New treatments for HIV and hepatitis C co-infection and the impact in nursing practice

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There have been significant developments in how chronic hepatitis C (HCV) can be treated in the last few years, since the advent of direct-acting antivirals (DAAs) (Figure 1).

The current BHIVA guidelines on the management of hepatitis viruses in adults infected with HIV were published in January 2014 [1]. At this time there were two DAAs for chronic hepatitis C (HCV) genotype 1 patients that had received both European Medicines Agency (EMA) and National Institute for Health and Care Excellence (NICE) approval: telaprevir [2] and boceprevir [3]. Since then, new data have been presented confirming the benefits of individual DAAs with pegylated interferon (PEG) and ribavirin (RBV); and DAAs in combination, in interferon-sparing regimens, with or without ribavirin, for the treatment of chronic HCV. There are now several of these DAAs that have received EMA approval, with other drugs in the pipeline, which are likely to be licensed in 2015. BHIVA provided a consensus statement on the guidelines on the management of hepatitis viruses in adults infected with HIV in September 2014 [1], addressing the impact of these developments on the management of both acute and chronic HCV/HIV co-infection, and upon patient choices and decisions on treatment. A further update to the guidelines is due in early 2015, though this might be delayed pending the outcome of the submissions for recommendations before NICE on the newer agents.

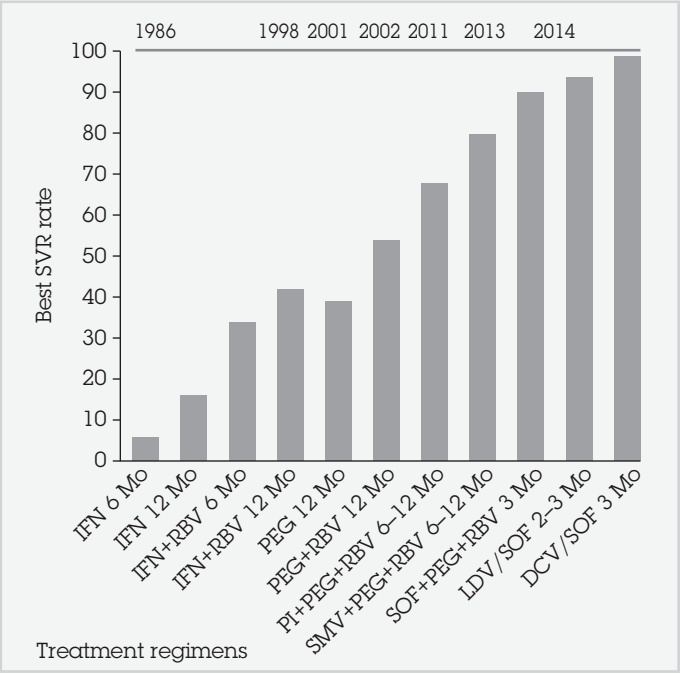

Figure 1: *A timeline for HCV therapy.*

Preparation, planning and good provider–patient communication have been cornerstones of successful treatment and the general principles of adherence [4–6]. Discussing possible side effects, including potential drug and food interactions, prior to a person beginning a new treatment regimen, and concentrating efforts to plan for and to manage side effects at times when a new drug or regimen is being started (and thus medication side effects are most likely to occur), promotes adherence [7,8]. Therapeutic education by a specialised nurse has been demonstrated to increase the response of patients with hepatitis C to therapy, particularly in difficult-to-treat patients [9]. Simplification of treatments, with fewer or milder adverse effects, shorter duration of treatment and good efficacy has always been the 'Holy Grail' of HCV therapy.

Treatment-experienced patients who have undergone a PEG/RBV regimen of up to 48 weeks will probably see the new treatment as a significant improvement. Aside from the potentially more favourable side-effect profile should a PEG- or RBV-sparing regimen be used, the fact that even PEG/RBV-containing therapies will have the shorter treatment duration of 12 to 24 weeks will be seen as advantageous. It must be borne in mind that unlike healthcare staff and many treatment-experienced patients, treatment-naïve patients will not have the same reference point with which to compare past to current treatment options. The fact that there may be fewer adverse effects than with the previous standard of care is unlikely to be a motivating or encouraging factor for these individuals. They will need to be informed and supported in just the same way as patients who received the older treatment regimens. In a bid to highlight the improvements in treatment and the reduction in adverse effects it can be easy to inadvertently under-represent the potential impact of adverse effects of HCV therapy.

Within the preliminary work of the nursing assessment and giving information on treatment success rates, potential adverse effects, symptom control and drug–drug interactions etc., there may now need to be a greater focus on managing patient expectations.

As BHIVA states, the availability of drugs and national or local directives may restrict the choice of options [1].

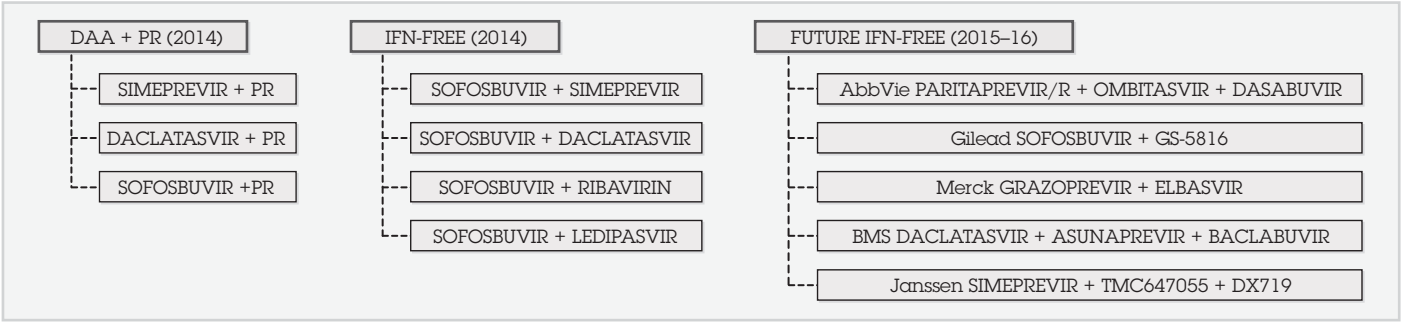

Figure 2: *DAA treatment options.*

The wider general media tend to promote news items that 'sell' and so often omit the finer details of the process involved between a scientific discovery and patient access to new medicines. Although there were four DAAs licensed in Europe in 2014 [10–13] (see Figure 2) we are yet to receive a decision on access to any of these agents from NICE. While BHIVA recommends that DAAs should form the backbone of all treatment options, irrespective of genotype, fibrosis stage or past treatment status [1], combinations with PEG/RBV still have a significant role to play. The cost of the newer therapies is likely be an important factor in the decision for recommendations by NICE. There is a difference, which may be considerable, between list prices for pharmaceuticals and local contract prices. Currently, the list price of a 24-week course of PEG/RBV at full dose, excluding VAT, would be £4.5–5K, depending on product and patient weight. (PEG and RBV are available from two different companies and RBV dosage is usually calculated based on patient weight.) Of the DAAs that are already NICE recommended, boceprevir, which may involve 24 weeks of triple therapy regardless of any additional weeks with just PEG/RBV, would cost a further £16,800 for 24 weeks' treatment, whereas telaprevir would cost £22,398 for the 12 weeks' triple therapy component of treatment. Simeprevir, which is one of the newest DAAs, has been competitively priced and would equally cost £22,398 for the 12 weeks of triple therapy. Unfortunately, simeprevir has drug–drug interactions that make it contraindicated for any HIV antiretroviral therapy involving non-nucleoside reverse transcriptase inhibitors (NNRTIs) or any boosted protease inhibitor (PI). Patients on HIV antiretroviral therapy would require switching to, and stabilising on, a boosted PI- and NNRTI-sparing regimen, such as raltegravir and Truvada, prior to commencing simeprevir. Sofosbuvir would cost £34,982.94 for 12 weeks in whatever combination it was given. The co-formulated sofosbuvir, 400mg, and ledipasvir, 90mg, that is marketed as Harvoni would cost £38,979.99 for one tablet daily for 12 weeks.

With the high cost of the newer agents, ineligibility for interferon and ribavirin therapy is likely to be a determining factor, rather than patient preference, for access to PEG-sparing regimens.

Equally, the inclusion criteria for using more than one DAA will be strict if the recent Expanded Access Programme funded by NHS England [14] is any indication. It may be deemed prudent by NICE to offer wider access to DAAs to those with more significant liver disease for the immediate future, with broader access perhaps being granted in a later wave in years to come.

Historically, a trend has developed among liver specialists of 'warehousing' the more 'difficult-to-treat' patients in anticipation of the availability of more effective hepatitis C treatments in the future [15]. Among the HIV/HCV co-infected patients will be those who have been 'warehoused' until better treatment became available, such as those with decompensated cirrhosis or who are pre-/post-liver transplant.

BHIVA recommends that cirrhotic patients with chronic viral hepatitis and HIV infection should be managed jointly with hepatologists or gastroenterologists with knowledge of end-stage liver disease, preferably within a specialist co-infection clinic [1]. Common practice in the UK is that the management and monitoring of patients undergoing antiviral therapy for HCV has come under the remit of a specialist nurse. However, there are few dedicated HIV/hepatitis co-infection specialist nursing posts, with care for the HIV/HCV co-infected being managed by nurses specifically working in one specialty, be that HIV, infectious diseases, hepatology or gastroenterology. Because of 'warehousing' there is limited experience on managing HIV/HCV co-infected cirrhotic patients. Collaborative work and shared placements between the different related specialty nurses may prove beneficial in transferring appropriate skills to all the relevant areas where HIV/HCV co-infected patients undergo HCV antiviral therapy to better manage this patient group.

When PEG/RBV was the standard treatment, patients would be prepared for 48 weeks of treatment, with the potential of reducing this to 24 weeks if a rapid virological response was achieved (in the non-cirrhotic patient). The more recently licensed DAAs will require a shorter course of treatment as standard, from 8 to 24 weeks [12]. There is therefore a potential to increase the throughput of patients even if the same frequency

of monitoring visits is maintained. If treatments offered are either PEG- or RBV-sparing then the frequency of visits may be altered, as the haematinic effects, such as anaemia, neutropenia or thrombocytopenia, will be reduced. According to the National Institutes of Health, patient adherence is critical to the success of treatment of hepatitis C and physicians should discuss the importance of adherence with patients before embarking on therapy, and regularly assess and take steps to help their patients maximise their adherence [16]. There may be an increased willingness to consider treatment by those for whom a 48-week course of treatment was too onerous. Adherence levels are known to be low in chronic disease such as diabetes, asthma and hypertension, with only 50% of patients remaining adherent over time [17,18]. It is also known that adherence levels change over time. Those who might have experienced difficulty in long-term adherence over 48 weeks may find the prospect of between 12 and 24 weeks of treatment much more tolerable and achievable. Considering that many HIV/HCV co-infected patients on HCV treatment are also on HIV antiretroviral treatment, there are additional challenges due to the interactions between HIV and HCV therapies and further research is probably required on co-infection population-specific issues [19].

With reduced treatment times and a lower side-effect profile during treatment, it may be possible to treat patients who have had difficulties in committing to a long period of treatment in a hospital outpatient setting. This may now increase the opportunities for development of satellite clinics and shared care in the community. Models of shared care with community outreach with prison services, homeless persons, and drug and alcohol services, are further areas for exploration and development. There is evidence to suggest that illicit drug users would accept referrals for assessment, treatment and monitoring at a multidisciplinary health centre where they also accessed a weekly HCV peer-support group [20]. Anecdotally, the Liver and Antiviral Centre at Imperial College Healthcare NHS Trust already provides a weekly clinic at North Westminster Drug and Alcohol Service (Central North West London NHS Foundation Trust) where patients receive treatment for their HCV as a satellite service, reducing hospital appointments, which will include any HIV/HCV co-infected patients accessing this service. Additionally HCV oral swab testing is offered at St Mungo's Broadway homeless hostel, followed by full venous blood-borne virus testing for those who have reactive oral swabs. There are plans to expand further within Central and North West London NHS Foundation Trust and the feasibility of extending into local prison services is currently being explored.

Acute HCV: when to treat?

As stated in the latest BHIVA consensus statement [1], the options for treatment of acute HCV should be discussed with all patients and should cover the benefits of immediate versus deferred therapy. DAAs are not licensed for use in acute HCV and so currently the only available treatment outside a clinical trial would be PEG/RBV for a minimum of 24 weeks. However, if a patient's estimated duration of HCV infection has been greater than 24 weeks then they would technically now be classified as having a chronic infection and would be eligible for products licensed for chronic HCV, including the new DAAs (if the newer drugs meet NICE recommendations).

One of the rationales for early access to HCV treatment during the acute phase has been the higher treatment success rate for acute HCV when compared to chronic HCV, in HIV/HCV co-infection. Some patients might wish to wait for access to DAAs because the treatment period will be briefer with a lower side-effect profile, and clinical trial data have still suggested a high success rate. Fierer presented preliminary data at the *20th Conference on Retroviruses and Opportunistic Infections* (CROI) on the use of DAAs in acute HCV suggesting a reduction in total duration is possible to 12 weeks [21].

A further rationale for treatment during the acute phase of HCV has been from a public health perspective. Over the past decade a global epidemic of acute hepatitis C has been observed amongst HIV-infected men who have sex with men (MSM). The route of transmission seems to be permucosal and has an association with sex and drug-taking behavioural factors [22]. HCV/HIV co-infected patients have higher HCV viral loads and so treatment can reduce the HCV viral load and reduce the risk of onward transmission, thus also reducing the potential 'pool' of transmission within the MSM community.

Re-infection

Targeted interventions to prevent both initial HCV infection and the potential of re-infection in HIV-infected MSM will need to be considered if the DAAs make treatment shorter, more effective and more tolerable. Re-infection is a major issue for consideration both in injecting drug users and MSM. The rate of HCV re-infection in both groups for those who have previously cleared HCV infection, either spontaneously or through treatment, is significantly high. According to the EuroSIDA study of HIV-infected patients, 20% of MSM and injecting drug users who are cured of HCV will be re-infected subsequently [23,24]. As recently as 2012, in England, only around 3% of those with long-term HCV infection were starting treatment each year [25]. The NHS is not meeting demand for treating those naïve to HCV therapies. With the cost

implication of the new DAAs likely to limit access to treatment for some, how often can the NHS afford to offer re-treatment? This issue was recently explored at the *Five Nations Conference on HIV and Hepatitis* in December 2014, a joint initiative involving partner organisations from France, Germany, Italy, Spain and the United Kingdom, where the motion debated was 'Re-infections should not be retreated' [26,27].

Anecdotally, nurses have reported receiving a number of queries from patients about access to the 'new treatments' and to PEG-sparing therapy. Both patients and some of the 'front line' clinic and ward staff seem unaware of the timescale for access to newer therapies or the fact that although PEG-sparing therapies may be licensed, they are unlikely to be readily available. At the time of writing, according to *The Guardian*, in the final draft guidance on sofosbuvir from NICE, NHS England was to be allowed to postpone implementation for four months, until the end of July instead of the beginning of April [28]. Mark Thursz, Professor of Hepatology at Imperial College London and Chair of the Hepatitis C Coalition, described the delay as unprecedented. Charles Gore, chief executive of the Hepatitis C Trust, was reported to be very concerned about the delay and worried about the precedent it could set. 'It feels to me as if a whole new criterion has been invented by the back door,' he said [28].

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