The Impact of Stress on AIDS Progression among Chicago Residents Living with HIV: A Prospective Cohort Study

Alexandra Chang[1]

1. Epidemiologic Methods (PBHS 31001, Winter 2024)
2. The Department of Public Health Sciences, The University of Chicago (al8xi8@uchicago.edu)

This prospective cohort study outlines a research design aimed at exploring the association between chronic stress exposure and an increased risk of AIDS development. This study plans to monitor stress levels and AIDS status among a population of Chicago-based adults aged 18 to 50 with positive HIV diagnosis at baseline. Over five years, this research will utilize the Perceived Stress Scale (PSS) for evaluating stress and employ standard serological tests for AIDS detection, both being detected every six months. The objective is to determine whether changes in immune function induced by stress lead to greater susceptibility to AIDS, the importance of understanding local factors influencing disease progression, and, more specifically, the potential role of urban stressors unique to Chicago residents. This study design details the aspects of a prospective cohort study, assessing its ability to investigate the time-based relationship between stress exposure and the risk of AIDS. The ultimate goal is to contribute to effective HIV/AIDS prevention strategies by underscoring the significance of stress management in reducing the likelihood of infection.

Keywords: Stress, HIV, Immune funtion, Observational cohort study, Perceived Stress Scale, AIDS.

Edited by:
Alexandra Chang

Reviewed by:
Brian Chiu, Bei Wang

Copy-edited by:
–

Received: Feburary 27th, 2024
Published: –

1 Objectives

1.1 Research Question

This study design aims to address the research question: "In Chicago residents aged 18 to 50 living with HIV, how does stress influence immune function and the progression to AIDS?"

1.2 Study Design

The research conducts a prospective cohort study to investigate this question by enrolling HIV-positive individuals to examine the impact of long-term stress exposure on the progression of Acquired Immune Deficiency Syndrome (AIDS).

2 Methods

2.1 Overview

Prospective cohort study design utilizes the ability to measure the incidence of HIV infection over time concerning stress exposure; this study design is not only scientifically valid for establishing temporal relationships but is also practical, given the widespread availability of stress measurement tools and HIV/AIDS diagnostic tests. An adequately designed cohort study enables direct observation of the progression from stress exposure to potential AIDS infection to facilitate a logical understanding of the causal relationship between stress and AIDS and the possible local stressors unique to Chicago residents. Hence, participants are followed longitudinally for five years to assess stress levels regularly alongside other clinical markers for diagnosis. By tracking stress levels and the disease progression over time, the study aims to analyze the relationship between chronic stress and accelerated AIDS development among individuals living with HIV.

2.2 Study Subjects

The sampling participants for this study will comprise adults aged 18 to 50 years residing in Chicago with HIV at baseline but not yet diagnosed with AIDS. The study employs a specific strategy to accompany these inclusion criteria by collaborating with hospital and healthcare providers in the Chicago area to recruit potential participants diagnosed within the last three months who have not yet initiated treatment for personal/hospital-related reasons at baseline. Individuals afflicted with a previous diagnosis of HIV/AIDS of more than three months or other pre-existing immunodeficiency disorders, as well as participants currently receiving antiretroviral therapy (ART) or any form of treatment for HIV, will be excluded from this cohort study. The sampling unit will be represented by a randomly selected Chicago adult resident meeting the inclusion and exclusion criteria for this study design.

Ethical Approval and Informed Consent. Participation eligibility is firmly based on individuals' consent and availability for follow-up assessments, and they have the unrestricted right to withdraw from the study at any time. Hence, this recruitment process will underscore the importance of voluntary participation and the strict confidentiality of all collected data, ensuring an ethical approach to gathering sensitive health information.

2.3 Measures and Data Collection

Before approving the eligibility of the participants to begin this research study, comprehensive baseline assessments upon enrollment are conducted to establish participants' health status (HIV-positive) and initial stress levels. For this specific prospective cohort study, the methodology for data collection encompasses surveys and medical testing conducted every six months. Regular intervals of follow-up evaluations are scheduled every six months over five years to track changes in HIV progression and stress levels/factors. The survey captures detailed scoring on participants' perceived stress levels through scenarios that could influence stress and potential AIDS susceptibility. Concurrently, medical tests are rigorously carried out to monitor AIDS status, providing a comprehensive dataset that links stress measurement with possible changes in infection status over the study period. This dual approach of psychological and physiological data collection is pivotal for elucidating the relationship between stress and AIDS infection risk:

Perceived Stress Scale (PSS) as an independent variable for stress. The PSS has demonstrated validity and reliability in numerous research studies, indicating its effectiveness in accurately capturing perceived stress

levels. [1] Incorporating PSS as a stress measurement enhances the credibility of the study findings and increases confidence in the measured outcomes from a quantitative perspective. Depending on participants' access and preferences, the PSS self-reported questionnaires can be administered electronically, by paper mail, or in person.

Laboratory measurement of CD4+ T-cell counts as an outcome variable for AIDS. Evaluation for AIDS status is based upon CD4+ T lymphocyte count as an essential indicator of disease progression, clinical use of medications, efficacy, and prognosis. [2] Cut-off for AIDS is that the CD4+T lymphocyte count falls below 200/mL. [2] Depending on participants' access and preferences, data can be collected through participants' medical records from healthcare professionals or rely on patient disclosure of their diagnosis.

The Relative Risk (RR). RR is used in prospective cohort studies where the outcome of interest is binary (progression to AIDS yes/no), and all participants are followed for the same fixed period (5 years). RR interprets how much more (or less) likely the event of interest is to occur in the exposed group (stressed) compared to the unexposed group.

2.4 Independent Variables

The design study will utilize the Perceived Stress Scale (PSS) to assess individual stress levels within the cohort. This tool has gained widespread validation for its consistency and reliability among various demographic groups and applications. Since its development in 1983, the PSS has been a preferred instrument for gauging how individuals perceive stress in response to different circumstances. [1] The PSS prompts the participants to reflect on their feelings and thoughts in response to 10 scenarios. [1] Participants will be encouraged to respond swiftly, basing their answers on a general estimation of their experiences rather than attempting to tally specific occurrences; this method aims to gather an authentic snapshot of perceived stress levels by emphasizing intuitive responses over precise recollection. [1] Scores will be tallied after the adjustment from its specially designed criteria to determine the final score ranging from 0 to 40, with higher scores indicating increased levels of perceived stress:

- Scores ranging from 0-13 would be considered low stress.
- Scores ranging from 14-26 would be considered moderate stress.
- Scores ranging from 27-40 would be considered high perceived stress.

For this study, the PSS score for each observation count is re-categorized into two groups, with low stress as "unexposed" and moderate and high counting as "exposed" for stress. Optional interviews can be conducted to uncover particular stressors and life scenarios relevant to HIV patients in Chicago to enhance the understanding of perceived stress levels and participants' corresponding scores on the PSS to offer a more affluent, qualitative insight into their experiences.

Life Change Index (LCI) as a potential independent variable? Similar to PSS, this stress assessment also quantifies the level of change a person has undergone by three categories and adapted to over the past year by assigning Life Change Units to 31 events, aiming to gauge the risk of illness following stressful life occurrences. [3] Each event is assigned a score reflecting the degree of adjustment required by an individual due to that event, acknowledging that not every event measured may be harmful. [3] Regardless of the identification of stress through the occurrence of applicable events in one's lifetime, subjective experience is particularly relevant in HIV/AIDS, where individual variances in coping with the diagnosis and life management of the disease significantly impact health outcomes.

Brainwaves as a potential independent variable? Electroencephalography (EEG) is commonly used to record

Table 2.1: PERCEIVED STRESS SCALE

SCALE (0 - 4)*	QUESTIONS (10)
0 1 2 3 4	1. In the last month, how often have you been upset because of something that happened unexpectedly?
0 1 2 3 4	2. In the last month, how often have you felt that you were unable to control the important things in your life?
0 1 2 3 4	3. In the last month, how often have you felt nervous and "stressed"?
0 1 2 3 4	4. In the last month, how often have you felt confident about your ability to handle your personal problems?
0 1 2 3 4	5. In the last month, how often have you felt that things were going your way?
0 1 2 3 4	6. In the last month, how often have you found that you could not cope with all the things that you had to do?
0 1 2 3 4	7. In the last month, how often have you been able to control irritations in your life?
0 1 2 3 4	8. In the last month, how often have you felt that you were on top of things?
0 1 2 3 4	9. In the last month, how often have you been angered because of things that were outside of your control?
0 1 2 3 4	10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

*0 (Never), 1 (Almost Never), 2 (Sometimes), 3 (Fairly Often), 4 (Very Often)

brainwave patterns, with studies that indicate that these patterns can reliably assess stress reactions. [4] Specifically, research from Saeed (2020) has shown that alpha asymmetry, a variation in the activity of alpha brainwaves across different brain hemispheres, might serve as a significant indicator of stress. [4] Despite being an accurate method to measure long-term physiological stress, EEG lacks in capturing direct correlations between perceived stress and participants' subjective interpretation of stressors, which is more crucial in understanding the impact of stress on immune function and, ultimately, HIV/AIDS susceptibility.

2.5 Confounding Variables

Socioeconomic Status (SES) as a confounder? The concern is that high levels of stress are most prevalent in lower socioeconomic status (SES) groups within populations, with known examples of the socioeconomic gradient in the incidence of many diseases, such as ischemic heart disease (IHD). [5] Lower SES exacerbates stress levels through poverty, economic instability, and job insecurity, with limited access to healthcare resources and support systems. [5] SES discrepancy can additionally delay HIV diagnosis and treatment (worsen disease progression to late HIV Stage III, AIDS). To accommodate the complex interplay between SES, stress, and susceptibility in AIDS patients, stratification methods are implemen-

ted: dividing participants into strata based on levels of the potential confounding factor, in this case, SES (e.g., low, medium, high). [6] Hence, this allows for an SES-stratified sample of Chicago men and women to observe if and how SES influences the outcomes for participants around the city and suburbs of Chicago.

Mental disorder as a confounder? The concern is that individuals dealing with pre-existing mental health issues may experience increased levels of exposure to stress compared to those with minimum stress. This impact may further be exaggerated, given that mental health conditions may worsen throughout a cohort study, with HIV-positive individuals being at a higher risk for developing mental disorders. [7] Limitations on controlling mental health status can increase vulnerability and affect their progression from HIV to AIDS. [7] To accommodate the biopsychosocial mechanisms between mental disorders, stress, and susceptibility in AIDS patients, multivariate analysis can be employed: techniques such as regression modeling can adjust for the various causes of mental disorders unique to Chicago residents. Hence, this allows for the isolation of each specific impact of stress on mental health.

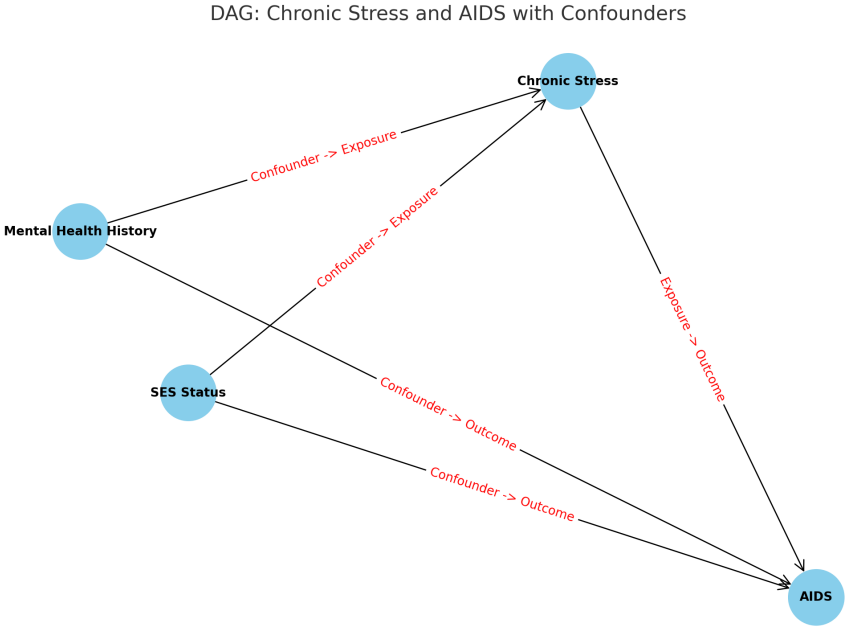

Figure 2.1: Directed Acyclic Graph (DAG) between chronic stress (exposure) and AIDS (outcome), with SES status and mental health history as confounders

2.6 Outcome Variables

The design study will utilize CD4+ T lymphocyte count to assess the individual progression of HIV to AIDS within the cohort. Evaluation for AIDS status is based upon CD4+ T lymphocyte count as an essential indicator of disease progression, clinical use of medications, efficacy, and prognosis. [2] The "golden standard" criteria for AIDS is that the CD4+T lymphocyte count falls below 200/mL. An infection for non-HIV individuals may cause a low CD4+ T lymphocyte count. As a result, constant monitoring for positive HIV status is necessary. For this study, each observation's CD4+ T lymphocyte count counts as a binomial variable categorized as "diseased" and "undiseased" based on the clinical cut-off value.

Clinical symptoms as a potential outcome variable? HIV positive adults and adolescents aged 15 years and

older can receive an AIDS diagnosis if they meet at least one of the following conditions: (1) Sustained, unexplained fever above 38°C for more than one month; (2) Persistent diarrhea occurring more than three times daily for over a month; (3) A loss of more than 10% of body weight within six months; (4) Repeated occurrences of oral yeast infections; (5) Frequent infections with herpes simplex or zoster virus; (6) Pneumocystis jirovecii pneumonia (PCP); (7) Multiple episodes of bacterial pneumonia; (8) Active cases of tuberculosis or infection with nontuberculous mycobacteria (NTM); (9) Infections by fungi that are not just skin-deep; (10) Brain lesions; (11) Dementia in adults who are neither elderly nor very young; (12) Active infection with cytomegalovirus (CMV); (13) Brain infection with Toxoplasma gondii; (14) Infection with Talaromyces marneffei; (15) Repeated episodes of blood poisoning; and (16) Development of Kaposi's sarcoma or lymphoma. [2] Participants are assumed to have a confirmed HIV diagnosis upon enrollment, making this approach less efficient compared to directly assessing CD4+ T lymphocyte count. Diagnosing AIDS by solely examining CD4+ T lymphocyte levels can be more time efficient, as the focus shifts from identifying symptoms to establishing the status of the disease.

3 Statistical Analysis

Logistic Regression. Logistic regression models the log odds of the dichotomous outcome (AIDS/no AIDS) as a linear combination of the exposure and other covariates (predictors or confounding variables). Utilizing logistic regression for this cohort study is appropriate in predicting the RR of a participant developing AIDS based on specific characteristics focusing on binary outcomes like AIDS/no AIDS, taking into account the effect of other covariates. Examining the presence of stress exposure from PSS scores provides visualization of the magnitude of exposure effect on outcomes to assess the significance of observed AIDS susceptibility. Additionally, analyzing stress levels assists in controlling for potential confounding factors and detecting interactions/effect modifiers that may distort the relationship between stress and AIDS susceptibility.

Proposed potential confounders, such as socioeconomic status (SES) and mental health history, are being controlled by the completion of the research in the logistic regression model and can be confirmed through stratification and multivariate analysis to isolate the actual effect of stress on AIDS susceptibility across the entire population in Chicago. By categorizing participants into SES-based strata (low, medium, and high), the study closely examines the impact of SES on the outcomes across Chicago's diverse urban and suburban populations. For multivariate analysis, techniques like regression modeling apply control for the various determinants of mental health problems specific to individuals living in Chicago. Interaction/effect modifiers can similarly be explored through stratified analyses to identify subgroups where the relationship between stress and AIDS risk may vary across populations in Chicago. As stated, stratification methods divide participants into strata based on levels of the potential factor, and multivariate analysis of regression modeling can adjust for the various causes of mental disorders unique to Chicago residents. Finally, the logistic regression model is fitted to adjust confounding for all baseline covariates simultaneously for data analysis. The coefficients in logistic regression are interpreted as the log odds for a one-unit change in the predictor variable while holding all other variables constant. Exponentiating the coefficients gives the odds ratio (OR) for a one-unit increase in the corresponding independent variable and can be used to estimate RR for this cohort study.

4 Limitations

Migration Bias. Participants enrolled in the study might relocate out of Chicago for various reasons, including seeking better healthcare for HIV, employment opportunities, supportive communities, or

educational pursuits. Such differential migration patterns could lead to loss of follow-up, resulting in incomplete data regarding individuals' progression of AIDS and their stress levels. This issue is particularly observant if the migrating groups have distinct stress levels or differential risks of AIDS progression, driven by variations in stress exposure and coping mechanisms across different demographic groups, underscoring the challenge of accurately assessing the impact of stress on disease progression in dynamic urban populations.

Participant comparisons between movers and non-movers from Chicago can be implemented using current information collected through improved active follow-ups to explore the presence of this potential phenomenon (following participants regularly over the study period through phone calls, emails, and home visits to help maintain contact and present information from participants). This approach assesses significant and differential movement to determine whether potential migration bias exists or whether migration among exposure groups is random. Therefore, addressing migration bias could indicate if potential limitation obscures the actual influence of stress on susceptibility to AIDS, especially since specific populations might be more inclined to move out of the city.

Recall Bias. The methodology for this prospective cohort study involves participants periodically reporting their perceived stress and experiences via PSS surveys over the past six months for five years. Participants may encounter challenges in precisely recalling and evaluating their stress levels due to the emotional and psychological ramifications of managing a chronic condition. This variability in memory and perception can introduce a range of stress responses among participants, indicating that the study's outcomes may more likely be subjective interpretations rather than objective measures for assessing the impact of stress on HIV progression. Such an effect is particularly relevant in dynamic urban populations like Chicago, where diverse lifestyles and environmental factors may further underscore individuals' stress perceptions and reporting accuracy.

Additional cognitive interviews can be adopted to investigate the potential presence of this phenomenon (integrated phone or in-person sessions into each follow-up phase), aiming to deeply understand the specific stressors and life circumstances of participants, designed to ensure the data's validity and reliability, aligning closely with the Perceived Stress Scale (PSS) results. By comparing the outcomes from the PSS with insights gained from direct interviews, the study can identify any discrepancies in the interpretation of PSS questions or issues related to memory recall. This approach assesses whether recall bias exists or whether participants can accurately recall and express their experiences and stress levels. Therefore, addressing recall bias could indicate if potential limitations obscure the true impact of stress on the progression to AIDS, particularly in a dynamic urban setting like Chicago.

Acknowledgements

We extend our heartfelt gratitude to Dr. Brian Chiu for his invaluable mentorship and guidance throughout the course of this study. His insights and expertise was instrumental in shaping both the design and direction of the research.

Our sincere thanks go to The University of Chicago of the Department of Public Health Sciences, for providing the necessary resources and environment to design this study. We are also grateful to our peers and teammate for their constructive feedback during the various stages of this research.

Special thanks to my group member Diego Mendoza-Martinez for his assistance and support.

References

1. State of New Hampshire Employee Assistance Program. Perceived Stress Scale [Internet]. 1983. Available from: https://www.das.nh.gov/wellness/docs/percieved%20stress%20scale.pdf

2. AIDS and Hepatitis C Professional Group, Society of Infectious Diseases, Chinese Medical Association; Chinese Center for Disease Control and Prevention. Chinese guidelines for the diagnosis and treatment of HIV/AIDS (2021 edition). Infectious Diseases & Immunity. 2022 Jul 20;2(03):145-67.

3. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. J Psychosom Res. 1967;11(2):213-218. doi:10.1016/0022-3999(67)90010-4

4. Saeed SMU, Anwar SM, Khalid H, Majid M, Bagci AU. EEG-based Classification of Long-term Stress Using Psychological Labeling. Sensors (Basel). 2020;20(7):1886. Published 2020 Mar 29. doi:10.3390/s20071886

5. Andersen I, Osler M, Petersen L, Grønbaek M, Prescott E. Income and risk of ischaemic heart disease in men and women in a Nordic welfare country. Int J Epidemiol. 2003;32(3):367-374. doi:10.1093/ije/dyg073

6. Jager KJ, Zoccali C, Macleod A, Dekker FW. Confounding: what it is and how to deal with it. Kidney international. 2008 Feb 1;73(3):256-60.

7. Collins PY, Holman AR, Freeman MC, Patel V. What is the relevance of mental health to HIV/AIDS care and treatment programs in developing countries? A systematic review. AIDS (London, England). 2006 Aug 8;20(12):1571.