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Challenges and opportunities for hepatitis B virus screening in people attending PrEP services: a retrospective prevalence study

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ABSTRACT

Objectives Pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir to prevent HIV in individuals with hepatitis B virus (HBV) raises concerns about HBV reactivation when stopping event-driven PrEP or redundancy in HBV treatment for continuous PrEP (since tenofovir alone would be enough for HBV). Real-world data from PrEP services could provide useful epidemiological information on HBV prevalence in PrEP attendees in low-prevalence countries.

Methods A retrospective analysis on PrEP attendees of three services in northern Italy were conducted to assess HBV prevalence among PrEP attendees and the need for primary cycle/booster dose HBV vaccination despite previous vaccination during childhood (at birth or 12 years). Risk factors possibly associated with HBV exposure were evaluated with a binary logistic regression analysis, controlling for age, gender, place of birth (Italy vs abroad) and chemsex use (as a proxy of high-risk sexual behaviour for contracting sexually transmitted infections).

Results Among 10 hepatitis B surface antigen (HBsAg)-positive out of 2152 PrEP attendees (0.46%), PrEP was started in 7 subjects mainly with a daily schedule, 1 has declined after counselling, 2 were lost to follow-up. Around three-fourth of the 2152 PrEP attendees were born in Italy after 1979, thus were previously vaccinated during childhood. The probability of needing a booster for low-titre HBs antibodies was higher among those vaccinated at birth with respect to those vaccinated at 12 years (OR 2.30, 95% CI 1.80 to 2.96). The risk of previous HBV exposure (resulting in either HBsAg+ or antibodies against HBV core antigen [HBcAb]+) was higher for increasing age (OR 3.07, 95% CI 2.49 to 3.78 per 10 years more) and lower for being born in Italy (OR 0.23, 95% CI 0.14 to 0.36).

Conclusions Our real-world data on a large PrEP cohort suggest that, although uncommon, HBV infection in PrEP users in low-prevalence countries should be considered and managed. In addition, HBV screening offers the opportunity to expand prevention services through vaccination.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pre-exposure prophylaxis (PrEP) for HIV with emtricitabine/tenofovir in people with hepatitis B (HBV) raises concern on HBV reactivation when stopped. Limited data exist on HBV prevalence in PrEP users in low-prevalence settings like Italy.

WHAT THIS STUDY ADDS

⇒ In a large cohort of PrEP users in Italy, HBV was uncommon but affected foreign-born and vaccinated individuals differently, indicating a need for tailored HBV vaccination or booster support.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This study suggests that HBV screening within PrEP services can improve preventive care and vaccine strategy, particularly for diverse or high-risk populations.

Access to PrEP could be limited by cost in countries where PrEP is not publicly funded. Some clinical conditions could influence PrEP uptake: Renal impairment or hepatitis B virus (HBV) infection. The drugs used in oral PrEP, indeed, exert antiviral activity also on HBV: In case of event-driven PrEP or suboptimal adherence in daily PrEP in people with concurrent chronic HBV infection (CHB), a risk exists of HBV viral reactivation, hepatitis flare and liver damage.^{2–4}

Concerns on PrEP use in people with CHB could affect PrEP scale-up in this subpopulation, particularly in untreated 'inactive HBV carriers' (HBV e antigen [HBeAg]-negative, HBV-DNA <2000 UI/mL),⁵ in whom it would be preferable to offer a daily rather than an event-driven PrEP to reduce the risk of viral reactivation for repeated treatment interruptions but this means increased cost and toxicity.

Conversely, there is no clear guidance on how to manage patients with CHB treated with tenofovir or entecavir who start PrEP. The options are keeping TDF, TAF or entecavir on therapy, instructing the patient to switch to FTC/TDF (or FTC/TAF) whenever needs PrEP or directly switching ongoing



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INTRODUCTION

Pre-exposure prophylaxis (PrEP) with oral emtricitabine (FTC) and tenofovir (disoproxil fumarate, TDF or alafenamide, TAF) is contributing to decreasing HIV incidence in Western countries.¹

treatment to FTC/TDF (or FTC/TAF), forcing a continuous PrEP schedule, with additional costs.

Given the increasing number of PrEP users and the lack of data on the burden of HBV infection in people on PrEP in Italy, we conducted a retrospective analysis on a large cohort of people attending PrEP services to assess the magnitude of this issue and the real-world clinical management in a low HBV prevalence country.

METHODS

A retrospective analysis included all the subjects attending three different PrEP services in the Lombardy region, Northern Italy, from January 2018 to April 2024: One community-based, peer-ran service for sexual health (Milano Checkpoint ETS), two public tertiary hospitals (Niguarda Hospital, Milan and San Gerardo Hospital, Monza). Milano Checkpoint ETS is a non-governmental organisation launched in July 2018 from the collaboration of several associations working in the field of HIV prevention in Milan (ANLAIDS sezione Lombarda ETS, ASA Milano ODV, CIG-Arcigay Milano ODV, Fondazione LILA Milano Onlus, NPS Italia APS). Milano Checkpoint provides free medical assistance to one of the largest cohorts of PrEP users in Italy.

Volunteer physicians of Milano Checkpoint work in the Infectious Diseases (ID) Unit of Niguarda and San Gerardo hospitals and are in a network with other ID doctors in other hospitals, thus allowing information retrieval of patients with HBV who entered a PrEP service.

Italy is considered a low-prevalence HBV country due to Law 165, issued in 1991, which mandated HBV vaccination for those born from 1979 onwards. Those born from 1979 to 1991 were vaccinated at age 12 while those born from 1992 onwards were vaccinated in their first year. This law applies only to individuals who fall into these two categories meaning that a foreign-born person who did not comply with these conditions did not undergo compulsory vaccination. Nevertheless, they may receive HBV immunisation at any age if required even though the vaccination is free of charge only for some groups (including men who have sex with men). According to the Ministry of Health official data, the rate of HBV vaccine completion for the groups identified by the 165/1991 Law is high (above 97%). Thus, we assumed with a satisfactory margin of approximation that a person born in Italy from 1979 onwards received a full immunisation course. On the contrary, most foreign-born individuals included in the analysis come from low-income countries where HBV vaccination is not mandatory and is not widely available so we assumed that a positive serology could be the result of a previous voluntary vaccination that they decided to complete either in their own country or on their arrival in Italy. Information about vaccination course for Italians born before 1979 and for foreign-born persons were retrieved from medical charts. Data about the time of vaccine injections were largely unavailable and then were not collected.

Data were recorded in pseudo-anonymised forms using unique alphanumeric codes to identify participants. Demographic, clinical and baseline laboratory characteristics including HBV serostatus, HBV vaccination history and prescriptions were retrieved from medical charts by electronic data extraction (in case of electronic medical record) or by manual data entry. The type of data collected was homogeneous in the three services; in case of missing information, a dropping data (listwise deletion) approach was applied.

Descriptive statistics (median and interquartile range [IQR] for continuous variables, absolute [n] and relative [%] values for categorical variables) were used. A binary logistic regression analysis was conducted to assess the probability of needing a booster HBV vaccination (defined as anti-HBs antibodies [HBsAb] <10 mIU/mL) among those who have been vaccinated according to the 165/1991 Law directives calculating odds ratio (OR) and their 95% Confidence Intervals (CIs). A second binary logistic regression evaluated the risk of previous exposure to HBV (defined as HBsAg-positive, HBsAb-positive/anti-HBc-positive and HBsAb-negative/anti-HBc-positive) at baseline clinical evaluation for PrEP. Multivariable binary logistic regression for each outcome was fitted on variables selecting relevant risk factors based on both clinical knowledge and unadjusted analyses. Thus, final models were adjusted for age, gender, country of birth (Italy vs abroad) and chemsex use (as a proxy of higher risk behaviour for contracting sexually transmitted infections).

Analyses were performed using Stata V.16.1 (College Station, TX, StataCorp 2019).

RESULTS

The study included 2152 subjects attending one of three different PrEP services. Table 1 shows their main characteristics. The majority (1734, 80.58%) were already vaccinated, 143 subjects (6.64%) had been previously exposed to HBV (133 anti-HBc-positive with or without HBsAb and 10 HBsAg-positive) and 284 persons (13.20%) have never been exposed to the virus or to the vaccine. Of note, nine individuals (0.42%) acquired the infection despite the vaccination.

10 subjects (0.46%) were HBsAg-positive: 9 men, 1 transgender woman, 6 born in Italy (age range 43–57 years), 4 born abroad (age range 25–37 years). Six started daily PrEP with FTC/TDF (one switching from entecavir), one who was already on treatment with entecavir for CHB switched from entecavir to FTC/TDF only during event-driven PrEP (meaning that he alternates entecavir with on-demand FTC/TDF according to his sexual activity). None of them experienced treatment failure, viral blip or liver enzymes elevation during PrEP. One chose not to start PrEP after counselling about potential management issues while two were lost to follow-up (table 2).

The other individuals exposed to HBV were 50/2152 (2.32%) with protective immunity after infection (HBsAb-positive/anti-HBc-positive serology) and 83/2152 (3.86%) with potential occult infection (HBsAb-negative/anti-HBc-positive serology).

Considering these three groups together, in the multivariable logistic regression analysis to estimate the risk of previous HBV exposure in PrEP attendees, after adjustment, age was associated with a higher risk (OR 3.07 per 10 years more, 95% CI 2.49 to 3.78, $p < 0.001$) while being born in Italy was protective (OR 0.23 95% CI 0.14 to 0.36, $p < 0.001$).

Among HBV-vaccinated individuals, 1281 had been vaccinated according to the 165/1991 Law (888 in the 1979–1991 cohort and 393 in the 1992 onwards cohort), 453 had been vaccinated on their request because born before 1979 or were foreign-born. They were mainly Italian (1503/1734, 84.82%). Among the 379 individuals born abroad, 231 (60.95%) were vaccinated. Almost one-third of those vaccinated according to the 165/1991 Law (396/1281, 30.91%) required a booster dose because of insufficient serological response. They belonged more commonly to the younger cohort (172/393 (43.8%) vs 224/888 (25.2%), $p < 0.001$). Indeed, the only factor significantly associated with the need for a booster dose was being vaccinated at birth (cohort 1992 onwards) as compared with having been

Table 1 Characteristics of subjects taking PrEP in three different PrEP services in Lombardy, Northern Italy

		N=2152
Age, years, median (IQR)		35 (30–42)
Age classes, n (%)	Young adulthood (below 39 years)	1432 (66.54)
	Middle adulthood (40–59 years)	683 (31.74)
	Old age (above 60 years)	37 (1.72)
Born from 1979 onwards, n (%)		1612 (74.91)
Gender, n (%)		
	Men	2108 (97.96)
	Women	25 (1.16)
	Transgender women	19 (0.88)
Foreign born, n (%)		379 (17.61)
Chemsex user, n (%)	Yes	105/1749 (6.00)
	Missing	403
HBsAg positive, n (%)		10 (0.46)
Previous HBV infection (with or without anti-HBs>10 mUI/mL), n (%)		133 (6.18)
Already vaccinated for HBV, n (%)		1734 (80.58)
Vaccinated after mandatory immunisation law in 1991*, n (%)		1281 (59.53)
	1979–1991 cohort	888 (69.32)
	1992 onwards cohort	393 (30.68)
Vaccinated individuals who needed a booster injection, n (%)		488/1734 (28.14)
Eligible† for HBV vaccination, n (%)		284 (13.20)
Individuals who started HBV vaccination after PrEP consultation, n (%)		104/284 (36.62)
Non-responder to primary and secondary immunisation courses, n (%)		14/1794 (0.78)

Exceptions: One subject with positive HBsAg was vaccinated within the 1979–1991 cohort and acquired the infection through sexual contact; eight individuals with anti-HBs/anti-HBc positive titres were vaccinated after mandatory immunisation law in 1991.

*Mandatory immunisation law of 1991 established that HBV vaccination should have been done at birth for those born from 1992 onwards and at 12 years for those born from 1979 to 1991. This approach extended the HBV vaccination coverage on all the young people of less than 25 years in a 12-year period.

†People born in Italy before 1 January 1979 or abroad with no evidence of previous vaccination or HBsAg+ or HBcAb+.

HBcAb, antibodies against hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PrEP, pre-exposure prophylaxis.

vaccinated at 12 years of age (1979–1991 cohort): OR 2.30, 95% CI 1.80 to 2.96, $p < 0.001$.

DISCUSSION

In our large real-life cohort of PrEP attendees, we showed that CHB was very uncommon. The low prevalence may be due to our population being mainly young Italian-born subjects with a low risk of being HBsAg-positive because of previous vaccination. In Italy, vaccination against HBV was made mandatory by law from 1991: Thus, most PrEP users in Italy are supposed to be vaccinated for HBV. Nevertheless, we still observed nine cases of Italian vaccinated men who were subsequently infected by HBV, one developing chronic infection. This suggests a possible advantage in the screening for HBV serology because it gives the opportunity to reinforce HBV prevention through vaccination in those who missed it during childhood and could be the chance to offer a booster to those who received prior vaccination and have negative HBsAb. Notably, we observed a double risk of needing a booster in people vaccinated at birth with respect to those vaccinated at 12 years consistently with published literature.^{6,7} Moreover, among people attending a PrEP service, there is a growing number of foreign-born individuals who missed HBV vaccination during childhood and may come from endemic HBV countries.

Literature on HBV reactivation risk in patients with CHB on PrEP is limited. There is no data on using FTC/TDF PrEP in those already treated with entecavir. Recent findings suggest PrEP can be safely started in patients with HBV despite adherence or discontinuation risks as advanced liver disease is rare but protocol eligibility criteria of clinical trials could have excluded individuals with more active forms of CHB.^{8,9} However, patients with CHB starting PrEP should be counselled on the risks of stopping FTC/TDF and the need for close monitoring for HBV reactivation.

For people without HBV infection, PrEP could unintentionally reduce the risk of contracting HBV.¹⁰ However, vaccination remains the main preventive strategy for HBV infection. Screening for HBV is essential before starting PrEP and represents an excellent opportunity to offer vaccination to individuals who are HBsAb-negative.

Our study has limitations. It is a retrospective study: It does not provide HBV incidence in PrEP attendees but it only gives a snapshot of HBV prevalence in a large cohort of people who asked for PrEP (ie, individuals who are supposed to be at risk of

Table 2 Demographic and clinical features of the 10 PrEP attendees with baseline HBsAg-positive serology

	Age (years)	Gender	Place of birth	Vaccine status	PrEP started	PrEP schedule
ID#1	29	Man	Southeastern Europe	Not vaccinated	Yes	Daily
ID#2	43	Man	Italy	Vaccinated*	Yes	Event driven
ID#3	48	Man	Italy	Not vaccinated	Lost to follow-up	--
ID#4	46	Man	Italy	Not vaccinated	Lost to follow-up	--
ID#5	43	Man	Italy	Not vaccinated	No	--
ID#6	25	Man	Africa	Not vaccinated	Yes	Daily
ID#7	46	Man	Italy	Not vaccinated	Yes	Daily
ID#8	37	Transgender woman	South America	Not vaccinated	Yes	Daily
ID#9	34	Man	Southeastern Europe	Not vaccinated	Yes	Daily
ID#10	57	Man	Italy	Not Vaccinated	Yes	Daily

*Individual ID#2 belongs to the 1979–1991 cohort; thus, he was vaccinated at the age of 12. According to the Italian law, serology testing was not required before compulsory vaccination so it is not possible to ascertain whether he acquired the infection during childhood (horizontal intrafamilial transmission) or after vaccination through sexual contact.

HBsAg, hepatitis B surface antigen; PrEP, pre-exposure prophylaxis.

sexually transmitted infections). Additionally, the limited number of HBsAg-positive subjects does not allow to draw conclusions on the risk of HBV reactivation in case of PrEP withdrawal: However, our effort was essentially focused on describing real-world numbers, notably the prevalence of HBsAg-positive serology in a group of PrEP attendees. Lastly, until June 2023, Italy's public health system did not cover PrEP, limiting access for economically constrained individuals like those born abroad. This may have caused selection bias in enrolled foreign subjects.

Our experience, while giving a real-life proportion of the magnitude of HBV infection among PrEP attendees in a low-prevalence country, highlights the prevention opportunity of HBV vaccination for those who are still at risk.

In conclusion, in the current limited epidemiological data on HBV prevalence in people who attend a PrEP service, our real-world data offer a size of this medical issue and point out the positive effects of a prevention service for HIV as an opportunity to expand prevention also on other sexually transmitted infections such as HBV.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants. As anonymised data generated from routine clinical practice were retrospectively managed in aggregated form, formal approval by the ethics committee (EC) was not mandatory due to the epidemiological non-pharmacological nature of the study as by Italian law. The study was notified to the local EC. Patients gave written informed consent for data management according to European General Data Protection Regulation. As there was no specific submission to EC (only a notification) for the retrospective nature of the study, there was no specific consent.

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Abstract

Obiettivi

La profilassi pre-esposizione (PrEP) con emtricitabina/tenofovir per prevenire l'HIV in persone con epatite B (HBV) pone il problema della riattivazione di HBV in caso di interruzione della PrEP “*on demand*”, mentre può essere ridondante in caso di PrEP continuativa poiché il tenofovir da solo sarebbe sufficiente per trattare l'epatite B. Dati *real-world* sulla prevalenza di HBV tra gli utenti della PrEP possono fornire informazioni epidemiologiche utili nei paesi a bassa prevalenza come l'Italia.

Metodi

È stata condotta un'analisi retrospettiva tra gli utenti PrEP di tre servizi nel nord Italia per valutare la prevalenza di HBV e la necessità della vaccinazione HBV o di una dose *booster* nonostante la pregressa vaccinazione in età pediatrica (alla nascita o a 12 anni). I fattori di rischio potenzialmente associati all'esposizione a HBV sono stati valutati tramite un'analisi di regressione logistica binaria, controllando per età, sesso, luogo di nascita (Italia o estero) e uso di chemsex (come indicatore di comportamenti sessuali ad alto rischio per infezioni sessualmente trasmesse).

Risultati

Tra 10 soggetti HBsAg-positivi su 2152 utenti PrEP (0,46%), 7 hanno iniziato la PrEP, principalmente con schema giornaliero; uno ha rifiutato dopo il *counselling* e due sono stati persi al follow-up. Circa 3/4 dei 2152 utenti PrEP erano nati in Italia dopo il 1979 e quindi vaccinati in età pediatrica. La probabilità di dover fare un *booster* vaccinale HBV per basso titolo di HBsAb era più alta tra i vaccinati alla nascita rispetto a quelli vaccinati a 12 anni (odds ratio [OR] 2,30, intervalli di confidenza al 95% [CI] 1,80-2,96). Il rischio di esposizione pregressa a HBV (espresso come HBsAg+ o HBcAb+) aumentava con l'età (OR 3,07, 95% CI 2,49-3,78 per ogni 10 anni in più) e diminuiva per i nati in Italia (OR 0,23, 95% CI 0,14-0,36).

Conclusioni

I nostri dati *real-world* su un'ampia coorte di utenti PrEP suggeriscono che, sebbene rara, l'infezione da HBV negli utenti PrEP in paesi a bassa prevalenza debba essere considerata e gestita appropriatamente. Lo screening HBV inoltre offre l'opportunità di ampliare l'offerta di prevenzione delle infezioni sessualmente trasmesse tramite la vaccinazione.