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Hepatitis A Screening and Vaccination Among People Living with HIV: When is the Ideal Time?

HIV ile Yaşayan Bireylerde Hepatit A Taraması ve Aşılama: İdeal Zaman Ne Zaman?

Ceylan et al. Hepatitis A and HIV: Timing for Vaccination

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Abstract
Introduction: This study aimed to determine the hepatitis A seroprevalence and vaccination status among [people living with Human Immunodeficiency Virus (HIV) (PLWH)], assess serologic responses to vaccination, and identify age groups for which hepatitis A vaccination is recommended.
Materials and Methods: This research was conducted between January 2019 and 2024, comparing groups with positive and negative anti-hepatitis A virus (HAV) immünoglobulin G (IgG) antibodies based on age and sex. A receiver operating characteristic (ROC) analysis was performed to identify the optimal age cutoff for predicting anti-HAV IgG positivity. Anti-HAV IgG serology was screened at least 1 month after the second vaccine dose to evaluate antibody formation.
Results: Of the 1,140 participants, 61.5% tested positive for anti-HAV IgG at baseline. Those with positive results exhibited significantly higher mean age (44.6±11.6 years) than those with negative results (33.7±8.6 years; p<0.001). Seropositivity was significantly higher among women (75.0%, n=87/702; p=0.002) and individuals >40 years of age (83.3%, p<0.001). The ROC analysis identified 40 years as the optimal age cutoff, with an area under the curve of 0.78 (95% confidence interval, 0.75-0.81), a sensitivity of 61.6%, and a specificity of 80.1%. Of the seronegative individuals, 86.1% received two vaccine doses; of the 268 with follow-up anti-HAV IgG serology, 86.1% had seroconverted and the results of 109 patients are still awaited.
Conclusion: Examining individuals living with HIV for hepatitis A antibodies at their initial hospital admission is critical so that those with seronegativity can be vaccinated with two doses of hepatitis A. Vaccination can be administered to those <40 years of age without prior serological testing. These findings provide valuable insights for developing hepatitis A vaccination policies and monitoring strategies for PLWH.
Keywords: HIV, HAV, vaccination, prophylaxis

Öz
Giriş: Bu çalışmanın amacı, İnsan Bağışıklık Yetmezliği Virüsü (HIV) ile yaşayan bireylerde (PLWH) hepatit A seroprevalansını ve aşılanma durumunu belirlemek, aşılara karşı serolojik yanıtı değerlendirmek ve hepatit A aşısının önerileceği yaş gruplarını saptamaktır.
Gereç ve Yöntem: Çalışma, Ocak 2019-2024 yılları arasında yürütülmüş ve anti-hepatit A virüsü (HAV) immünoglobulin G (IgG) antikoru pozitif olan bireyler ile negatif olan bireyler, yaş ve cinsiyet açısından karşılaştırılmıştır. Anti-HAV IgG pozitifliğini öngörmede en uygun yaş sınırını belirlemek amacıyla alıcı işletim özelliği (ROC) analizi uygulanmıştır. Antikor yanıtını değerlendirmek için ikinci aşı dozundan en az bir ay sonra anti-HAV IgG serolojisi taranmıştır.
Bulgular: Toplam 1.140 katılımcının %61,5'inde başlangıçta anti-HAV IgG pozitifti. Anti-HAV IgG pozitif saptanan bireylerin yaş ortalaması (44,6±11,6 yıl), negatif saptanan bireylerin yaş ortalamasına (33,7±8,6 yıl) kıyasla anlamlı derecede daha yüksekti (p<0,001). Seropozitivite oranı kadınlarda (%75,0; n=87/702; p=0,002) ve 40 yaş üzerindeki bireylerde (%83,3; p<0,001) belirgin olarak daha fazlaydı. ROC analizine göre anti-HAV IgG pozitifliğini öngörmek için en uygun yaş sınırı 40 olarak belirlendi (eğri altı alan: 0,78; %95 güven aralığı: 0,75-0,81; duyarlılık: %61,6; özgüllük: %80,1). Seronegatif bireylerin %86,1'ine iki doz aşı yapıldı ve aşılama sonrası 268 kişinin %86,1'inde serokonversiyon saptandı. Ancak 109 olgunun seroloji sonuçları henüz beklenmektedir.

Sonuç: HIV ile yaşayan bireylerin ilk sağlık kuruluşu başvurusunda hepatit A antikorları yönünden taranması ve seronegatif olanlara iki doz hepatit A aşısı uygulanması önem arz etmektedir. Serolojik test yapılmaksızın doğrudan aşılama, 40 yaş altı bireyler için uygun bir strateji olabilir. Bu çalışma, HIV ile yaşayan bireylere yönelik hepatit A aşı politikalarının geliştirilmesine ve izlem stratejilerinin oluşturulmasına katkı sağlamaktadır.
Anahtar Kelimeler: HIV, HAV, aşı, profilaksi

Introduction

Hepatitis A infection is a global public health threat and is common in underdeveloped and developing countries because of poor hygiene conditions. The virus mainly spreads through the fecal-oral route via contaminated food, water, or close physical contact such as oral-anal sex. In regions with high endemicity, most hepatitis A infections occur in early childhood[1]. In contrast, in developed and resource-rich regions, hepatitis A outbreaks are generally restricted to vulnerable populations, such as homeless people, drug users, and men who have sex with men (MSM), transmitted via direct person-to-person contact[2]. The seroprevalence of hepatitis A infection in [people living with human immunodeficiency virus (HIV) (PLWH)] is higher than that in HIV-negative individuals[1], which could be attributed to the higher prevalence of oral-anal sex, the higher number of sexual partners, and on rare occasions, intravenous drug use, a common risk factor for both conditions[1,3]. Screening for hepatitis A and vaccinating seronegative individuals is crucial for PLWH. Although the guidelines for hepatitis A screening and vaccination are clear, several factors, including test kit and vaccine shortages, antivaccine attitudes, and non-compliance with follow-up visits, may hinder effective screening and vaccination practices[4].

Hepatitis A remains endemic in our country, and the age of exposure to the virus has shifted toward adolescence and young adulthood. The introduction of the hepatitis A vaccine in our country in 2012, along with improved hygiene, increased socioeconomic status, and enhanced vaccination coverage, has led to a decrease in the incidence of hepatitis A virus (HAV). However, this scenario has escalated the population susceptible to the virus among unvaccinated groups[5]. This study aimed to assess the seroprevalence of hepatitis A, the vaccination status of individuals susceptible to it, and the serologic response to vaccination among PLWH in our cohort. The secondary aim was to determine the specific age groups for which the hepatitis A vaccine could be recommended without serology screening owing to recent changes in hepatitis A epidemiology in our country.

Materials and Methods

This study included PLWH registered in our cohort who attended follow-up visits between January 2019 and January 2024. Screening for anti-HAV immünoglobulin G (IgG) antibodies at baseline is routinely performed for PLWH presenting to our clinic using the Alinity i anti-HAV IgG (Abbott, USA) antibody kit. Those who test negative are scheduled to receive two subcutaneous shots of hepatitis A vaccination, administered 6 months apart. Anti-HAV IgG antibodies are rescreened at least 1 month after completing the vaccination schedule.

The baseline screening results were retrospectively derived from the medical records and outpatient clinic notes. Groups with positive and negative anti-HAV IgG antibody results were compared in terms of sex and age. Data regarding hepatitis A vaccination of individuals susceptible to hepatitis A were derived from the National Vaccine Tracking System and hospital records. In contrast, postvaccination rescreening data were obtained from medical records.

Statistical Analyses

Statistical analyses and visualizations were performed using R version 4.3.1, a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). Categorical variables were compared using the Pearson chi-square test, and continuous variables were compared using Student's t-test. A p-value of <0.005 was considered statistically significant. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff point for age in predicting anti-HAV IgG positivity.

Ethical Approval

This study was approved by the Ege University Medical Research Ethics Committee (approval number: 2023-1702, dated: 31.10.2023).

Results

This study included 1,140 PLWH [average age 40.4±11.8 years; 1,024 (89.8%) men]. Anti-HAV IgG antibodies were positive at baseline in 61.5% (n=702/1140). None of the patients presented with acute hepatitis A. Patients with anti-HAV IgG positivity at baseline exhibited a higher mean age than those who were negative (44.6±11.6 and 33.7±8.6, respectively; p<0.001). Anti-HAV IgG positivity was significantly higher among women (n=87/702; 75.0%) than men (n=615/702; 59.6%) (p=0.002). The seropositivity rate was 83.3% in individuals >40 years of age and 42.9% in the ≤40 age group (p<0.001). According to the ROC analysis, the optimal cutoff point was 40 years (area under the curve, 0.78; 95% confidence interval, 0.75-0.81; sensitivity, 61.6%; specificity, 80.1%) (Figure 1). Of the 438 seronegative individuals, 377 (86.1%) received two doses of the hepatitis A vaccine. Analysis of 61 individuals who did not receive the vaccine revealed that 21 were lost to follow-up, 2 had died, and 38 were referred to their family doctor owing to a temporary stockout of the hepatitis A vaccine in our hospital; however, they did not receive the vaccination (Figure 2). Of the 377 individuals who received two doses of hepatitis A vaccine, follow-up anti-HAV IgG serology was available for 268 (71.1%) and 86.1% had seroconverted; the results are still awaited for 109 patients.

Discussion

The World Health Organization has provided guidelines for achieving the goal of eradicating viral hepatitis infections by 2030 via improved sanitation, food safety, and vaccination practices[6]. The introduction of the hepatitis A vaccine in our country in 2012, along with improvements in living conditions, socioeconomic status, and vaccination coverage, has led to a decrease in HAV incidence[5,7]. In middle-to-high-income societies, the lack of exposure to HAV during childhood may result in a young adult population susceptible to hepatitis A outbreaks. A study involving 22 European countries reported that most hepatitis A patients were MSM, including those coinfected with HIV[8]. HAV and HIV coinfection may lead to a higher hepatitis A viral load and a longer duration of viremia than monoinfection, extending the transmission period and resulting in more severe liver damage[9]. In addition, the presence of HAV infection can increase the HIV viral load and the probability of HIV transmission[9]. Thus, screening for hepatitis A antibodies in PLWH at presentation and vaccinating those who test negative is critical from both individual and public health perspectives. The prevalence of hepatitis A exposure in Europe has been reported to vary between 0.00055‰ and 0.0001%[10]. However, screening rates show significant variations throughout the continent, with very low rates in Central and Eastern European countries (54.5% in 2019 and 47.4% in 2022)[11].

Our study revealed that most PLWH were already seropositive for hepatitis A at baseline. Other studies from Türkiye have obtained similar results[12-14]. The introduction of the hepatitis A vaccine into the national vaccination program in Türkiye was delayed until 2011. Therefore, the high positivity rate in our study was due to past infection rather than childhood vaccination. However, because of the retrospective design of the research, distinguishing between the two is challenging.

Recent reports have highlighted the changing epidemiological profile of hepatitis A, with outbreaks appearing more among homeless individuals, drug users, and MSM than other segments of the society, resulting in severe adverse outcomes[2,15]. During 2017, 1,521 outbreak-associated HAV cases were reported from California, Kentucky, Michigan, and Utah, with 1,073 (71%) hospitalizations and 41 (3%) deaths. Overall, 866 (57%) patients stated drug use, homelessness, or both. Of all cases, 818 (54%) had an indication for hepatitis A vaccination before becoming infected (i.e., using drugs or being MSM), as recommended by the Advisory Committee on Immunization Practices (ACIP)[16]. Similarly, between 2016 and 2017, a large outbreak of >4000 acute hepatitis A cases were reported from the European Union and European Economic Area countries, of which 84% were MSM[17]. In an outbreak in Canada between 2017 and 2018, 52 acute hepatitis A

cases were reported; 64% were MSM, and 36% of the possible or confirmed cases were coinfected with HIV[18]. These reports suggest that even in developed countries, vaccination rates among vulnerable populations remain low and the disease is overlooked.

Vaccines coupled with safe sexual behaviors are known to be highly effective in preventing acute hepatitis A infection. The Centers for Disease Control and Prevention (CDC) and the ACIP recommend vaccinating individuals at risk of HAV infection, such as those aged ≥1 year, homeless individuals, and MSM, or those at high risk of severe HAV infection (e.g., individuals with chronic liver disease or those living with HIV) with the hepatitis A vaccine[19]. Furthermore, their prioritization for vaccination during outbreaks is recommended[19]. The vaccination acceptance rate was exceptionally high in our study, with 86% of the nonimmune individuals receiving the full dose hepatitis A vaccine. Referrals to other healthcare facilities owing to vaccine stockouts in the clinic appeared to be a major obstacle to vaccination, highlighting the importance of integrating healthcare services in a single setting. Questioning the reason for not being vaccinated was not possible because of the retrospective design of the study.

The antibody response to vaccination may be lower in PLWH than in HIV-negative individuals. Vaccine response rates may be low after the first dose but usually increase significantly after the second dose[1,3,19]. The response rates to the two doses of hepatitis A vaccine were considerably high in our cohort. Reports suggest that 85% of PLWH remain seropositive 6-10 years after the two-dose vaccine series[20]. A higher CD4 T cell count at the time of vaccination has been shown to enhance the vaccine response[21]. Our local guidelines recommend testing for anti-HAV IgG in PLWH at baseline and vaccinating seronegative individuals with two doses if the CD4 T lymphocyte count is >350 cells/mm^3 and with three doses if it is <350 cells/mm^3[22]. A third dose of the vaccine is planned for our patients who did not develop an antibody response after receiving a full dose of vaccination. According to CDC recommendations, immunoglobulin (IG) administration may be necessary for PLWH who do not seroconvert after two doses of vaccine in high risk contact situations (e.g., sexual or household contact); however, this issue is controversial[23]. Indications for IG use are based on ACIP recommendations published in 2007 for the prevention of hepatitis A infection after exposure to HAV and in international travelers. Information about the relative efficacy of the vaccine compared with IG postexposure is limited, and no data are available for individuals aged >40 years and those with underlying medical conditions[24].

Interruptions in the availability of antibody screening tests for hepatitis A may hamper vaccination practices. Screening rates are considerably low in several countries in our region[11]. The findings of our study suggest that individuals <40 years of age and who do not have a history of receiving the hepatitis A vaccine can be vaccinated even if antibody testing is not available. The hepatitis A vaccine does not increase the HIV viral load, influence the CD4 T lymphocyte count, or accelerate the progression to acquired immunodeficiency syndrome (AIDS); thus, vaccination is a safe practice for PLWH[19].

Although there seems to be a consensus on vaccinating individuals with negative hepatitis A serology, guidelines on serological follow-up and booster vaccination differ[1,2]. The British HIV Association recommends HAV vaccination every 10 years for PLWH with an ongoing exposure risk, whereas the European AIDS Clinical Society advises periodic monitoring of hepatitis A serologies[2].

Study Limitations

The primary limitation of our study is the inability to reach all patients, preventing the evaluation of postvaccination control serologies. Moreover, the retrospective, single-center design may limit the generalizability of the findings. Further multicenter, prospective studies are needed to validate our results.

Conclusion

Although most of our cohort seems to have been exposed to hepatitis A, either via vaccination or via infection, there remains a susceptible group who would benefit from late vaccination. As recommended by international and national guidelines, screening PLWH for hepatitis A antibodies at baseline and administering two doses of hepatitis A vaccine to those who are seronegative is critical for preventing adverse outcomes due to acute hepatitis A infection. The inability to perform hepatitis A serology is not a barrier to vaccination. Our study suggests that individuals <40 years of age can be vaccinated without serological testing as the seropositivity rates are extremely low in this group. We believe that the findings from this research will inform the development of policies on hepatitis A vaccination and the monitoring of serologic responses in PLWH.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (approval number: 2023-1702, dated 31.10.2023).

Informed Consent:

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.P., M.T., D.G., Concept: A.N.E., H.P., M.T., D.G., Design: .N.E., H.P., M.T., Data Collection or Processing: C.T., D.G., Analysis or Interpretation: M.C., A.K., Literature Search: M.C., C.T., Writing: M.C., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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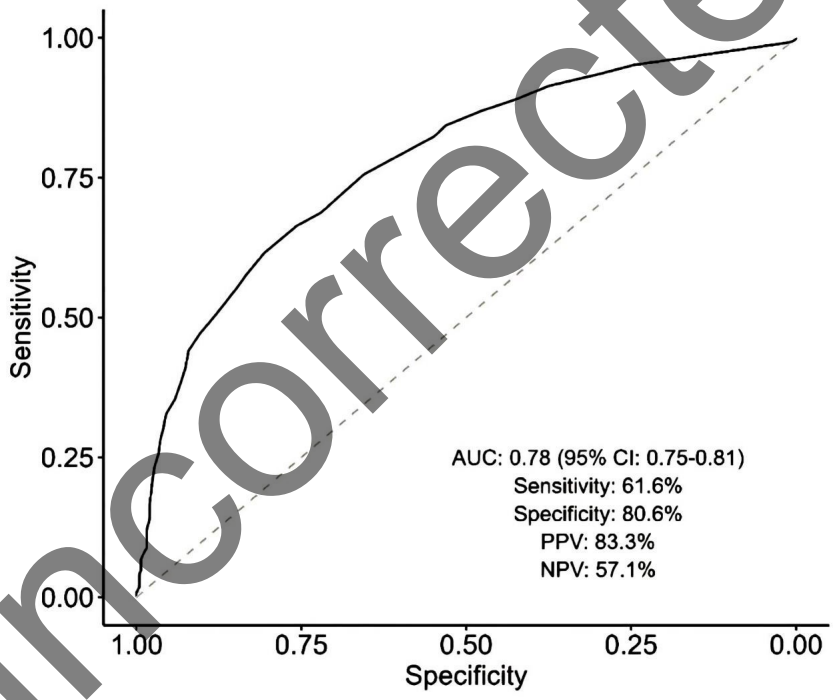

Figure 1. Receiver operating characteristic curve to find best cutoff of age for anti-hepatitis A virus IgG positivity

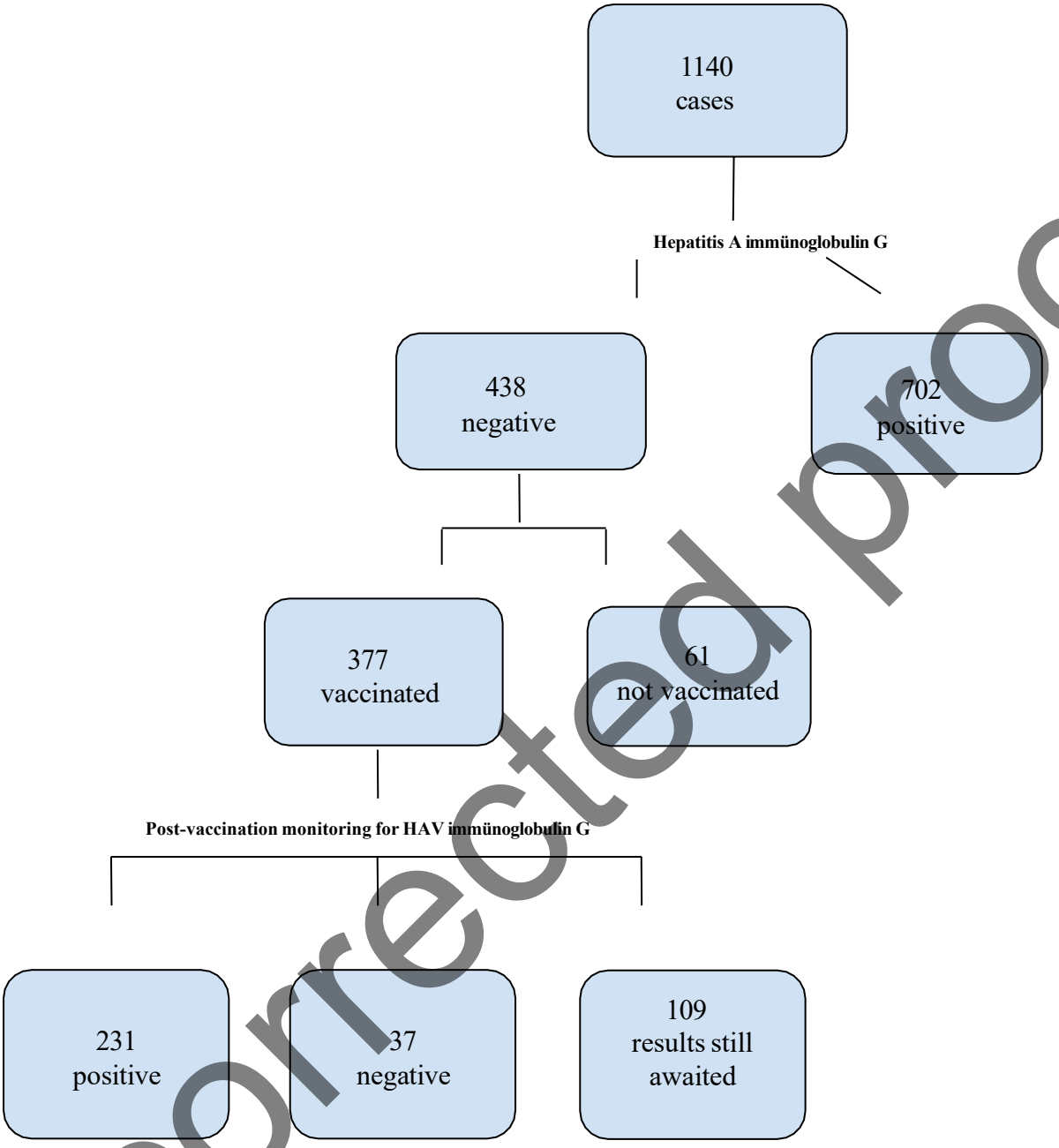

Figure 2. Schematic summary of the cases included in the study