



Occult Hepatitis B and C among injection drug users (IDUs): An Overlooked Obstacle in Global Health Efforts

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Abstract

Occult hepatitis B (OBI) and C (OCI) infections represent hidden viral states that evade standard serum diagnostics, posing a significant challenge to global hepatitis control, particularly among high-risk groups like injection drug users (IDUs). OBI is characterized by the persistence of replication-competent hepatitis B virus (HBV) DNA within the liver, often as covalently closed circular DNA (cccDNA), or in blood, in individuals who consistently test negative for hepatitis B surface antigen (HBsAg) through conventional assays. This form of HBV infection is marked by low-level replication within hepatocytes, evading immune detection and remaining undetectable by standard HBsAg tests, thus complicating diagnosis and management. OCI, similarly, is characterized by hepatitis C virus (HCV) RNA in liver cells or peripheral blood mononuclear cells (PBMCs) despite undetectable serum levels. OCI can be seropositive, with anti-HCV antibodies indicating past infection, or seronegative, lacking these antibodies and suggesting minimal immune recognition. Due to practices like needle sharing, IDUs face heightened risks of OBI and OCI, which can silently progress to severe liver disease, including cirrhosis and hepatocellular carcinoma (HCC). The frequent co-occurrence of HIV among IDUs further complicates clinical care, emphasizing the need for multi-disease, integrated screening strategies. The development of sensitive diagnostic tools capable of accurately identifying OBI and OCI in high-risk populations is essential to advance the World Health Organization's (WHO) hepatitis elimination targets for 2030. Enhanced diagnostics and targeted interventions will support early detection, reduce transmission, and contribute to global efforts to eradicate hepatitis in vulnerable populations.

Keywords: Occult hepatitis B; Occult hepatitis C; Injection drug users; HCV; HBV.

1. Introduction

Hepatitis B and C represent major public health concerns due to their transmissibility via blood contact, including through intravenous drug use,

medical procedures, tattooing, and body piercing. These transmission routes contribute to a spectrum of liver diseases and increase the risk of outbreaks and epidemics (Ahmed et al., 2024; Vilibic-Cavlek et al., 2023). Egypt, in particular, faces an exceptionally high prevalence of HCV, ranking

among the highest globally and is considered an area of intermediate endemicity for HBV infection (Azzam et al., 2023).

Individuals who inject drugs are exposed to multiple health risks and adverse outcomes (Collins et al., 2019). Injection practices significantly increase the transmission of blood-borne viruses, notably hepatitis B virus (HBV) and hepatitis C virus (HCV), leading to considerable morbidity and mortality (Degenhardt et al., 2023).

Occult hepatitis provides a greater issue since it cannot be identified using normal diagnostics, resulting in a substantial proportion of cases being undiscovered. This is particularly troublesome among high-risk populations, such as injection drug users (IDUs), who increase the chance of transmission within their demography (Ondigui et al., 2022). Unfortunately, the issue of occult infections within this population has been largely neglected in Egypt, a country previously recognized for having the highest global prevalence of chronic HCV.

2. Occult HBV among Injection Drug Users

Occult hepatitis B infection (OBI) is a distinct virological condition where replication-competent HBV DNA persists in the liver without detectable hepatitis B surface antigen (HBsAg) in the blood. This state is maintained by the covalently closed circular DNA (cccDNA), which enables low-level intrahepatic replication and the production of infectious HBV virions (Fu et al., 2024).

Occult hepatitis B infection (OBI) can be categorized into two distinct serological subtypes based on the presence or absence of specific antibodies. The more common subtype, seropositive OBI, is characterized by the presence of hepatitis B core antibody (HBcAb) and/or hepatitis B surface antibody (HBsAb), suggesting some level of immune recognition of the virus. In contrast, seronegative OBI represents a smaller fraction of cases (approximately 1%-20%) and is defined by the absence of both HBcAb and HBsAb, indicating a complete lack of detectable hepatitis B antibodies. This classification underscores the variability in immune response among individuals with OBI and offers valuable insights that could improve diagnostic accuracy for this often-undetected infection (Jafari et al., 2024).

Despite the main focus on eliminating HBV, OBI warrants attention due to its clinical implications. OBI remains challenging to diagnose. Detection often relies on nested, real-time, or digital PCR assays in blood samples, but the intermittent nature of HBV DNA in circulation and the lack of standardized, sensitive assays hinder accuracy. Ideally, OBI diagnosis would involve liver-based identification of replication-competent HBV DNA; however, validated tests for this purpose are currently unavailable, underscoring a significant gap in hepatitis research (Bucio-Ortiz et al., 2024).

Injection drug users comprise a demographic that is consistently exposed to a wide range of viral pathogens due to their involvement in injecting activities. Particularly, among IDUs with occult HBV infections, exposure to the virus through parenteral behaviors (such as sharing syringes/needles and tattooing) was identified. Furthermore, secondary risk factors, including a prior record of incarceration, thought to be taken into account. Limited research has examined the prevalence of OBI among IDUs and the impact of injecting bad behaviors on the transmission of OBI (Matos et al., 2013).

For OBI prevalence, few research among IDUs were conducted, with varying prevalence rates identified. For example, a research done in Taiwan indicated an OBI prevalence of approximately 41.1% among Taiwanese IDUs (Lin et al., 2007), whereas another conducted in Iran discovered an overall frequency of 5.6% (Asli et al., 2016). These variances may be due to differences in viral endemicity, sample size, and viral detection technological advances.

For OBI transmission risk factors among IDUs, a research investigation carried out in Baltimore revealed a significant incidence of OBI among IDUs who engaged in unacceptable behaviors such as parenteral behaviors (e.g., sharing syringes/needles, which accounted for approximately 68.4%, and tattooing, which accounted for 57.9%) (Matos et al., 2013). The potential significance of prolonged injection duration in the transmission of OBI has been demonstrated in two studies conducted in Iran and Taiwan. These studies found that elderly injecting drug users might have a more extensive history of drug use, which is indicative of the cumulative exposure effect (Asli et al., 2016).

OBI is regarded as a potential risk factor for chronic liver disease across a range of demographic populations. Moreover, it makes a substantial contribution to the progression of severe hepatic diseases such as cirrhosis. Unfortunately, few studies have examined the detrimental effects of OBI on IDUs. An investigation carried out in Baltimore in 2004 discovered that there was no correlation between AST and OBI. However, ALT levels demonstrated a statistically significant difference (**Torbenson et al., 2004**), while two studies conducted in Iran on IDUs infected with viral hepatitis and HIV identified elevations in AST and ALT levels (**Azadmanesh et al., 2008; Jamshidi et al., 2020**).

Despite the existence of numerous studies examining the prevalence of OBI in Egypt, there is a notable absence of research on OBI among IDUs. This creates a critical need for studies that focus on demographic parameters and clinical outcomes associated with the transmission of OBI among this high-risk population.

3. Occult HCV among Injection Drug Users

Occult hepatitis C infection (OCI), first identified by Castillo et al. in 2004, is a distinct form of hepatitis C characterized by the absence of detectable viral RNA in serum, with its presence confirmed in hepatocytes, peripheral blood mononuclear cells (PBMCs), or in serum after ultracentrifugation. OCI is classified into two types: seronegative OCI, which occurs in individuals without anti-HCV antibodies, and seropositive OCI, found in those who are anti-HCV positive. Seropositive OCI often represents individuals who were chronically infected with HCV and have since cleared the virus from their serum, either spontaneously or through treatment (**Mbaga et al., 2022**).

Clinically, OCI presents a varied profile. While some carriers are asymptomatic with normal liver enzyme levels, others exhibit abnormal liver function. Importantly, OCI can progress to more serious hepatic conditions, including liver cirrhosis, and in high-risk individuals, hepatocellular carcinoma (HCC). This hidden form of hepatitis C underscores the need for careful monitoring in at-risk populations, as standard HCV testing may fail to detect this elusive infection (**Mbaga et al., 2022**).

Injection drug users have a significant risk of HCV infection (**Khalsa & Mathur, 2021**). This is due to the widespread adoption of high-risk activities such as needle sharing, sharing of other injecting equipment, drug use in social settings, and insecure living situations. Sharing injection equipment, in particular, increases the risk of HCV infection among IDUs. It is worth emphasizing that there is a lack of critical data on the current state of injectable drug users and the frequency of HCV infection among IDUs in various countries, including Egypt (**Karimi et al., 2020; Mateu-Gelabert et al., 2022**).

Castillo et al. (2004) presented a complete description of OCI, a different kind of HCV infection with unique characteristics. OCI is diagnosed when a patient has positive viral HCV RNA in their PBMCs but negative HCV RNA in their plasma. Sixty percent of OCI patients are successfully detected utilizing the noninvasive approach of OCI detection in PBMCs (**Elkashef et al., 2022**). Previous research revealed that OCI might be present in many people who had spontaneously "cleared" the virus from their blood (**Mashaal et al., 2022; Wang et al., 2019**). Furthermore, the prevalence of OCI has been recorded in populations with risk features, such as those with tattoos and those who have had acupuncture, as well as in apparently healthy persons (**Helaly et al., 2017; Martínez-Rodríguez et al., 2018**). OCI has been seen in IDUs (**Sheikh et al., 2019**). Given that this group is deemed high-risk for the transmission of blood-borne illnesses, the existence of OCI positive persons may contribute to the spread of HCV, impeding the vision of WHO for eradicating HCV by 2030 (**Khalsa & Mathur, 2021**).

Occult HCV infection has been documented across various global regions and among diverse populations. For instance, it has been identified in patients undergoing hemodialysis (**Naguib et al., 2024**), those diagnosed with cryptogenic liver disease, those diagnosed with thalassemic patients (**Franzè et al., 2022**), those diagnosed with lymphoproliferative disorders (**Elkashef et al., 2022**), those living with HIV infection (**Bokharaei-Salim et al., 2016**), blood donors, and those diagnosed with hepatocellular carcinoma (**An et al., 2020**). Sadly, there is a severe dearth of information regarding the prevalence of OCI among IDUs. Two investigations regarding the prevalence of OCI in Iranian IDUs were examined.

There is currently no data on the incidence of OCI among Egyptian IDUs; therefore, epidemiological studies are being conducted to determine the circumstances surrounding this prevalence.

There was insufficient evidence available on the risk variables that potentially lead to illness transmission among IDUs. For example, **Donyavi et al. (2019)** found a substantial association between OCI and level of education. Additional risk factors, including a history of incarceration and the practice of sharing syringes, were examined in relation to OCI. The results revealed a significant correlation between the presence of OCI and the transmission of the disease, underscoring the importance of implementing interventions within correctional facilities that reduce its transmission (**Sheikh et al., 2019**).

Regarding to the clinical consequences of OCI presence, prior research has indicated that OCI may induce mild hepatic impairment. Hence, it is recommended that individuals diagnosed with OCI undergo subsequent examinations to monitor the progression of apparent illness (**Saad et al., 2011; Elkashef et al., 2022**).

The identification of OCI in IDUs is significant because of its possible function as a viral reservoir and subsequent spread to others. Furthermore, IDUs often fail to attend to treatment programs. According to hepatologists, therapy for these patients should begin 6-12 months after de-addiction. Individuals infected with HCV who are also IDUs have been successfully treated with continued monitoring by medical specialists with experience in addiction medicine and hepatology (**Sheikh et al., 2019**).

OCI prevalence among IDUs is not similarly documented as OBI prevalence in Egypt. Among this high-risk population, there is an urgent need for research focusing on demographic and clinical outcomes associated with the transmission of OCI.

4. Viral coinfections

The growing epidemic of HBV and HCV, together with HIV infection, presents a major public health concern. Due to a lack of evidence, it has been difficult to diagnose and treat these patients.

In an Iranian study of OBI and OCI patients, viral coinfection with HIV IDUs occurred at rates of 3.1% and 11.4%, respectively. Another Iranian

research on IDUs discovered that OCI-HIV coinfection occurred in 18.1% of the sample group. Co-infection with the occult forms, OBI and OCI, complicates HIV patients' treatment and overall care, emphasizing the need of integrated healthcare for this group (**Donyavi et al., 2019; Jamshidi et al., 2020**).

It is noteworthy that one study identified the existence of OBI-OCI coinfection. Based on the findings of this study, it appears that further research is warranted to examine this matter in a more extensive sample size and across diverse populations situated in various global locations (**Jamshidi et al., 2020**).

5. Conclusion

Occult hepatitis infections in injection drug users (IDUs) represent a hidden yet significant health risk, especially in high-prevalence regions like Egypt. These undetected infections contribute to disease progression and continued virus transmission, exacerbated by unsafe practices like needle sharing. Addressing this gap through targeted screening for occult infections and enhanced harm reduction strategies is crucial for reducing transmission and supporting global hepatitis elimination goals.

6. Recommendations

Effective management of OBI and OCI among IDUs requires a strategic enhancement of screening protocols, utilizing advanced diagnostics such as PCR to identify viral DNA/RNA undetectable by standard serum tests. The optimization of these screening practices is critical for early detection of hidden infections, particularly in high-prevalence regions. Incorporating improved diagnostics into harm reduction and healthcare programs can enable timely intervention, significantly lowering transmission risks. This focused approach is essential for advancing the WHO's 2030 hepatitis elimination goals and ensuring that occult infections receive necessary attention within high-risk populations.

Conflict of interest

None of the authors have any conflicts of interest.

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