tbody>
<tr>
<td>London, Chelsea and</td>
<td>50</td>
<td>transmission risk: unprotected anal intercourse, 44/50 (88%); male, 50/50 (100%); genotype 1, 31/36 (86%)</td>
<td>27 patients treated pegylated interferon: alfa-2b 1.5 μg/kg/week ribavirin: weight-based 800–1200 mg/day duration: 24 weeks</td>
<td>SVR 16/27 (59%) predictors for SVR: • high peak ALT* • high CD4 cell count* • all 4 non-genotype 1 infections reached SVR</td>
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<td>Westminster38</td>
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<td>Germany35</td>
<td>47</td>
<td>transmission risk: unprotected anal intercourse, 38/47 (81%); male, 47/47 (100%); genotype 1/4, 37/47 (79%)</td>
<td>36 patients treated pegylated interferon: alfa-2a/2b standard dosage ribavirin: 800–1200 mg/day duration: 24–48 weeks</td>
<td>SVR 22/36 (61%) predictors for SVR: • longer duration of therapy* • 5/7 genotype 2/3 infections reached SVR • 10/22 on ribavirin versus 12/15 off ribavirin reached SVR</td>
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<tr>
<td>New York39</td>
<td>45</td>
<td>transmission risk: unprotected anal intercourse, 17/21 (81%); male, 45/45 (100%); genotype 1, 41/45 (91%)</td>
<td>15 patients treated pegylated interferon: alfa-2a 180 μg/week ribavirin: 1000–1200 mg/day duration: 24–48 weeks</td>
<td>SVR: 8/10 (80%)</td>
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<td>Paris, CHU Pitie´-Salpe´trie`re/ Tenon40</td>
<td>38</td>
<td>transmission risk: unprotected anal intercourse, 44/50 (88%); male, 50/50 (100%); genotype 1 or 4, 33/38 (87%)</td>
<td>20 patients treated pegylated interferon: alfa-2a 180 μg/week ribavirin: weight based 1000–1200 mg/day duration: IQR 24–36 weeks</td>
<td>SVR 13/20 (65%)</td>
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<td>Australia12</td>
<td>27</td>
<td>transmission risk: unprotected anal intercourse, 56%; male, 100%; genotype 1, 60%</td>
<td>22 patients treated pegylated interferon: alfa-2a 180 μg/week ribavirin: 20/22 (91%) duration: 24 weeks</td>
<td>SVR: 16/22 (73%); 16/20 (80%) with pegylated interferon + ribavirin • all genotype 2 or 3 infections reached SVR • all 7 patients with RVR reached SVR</td>
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<td>Paris, CHU Pitie´-Salpe´trie`re/ Tenon41</td>
<td>25</td>
<td>transmission risk: unprotected anal intercourse, 24/25 (96%); male, 25/25 (100%); genotype 1 or 4, 9/14 (64%)</td>
<td>19 patients treated pegylated interferon: alfa-2a 180 μg/week ribavirin: 800 mg/day duration: 24 weeks</td>
<td>SVR: 10/14 (71%) • 5/5 genotype 3 infections reached SVR</td>
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<tr>
<td>Moscow15</td>
<td>17</td>
<td>transmission risk: intravenous drug use (87%); male (79%); genotype 1 or 4 (31%)</td>
<td>17 patients treated pegylated interferon: alfa-2b 1.5 μg/kg/week ribavirin: 800–1000 mg/day duration: 24 weeks</td>
<td>SVR: 9/17 (53%)</td>
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<td>transmission risk: unprotected anal intercourse, 12/12 (100%); male, 12/12 (100%); genotype 4, 10/12 (83%)</td>
<td>10 patients treated standard interferon: 9/10 (90%) ribavirin: 2/10 (20%) duration: 24–48 weeks</td>
<td>SVR: 0/10 (0%)</td>
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<td>Hopital/Ambroise Pare´42</td>
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<td>San Francisco3</td>
<td>9</td>
<td>transmission risk: unprotected anal intercourse, 6/9 (67%); male, 9/9 (100%); genotype 1, 3/4 (75%)</td>
<td>4 patients treated pegylated interferon: alfa-2a 180 μg/week ribavirin: 1000 mg/day duration: 24–48 weeks</td>
<td>SVR: 2/3 (67%)</td>
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</table>
Conclusions

The high SVR rates observed after early treatment of acute HCV infection in HIV-positive individuals even in the unfavourable genotypes 1 and 4 make early treatment of acute HCV an attractive therapeutic intervention. Therefore treatment should be initiated in every patient who is still HCV RNA positive 12 weeks after the presumed date of acute HCV infection. Controlled trials on the best management strategy are still lacking for HIV-positive patients and are urgently needed.

Transparency declarations

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References


