HIV co-infections: TB, HCV and HBV

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Abstract
Immunodeficiency caused by suboptimally treated HIV infection increases the risk of additional concurrent infections, both opportunistic and those that occur in spite of a relatively robust immune system. In relation to the latter, this article identifies three such infections that continue to cause significant morbidity and mortality in people living with HIV globally. These are *Mycobacterium tuberculosis* (MTB), hepatitis C virus (HCV) and hepatitis B virus (HBV). Knowledge of the complex interaction between HIV and these co-infections is central to developing new strategies for optimal prevention, treatment and care.

Keywords: co-infections, MTB, hepatitis C virus, hepatitis B virus, HIV

A. Revalidation

This article has been prepared with continuing professional development (CPD) in mind and can be used to support your revalidation. It is estimated that 5 hours of CPD activity will be required for completion of the reading, 'time out' activities and writing a brief reflective account in relation to your learning and its applicability to your practice. There is a self-assessment quiz at the end of this article for you to assess what you have learnt.

B. Aims and intended learning outcomes

The article aims to increase knowledge and confidence in assessing and caring for people living with HIV (PLWH) who may be at risk of, or diagnosed with, both HIV and one of the three significant co-infections described. After reading this article, undertaking the activities and completing the self-assessment quiz you should be able to:

- Outline the current global and national trends and prevalence of *mycobacterium tuberculosis* (MTB), hepatitis C virus (HCV) and hepatitis B virus (HBV) particularly in relation to HIV co-infection;
- Understand the basics of screening for and diagnosing these three conditions;
- Describe the risk factors for, and identify those who are more vulnerable to these infections; and
- Describe the specific challenges arising from treating these conditions in PLWH, especially with regards to concurrent antiretroviral therapy (ART).

C. *Mycobacterium tuberculosis*

Mycobacterium tuberculosis (MTB) is an intracellular bacterial pathogen that infects approximately one-third of the world's population (about 2 billion people) [1]. Primary infection affects the lungs generating an immune response that may either resolve the infection or lead to active primary pulmonary tuberculosis (TB). The majority of those infected achieve long-term control of the bacterium resulting in latent infection. About 5–10% of those with latent TB infection (LTBI), and without concurrent HIV, will experience a reactivation of the infection at some time during their lifetime. This is usually associated with ageing, medications or illness that impairs immune-competence.

The global challenge is exacerbated by the growing prevalence of multidrug-resistant TB (MDRTB) and extensively drug-resistant TB (XDR-TB). In 2008, the World Health Organization (WHO) released the findings of a survey covering 80 countries and confirmed that the spread of MDRTB is reaching all corners of the world [2]. Extensively drug-resistant TB (classified as resistant to four or more drugs) has also increased dramatically in the last few years in most regions [3].

Time out activity 1

Go to the WHO website and view recent data on worldwide incidence of MTB by country.

www.gov.uk/government/uploads/system/uploads/attachment_data/file/677927/WHO_estimates_of_tuberculosis_incidence_by_country__2016.pdf

D. Screening for MTB

Late detection of TB increases risk of onwards transmission, poor health outcomes, distress and economic hardship so early diagnosis and treatment is imperative [4]. Systematic screening has the potential to detected TB in people who would otherwise go undiagnosed or would be diagnosed too late, however, potential benefits need to balanced against the risks and costs of screening. In the UK today the Department of Health no longer views mass screening as cost effective and screening is considered a complementary and targeted approach [5].

Given that people with LTBI can be asymptomatic for years until reactivation occurs, it is likely that this is the cause of most active MTB cases in the UK. Individuals who were born in or spend considerable time in a country where TB is very common are more likely to have LTBI. It is not deemed feasible or cost effective to screen an entire population for LTBI but the National Institute for Health and Care Excellence (NICE) currently recommends screening specific high-risk groups (See Box 1), alongside awareness raising activities [6].

Box 1. TB screening recommendations

NICE recommends that the following cohorts are screened:

- close contacts of patients with TB;
- healthcare workers;
- migrants from countries where TB is common; and
- immune-suppressed patients (e.g. people living with HIV).

Source: NICE tuberculosis guideline [6]
BHIVA advise screening for LTB in PLWH where individuals are from countries of medium or high risk. In those from low-prevalence countries screening should occur where there are additional risk factors for LTB [7].

Since 2012 the UK Home Office policy [8] is to screen all applicants who apply for a UK visa, intend to stay ≥6 months and are resident in a country where TB is common. Active case finding (ACF) is a strategy used to identify and treat people with TB who would otherwise not seek prompt medical care. This strategy usually focuses on detecting pulmonary TB. In the UK this is targeted at high-risk groups, in addition to those described above and includes people with social risk factors such as homelessness, prisoners and people with drug and/or alcohol problems [6].

E. Testing for MTB

Several tests are used depending on the type of disease suspected. Diagnosing pulmonary TB can be difficult and several tests are usually needed [9]. NICE describes the process for diagnosing active TB in all age groups [6]. Box 2 summarises key points.

Box 2. Summary of key points for diagnosing TB in all age groups

- Where there are clinical signs and symptoms consistent with a diagnosis of TB, especially in the severely unwell patient, starting treatment without waiting for culture results is recommended
- Chest X-ray, ideally *before* starting treatment (for pulmonary disease). If chest X-ray suggestive of TB, then three deep cough sputum samples should be obtained (mechanically induced sputum or bronchoscopy with lavage may be necessary to obtain samples)
- Rapid nucleic acid amplification tests should be requested in some cases, e.g. for people living with HIV, where rapid information would alter care or if a large contact-tracing initiative is being considered

Source: NICE tuberculosis guidelines [6].
BHIVA also recommend rapid detection of rifampicin resistance prior to commencing treatment, in specific cases or when the clinical course suggests MDRTB [7].

For extra-pulmonary TB several tests can be used to confirm a diagnosis. The choice will depend on the site causing concern. Tests might include, CT and MRI scans, echocardiogram, ultrasound, endoscopy, laparoscopy, urine analysis, biopsy and lumbar puncture.

The Heaf test was used until 2005 in the UK, when it was replaced by the Mantoux test: where a small amount of purified tuberculin is injected intradermally, into the forearm. In the presence of infection the skin will react with localised inflammatory changes usually within 72 hours of the test. The reaction is measured carefully. Whether the extent of the localised reaction is classed as a positive result will depend on underlying risk factors. Induration of 15 mm or more is considered positive in those without any known risk factors. False results can occur, for example, due to very recent TB infection, a local hypersensitivity reaction, in those taking (cortico)steroids or in immune compromised individuals. Serum interferon-gamma release assays can be a useful test to help diagnose latent TB following a positive Mantoux test or in those who have previously had a bacille Calmette–Guérin (BCG) vaccination.

Key point

The bacille Calmette–Guérin (BCG) vaccine has existed for 80 years and is one of the most widely used of all current vaccines. According to the WHO, 'BCG vaccine has a documented protective effect against meningitis and disseminated TB in children. However it does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. The impact of BCG vaccination on transmission of MTB is therefore limited' [10].

F. Risk factors for MTB infection

MTB is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty [11]. Chronic lung disease is another significant risk factor and smokers have nearly twice the risk of MTB compared to non-smokers [12]. Other concurrent diseases such as renal disease and diabetes mellitus increase susceptibility [13]. Genetics also appear to play a role [14] and certain medications, such as long-term use of corticosteroids also enhance risk of infection.

Time out activity 2

Knowing how MTB is spread: take 5 minutes to consider what factors you might incorporate in devising an assessment tool for exploring risk of TB infection.

Box 3 shows what your list, exploring the risk of TB infection, might include.

G. MTB and HIV co-infection

Notably the presence of HIV infection increases the risk of reactivation of subclinical MTB by about 20 fold [15]. Globally the main risk factor for TB infection is HIV. The WHO has estimated that HIV and TB co-infection has accounted for about 26% of AIDS-related deaths [16].

The presence of both pathogens can potentiate one another, causing an acceleration of deterioration of immunological functions if untreated [15]. CD4 cell depletion appears to be particularly significant and those with CD4 counts <200 cells/mm^3, or rapidly declining counts, seem to be particularly susceptible both to reactivation of latent disease and also to disseminated TB infection. Active TB has also been reported to exacerbate HIV infection.

Box 3. Risks of TB

Aside from those who have had recent contact with an index case, you might assess whether the individual is or has:

- lived in or originated from a high-prevalence area such as sub-Saharan Africa
- lived in overcrowded conditions
- served a prison sentence
- worked in an area where vulnerable people gather (e.g. prisons and homeless shelters) or overseas in a high-prevalence area
- Immune-compromised, such as people living with HIV with CD4 count of <200 cells/mm^3, a current recipient of chemotherapy or post organ transplant
- a cigarette smoker
- suffering from concurrent and chronic respiratory disease
- malnourished or alcohol dependent
- other underlying chronic diseases, such as diabetes mellitus or end-stage renal disease

H. Impact of antiretroviral therapy on MTB infection

As expected an improvement in the state of the immune system is associated with a significant reduction in rates of both primary TB and reactivation of latent disease. This benefit occurs regardless of the CD4 T cell count at which ART is commenced. However during the first 3 months on ART, while restoration of the immune system takes place the incidence of acute disease increases. This is more likely to occur in those who start treatment with CD4 T cell counts of <50 cells/mm^3 [15].

Recent data suggest early treatment reduces morbidity and mortality. BHIVA, therefore, recommend, in most cases, starting ART as soon as practicable/tolerable after starting TB therapy, however, treatment plans are complex and a specialist field [7]. In addition to the issue of immune reconstitution, there are also overlapping toxicities, drug–drug interactions and high pill burdens, which may impact on adherence. Drug interactions are common. Rifampicin is a powerful cytochrome 450 inducer and has effects on several metabolic pathways. It interacts with protease inhibitors, non nucleosides and CCR5 antagonists, as well as some antimicrobials. In some of these cases a longer duration of TB treatment (up to 10 months) may be necessary. In general, for drug-sensitive TB (not involving the central nervous system) regimens of 6 months are recommended [7].

Time out activity 3

If you are unfamiliar with or need a refresher on TB drug treatments, go to:

www.bhiva.org/TB-HIV-coinfection-guidelines.aspx

Find page 3, section 1.60 of *the British HIV Association guidelines for the treatment of TB/HIV coinfection 2011* and take a few minutes to view the co-administration guidance for first-line ART and TB treatment [7].

I. Hepatitis C

Hepatitis C virus and related diseases are found worldwide. An estimated 2% of the world's population were infected with HCV in 2015. Figure 1 illustrates the WHO's estimated numbers. The most affected regions are the Eastern Mediterranean and Europe (2.3% and 1.5% respectively) and 1% of the African region [17]. Depending on the country, infection is often concentrated in certain populations, e.g. in those who inject drugs. There are multiple genotypes of the virus and their distribution varies by region.

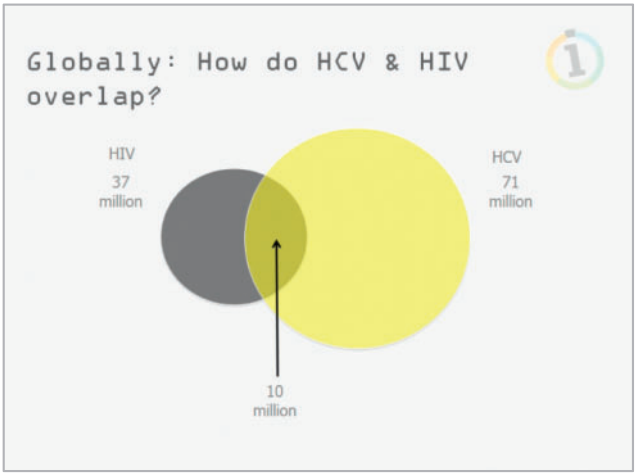

Figure 1: Global overlap of HCV and HIV. Published with kind permission from www.treat-hiv.com.

Without treatment chronic HCV can cause severe liver dysfunction, cirrhosis, oesophageal varicies and liver cancer. Most people with acute infection do not have symptoms and chronic HCV is often discovered during routine liver function tests. However some people do develop symptoms soon after infection. Symptoms can include jaundice, fatigue, anorexia, nausea and myalgia.

J. HCV and HIV co-infection

As HCV is a blood-borne virus, sharing equipment for injecting drugs is the most common route of transmission for HCV, but sexual transmission can also occur and there has been an increase in the number of men who have sex with men (MSM) acquiring HCV through sexual contact in this decade. Recent estimates believe that about one-third of PLWH are co-infected [18]. BHIVA reports an epidemic of acute HCV infection amongst MSM who are living with HIV in the UK and Western Europe. This appears to be linked with mucosal traumatic sexual practices and chemsex and is often transmitted alongside other sexually transmitted infections [19]. In some studies participants had been treated and re-infected multiple times [20]. This highlights the need for ongoing safer sex advice even if partners are HIV seroconcordant, virologically suppressed on ART or taking ART as prevention.

HCV does not appear to impact directly on HIV infection but PLWH are less likely to naturally clear the virus, and, especially with lower CD4 cell counts, are more prone to subsequent aggressive liver disease.

There is also an increased risk of liver carcinoma, which tends to occur at a younger age and within a shorter time period than in those with HCV only [19]. Where HIV viral load is effectively suppressed with ART, HCV disease progression is similar to that of the HIV-negative cohort [19]; however, there are treatment challenges; PLWH do not respond as well to the older interferon-based therapies, but with newer direct-acting antivirals (DAAs) cure rates appear similar for all individuals regardless of HIV status.

K. Testing/screening for HCV

It is recommended that individuals receiving a positive HIV test have an HCV antibody test and that this is subsequently repeated at least annually. Guidelines also recommend individuals who achieve a sustained virological response following treatment, or those who have spontaneously cleared HCV infection, should be offered annual HCV-PCR and more frequent testing should they have an unexplained rise in liver function test results [21].

L. HCV treatment

BHIVA's recently updated treatment guidelines recommend commencing ART in all PLWH [22], regardless of CD4 cell count. Once established on ART, HCV treatment can be initiated, unless HCV treatment takes precedence due to clinical conditions. The choice of treatment depends on the genotype and existence of liver disease, in particular the presence of cirrhosis. Antiretroviral (ARV) regimens should be selected or modified to suit the planned HCV treatment [19].

Until relatively recently, treatment for chronic HCV (as well as HBV) usually involved interferon, with a view to strengthening the immune response; used together with the antiviral ribavirin. Pegylated interferon has an improved pharmacokinetic and pharmacodynamic profile. There remains opinion that adding this to the treatment plan may increase the likelihood of positive clinical outcomes, although viral clearance is not common [23]. Pegylated interferon is injected once weekly but the toxicity profile is high. The most common side effects include flu-like symptoms, loss of appetite, insomnia, depression and other mood changes; symptoms which many find difficult to tolerate.

Recent data shows that interferon-free DAAs clear HCV in the vast majority of PLWH co-infection and appear effective with good tolerability and low toxicity [24]. DAAs are taken orally 8–48 weeks, depending on the genotype and the severity of liver disease. NICE recommends several DAA combinations that are appropriate, however, a number of these recommendations are made within the caveat of a cost reduction by the manufacturers [25]. Importantly when DAAs are chosen for PLWH, some restrictions on first-line ARV choice exists due to drug–drug interactions. For example, boceprevir and telaprevir are inhibitors of cytochrome P 3A4/5 and therefore interact with several ART medications.

Time out activity 4

Different viewpoints

First visit: www.cochrane.org/CD012143/LIVER_direct-acting-antivirals-chronic-hepatitis-c and read the Cochrane Review from 2017.

Then go to: www.journal-of-hepatology.eu/article/S0168-8278(17)32129-3/fulltext. Read the conclusions of the response to the above Cochrane review by the European Association for the Study of the Liver.

In January 2018 NHS England announced that it aims to eliminate hepatitis C by 2025 [26].To achieve this target substantial reductions in drug pricing with improved access to these, alongside increased uptake of testing will be essential. Public Health England believes approximately 50% of people with HCV may have already been diagnosed in England and Wales but according to the CEO of the Hepatitis C Trust there are at least 100,000 more people to identify [27].

Key point

Due to the cost of these new treatments the NHS has had to phase in access with waiting lists amongst other measures. According to HIV i-base, at the end of 2017 around 10,000 people had been treated with DAAs. People with long-term co-infection are prioritised because of the higher risk for liver cancer and faster HCV progression. As more people are treated with DAAs, the access problem is likely to affect hard-to-reach groups, the small numbers who have had DAA failure and people who become re-infected [28].

Time out activity 5

The 'I'm Worth Campaign' aims to address the stigma that many people with hepatitis C face and encourages access care and services. Take 10 minutes and visit the website to read more about this useful resource: www.imworth.co.uk

M. Hepatitis B

Hepatitis B (HBV), a BBV infection, can also cause severe liver disease including cirrhosis and hepatocellular carcinoma. In up to 10% of chronic carriers viral DNA and proteins have also been detected in extra-hepatic sites [29].

Time out activity 6

Go to the *British HIV Association guidelines for the management of coinfecion with HIV-1 and hepatitis B or C virus 2010*: www.bhiva.org/documents/Guidelines/HepBC/2010/hiv_781.pdf [19],

Find section 4.2.2 and take a few minutes to study Table 2. This clarifies how HBV serology is interpreted.

About one-third of the world's population has been infected at some point in their lives. It is especially common in sub-Saharan Africa, the Indian subcontinent and the rest of Asia where many people have been

infected by vertical transmission or during early childhood [30]. Up to 50% of children infected under the age of 5 years go on to develop chronic infection [31]. HBV can be transmitted between family members within households, by contact of non-intact skin or mucous membrane with secretions or saliva. In the UK, HBV mainly affects MSM and people who inject drugs [32].

For most people (around 95%) who get HBV as adults, the infection is self-limiting without treatment. People who naturally clear the virus recover fully and develop lifelong immunity but DNA remains present in the liver and may reactivate later. However a proportion of people, including those with compromised immune systems can go on to have chronic infection beyond 6 months. There are four stages of chronic hepatitis B infection outlined in Box 4.

Box 4. Four stages of chronic hepatitis B infection

1. Immune tolerant	HBV e antigen (HBeAg) positive, normal liver function tests (LFTs), high viral load, little or no inflammation on liver biopsy
2. Immune active	HBeAg positive, raised LFTs, high viral load, progressive inflammation and fibrosis of the liver
3. Inactive carrier	HBV surface antigen (HBsAg) positive, HBeAg negative with low viral load and normal LFTs
4. Chronic active hepatitis	HBeAg negative, moderate viral load levels, progressive inflammation and fibrosis of the liver

Source: adapted from Brook G *et al.* 2010 [33].

N. HIV and HBV co-infection

Around 7% of PLWH in the UK also have HBV [32]. Liver complications due to HBV (and HCV) infections have become one of the most common non-AIDS-related cause of death for PLWH [34] as shown in Figure 2.

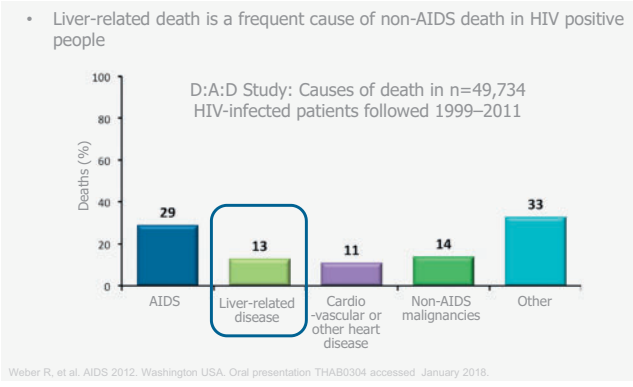

Figure 2: Liver-related death in HIV positive people. Published with kind permission from www.treat-hiv.com

There are reports of PLWH clearing chronic HBV infection with the recovery of their immune system following commencement of ART [35]. Nevertheless co-infection presents some unique challenges as listed in Box 5.

Box 5. Challenges in the management of HBV/HIV co-infection

- People living with HIV are about 60% less likely to clear HBV without treatment and liver disease progression can be more rapid.
- Poor prescribing or reduced treatment adherence can cause resistance to develop in either virus as many ART drugs are dually active against both HIV and HBV.
- Discontinuing ART can lead to temporary worsening of liver disease known as 'flares'.
- In resource-limited countries HBV is not always routinely tested before starting ART. This increases the risk of resistant HBV and can limit future treatment options.
- For those not already receiving ART, treating HBV with these dually active drugs, but without a potent antiretroviral agent, such as a protease inhibitor or non-nucleoside reverse transcriptase inhibitor, can lead to HIV resistance [36].
- All ART drugs have the potential to cause acute and long-term hepatotoxicity and this risk is increased up to three fold in the presence of chronic liver disease [19].
- Although rare, people living with HIV who appear to have cleared HBV infection can present with a further episode of either acute HBV reactivation or re-infection [19].

It is important that people diagnosed with HIV are screened for and vaccinated against HBV if they are not already immune. BHIVA advises that the schedule used in the HIV-negative population of several doses over a 12-month period is usually suitable for PLWH. The organisation have identified a number of priorities for the management and care of PLWH at risk of, or co-infected with HBV, as outlined in Box 6 [19].

Box 6. Priorities for the management and care of people living with HIV at risk of, or co-infected with, HBV

- Screening for all those with a new HIV diagnosis for HBV and HCV markers
- An offer of vaccination for HBV if not already immune
- Screening tests should be repeated before commencement of ART and annually
- People with HBV should have their 'e' status and HBV viral load checked
- Those with active hepatitis must be given advice on alcohol avoidance and how to reduce the risks of transmission
- People living with HIV and chronic HBV (or HCV) should be offered an assessment of liver fibrosis
- Those with cirrhosis should be jointly treated by a hepatologist and have regular checks for hepatocellular carcinoma

Source: *BHIVA guidelines for the management of coinfection of with HIV-1 and hepatitis B or C virus 2010* [19]

O. Transmission and prevention of HBV

Time out activity 7

Using what you understand of blood-borne viruses and HBV in particular, take 5 minutes to consider some strategies for reducing transmission of HBV. Before you read on try to list four prevention methods.

Given the wealth of evidence for condom use in the prevention of many STIs it is logical that they are also effective for preventing transmission of both HBV and HCV during forms of penetrative sex. Furthermore, harm reduction strategies for those who inject drugs, including needle exchanges, are likely beneficial, however due to the high infectivity of HBV the sharing of all injecting 'works' (not just 'sharps') carries significant risk. Counselling those who inject drugs and facilitating sustained access to care is essential. High standards of infection control in clinical settings as well as tattooing, body piercing and acupuncture are also important.

Infection rates in many countries have fallen dramatically thanks to routine infant vaccination. The highly effective vaccine has been widely available since 1982 and is recommended by WHO in the first day of life if possible, with 2–3 subsequent doses. About 180 countries gave the vaccine as part of national programmes from 2006 [37]. Vaccinating those working in high-risk areas such as medical settings and prisons is now standard practice in Europe.

Key point

In the UK all children born since August 2017 are vaccinated routinely as part of their 6-in-1 vaccine at 8, 12 and 16 weeks of age [31].

P. Treatment for HBV

The type of treatment recommended will depend on the extent of liver inflammation and disease, e.g. fibrosis, cirrhosis, or persistently or marked elevation of liver function tests (especially alanine transaminase [ALT]). Effective treatment suppresses HBV reproduction and reduces viral load, which in turn can reduce inflammation and liver enzyme levels revert. Less often, treatment can lead to loss of HBV antigens and promote the production of antibodies. For people with HIV co-infection, seroconversion appears to be more likely if they are also on ART for HIV [38]

Several antiviral drugs are effective for those who do not clear the virus spontaneously but treatment is usually lifelong. Nucleoside or nucleotide analogues including some commonly used to treat HIV alone, such as tenofovir, lamivudine and emtricitabine, are also active against HBV. The use of a regimen containing one of these is advised [39] and simplifies treatment for co-infection although great care needs to be taken to avoid drug resistance for either virus. Other antiviral drugs effective against HBV include adefovir, entecavir and telbivudine but these are no longer recommended for use in HIV co-infection [39]. Pegylated interferon, as described in Section L, has also been widely used for the treatment of HBV with similar associated challenges.

Q. Conclusions and the nurse's role

With increased access to ART, improved monitoring of treatment effectiveness and effective management of toxicities and comorbidities fewer people are dying from HIV-related causes and are living longer. However among PLWH morbidity and mortality is increasingly driven by co-infections including HCV, HBV and TB. Successfully addressing the challenge of co-infections requires tackling structural inequalities both globally and nationally, managing the complexities of multiple epidemics, targeting vulnerable populations, reducing stigma, improving access to new treatments and investing in research and clinical development. Nurses have a clear role to play in raising awareness of these conditions, in the assessment of risk, screening and diagnosis and in reaching and maintaining relationships with the hard-to-reach. As always a holistic and multidisciplinary approach is imperative alongside an emphasis on educating and empowering PLWH in relation to risk reduction and maximising health and well-being.

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Conflicts of interest

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