RESEARCH ARTICLE

Cross-sectional Assessment of HIV and Hepatitis A, B, C, D, and E among Individuals Surveyed in National Health and Nutrition Evaluation Survey, 1999–2018

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Abbreviations: National Health and Nutrition Examination Survey (NHANES); Human Immunodeficiency Virus (HIV)

Abstract

Objective: To assess the association with HIV with five strains of viral hepatitis, in adults 18-59 years, who have taken the NHANES survey for HIV, and to determine if there is a positive association with HIV in each of the five viral hepatitis strains adjusted by age, gender, and race.

Methods: Cross-sectional analysis of HIV Screening Test by Laboratory test results for Hepatitis A, B, C, D, and E screenings, using 10 pooled datasets from the 1999-2018 biennial National Health and Nutritional Examination Surveys. Statistical analyses performed included Spearman's Correlations, weighted Rao-Scott Chi-Square tests, and weighted binary logistic regression modeling.

Results: In the subset of 33,214 adult participants surveyed in the 1999-2018 NHANES the percentage of HIV positivity was 0.44% (standard error=0.05), with 56% occurring in 2009-2018. Weighted Rao-Scott Chi-Square Tests had a statistically significant association between HIV and the five hepatitis strains, with four having a p-value <=0.0001, except for Hepatitis D. After adjustment by age, race, and gender HIV was positively associated odds ratios. Hepatitis A had a statistically significant odds ratio for 1999-2018 but was not significant for 1999-2006 and 2007-2018. Hepatitis B and Hepatitis C had a statistically significant association in all three subsets. Hepatitis D had no HIV coinfection in 1999-2006, so it was not reported, and a nonsignificant association in 2009-2018. Hepatitis E, which started collection in 2009, had a nonsignificant association with HIV in 2009-2018.

Conclusion: Based on this analysis and the review of HIV and viral hepatitis guidelines it is suggested that immunocompromised individuals, including HIV positives, should be screened for all five strains of viral Hepatitis. Further research is needed in order to better understand the connection between HIV and viral hepatitis strains, especially Hepatitis A, Hepatitis D, or Hepatitis E.

Keywords: NHANES; HIV; Viral Hepatitis A-E

1. Introduction

In the United States there has been a chronic epidemic of people who are infected with HIV, which has a link between viral liver infection also known as hepatitis. Currently there are five strains of the Hepatitis Virus that were reported in NHANES 1999-2018. However most studies have only focused on Hepatitis B and Hepatitis C. This is one of the first studies to look at all 5 strains of Hepatitis Viruses and its connection to HIV using ten cycles of NHANES, collecting in a 10-20-year time frame.

1.1.Viral Hepatitis

Hepatitis A is a short-term infection with no complications which typically lasts a few weeks, which is typically spread by contaminated food or water. Hepatitis B is a virus that lasts 2 months and may be co-infected with Hepatitis D Virus by contaminated blood products and unprotected sex. Hepatitis C is a long-term infection that can lead to cirrhosis of the liver, cause by contaminate blood or needles. Finally, Hepatitis E Virus is found in underdeveloped areas and can be spread by fecal-oral route and causes acute symptoms.

1.2.HIV and Viral Hepatitis

Previous studies have supported a link between HIV and all five hepatitis strains. In two case studies there was a prolonged hepatitis A infection in a HIV-1 seropositive patient,[1] which can lead to fulminant hepatitis if coinfected with HIV.[2] There also was an increase in Hepatitis D mortality in HIV/Hepatitis B-coinfected patients.[3] In addition Hepatitis E infection in immunosuppressed HIV patients could rapidly progress to cirrhosis, but it can be effectively treated using interferon and ribavirin therapy with a longer period of treatment,[4] including a high prevalence for IgG anti-Hepatitis E antibodies in Spain.[5] There also over 10,000 articles that focused on HIV and Hepatitis B and C.

1.3.*Objectives*

The first aim of this analysis is to assess the association with HIV with five strains of viral hepatitis, in adults 18-59 years, who have taken the NHANES survey for HIV. The second aim is to determine if there is a positive association with HIV in each of the five viral hepatitis strains adjusted by age, gender, and race.

2. Material and Methods

I used pooled data from the 10 biennial NHANES surveys from 1999-2018 to investigate the connection between Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, and Hepatitis E to HIV. NHANES is a cross-sectional study that accesses diet and health of the non-institutional United States population using a multistage clustered design, as established by the Centers for Disease Control and Prevention.

2.1.Study Population

Laboratory results were restricted our analysis to individuals 18-59 years old, who completed the HIV laboratory questionnaire in 1999-2018 (N=33,214). The data was then split between 1999-2006 and 2007-2019. The rational was that HIV-1 and HIV-2 testing was started in 2007. Also the Hepatitis E screening did not start until 2007 and very limited number of Hepatitis D testing occurred before 2006. Prior to 2006 there was indeterminate cases for HIV which where redefined as negative cases in later years.

2.2.Statistical analysis

The sampling design of NHANES requires sample weights in order to improve external validity to the general adult population. I conducted a weighted analysis using one combined population weight variable for the ten cycle subsamples in which HIV and the

five viral hepatitis strains were measured. For Hepatitis A-D, I used the 10-cycle weighed variable, whereas for Hepatitis E, I used a five cycle weighted variable. The survey design variables were incorporated using the NHANES guidelines. Some confounder variables included: sex, age, and race/ethnicity.

Some statistical analysis performed were Spearman's Correlations, weighted Rao-Scott Chi-Square tests and weighted binary logistic regression, I modeled HIV screening separately in the weighted binary logistic regression models to allow for nonlinear connections. I used five separate logistic regression models using Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, and Hepatitis E to assess the association between HIV adjusted by gender, race, and age. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Results were considered statistically significant at <0.05 levels using a two-sided statistical test.

3. Results

In the subset of 33,214 adult participants surveyed in the 1999-2018 NHANES the percentage of HIV positivity was 0.44% (standard error=0.05), with 56% occurring in 2009-2018. Spearman's Correlations indicated a positive association between HIV and Hepatitis A-E, except for HIV and Hepatitis E, which had a small nonsignificant relationship (Table 1). It was also observed that there was a weak positive monotonic relationship between the five hepatitis strains. The sample size was lowest for the Hepatitis E, because it did not exist until 2007, and the lowest between Hepatitis C and Hepatitis E.

Table 1: Spearman Correlation Coefficient Matrix to measure monotonic association between HIV and Hepatitis A-E, among pooled 1999-2018 NHANES Sample

	HIV	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
HIV	1.0000	0.0174	0.1197	0.0477	0.0123	-0.0005
		0.0018	<0.0001	<0.0001	0.0469	0.9452
	33,214	32,349	32,607	32,510	26,205	18,379
Hepatitis A	0.0174	1.0000	0.1124	0.0081	0.0258	0.0781
	0.0018		<0.0001	0.1418	<0.0001	<0.0001
	32,349	32,730	32,727	32,628	26,326	18,369
Hepatitis B	0.1197	0.1124	1.0000	0.1585	0.1291	0.0721
	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001
	32,607	32,727	32,991	32,887	26,512	18,626
Hepatitis C	0.0477	0.0081	0.1585	1.0000	0.0040	0.0151
	<0.0001	0.1418	<0.0001		0.5183	0.0397
	32,510	32,628	32,887	32,889	26,474	18,537
Hepatitis D	0.0123	0.0258	0.1291	0.0040	1.0000	0.0336
	0.0469	<0.0001	<0.0001	0.5183		0.0002
	26,205	26,326	26,512	26,474	26,512	12,148
Hepatitis E	-0.0005	0.0781	0.0721	0.0151	0.0336	1.0000
	0.9452	<0.0001	<0.0001	0.0397	0.0002	
	18,379	18,369	18,626	18,537	12,148	18,627

Weighted Rao-Scott Chi-Square Tests had a statistically significant association between HIV and the five hepatitis strains, with four having a p-value <=0.0001, except for Hepatitis D (Table 2). Also in Table 2 are the results of the weighted logistic regression analysis for all sample (1999-2018), 1999-2007, and 2009-2018, with adjustment by gender, age, and race/ethnicity. Hepatitis A had a statistically significant odds ratio for 1999-2018 but was not significant for 1999-2006 and 2007-2018. Hepatitis B and Hepatitis C had a statistically significant association in all three groups. Hepatitis D had no HIV coinfection in 1999-2006, so it was not reported, and a nonsignificant association in 2009-2018. Hepatitis E, which started collection in 2009, had a nonsignificant association with HIV in 2009-2018.

Table 2: Frequency analysis of odds ratios and 95% confidence intervals of prevalent HIV and Hepatitis A-E in pooled 1999-2018 NHANES Sample

	HIV % (SE)	General Population % (SE)	1999-2018 OR (95% CI)*	1999-2008 OR (95% CI)*	2009-2018 OR (95% CI)*
Hepatitis A 1999-2018	0.25 (0.04) p<0.0001	0.19 (0.03)	2.02 (1.13, 3.63)	1.78 (0.87, 3.62)	2.23 (0.95, 5.21)
Hepatitis B 1999-2018	0.17 (0.03) p<0.0001	0.25 (0.57)	11.54 (6.76, 19.72)	15.74 (7.64, 32.48)	8.70 (4.25, 17.78)
Hepatitis C 1999-2018	0.03 (0.01) p<0.0001	0.40 (0.05)	3.58 (1.77, 7.21)	3.10 (1.29, 7.40)	3.57 (1.23, 10.40)
Hepatitis D 1999-2018	0.002 (0.002) p=0.0251	0.46 (0.05)	3.14 (0.46, 21.38)	--	4.38 (0.67, 28.84)
Hepatitis E 2007-2018	0.35 (0.05) p<0.0001	0.09 (0.01)	--	--	1.18 (0.43, 3.27)

*Logistic regression models were adjusted by gender, age (continuous years), and race (non-Hispanic white vs. all others). OR=Odds Ratio; SE=Standard Error; 95%CI=95% Confidence Interval.

4. Discussion

In this cross-sectional analysis of pooled 1999-2018 NHANES data HIV were associated with the five strains of viral hepatitis. This analysis takes into consideration a large biennial dataset with consistent measures of laboratory results such as HIV or five strains of Hepatitis. Out of all the five strains investigated there may be a positive association between HIV and the five viral hepatitis strains. The analysis also supports the need for testing HIV infected people with all five strains of hepatitis. The nonsignificant odds ratios for Hepatitis D and E might be caused by the lack of screening for these conditions among HIV infected individuals. For Hepatitis A the overall significant association warrants further investigation and stresses the importance of promotion of vaccination. Not surprisingly Hepatitis B and C were the most significant and supports the larger literature of coinfection with HIV. This analysis also suggests that HIV may mediate Hepatitis, but mediation analysis should be performed in other datasets.

In previous United States and Canadian studies, the association between HIV and viral hepatitis strains were constant with this analysis. Hepatitis E was reported to be 6% seropositivity in the 2009-2010 NHANES sampling,[6] which is close to the general

population (9%), but lower than the HIV infected subpopulation (35%). In 2011-2016, the estimated prevalence of Hepatitis B was 0.46% with 42% having antibodies for Hepatitis D,[7] which is comparable to the 0.44% Hepatitis B and 43% having antibodies for Hepatitis D, observed in our sample. There also is a problem with decreasing immunity to Hepatitis A that was observed in NHANES 1999-2012 by age that increases the severity of catching this virus.[8] Another study in Asian Americans in United States and Canada with Hepatitis B, found a high seroprevalence of anti-HEV IgG among the chronic HBV patients.[9] Although none of these studies adjusted for HIV status, there needs to be an urgent need for revaccination, for Hepatitis A and B, and enhanced hepatitis screening, for Hepatitis A-E, among HIV infected individuals.

In third world counties, viral hepatitis can progress to chronic hepatitis and cirrhosis. Globally the mortality rate from viral hepatitis increased from 980,9 thousand in 1990 to 1,412.3 thousand in 2017, with Hepatitis B and C account for 97.6% of viral hepatitis-related deaths.[10] Currently the trends of hepatitis A incidence rates are decreasing non-uniformly, with the lowest-risk counties have high incidence but low disease burden; higher-income have low incidence rate but higher likelihood of requiring hospitalization.[11] Though Hepatitis D is rarer than other strains at a prevalence of 0.80% and 13.02% among Hepatitis B carriers, there is estimated to be 48-60 million infections globally, with a progression to cirrhosis within 5 year and hepatocellular carcinoma within 10 years.[12]

Out of all the strains Hepatitis E remains the least understood especially in third world counties, such as Brazil[13], Central African Republic[14], Nigeria[15], Nepal[16], and India.[17] There is limited treatment for acute hepatitis E, but chronic in the immunosuppressed can be treated with ribavirin, and people living in China can be vaccinated against hepatitis E, but the vaccine is not widespread.[18] In South America alone Hepatitis E is widely distributed in humans, animals, environmental samples and food, suggesting the need for public health officials to improve testing.[19] The challenge is the there is wide spread discordance between screening assays for hepatitis E, from those used in China, Italy, NIH, and standard western blots.[20] There is a need for better understanding the impact of hepatitis E and the connection to HIV.

The cross-sectional nature of NHANES prevents me from making any causal inferences that HIV led to Hepatitis A-E or vice versa. The data is not identified so it is not possible to determine the geographic location or determine date of infection or death longitudinally. The laboratory results only confirm the present or absence of antibodies for Hepatitis not the viral strain. Despite these issues this study does support the need for further investigation of the association between Hepatitis A, D, and E with HIV.

Currently, the Centers for Disease Control and Prevention recommended that all people with HIV who are greater than 1 year be vaccinated against Hepatitis A and receive post-vaccination testing one month after completing Hepatitis A vaccination.[21] Also unvaccinated people with HIV receive Hepatitis B vaccination.[22] Also all adults 18 age years and older should be screened for hepatitis C.[23] Moreover, the American Association for the Study of Liver Disease recommends Hepatitis D testing for Hepatitis B carriers who are at high risk of Hepatitis D infection. [7] For Hepatitis E, the European Association for the Study of the Liver recommends Hepatitis E testing in all immunosuppressed patients with unexplained abnormal liver functioning

tests.[24] Based on these guidelines it is suggested that immunocompromised individuals, including HIV positives, should be screened for all five strains of viral Hepatitis. Further research is needed in order to better understand the connection between HIV and Hepatitis A, Hepatitis D, or Hepatitis E.

Acknowledgements: None

Conflicts of Interest: None declared

Financial Disclosure: None

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