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Investigations of the Effect of HIV Status on Lead in the Body

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Bachelor of Science
Sewanee: The University of the South
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An abstract of
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Abstract

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By Catherine G Evans

Blood lead levels in the United States are declining with time mostly due to the removal of lead from paint and gasoline. However, with no safe level of blood lead their resultant health effects still merit study, especially in vulnerable populations. HIV infection can alter many functions of the human body including how lead is processed in the body. New research shows that ART therapy can increase the rate at which bone (the primary lead storage place) is digested. This study parses out the benefits and complications of evaluating this potential interaction in NHANES data collected from 1999 to 2014. Weight adjusted t tests show that HIV positive participants have a higher blood lead level than HIV negative participants (1.5461, [95%CI 1.4455, 1.6540] and 1.2055 [95% CI 1.1996, 1.2114] respectively. A linear regression model with blood pressure (an associated health outcome for elevated blood lead levels) however shows no statistical significance and does not fit the data well in basic format or when controlling for age, race, age, ratio of family income to poverty, sex, CD4 count, and education level. Further research that accounts for duration of lead levels and time since HIV infection is needed to investigate if HIV is an effect modifier of the impact of lead on the body. This research is vital to adequately protecting vulnerable populations with chronic diseases that may need different response aid during a toxic release disaster such as the one in Flint, Michigan.

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Introduction and Background Information

Lead has well documented effects on the human body from impaired cognition development in children to cardiovascular changes in adults (Juberg, Kleiman, & Simona, 1997). Impaired cognition happens as a result of alterations in synapse formation (Gassowska et al., 2016) and literature suggests the decline centers around executive functions, short time memory and psycho-emotional variables (Fenga, Gangemi, Alibrandi, Costa, & Micali, 2016).

Blood lead levels have continued to decrease in the United States population (Tsoi, Cheung, Cheung, & Cheung, 2016) but impaired health outcomes documented at any measured blood lead level (Rogan & Ware, 2003) and continual technological disasters such as the emergency situation in Flint, Michigan demand continued research towards a greater understanding of how lead affects the body in complex circumstances, especially pertaining to comorbidities.

Lead is not needed for any known process in the human body but is prevalent in the environment. The National Health and Nutrition Examination Survey provides a valuable resource for exploring blood lead levels and their affects across different sub populations in the United States of America. Previous research has highlighted lead levels in children (Benson et al., 2016) (Jain, 2016b), adults, and the elderly (Jain, 2016a).

Research has shown an association between blood lead levels and elevated blood pressure in animals (Nowack, Wiecek, Exner, Gretz, & Ritz, 1993) and in humans; this relationship is notably confounded by medications, cardiovascular birth defects, age, race, and socioeconomic status (Alghasham, Meki, & Ismail, 2011; Hu et al., 1996; Kopp, Barron, & Tow, 1988). Lead, once in the body, is stored in the bone and is reintroduced to the blood stream as bone is digested by the body in normal aging (Hu et al., 1996). Blood lead levels can indicate how much lead is in

the bone based on the rate at which bone is digested if bone turnover rate releases more lead than the new amount from external exposure (Sakai, 2000).

The common risk factors for high blood pressure center around high levels of chronic stress and unhealthy diet and exercise routines. These behaviors are also associated with low socioeconomic status. The same group of people that are at risk for elevated blood pressure are likely at risk for many other things such as elevated blood lead and HIV.

Human Immunodeficiency Virus (HIV) has varied effects on human health and those effects are further complicated by medications taken to control the disease. Additionally, HIV positive persons on combined therapies are now living longer, but having worse outcomes from diseases due to aging (Lacson, Barnes, & Bahrami, 2017). Blood pressure, cognition, and bone density can be used as markers of HIV symptom severity (Ofotokun et al., 2016; Weitzmann, Ofotokun, Titanji, Sharma, & Yin, 2016). Research suggests that as HIV positive adults age their cognitive complaints are worse than those of HIV negative adults but they are not being screened properly for this mental decline (Kamkwalala, Hulgan, & Newhouse, 2017). Arterial degeneration is a side effect of many HIV medications and is a symptom of aging that is exacerbated by HIV by an unknown mechanism or mechanisms (Paisible et al., 2015).

The Womens' Interagency HIV Study (WIHS) recently published findings indicating that ART therapy increases the speed at which bone is digested by the body (Ofotokun et al., 2016). This acts as either part of the causal chain or as a side effect of immune reconstitution (Ofotokun et al., 2016).

Side effects in general are influencers of HIV ART medication prescription and use and maintaining quality of life related to medications is a topic of research (Maiese, Johnson, Bancroft, Goolsby Hunter, & Wu, 2016). Historically, complicated medication routines were

difficult to maintain especially for patients with low health literacy. This has been eased by simpler medication routines but the side effects of the medications and symptoms of HIV continue to burden patients. Blood pressure is a biometric of concern when evaluating usefulness of a drug to a patient and is a commonly assessed as both a comorbidity and as a side effect of HIV and HIV related therapies (Hogg et al., 2017). This blurring of lines between risk factor, comorbidity, side effect, and symptom makes detangling the effect of one change difficult to define in the context of a dynamic human population.

Disasters are events where the needs of a population exceed the resources of that community and a hazard has impacted a vulnerable population. Technological disasters are disasters that occur as a result of human actions or technological failures (Keim, 2011). According to the United Nations Office for Disaster Risk Reduction the incidence of technological disasters is increasing at an alarming rate as the world moves into more industrialized practices (UNODRR, 2016). Lead exposure can be an issue in both developed and developing nations. It can contaminate agriculture settings especially those in low resource or developing nations where restrictions are less intense (Keim, 2011) and often, HIV prevalence is also elevated (WHO, 2007). Most technological disasters happen in developing countries because of fewer controls on industry, fewer worker safety measures, and a lower capacity for emergency response (Codreanu, Ngo, Robertson, & Celenza, 2017). These same regulation holes have led to an exportation of risk from high resource countries to low resource countries (Codreanu et al., 2017). Lead disaster like the structural failure in Flint, Michigan highlight how poverty increases vulnerability to these disasters. The town was exposed to critically high levels of lead in their drinking water but did not have the financial or political power to change their situation until national outcry motivated action (CDC, 2016).

Using data from the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control (CDC) this project investigates the potential impact of HIV status on lead exposure health outcomes while taking into account common confounders that are also key vulnerabilities in disaster situations. The cross sectional nature of the investigation limits conclusions but will direct further research.

Methods

NHANES data collected between 1999-2014 with established protocols and data packages were used to answer two main research questions: do HIV positive persons have different blood lead levels than HIV negative persons; do HIV positive persons have different blood pressure than HIV negative persons. Additionally, a linear model was created to assess the relationship between lead level and blood pressure while controlling for significant confounders and assessing HIV status for effect modification. SAS version 9.4 with SAS-callable-SUDAAN was used to analyze differences in HIV positive and HIV negative groups. Out of 248,403 respondents 85141(0.343%) had a laboratory examination. Of those tested 589 (0.69%) tested positive for HIV antibody, 84,507 (99.26%) tested negative for HIV antibody, and 45 (0.05%) had inconclusive tests and were therefore excluded from analysis. Individuals were further excluded if they did not have blood pressure or blood lead level data. NHANES protocol dictates four systolic blood pressure readings. All available readings for each participant were averaged together to get one average systolic blood pressure value. Appropriate sample weights were constructed to account for 16 years of NHANES data spanning three weighting schemes (4 year MEC weights for 1999-2002, 2 year MEC weights for 2003-2012, and 2 year blood metal

weights for 2013-2014). This leaves a sample of 473 HIV positive and 75511 HIV negative individuals. Sample means were compared with a pearson t test and linear models were built using backwards elimination with standard effect modification and confounding assessment.

Results

Figure 1 shows demographic characteristics of the sample used for this project. HIV positive persons have a higher average blood lead level than HIV negative persons (1.5461, [95%CI 1.4455, 1.6540] and 1.2055 [95% CI 1.1996, 1.2114] respectively (figure 2). HIV positive persons have slightly elevated systolic blood pressure as compared to HIV negative persons (119.4 [95% CI 118.2, 120.5] and 117.0 [95% CI 116.9, 117.1] respectively (figure 3). Blood lead level and blood pressure is weakly positively correlated (0.14637 $p<0.0001$). When a model is constructed and race, age, ratio of family income to poverty, sex, CD4 count, and education level, neither HIV status nor blood lead levels are significant predictors of systolic blood pressure. A backwards elimination procedure leaves a model with blood lead level (3.52 $p=0.0167$) sex(female 10.13$p=0.0019$) , race (only non-Hispanic black was significant 9.36$p=0.0112$), cd4 count (0.01 $p=0.0006$), education (only some college 10.56 $p=0.0362$ and not remembering education level 25.15 $p<0.0001$ were significant), with a significant sex and blood lead interaction term (3.57 $p=0.0212$). This model has an R^2 of 0.218. Controlling for sex, race, age, cd4 count, education blood lead levels have minimal impact on systolic blood pressure and that impact is not affected by hiv status but is affected by the interaction of sex and blood lead.

Discussion and Conclusions

The original question of this project directed inquiry to the effect of HIV on the relationship between blood lead levels and systolic blood pressure in US adults. One major barrier is that the risk factors for each of these three points of interest (HIV status, elevated blood lead level, and elevated blood pressure) have intertwining risk factors that can be difficult to parse out in a model.

As blood lead levels decline the investigation into the relationship between blood lead levels and blood pressure has evolved. New analyses show that as blood lead levels decline the impact on blood pressure has weakened except in African Americans where it can still be detected (Vupputuri et al., 2003). Other research has shown an association between blood lead levels and blood pressure in hypertensive patients and linked them via oxidative stress ((Alghasham et al., 2011). While NHANES data is easily available and provides a view of the US population overtime its limitations for this inquiry were many. There were an adequate number of HIV positive individuals for statistical significance but the lack of time series data prevented deeper investigation. By looking at cumulative lead exposure over time with temporal changes in blood pressure more conclusive results and confounding assessment could be possible. Research where blood lead levels are collected overtime in an HIV prospective cohort would be ideal. Access to more detailed data such as length of time on ART therapy, length of time since HIV diagnosis would also improve this analysis.

Of the covariates assessed for effect modification and confounding the poverty income ratio had the most interesting effect on the relationship between blood lead level and blood pressure. When household income was used in the model there was worse fit to the data but the exposure was closer to being significant. When poverty index ratio was used instead the model

fit the data better but lead was even less significant as a predictor of average systolic blood pressure. This is an important indicator that the poverty income ratio (which is a ratio of the household income to the regional poverty level) is a better indicator of economic status that just income.

Understanding how chronic diseases such as HIV can change a population's health outcomes from a toxic exposure are vital to inform treatment options and to inform policy that has potential to protect these vulnerable populations. Clearly HIV positive individuals have a higher blood lead level which is concerning and further investigation is needed to determine if these levels are the result of a biological characteristic of infection or treatment or if the levels are elevated due to time based confounding characteristics.

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Figures

	HIV + (n=420)		HIV - (n=69621)		Total (n=70041)	
	N	%	N	%	N	%
Annal Household Income						
$ 0 to $ 4,999	56	0.05%	3270	3.86%	3326	3.91%
$ 5,000 to $ 9,999	45	0.07%	3505	5.01%	3550	5.08%
$10,000 to $14,999	33	0.05%	4691	6.38%	4724	6.43%
$15,000 to $19,999	39	5.89%	4189	5.83%	4228	5.89%
$20,000 to $24,999	25	0.04%	4684	7.33%	4709	7.37%
$25,000 to $34,999	35	0.04%	6344	10.90%	6379	10.94%
$35,000 to $44,999	10	0.02%	4956	9.06%	4966	9.09%
$45,000 to $54,999	10	0.02%	4485	9.38%	4495	9.40%
$55,000 to $64,999	0	0.00%	3097	6.63%	3097	6.63%
$65,000 to $74,999	0	0.00%	2670	7.15%	2670	7.15%
$75,000 to $99,999	16	0.05%	9714	24.65%	9730	24.70%
Refused	5	0.01%	490	0.68%	495	0.69%
Don't know	10	0.02%	685	0.74%	695	0.76%
Total	299		54613		54912	
Missing	121		15008		15129	
Age						
18-29	100	0.16%	32189	39.03%	32289	39.19%
30-39	98	0.12%	16940	26.65%	17038	26.78%
40-49	196	0.21%	18218	30.71%	18414	30.92%
50-59	26	0.03%	2258	3.06%	2284	3.09%
59+	0	0.00%	16	0.04%	16	0.04%
Education						
Less than 9th grade	18	0.02%	5093	4.24%	5111	4.26%
9-11th grade (Includes 12th grade with no diploma)	119	0.12%	9886	12.14%	10005	12.26%
High school graduate/GED or equivalent	72	0.08%	14055	24.69%	14127	24.76%
Some college or AA degree	150	0.24%	17937	32.55%	18087	32.79%
College graduate or above	41	0.08%	11877	25.77%	11918	25.85%
Refused	0	0.00%	11	0.01%	11	0.01%
Don't Know	5	0.01%	27	0.06%	32	0.07%
Total	405	0.54%	58886	99.46%	59291	100.00%
Missing	15		10735		10750	
Sex						
Male	286	0.38%	31985	48.23%	32271	48.61%
Female	134	0.14%	37636	51.25%	37770	51.39%
Race						
Mexican American	41	0.03%	17245	9.39%	17286	0.67%
Other Hispanic	33	0.04%	4019	5.65%	4052	5.69%
Non-Hispanic White	62	0.19%	30007	67.47%	30069	67.66%
Non-Hispanic Black	283	0.25%	15075	11.44%	15358	11.70%
Other Race - Including Multi-Racial	1	0.00%	3275	5.53%	3276	5.53%

Figure 1: Demographic characteristics of the sample indicating unweighted counts and weighted percentages. If no total is indicated then there were no missing data points.

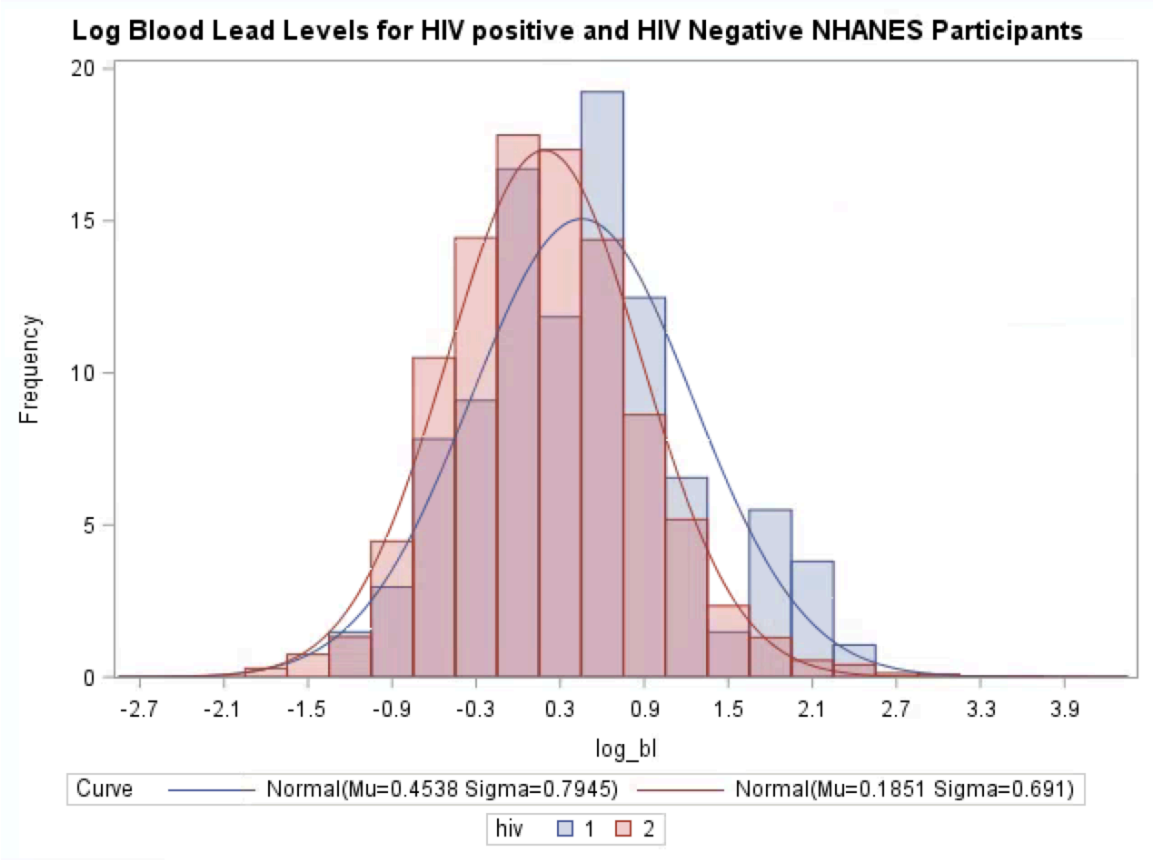

Figure 2: Weighted distribution of log transformed blood lead levels for HIV positive (hiv=1) and HIV negative (hiv=2) participants. HIV positive participants have a higher average blood lead level when compared to HIV negative participants.

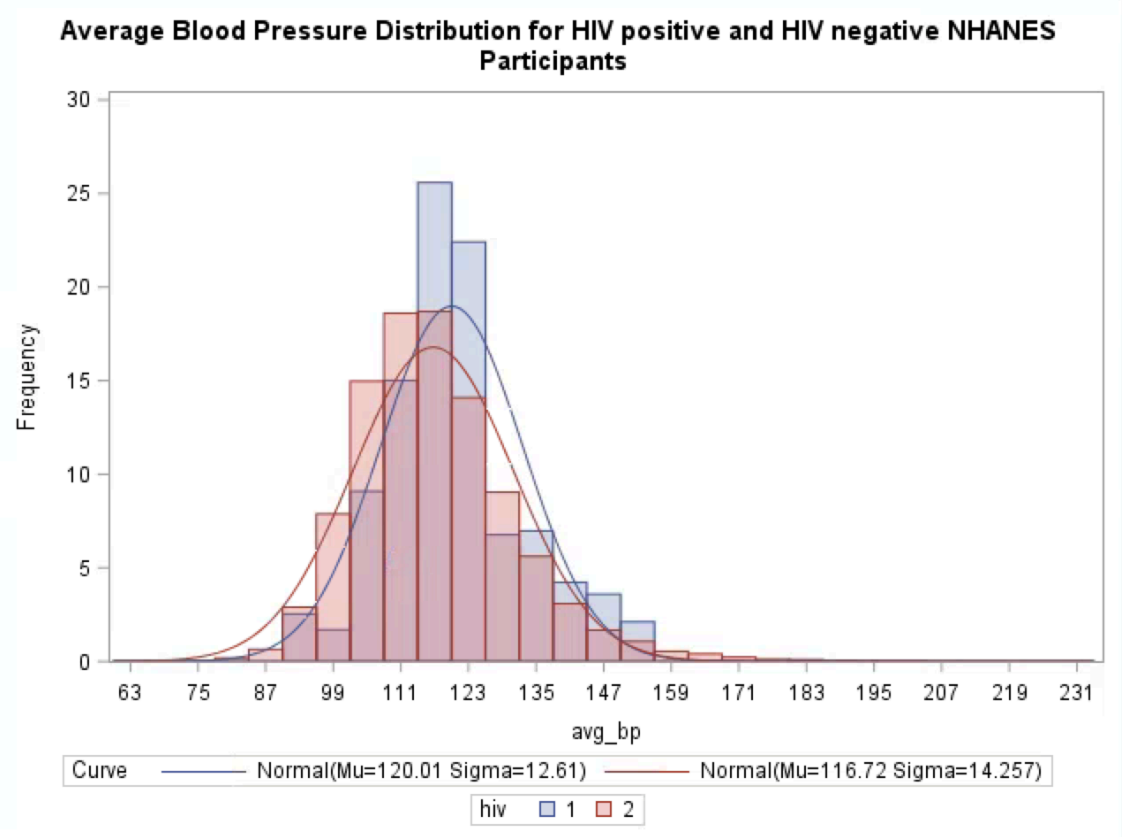

Figure 3: Weighted distribution of Average Systolic Blood Pressure for HIV positive (hiv=1) and HIV negative (hiv=2) participants. HIV positive participants have a higher average blood pressure when compared to HIV negative participants.