The HBV/HDV screening and linkage to care in drug users: A therapeutic diagnostic pathway (PDTA)

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Summary

■ ***The infectious diseases are an important comorbidity in drugs users and a health warming.***
Today only a few percentages of drug users are subjected to screening for hepatitis and human immunodeficiency virus (HIV).
In the recent years an effort has been made in drug users for the elimination of hepatitis C virus (HCV). Unfortunately, several barriers are now limiting the achievement of the goal of HCV elimination, as suggested by WHO.
Drug users are people highly at risk to contract HBV and HDV infections. Only a few percentages of drug users receive HBV/HDV treatments, although they are effective and safe. The lack of treatment for drug users may be due to several factors. The main is that only a few percentages of drug users are tested for HBV and linked to treatment.
The principal aim of this work is to define a therapeutic diagnostic pathway (Percorso Diagnostico Terapeutico Assistenziale – PDTA) able to favorite HBV/HDV screening and linkage to care in drug users. ■

Keywords: ***Hepatitis D virus (HDV), Hepatitis B virus (HBV), Drug users, Harm reduction, Bulevirtide.***

Introduction

Approximately 587 million people are infected with chronic HBV infection and 62-72 million chronically infected with HDV (Botelho-Souza, Vasconcelos, 2017). Several people are at risk of HBV infection: people that come from endemic areas, intravenous drug users (IDUs), men who have sex with men, individuals with human immunodeficiency virus (HIV) or hepatitis C (HCV) and patients with multiple sexual partners (Kushner *et al.,* 2015; Lempp *et al.,* 2016; Perez-Vargas *et al.,* 2019; Shih *et al.,* 2008).
The evidence suggests that drug users are commonly exposed to hepatitis B virus (HBV) and hepatitis D virus (HDV) (Aguilera *et al.,* 2018; Chen *et al.,* 2017; Hsiech *et al.,* 2016; Lu *et al.,* 2021; Mahale *et al.,* 2018; Vlachogiannokos, Papatheodoridis, 2020). The Italian epidemiological data indicate that only a few percentages of drug users inside the Drug Abuse Services (Servizi per le Dipendenze – SerDs) are subjected to HBV screening. In particular, the data suggest that inside SerDs only the 25.1% of drug users are tested for HBV and of them only the 2.4% were positive (Italian report on drug dependence at Parliament, 2023). Moreover, there no data no data on the prevalence of HBV vaccination in drug users inside SerDs.

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Worldwide the epidemiology of HDV infection is yet largely unknown. In Italy the prevalence of HDV is 3.2.% between the HBsAg positive subjects and 9.3% between the patients with chronic hepatitis B (Coco *et al.,* 2022). In Italy there are not data on the prevalence of HDV in drug users.
Drug users share several risk factors to contract HBV and HDV infections. Most of them are coming from endemic areas such as South Europe, South Africa and North America (Taylor *et al.,* 2013), most are IVDUs (Hercun *et al.,* 2020), some are practitioners of high-risk sexual behaviors (HRSBs) (Lin *et al.,* 2015; Stockdale *et al.,* 2020), some others are human immunodeficiency virus-positive (Stockdale et al, 2020), and others are (or were) incarcerated with a more elevated risk to contract infection diseases for the promiscuous conditions of life inside prisons (Grigolin *et al.,* 2021; Nava *et al.,* 2021; Simpson, 2019).
Today, the are some important and effective options for the treatment of HBV and HDV infections but several barriers are now limiting these treatments in drug users. The first is the low percentage of drug users subjected to screening and linkage to care; the second is the lack of knowledge of HDV between specialists working inside SerDs; the third is the lack of support of the patients on treatment persistence and adherence.
The treatment of HBV and HDV positive drug users is an essential action of public health able to limit the spread of the infections in general population.
The principal aim of this work is – starting from the main international guidelines/recommendations – to propose a therapeutic diagnostic pathway (Percorso Diagnostico Terapeutico Assistenziale – PDTA) for the treatment of HBV and HDV infections in drug users.

Aims of the PDTA

The therapeutic diagnostic pathway (PDTA) is a tool of clinical governance that allow the definition of the best practicable pathways within the health organization and the network in which it is inserted.
The aim of this PTDA is to guarantee inside SerDs the:

- early detection of HBV and HDV infections in drug users;
- diagnosis;
- linkage to care;
- treatment persistence and adherence;
- follow up and the harm reduction.

Stages of PDTA

A. The early detection of HBV and HDV infections

Drug users are at risk to contract infectious diseases. All drug users should be subjected to screening for HBV (including for HCV and HIV) at service admission, every 6 months and at each risk behavior. The principal goal of the screening is the early detection of the HBV/HDV disease.

Early detection: red flag
Elevated transaminase: test for HBV, HCV, HAV;
No HBV vaccination: test and vaccine, if necessary.
Priority screening for infection diseases and harm reduction action should be reserved for IVDUs.

The HBV screening should be proposed to all drug users through a blood sampling and in hard-to-reach people through a rapid test.
The screening should be associated in drug users with:

- motivational counseling;
- educational training (e.g. Informative booklet about infectious diseases);
- risks behavior diary.

The first line HBV tests for drug users are (Aghemo *et al.*, 2023; Buti *et al.*, 2023; EASL, 2017; 2021):

- Hepatitis B surface antigen (HBsAg);
- Hepatitis B surface (anti-HBs);
- Antibody to hepatitis B core antigen (anti-HBc).

The above tests are needed to evaluate the characteristics of HBV disease.

Interpretation of hepatitis serologic test
Hepatitis B surface antigen (HBsAg)
The body normally produces antibodies to HBsAg as part of the normal immune response to infection. The HBsAg is a protein on the surface of hepatitis B virus that can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. HBsAg is the antigen used to make HepB vaccine
Hepatitis B surface antibody (anti-HBs)
The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B. Among vaccine responders who completed a vaccine series, anti-HBs levels can decline over the time, however the majority are still immune and will mount a response when exposed to HBV.

Antibody to hepatitis B core antigen (anti-HBc)
Appears at the onset of symptoms in acute hepatitis B, is a measure of both IgM and IgG, and persist for life. The presence of total anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame. People who have immunity to hepatitis B from a vaccine do not develop anti-HBc.

The HBV test should be integrated in all drug users with HIV, HAV and HCV tests.

B. Diagnosis

The HBV positive patients should by subjected to further diagnostic work-up by infectious disease specialists. The virological and the disease evaluation is an essential step to characterize HBV and/or HDV disease (Aghemo *et al.*, 2023; Buti *et al.*, 2023; EASL 2017; 2021; Negro, Loks, 2023; Niro *et al.*, 2021; Schaper *et al.*, 2010).
The aim of the virological evaluation is to characterize the replicative profile of HBV and HDV. All HBsAg positive patients should be tested with anti-HDV (IgG + IgM), at least once during their clinical history. In case of anti-HDV positive is recommended the HDV-RNA quantitative test. Contextually is recommended the virological characterization of HBV (HBsAg quantitative, HBeAg, anti-HBe, HBV quantitative), because in some cases HDV may suppress HBV replication. The characterization of HDV may completed by HDV genotype.
The monitoring of HDV patients is made with HDV-RNA quantitative test, once a year in patients that are not in treatment and every 2-4 months during treatment.

Interpretation of hepatitis serologic test for virological evaluation
Antibody to HDV
Negative results indicate the absence of HDV infection and no past exposure to HDV. A positive anti-HDV associated with a positive HDV-RNA defines a chronic HDV infection.
HDV-RNA quantitative
HDV RNA levels may help to identify the subgroup of patients with less or more progressive liver disease.
Hepatitis B surface antigen (HBsAg) quantitative
Quantification of serum hepatitis B antigen (HBsAg) is an important test that marks active infection with hepatitis B and helps in the prediction of the clinical outcome and management of hepatitis B virus (HBV) infection.
Antibody to HBeAg
An ***anti-HBe*** test that is non-reactive (negative) may mean the infection is very recent and viral replication has not yet peaked.

The aim of HBV and/or HDV disease evaluation is to define the stage of fibrosis, the prognosis, the indication for therapy, the Hepatocellular Carcinoma (HCC) surveillance and the management of portal hypertension. The disease evaluation is made through hematological tests (blood count, AST/ALT, GGT, alkaline phosphatase, direct and indirect bilirubin, prothrombin time or INR, protein electrophoresis, albumin, creatinine); abdominal ultrasonography; and fibrosis assessment (with Fibroscan and APRI or FB4).

APRI score
The APRI score measures the amount of fibrosis in the liver. The formula for the APRI score is [(AST/upper limit of the normal AST range) X 100]/Platelet Count. The score is less than or equal to 0.5, the liver is either completely free of fibrosis or has a tiny bit of scarring. If the APRI score is more of 1.5 or greater the liver has scarring and likely some cirrhosis.

FB4 score
The FB-4 is noninvasive diagnosis of hepatic fibrosis. The formula for FIB-4 is: Age ([yr] x AST [U/L]) / ((PLT [10(9)/L]) x (ALT [U/L])(1/2)). Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

Both virological and disease evaluation are elements able to characterize the HBV infection (Aghemo *et al.,* 2023; Buti *et al.,* 2023).

Natural history of chronic HBV

	Phase 1 Chronic infection HBeAg+	*Phase 2 Chronic hepatitis HBeAg+*	*Phase 3 Chronic infection HbeAg-*	*Phase 4 Chronic epatitis HBeAg-*
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2.000 IU/mL*	>2.000 IU/mL
ALT	Normal	High	Normal	High**
Liver damage	Any/Minimal	Moderate/Severe	Any	Moderate/Severe

* The level of HBV DNA may be between 2.000 and 20.000 UI/ml in some patients with no chronic hepatitis.
** Persistent or intermittent.
EASL, 2017

The diagnosis should be associated in drug users with:
- disease counseling;
- individual and community prevention.

C. Linkage to care and treatment

The HBV and HDV patients should be referred to specialists for treatment (Aghemo *et al.,* 2023; Buti *et al.,* 2023; Degasperi *et al.,* 2022; De Lédinghen *et al.,* 2022; EASL 2017; 2021; Fontaine *et al.,* 2022; Lampertico *et al.,* 2022; Loglio *et al.,* 2022; Wedemeyer *et al.,* 2022).

Treatment options for HBV infections
- PEG-INFa inhibits replication. The efficacy of treatment is limited and, in some cases, there are important side effects. The treatment is usually for 48 weeks.
- Nucleoside analogues act by inhibition of HBV polymerase activity resulting in decrease of viral replication. They are administered orally, and most of them have an excellent tolerance and safety profile. They are for most of patients the first line treatment and they may be administered also for several years.

Treatment options for co-infection HBV/HDV
- Bulevirtide blocks the entry of HBV and HDV into hepatocytes by binding to and inactivating NTCP, a bile salt liver transporter serving as essential HBV/HDV entry receptor. The duration of treatment is yet unknown and it is recommended if a clinical benefit as measured by a decrease viral load (virological response) and/or normalization of ALT values (biochemical response).

The linkage to care should be associated in drug users with:
- therapy monitoring and counseling (focus on adherence and persistence);
- therapy and follow-up diary.

D. Follow up and harm reduction

In drug users the follow up able to reduce relapse in drug use and re-infection include serological tests and harm reduction measures.

Follow up post treatment
- After discontinuation of PEG-INFa and/or nucleoside analogues: HBV DNA, ALT and liver function for several years (risk of infection reactivation);
- After discontinuation of Bulivertide: HBV DNA, HDV RNA, ALT and liver function for several years.

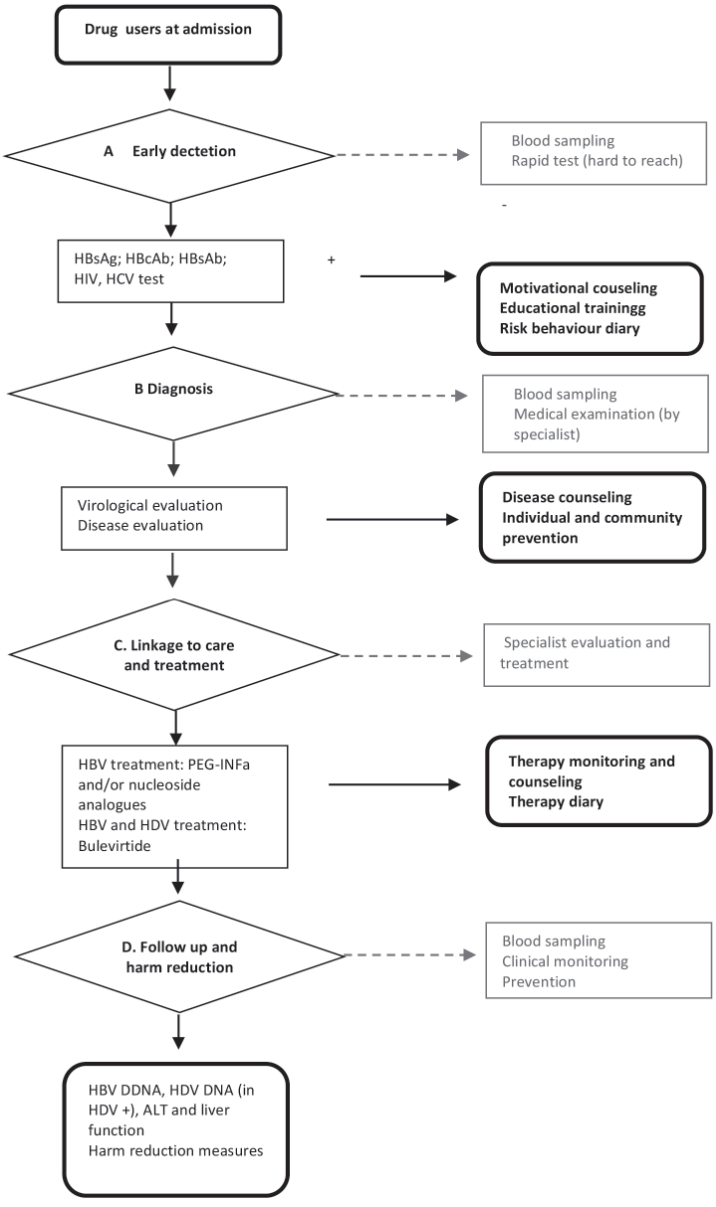
Harm reduction measures
- Needle and syringe programs;
- Agonist therapy and other drug dependence treatment;
- HIV, HAV, HBV, HCV, and HDV (in HBV +) testing and counseling;
- Treatment for infectious diseases for those who are eligible to receive it;
- Package of harm reduction services:
  - Prevention and treatment of sexually transmitted infections (STIs)

- **Condom programs for IDUs and their sexual partners;**
- **Targeted information, education, and communication (IEC) for IDUs and their sexual partners;**
- **Vaccination, diagnosis, and treatment of viral hepatitis;**
- **Prevention, diagnosis, and treatment of tuberculosis (TB).**

During HBV and HDV treatment the focus on harm reduction is on:

- Treatment compliance;
- Prevention of re-infection.

Fig. 1



Conclusion

Today, most of drug users are excluded from HBV and HDV treatment for several reasons that are the lack of patient's support to treatment persistence and adherence. Moreover, a barrier for the HBV/HDV treatment in drug uses is the "believe" that the parenterally therapies for HBV/HDV may induce craving and relapse in drug use.

The present PDTA define the patient's clinical course of drug users with HBV/HDV infections, starting from assessment and staging, up to the aspects of treatment, stabilization, and follow up to facilitate screening and treatment and to promote in the treatment persistence and adherence.

This PDTA represent the first tentative to create a PDTA for drug users for the access to HBV/HDV treatment and to support the clinicians inside SerDs as guide in the steps of the patient's journey of drug users with HBV and HDV infection.

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