UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Prevalence of Loneliness and its Predictors and Outcomes in People with HIV

A dissertation submitted in partial satisfaction of the
requirements for the degree of Doctor of Philosophy

in

Clinical Psychology

by

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2022

The Dissertation of Mariam Ayesha Hussain is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California San Diego

San Diego State University

2022

DEDICATION

This dissertation is dedicated to my faith, my family, and my friends. Without these pillars in my life, this accomplishment would not have been possible. Alhamdulillah to be able to reach this milestone, and for all the blessings that He granted for this moment to happen. To my life partner, Amir, you have been my constant through unsteady waters; thank you for your unwavering love and support. To my parents and my family, thank you for instilling in me a love of learning and the pursuit of a higher calling, despite the challenges it may entail. And to my friends who cheered me on from near and far, thank you for your kindness as I navigated the professional and personal demands necessary to reach this achievement. More than a representation of individual success, this milestone reflects the efforts of numerous individuals, and I wholeheartedly give thanks and dedication to my Creator and my "village".

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LIST OF ABBREVIATIONS

HIV = human immunodeficiency virus

PWH = people with HIV

PWoH = people without HIV

ART = antiretroviral therapy

AIDS = acquired immunodeficiency syndrome

CRP = C-reactive protein

IL-6 = Interleukin-6

CCL2 = Chemokine (C-C motif) ligand 2

MCP-1 = monocyte chemoattractant protein-1

sCD14 = soluble cluster of differentiation 14

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Chapter 1, “Prevalence of Loneliness, its Associations with Psychological and Social Resources, and its Impact on Depressive Symptoms among Adults with and without HIV,” is coauthored with Hussain, Mariam A.; Kohli, Maulika; Karris, Maile; Iudicello, Jennifer E.; Heaton, Robert K.; Jeste, Dilip V.; Moore, David J. The dissertation author was the primary author of this chapter.

Chapter 2, “Combined Effects of Loneliness and Inflammation on depression in People with HIV,” is coauthored with Hussain, Mariam A.; Watson, C. Wei-Ming; Morgan, Erin E.; Heaton, Robert K.; Letendre, Scott L.; Jeste, Dilip V.; Moore, David J.; Iudicello, Jennifer E. The dissertation author was the primary author of this chapter.

Chapter 3, “Understanding the Longitudinal Impact of Loneliness on Depressive Symptoms in People with and without HIV,” is coauthored with Hussain, Mariam A.; Umlauf, Anya; Iudicello, Jennifer E.; Morgan, Erin E.; Heaton, Robert K.; Jeste, Dilip V.; Moore, David J. The dissertation author was the primary author of this chapter.

VITA

Education

2021-2022	**Pre-Doctoral Internship** in Clinical Psychology West Los Angeles VA Healthcare Center Track: Geropsychology Director of Training: Stephanie Cardoos, Ph.D. Rotations: Neuropsychology, Rehabilitation Psychology, Geriatric Medicine, Geropsychology
2016-2022	**Doctor of Philosophy** in Clinical Psychology San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology Major Area of Study: Neuropsychology (GPA: 4.0) *Emphasis* in Quantitative Methods Dissertation Chair: Jennifer E. Iudicello, Ph.D. Dissertation Title: *Prevalence of Loneliness, and its Predictors and Outcomes in People with HIV* Dissertation Status: Successfully defended May 2022
2016-2018	**Master of Science** in Clinical Psychology San Diego State University (SDSU) Thesis Chair: Jennifer E. Iudicello, Ph.D. Thesis Title: *Use of a Novel Virtual Reality Measure to Assess Everyday Functioning Difficulties Associated with HIV Infection, Methamphetamine Use and/or Aging*
2010-2014	**Bachelor of Science** in Psychology & Neuroscience The Ohio State University (OSU) *Magna Cum Laude* w/*Honors Research Distinction* in the Major of Psychology Honors Thesis Advisor: Ruchika S. Prakash, Ph.D. Honors Thesis Title: *Mindfulness and Stress in The Elderly- Identifying Potential Mediators*

Honors, Distinctions, and Awards

2021	Asian Neuropsychological Association (ANA) Conference Award ($150)
2018	American Academy of Clinical Neuropsychology (AACN) Student Poster Merit Award
2017	Division 40-Clinical Neuropsychology Blue Ribbon Award ($1,000)
2017	American Psychological Association (APA) Student Travel Award ($300)
2016	SDSU Graduate Student Travel Fund Award ($555)
2014	*Magna Cum Laude, Honors Research Distinction* in the Major of Psychology
2014	Phi Beta Kappa Honor Society
2014	OSU Department of Psychology Conference Travel Scholarship ($800)

2014 2nd Place, OSU Department of Neuroscience Undergraduate Research Colloquium ($75)
2013 1st Place, OSU Department of Psychology Undergraduate Research Colloquium ($75)
2013 3rd Place in Psychology, OSU Denman Undergraduate Research Forum ($150)
2013 OSU College of Arts & Sciences Undergraduate Research Scholarship ($6,000)
2013 OSU Undergraduate Summer Research Fellowship ($3,500)
2013 OSU Research Academic Enrichment Grant ($1,600)
2013 OSU Social and Behavioral Sciences Undergraduate Research Grant ($1,000)
2013 Mortar Board Senior Class Honor Society
2012 OSU Pelotonia Undergraduate Cancer Research Fellowship ($12,000)
2012 Nu Rho Psi National Honor Society in Neuroscience
2011 Psi Chi International Honor Society in Psychology
2010-2014 Dean's List, Ohio State University (OSU)
2009 Cleveland Clinic Science Summer Internship and Research Fellowship ($9,000)

Funding

2016-2021 **T32 NIH Pre-Doctoral Fellow**, Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Training Program: "Training in Research on Addictions in Interdisciplinary NeuroAIDS" (TRAIN; DA031098). PI: Robert K. Heaton.

Teaching and Supervision

Spring 2021 **Teaching Assistant**, SDSU Department of Psychology: PSY 849 - Clinical Interventions
Spring 2020 **Peer Clinical Supervision**, SDSU Psychology Clinic
Spring 2014 **Peer Expert Statistics Tutor**, OSU Department of Psychology
Fall 2013 **Undergraduate Course Assistant**, OSU Psychology 1100
2010–2013 **Grade 4-6 Science/Math Tutor**, Ohio House of Science & Engineering Program

Ad Hoc Manuscript Reviews

2021 *Archives of Clinical Neuropsychology* (requested to review by journal's associate editor)
2020 *The Clinical Neuropsychologist* (requested as a reviewer by the journal's editor in chief)
2020 *Archives of Clinical Neuropsychology* (with David J. Moore, Ph.D.)

Peer-Reviewed Publications

Nguyen, A. L., **Hussain, M. A.**, Pasipanodya, E., Rubtsova, A. A., Moore, R. C., Jeste, D. V., Moore, D. J. (2022). The impact of life stress, psychological resources, and proactive

behaviors on quality of life among people living with HIV. *Aging and Mental Health*. doi:10.1080/13607863.2022.2068126.

Saloner, R., Morgan, E. E., **Hussain, M. A.**, Moore, D. J., Heaton, R. K., Cherner, M., Grant, I., Iudicello, J. E., & the TMARC Group (2022). The sensitivity of the balloon analog risk task to neurocognitive impairment differs by HIV serostatus and major depressive disorder. *Journal of NeuroVirology*. doi:10.1007/s13365-021-01046-z.

Hussain, M. A., Morgan, E. E., Iudicello, J. E., Montoya, J. L., Heaton, R. K., & Grant, I. (2022). Loneliness predicts risky sexual beliefs and intentions in methamphetamine dependent individuals. *Substance Use and Misuse*. doi:10.1080/10826084.2021.2003404.

Watson, C. W.-M., Kamalyan, L., Tang, B., **Hussain, M. A.**, Cherner, M., Rivera Mindt, M., Byrd, D. A., Franklin, D., Collier, A. C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., McCutchan, J. A., Ellis, R. J., Grant, I., Heaton, R. K., & Marquine, M.J. for the CHARTER group. (2022) Ethnic/racial disparities in longitudinal neurocognitive decline in people with HIV. *Journal of Acquired Immune Deficiency Syndromes*. doi:10.1097/QAI.0000000000002922.

Hussain, M. A., Iudicello, J. E., Morgan, E. E., Kamat, R., Heaton, R. K., & Grant, I. (2021). Apathy is associated with poorer abstinence self-efficacy in individuals with methamphetamine dependence. *Addictive Behaviors Reports, 13*, 100331. doi:10.1016/j.abrep.2020.100331.

Kamalyan, L., **Hussain, M. A.**, Diaz, M. M., Umlaf, A., Franklin, D. R., Cherner, M., Rivera-Mindt, M., Artiola i Fortuny, L., Heaton, R. K., & Marquine, M. J. (2021). Neurocognitive impairment in primarily Spanish-speaking Hispanics living with HIV in the US: Application of neuropsychological test norms. *The Clinical Neuropsychologist*. doi:10.1080/13854046.2019.1701084.

Pasipanodya, E. C., Montoya, J. L., Campbell, L. M., **Hussain, M. A.**, Saloner, R., Heaton, R. K., & Moore, D. J. (2021). Metabolic risk factors as differential predictors of profiles of neurocognitive impairment among older HIV+ and HIV- adults. *Archives of Clinical Neuropsychology*. doi:10.1093/arclin/acz040.

Sundermann, E.E., **Hussain, M.A.**, Moore, D.J., Horvath, S., Lin, D.T.S., Kobor, M.S., Levine, A., & the HNRP Group (2019). Inflammation-related genes are associated with epigenetic aging in HIV. *Journal of NeuroVirology*. doi:10.1007/s13365-019-00777-4.

Campbell, L. M., Fennema-Notestine, C., Saloner, R., **Hussain, M. A.**, Chen, A., Franklin, D., Umlauf, A., Ellis, R. J., Collier, A. C., Marra, C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., McCutchan, J. A., Letendre, S., Grant, I., Heaton, R.K., & The CHARTER Group. (2019). Use of neuroimaging to inform optimal neurocognitive criteria for detecting HIV-associated brain abnormalities. *Journal of the International Neuropsychological Society*. doi:10.1017/S1355617719000985.

Watson, C.W-M., Sundermann, E., **Hussain M.A.,** Umlauf, A., Thames, A., Letendre, S., Moore, R.C., Jeste, D., Morgan, E.E., & Moore D. (2019). Effects of trauma, economic hardship, and stress on neurocognition and everyday functioning outcomes in adults living with HIV. *Health Psychology.* doi:10.1037/hea0000688.

Moore, R. C., **Hussain, M. A.**, Watson, C. W-M., Fazeli, P. L., Marquine, M. J., Yarns, B. C, Jeste, D. V., & Moore, D. J. (2018). Grit and ambition are associated with better neurocognitive and everyday functioning among adults infected with HIV. *Aids and Behavior*. doi:10.1007/s10461-018-2061-1.

Prakash, R. S., **Hussain, M. A.**, & Schirda, B. (2015). The role of emotion regulation and cognitive control in the association between mindfulness disposition and stress. *Psychology and aging*, *30*(1), 160-171. doi:10.1037/a0038544.

Bethoux, F., Boulis, N., McClelland, S., Willis, M. A., **Hussain, M.**, Machado, A., Mychkovsky, L., Stough, D., Sutliff, M., & Pioro, E. P., (2013). Use of intrathecal baclofen for treatment of severe spasticity in selected patients with motor neuron disease. *Neurorehabilition and Neural Repair, 27*(9), 828-833. doi:10.1177/1545968313496325.

Book Chapters

Iudicello, J. E., Morgan E. E., **Hussain, M. A.**, Watson, C. W-M., & Heaton, R. K. (*2019*). HIV-Associated Neurocognitive Disorders (HAND). In R. A. Stern & M. L. Alosco (Eds.), *The Oxford Handbook of Adult Cognitive Disorders.* Oxford University Press.

Invited Presentations

Hussain, M. A. (2021, August). Presentation and discussion of "*Exploring the effectiveness of virtual compassionate presence sessions in reducing loneliness and isolation among assisted-living older adults: a pilot study*." Invited presentation at the T. Denny Sanford Institute for Empathy and Compassion Journal Club, the University of California, San Diego, CA.

Hussain, M. A., Iudicello, J. E., Morgan, E. E., Kamat, R., Heaton, R. K., Grant, I. & the TMARC Group (2018, April). *Apathy significantly predicts abstinence self-efficacy in methamphetamine users*. Selected oral presentation at the 13th Annual Lewis L. Judd Young Investigators Research Symposium, the University of California, San Diego, CA.

Hussain, M. A., Iudicello, J. E., Morgan, E. E., Villalobos, J., Watson, C. W., Minassian, A., Heaton, R. K., & Grant, I. (2017, August). *Age-Related Differences on The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) in HIV Infected (HIV+) and/or Methamphetamine Dependent (METH+) Adults*. Selected oral presentation and Division 40 Society for Clinical Neuropsychology Blue Ribbon Awardee at the 125th annual American Psychology Association (APA) conference, Washington D.C.

Bailie, J. M. & **Hussain, M. A**. (2015, September). *Anger Expression in the Military: Impact of Traumatic Brain Injury and Military Specific Demographic Factors*. Oral presentation

during September 2015 Defense and Veterans Brain Injury Center National Research Call, Camp Pendleton, CA.

Other Conference Presentations

Hussain, M. A., Morgan, E. E., Heaton, R. K., Iudicello, J. E., Jeste, D. J., & Moore, D. J. (February, 2022). *Effects of Loneliness and Wisdom on Physical and Mental Well-Being among People with and without HIV*. Poster to be presented to the International Neuropsychological Society (INS) Annual Meeting, New Orleans, LA.

Watson, C. W-M., Morgan, E. E., Sun-Suslow, N., Letendre, S., **Hussain, M. A.**, Heaton, R. K., Grant, I., & Iudicello, J. E. (February, 2022). *Worse alexithymia is associated with different patterns of pro-inflammatory and vascular biomarkers in people with HIV and/or methamphetamine dependence*. Paper abstract submitted to the International Neuropsychological Society (INS) Annual Meeting, New Orleans, LA.

Hussain, M. A., Watson, W-M. C., Morgan, E. E., Roesch, S. C., Iudicello, J. E., Heaton, R. K., Letendre, S. L., Jeste, D. J., & Moore, D. J. (February, 2021). *Combined effects of loneliness and inflammation on depression in people with HIV*. Paper abstract presented at the International Neuropsychological Society (INS) Annual Meeting, San Diego, CA.

Hussain, M. A., Kohli, M., Karris, M., Iudicello, J. E., Heaton, R. K., Jeste, D. J., & Moore, D. J. (October, 2020). *Loneliness is higher in people with HIV (PWH) versus HIV- individuals, and linked differently to psychological and social resources*. Poster presented at the International HIV & Aging Conference, Virtual meeting.

Hussain, M. A., Morgan, E. E., Iudicello, J. E., Heaton, R. K., & Igor, G. (February, 2020). *Methamphetamine dependence and low self-efficacy have an additive effect on impulsivity and disinhibition*. Poster presented at the International Neuropsychological Society (INS) Annual Meeting, Denver, CO.

Kamalyan, L., **Hussain, M. A.**, Morlett-Paredes, A., Umlauf, A., Franklin, D. R., Suarez, P., Rivera-Mindt, M., Artiola i Fortuny, L., Cherner, M., Heaton, R. K., & Marquine, M. J. (November, 2019). *Comparison of Rates of Impairment Between Three Sets of Normative Data for Spanish-speakers of Mexican Origin in a Healthy Cohort*. Paper talk presented at the 2019 National Academy of Neuropsychology (NAN) Meeting, San Diego, CA.

Paolillo E., **Hussain M. A.**, Moore R., Moore D., & Heaton R. (November, 2019). *Engagement in Cognitively-Demanding Activities in Daily Life is Associated with Neurocognitive Test Performance and Perceived Cognitive Difficulties Among Adults With and Without HIV*. Poster presented at the 2019 National Academy of Neuropsychology (NAN) Meeting, San Diego, CA.

Watson C., Kamalyan L., **Hussain M. A.**, Tang B., Collier A., Clifford D., Gelman B., Sacktor N., Morgello S., McCutchan J., Ellis R., Grant I., Heaton R., & Marquine M. (November, 2019). *Ethnic/Racial Differences in Longitudinal Neurocognitive Change*

among People Living with HIV. Poster presented at the 2019 National Academy of Neuropsychology (NAN) Meeting, San Diego, CA.

Sundermann, E. E., **Hussain, M. A.**, Moore, D. J., Horvath, S., Levine, A., & The HNRP Group (March, 2019). *Inflammation-related genes are associated with accelerated aging in HIV*. Poster presented at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, WA.

Montoya, J. L., Paolillo, E. M., **Hussain, M. A.**, Moore, A., Moore, D. J., & Moore, R. C. (March, 2019). *Concurrent Association between Substance Use and Social Interaction Ratings: An Ecological Momentary Assessment (EMA) study of Older Adults Living with HIV*. Poster presented at the 40th Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine (SBM), Washington, DC.

Hussain, M. A., Morgan, E. E., Iudicello, J. E., Heaton, R. K., & Igor, G. (February, 2019). *Loneliness Predicts Risky Sexual Beliefs and Intentions in Methamphetamine Dependent (MA+) Individuals*. Poster presented at the International Neuropsychological Society (INS) Annual Meeting, New York City, NY.

Hussain, M. A., Kamalyan, L., Diaz, M. M., Umlaf, A., Franklin, D. R., Cherner, M., Rivera-Mindt, M., Artiola i Fortuny, L., Heaton, R. K., & Marquine, M. J. (February, 2019). *Predictors of Neurocognitive Impairment in Spanish-Speaking Latinos Living with HIV in the United States using Newly Developed Neuropsychological Test Norms*. Poster presented at the Hispanic Neuropsychological Society (HNS) 2019 Meeting, New York City, NY.

Kamalyan, L., **Hussain, M. A**., Diaz, M. M., Umlaf, A., Franklin, D. R., Cherner, M., Rivera-Mindt, M., Artiola i Fortuny, L., Heaton, R. K., & Marquine, M. J. (2019, February). *Neurocognitive Impairment in Native Spanish-speaking Hispanics Living with HIV in the US: Validation of Neuropsychological Tests Norms for a Comprehensive Test Battery*. Poster presented at the Hispanic Neuropsychological Society (HNS) 2019 Annual Meeting, New York City, NY.

Campbell, L. M., Fennema-Notestine, C., Saloner, R., **Hussain, M. A.**, Chen, A., Franklin, D., Umlauf, A., Ellis, R. J., Collier, A. C., Marra, C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., McCutchan, J. A., Letendre, S., Grant, I., Heaton, R.K., & The CHARTER Group (2019, February). *Use of neuroimaging to inform optimal neurocognitive criteria for detecting HIV-associated brain abnormalities*. Oral presentation at the 47th Annual International Neuropsychological Society (INS) Meeting, New York City, NY.

Hussain, M. A., Iudicello, J. E., Morgan, E. E., Heaton, R. K., Grant, I. & the TMARC Group (2018, June). *Sensation-seeking behaviors persist in older (≥50 years) methamphetamine (METH)-dependent individuals and are associated with increased HIV transmission risk behaviors*. Poster presented at the 16th Annual American Academy of Clinical Neuropsychology (AACN) Conference, San Diego, CA.

Hussain, M. A., Iudicello, J. E., Morgan, E. E., Grant, I., & Heaton, R. K., (2018, June). *Associations between perceived stress and poor everyday functioning in methamphetamine (METH) dependence and/or HIV infection*. Poster presented at the 2018 College on Problems of Drug Dependence (CPDD) annual conference, San Diego, CA.

Morgan, E. E., **Hussain, M. A.,** Iudicello, J. E., Watson, C. W-M., Villalobos, J., Heaton, R. K., Grant, I. & the TMARC Group (2018, June). *Poor Social Cognition Negatively Influences Methamphetamine Addiction Characteristics*. Poster presented at the 16th Annual American Academy of Clinical Neuropsychology (AACN) Conference, San Diego, CA.

Iudicello, J. E., Morgan, E. E., **Hussain, M. A.**, Henry, S. M., Watson, C. W-M., Heaton, R. K., Grant, I. & the TMARC Group (2018, June). *Emotional and psychosocial functioning are problematic in HIV and methamphetamine use and associated with significant functional and health-related outcomes*. Poster presented at the 16th Annual American Academy of Clinical Neuropsychology (AACN) Conference, San Diego, CA.

Moore, R. C., **Hussain, M. A.**, Watson, C. W-M., Fazeli, P. L., Marquine, M. J., Yarns, B. C., Jeste, D. V., & Moore, D. J. (2017, October). *Grit as a protective factor for optimizing cognitive and everyday functioning among adults living with HIV*. Poster presented at the International Workshop on HIV and Aging, 8th Edition, New York City, NY.

Bailie, J. M., Karpel, H. M., Jolly, M. J., **Hussain, M. A.**, Andrews, T., Ritter, A. C., Mills, J., Sargent, & P. D., Duckworth, J. L. (2017, August) *The Impact of Lifetime Traumatic Brain Injury and Lifetime Blast Exposure History on Neurobehavioral Symptoms and Neuropsychological Functioning of Combat Specialists*. Poster presented at 2017 Military Health System Research Symposium, Kissimmee, FL.

Watson, C. W-M., Marquine, M. J., Moore, R. C., Heaton, A., Perez-Tejada, A., Umlauf, A., Morgan, E. M., **Hussain, M. A.**, Cherner, M., Ellis, R., Grant, I., & Heaton. R. K. (2017, August). *Racial/Ethnic Differences in Neurocognitive Performance among HIV-infected adults*. Paper talk presented at the 125th annual American Psychological Association (APA) conference, Washington, D.C.

Hussain, M. A., Iudicello, J. E., Morgan E. E., Kamat, R., Heaton, R. K., & Grant, I. (2017, June). *Apathy Significantly Predicts Abstinence Self-Efficacy (ASE) in Methamphetamine Users*. Poster presented at the 15th annual American Academy of Clinical Neuropsychology (AACN), Boston, MA.

Hussain, M. A., Bailie, J. M., Jolly, M. J., Powell, B. E., Sargent, P. D., & Duckworth, J. L. (2016, October). *The Impact of Traumatic Brain Injury and Heavy Weapons Blast Exposure on Neuropsychological Functioning in the Military*. Poster presented at the 36th annual National Academy of Neuropsychology (NAN) conference, Seattle, WA.

Jolly, M. J., Bailie, J. M., **Hussain, M. A.**, Sargent, P. D., & Duckworth, J. L. (2016, August). *The Impact of Lifetime Traumatic Brain Injury and Lifetime Blast Exposure History on Reported Neurobehavioral Symptoms of Service Members*. Poster presented at the annual Military Health System Research Symposium (MHSRS), Kissimmee, FL.

Hussain, M. A., Bailie, J. M., Ivins, B., Cole, W. R., Boyd, C., & Schwab, K. (2015, November). *Effect of Multiple Mild Traumatic Brain Injuries on the Experience and Expression of Anger in Military Personnel*. Poster presented at the 35th annual National Academy of Neuropsychology (NAN) conference, Austin, TX.

Hussain, M. A. & Prakash, R. S. (2014, April). *Mindfulness and Stress in the Elderly: Identifying Potential Mediating Factors*. Poster presented at the annual Cognitive Aging Conference (CAC), School of Psychology, Georgia Institute of Technology, Atlanta, GA.

Hussain, M. A., Jaremka, L. M., Bennett, J. M., Fagundes, C. P., Malarkey, W. B., Emery, C. F., & Kiecolt-Glaser, J. K. (2014, March). *Syndromal Depression, Intrusive Thoughts, and Heart Rate Variability among Cancer Survivors*. Poster presented at the 72nd annual American Psychosomatic Society (APS) meeting, San Francisco, CA.

Fink, C., **Hussain, M.**, Caine, K., Ely, R., Griffin, M., Ives, J., Craighead, T., Kirtz, T., Miller, D.M., Perryman, J., & Bethoux, F., (2012, May). *Effects of a fall prevention initiative on falls during outpatient visits in a MS center*. Poster presented at 26th annual The Consortium of Multiple Sclerosis Centers (CMSC) Meeting, San Diego, CA.

ABSTRACT OF THE DISSERTATION

Prevalence of Loneliness and its Predictors and Outcomes in People with HIV

by

Mariam Ayesha Hussain

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2022
San Diego State University, 2022

Professor Jennifer E. Iudicello, Chair

Rationale: Over half of people with HIV (PWH) report loneliness (i.e., perceived social isolation) in their lifetime. PWH may be at increased risk of loneliness compared to people without HIV (PWoH) due to stigma, discrimination, and objective social isolation. Depression can be a consequence of loneliness, which is problematic given its high prevalence in PWH. This dissertation aimed to address gaps in the literature related to loneliness in PWH by examining: 1)

the prevalence of loneliness and psychosocial factors that may mitigate it, 2) associations between loneliness and systemic inflammatory biomarkers, and 3) cross-sectional and longitudinal impacts of loneliness on depression. Design: Retrospective data from the Multi-Dimensional Successful Aging Among HIV-Infected Adults Study were extracted. Participants with UCLA Loneliness Scale-Version 3 data were included in analyses (*N*=202; PWH *n*=120, PWoH *n*=82). Studies 1 and 2 used multivariable regressions, and Study 3 used multilevel modeling. Results: Study 1 (cross-sectional; *N*=202) 41.7% of PWH reported clinically significant loneliness, exceeding rates for PWoH (29.3%; *p*=.049). Resilience, personal mastery, and affective wisdom were negatively associated with loneliness (*p*s<.05). PWH were more vulnerable to loneliness than PWoH when cognitive wisdom and emotional support were lower. Loneliness explained significant variance in depressive scores after accounting for demographic, psychological, and social variables. Study 2 (cross-sectional; *N*=82*)* In PWH, specific biomarkers of inflammation (D-dimer, CCL2/MCP-1, and sCD14) predicted loneliness after accounting for relevant covariates (*p*s<.05). There was also a combined association of loneliness and inflammation with depressive symptoms whereby higher D-dimer was associated with increased depressive symptoms only when loneliness was higher (*p*=.0497). Study 3 (longitudinal; *N*=139) Individuals who experienced more loneliness than their typical average reported higher depressive scores at the same visit *and* follow-up visits (*p*s<.05); however, only the latter relationship was stronger among PWH than PWoH (*p*=.03). Conclusion: Loneliness is more prevalent among PWH than PWoH, and impacts depression in the present and over time. Additionally, loneliness is linked to both psychological and biological processes, potentially explaining why individuals experiencing more loneliness are more depressed. Findings also

identified specific psychosocial variables (e.g., wisdom) as possible targets for loneliness intervention in PWH.

Introduction

Loneliness is an affective and cognitive discomfort, or uneasiness from perceiving oneself to be alone or otherwise solitary (Association, 2020a). Social isolation, by contrast, is defined as the voluntary or involuntary absence of contact with others (Association, 2020b). Though having few social interactions can contribute to feelings of loneliness, they remain distinct concepts. For example, individuals may feel lonely despite having many social interactions; similarly, those who prefer to live solitary lives may not necessarily feel lonely. Thus, loneliness is often described as discomfort associated with subjective, or perceived social isolation, which can be experienced regardless of the amount of social contact that one receives (Hawkley & Cacioppo, 2010). Moreover, loneliness and social isolation can lead to significant health consequences that occur independently of one another (Julianne Holt-Lunstad, 2018; Perissinotto, Stijacic Cenzer, & Covinsky, 2012; Rico-Uribe et al., 2018; Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016). The necessary key feature of loneliness includes the accompaniment of a distressing feeling related to the discrepancy between one's desired and actual social relations, in either quantity, quality, or both (Leigh-Hunt et al., 2017). Importantly, loneliness has been associated with a range of emotional, cognitive, and physical health problems, as well as increased risk for mortality (Julianne Holt-Lunstad, 2018; J. Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Holwerda et al., 2016; Luo, Hawkley, Waite, & Cacioppo, 2012). For example, chronic loneliness has been linked to poorer cardiovascular health (Friedler, Crapser, & McCullough, 2015; Hawkley, Thisted, Masi, & Cacioppo, 2010; Thurston & Kubzansky, 2009; Valtorta et al., 2016), reduced physical activity (Hawkley, Thisted, & Cacioppo, 2009), metabolic syndrome (Henriksen, Nilsen, & Strandberg, 2019; Shiovitz-Ezra & Parag, 2019), frailty (Ganesalingam, 2019), and cognitive decline/dementia

(Abell, Abell, Cadar, Llewellyn, & Steptoe, 2019; Lara, Martin-Maria, et al., 2019; Sundstrom, Nordin Adolfsson, Nordin, & Adolfsson, 2019; Wilson et al., 2007). Findings from the proposed cross-sectional and longitudinal studies below may help to elucidate the underlying mechanisms through which loneliness impacts clinical outcomes such as depression in people with and without HIV (PWH, PWoH, respectively), may provide a more nuanced understanding of the potential protective factors that may mitigate negative outcomes related to loneliness, and therefore help guide approaches for treatment targets.

The prevalence of loneliness in the general population can vary widely based on the different populations being studied, and may be affected by sample demographics, sample sizes, and differing measurement scales. Global estimates range from about 10-25% depending on the region, with the highest prevalence reported in European countries (Surkalim et al., 2022). However, the aforementioned meta-analysis may not have been fully inclusive of all studies that reported rates of loneliness. For example, Lee et al. (2019) reported that in sample of community-dwelling US adult, about 20% reported significant loneliness, as measured by high loneliness scores ($\geq$44) on the revised UCLA Loneliness Questionnaire. Of note, differing approaches have been used to define how people are classified as feeling "lonely." Some studies use a single-item direct measure of loneliness, while others have used a more comprehensive scale that does not even use the word "lonely", which can drastically change results (Ong, Uchino, & Wethington, 2016). For instance, according to a pre-COVID-19 Cigna report, which surveyed more than 10,400 Americans (18 years or older), more than half of respondents (52%) reported sometimes or always feeling alone (Cigna, 2020), much higher than reported elsewhere.

The prevalence of loneliness in PWH also varies widely for similar reasons. No large-scale surveys of loneliness across the lifespan in PWH have been conducted as of yet; however,

estimated prevalence rates of loneliness in PWH reported across the lifespan has ranged from 40-60% (Greene et al., 2018; Harris et al., 2020; Rodkjaer, Laursen, Balle, & Sodemann, 2010; Stanton, Moadel, Kim, Weinberger, & Shuter, 2015). Most studies investigating loneliness in PWH have focused on older adults, and their prevalence rates tend fall on the higher end compared to younger adults with HIV (Greene et al., 2018; Kane et al., 2018; Mazonson et al., 2020; Yoo-Jeong, Hepburn, Holstad, Haardorfer, & Waldrop-Valverde, 2019).

As noted, people can experience loneliness across the lifespan, with recent work illustrating that there are distinct periods in one's life that may be associated with higher loneliness than others. A study of community-dwelling individuals in California (*n*=340) found that while moderate to severe loneliness (as indexed by scores $\geq$28 on the well-validated revised UCLA Loneliness Questionnaire-Version 3) persisted across the lifespan, it was most pronounced during one's late-20s, mid-50s, and late-80s (Lee et al., 2019).

Risk factors for loneliness in older age included not being married/partnered and partner loss, limited social network, low level of social activity, poor self-perceived health, and depression/depressed mood (Dahlberg, McKee, Frank, & Naseer, 2022). In addition, different factors have been found to be associated with loneliness at different stages of life (Franssen, Stijnen, Hamers, & Schneider, 2020) such as lower education level and lack of contact with friends in young adulthood (19-34 years), financial instability in young adulthood (19-34) to early middle-age (35-49 years), lack of employment in early middle-age (35-49), and poor perceived health and low frequency of family contact in late middle-age (50-65). However, cohort-studies comparing Baby Boomers (born in 1948-1965) to those born in the previous generation (1920-1947) found no evidence of generational differences between loneliness prevalence, suggesting that loneliness is not increasing across generations (Hawkley,

Wroblewski, Kaiser, Luhmann, & Schumm, 2019). Nonetheless, the incidence of lonely individuals will likely increase given that a large proportion of the population will soon be entering into older adulthood (>65 years), one of the life stages associated with high loneliness, which could result in higher economic costs (Jeffrey, Abdallah, & Michaelson, 2017) and burden on healthcare systems (J. Zhang et al., 2018).

In general, there is evidence for the stability of loneliness over time (Mund, Freuding, Mobius, Horn, & Neyer, 2020), and the majority of research has investigated loneliness as a trait. However, it can also be experienced transiently in a state form. In this case, loneliness is more heavily influenced by the surrounding social context and will reflect "social loneliness" rather than the "emotional loneliness" that is experienced with trait loneliness. Thus, it can be conceptualized as both a subjective state, as well as a personality trait that can be heritable to some extent (J. T. Cacioppo & Cacioppo, 2018; Spithoven, Cacioppo, Goossens, & Cacioppo, 2019). However, given the transient nature of state loneliness, it is can be more difficult to measure in research. Recent studies have employed tools such as ecological momentary assessment (EMA) or social experimental designs in effort to overcome these limitations. Using EMA, van Roekel et al. (2018) found evidence for a differential reactivity hypothesis; adolescents who were considered having high trait-level loneliness experienced higher levels of state loneliness when alone compared to adolescents who had low trait-level loneliness. Notably, the high-lonely adolescents benefited more from being with intimate company than low-lonely adolescents, suggesting that the experience of loneliness can be modified even in people who are lonely at the trait-level.

Magnetic resonance imaging (MRI) studies have investigated the structural and functional brain connectivity associated with loneliness. Findings suggest that experience of

loneliness is generally associated with brain regions or circuitry involved in self-regulation, processing of social and emotional stimuli, social perception, and reward processing such as the amygdala, frontal cortex, insula, and ventral striatum (S. Cacioppo, Capitanio, & Cacioppo, 2014; Lam et al., 2021). Results differ by age such that loneliness in younger adults' impact white matter whereas loneliness impacted grey matter in older adults. In younger adults, loneliness was associated with smaller white matter density in areas linked to social cognition, judgement, and decision-making, including in the bilateral inferior parietal lobule (IPL), right anterior insula (AI), posterior temporoparietal junction (pep), left posterior superior temporal sulcus (pSTS), dorsomedial prefrontal cortex (dmPFC) and rostrolateral prefrontal cortex (RLPFC); (Nakagawa et al., 2015). Diffusion tensor imaging studies in younger adults have also found that loneliness is associated with significantly decreased fractional anisotropy of white matter fibers associated with the ventral attention network (Tian et al., 2014). In older adults, loneliness has been associated with smaller gray matter volumes of structures important for cognitive control and emotional regulation, after accounting for covariates such as social network size: left amygdala/anterior hippocampus, left posterior parahippocampus, and left cerebellum (Duzel et al., 2019). Functionally, when presented with pleasant pictures of people versus equally pleasant pictures of objects, lonely individuals showed weaker activation of the ventral striatum in response to the images of people, suggesting that those who experience loneliness may receive less pleasure during interpersonal interactions compared to other pleasant encounters, or compared to those who are not lonely (Hawkley, Preacher, & Cacioppo, 2007). Individuals who were lonely, compared to non-lonely individuals also have shown greater attention towards negative social information than to non-social information when presented with a modified emotional Stroop task (Bruce, Wu, Lustig, Russell, & Nemecek, 2019). These

findings provide support for an underlying neural pathway that may explain loneliness' impact on behavioral and cognitive outcomes. To our knowledge, there are no published imaging studies, to date, that have examined the association between loneliness and structural or functional brain regions in PWH.

A growing number of studies have been conducted to investigate the psychosocial risk factors that may increase the likelihood of feeling lonely, including relationship and socioeconomic status, education level, race/ethnicity, sex/gender, etc. Being single or unmarried (widowed, divorced, or never married), having lower education, and lower socioeconomic status independently increased the risk of loneliness (Cohen-Mansfield, Hazan, Lerman, & Shalom, 2016; Hawkley & Capitanio, 2015; Jakobsson & Hallberg, 2005). In addition, being an ethnic minority or recent immigrant has also been associated with higher loneliness (Parkhurst & Asher, 1992; Wu & Penning, 2015). In a sample of older U.S. participants (57 to 85 years), Black individuals reported experiencing significantly higher loneliness compared to non-Hispanic White and Hispanic people, but there was no difference on loneliness between non-Hispanic White and Hispanic individuals (Miyawaki, 2015). In a sample of younger Americans (18 to 25 years), Asian individuals reported feeling significantly lonelier than Hispanic individuals, but did not differ between non-Hispanic White or Black individuals (Hirsch, Chang, & Jeglic, 2012). In a comprehensive review of 38 studies, mixed findings related to sex/gender on loneliness was observed (Cohen-Mansfield et al., 2016). Some studies suggest that women experience greater loneliness (Jakobsson & Hallberg, 2005), although these effects may be attenuated when also accounting for age. Some studies suggested that the effects of gender on loneliness may differ depending on the age range studied. For exampl, women in the oldest age range (>85 years) reported feeling lonelier than their male counterparts (Zebhauser et al., 2014). Other studies

found that men were lonelier (Djukanovic, Sorjonen, & Peterson, 2015), or found no gender differences at all (Nicolaisen & Thorsen, 2014). Across studies, living alone was not consistently associated with loneliness, however, having fewer close relationships, poorer physical health, poorer functional status/physical activity, living in a rural area, identifying as LGBTQ, and alcohol and tobacco use were consistently associated with higher loneliness (Cohen-Mansfield et al., 2016; Greene et al., 2018; Jakobsson & Hallberg, 2005; Kumar et al., 2020; Zebhauser et al., 2014). Finally, other factors such as stigma (Nachega et al., 2012; Yoo-Jeong et al., 2019) and medical conditions that may be linked to inflammation and related process have also been associated with increased risk for loneliness (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012; Leschak & Eisenberger, 2019; Moieni & Eisenberger, 2018; Smith, Gavey, NE, Kontari, & Victor, 2020).

In PWH, some studies have found that the risk factors and/or consequences of loneliness may differ depending on demographic factors. For example, loneliness was significantly associated with illicit drug use and heavy drinking in older female, but not male PWH (Mannes et al., 2016). Studies conducted in PWH across the lifespan have consistently linked loneliness to poorer health and functional outcomes, including reduced physical activity, neurocognitive impairment, and poorer overall quality of life (Greene et al., 2018; Han et al., 2017; Harris et al., 2020; A. L. Nguyen, McNeil, Han, & Rhodes, 2018). These relationships are also observed after accounting for relevant demographics and biopsychosocial characteristics, including age, relationship status, education, living alone, substance use, and social connectedness (Han et al., 2017; Harris et al., 2020). Finally, there is evidence linking loneliness to poorer sleep (Fekete, Williams, & Skinta, 2018), as well as riskier sexual (Bryant et al., 2018; Golub et al., 2010;

Munoz-Laboy, Hirsch, & Quispe-Lazaro, 2009) and drug use behaviors (Greene et al., 2018; Hussain et al., 2022; Mannes et al., 2016; Stanton et al., 2015) in PWH.

In addition to the above risk factors and outcomes related to loneliness, loneliness has also been strongly associated with depression (Erzen & Cikrikci, 2018). Generally, it considered a contributor of depression. Yet, just as loneliness impacts depression, depression may also exacerbate feelings of loneliness. Notably, most longitudinal studies illustrate that loneliness generally predicts depression; however, depression does not always predict loneliness. Prospective studies have also shown that higher levels of loneliness were associated with more depressive symptoms in middle-aged and older adults. For example, across the lifespan (e.g., from mid-adolescents to older adults) and in ethnically diverse samples, loneliness predicted worsening of depression symptoms over time (Koenig & Abrams, 1999; Cacioppo, Hawkley, & Thisted, 2010), even after controlling for baseline depression symptoms. Another study of more than 5,000 community-dwelling older adults ($\geq$ 50 years), found evidence of a bidirectional relationship between loneliness and incidence of mood disorder (Green et al., 1992). While loneliness was a significant predictor of both Generalized Anxiety Disorder (GAD) and MDD, only GAD significantly predicted loneliness scores at two-year follow-up (Domenech-Abella, Mundo, Haro, & Rubio-Valera, 2019), suggesting that there is stronger directionality of loneliness influencing depression outcomes than depression influencing loneliness outcomes. Finally, among older adults (60-90 years) with late-life depression, loneliness was associated with less likelihood MDD remission after two years and more severe depressive symptoms, illustrating the adverse impact that loneliness can have on recovering from clinical depression, as well (Holvast et al., 2015).

Despite the multitude of studies investigating the link between loneliness and depression in the general population, research investigating this relationship in PWH has been limited to cross-sectional studies and has lacked comparisons with PWoH. In addition, most studies investigating depression and loneliness in PWH have had a limited focus on older (> 50 years) white males. The additive impact of loneliness and depression in PWH has also been associated with more risk-taking behaviors such as risky sexual behaviors and substance use (Siconolfi et al., 2013; Su et al., 2018; Wang et al., 2017). Both loneliness and depression symptoms also mediated the relationship between HIV-related stigma and medication adherence, as well as HIV-related stigma and sleep quality, suggesting independent effects of these constructs. However, results also suggest interconnected mechanisms between loneliness and depression in HIV, such that internalized stigma has predicted higher loneliness, which was associated with more depressive symptoms, poorer medication adherence, and sleep quality in PWH (Fekete et al., 2018; Turan et al., 2016). Although no longitudinal studies have specifically examined the relationship between loneliness and depression, there are studies that have looked at other psychosocial characteristics such as the impact of perceived support from spouse/partner or children on antiretroviral therapy adherence in PWH (Mao et al., 2019). However, loneliness was not specifically examined in this longitudinal study, and the potential impact of loneliness on depression symptoms over time in PWH has yet to be directly studied.

The mechanisms by which loneliness impacts depression are still being understood. Loneliness contributes to the affective (e.g., negative feelings of rejection, worthlessness, isolation), cognitive (e.g., negative self-conceptions, bias towards negative social cues, poorer self-efficacy), and behavioral (e.g., inhibited sociability, poor social skills, and social effectiveness) subcomponents of depression. Although some features of loneliness and

depression overlap (e.g., poorer sense of belongingness, and sadness; (Hagerty, Williams, Coyne, & Early, 1996), there is evidence that loneliness and depression are dissociable. For example, in loneliness, appraisals are specific to those pertaining to social aspects in one's life. In depression, appraisals are more global and encompass many multiple domains (e.g., cognitive, affective, somatic; van Winkel et al., 2017). Additionally, studies have found independent effects of loneliness on outcomes closely linked to depression, such as the quality of social interactions persists even after controlling for depression (L. C. Hawkley et al., 2003). Loneliness and depression may also be dissociable at the neural level. For example, in a sample of individuals with and without MDD, individuals who also reported higher loneliness showed greater prefrontal-anterior cingulate-parietal connectivity during a task of inhibitory control (Stroop) regardless of MDD status. In addition, those with MDD and higher loneliness showed weaker activation of the parietal and cerebellar regions during this task and overall reduced parietal-anterior cingulate connectivity during a resting state period, compared to those with MDD and lower loneliness (Shao et al., 2019).

Biological mechanism may also underlie the relationship between loneliness and depression. Loneliness and depression are independently associated with elevated systemic inflammation, which may result in further downstream consequences on health and well-being (Lam et al., 2021). Chronic inflammation can result in damage to healthy tissue, as well as the progression of disease processes such as cardiovascular disease. Although the relationship between depression and inflammation has been well-established, studies investigating loneliness and inflammation, and the combined effects between loneliness, depression, and inflammation are more limited.

Most cross-sectional studies of links between loneliness and inflammation in the general population have focused on a limited number of systemic biomarkers of inflammation (e.g., C-reactive protein [CRP], fibrinogen, and/or interleukin-6 [IL-6]). A recent meta-analysis found eleven studies that examined the association between loneliness and biomarkers of inflammation measured in plasma (CRP, fibrogen, IL-1RA, IL-6, or MCP-1) though noted limitations with regards to methodological heterogeneity across studies (Smith, Gavey, NE, Kontari, & Victor, 2020). The most consistent finding was an association between loneliness and IL-6 (a pro-inflammatory cytokine and an anti-inflammatory myokine that is produced in response to infections and tissue injuries). IL-6 mediates the body's inflammatory response but can play a pathological role in systemic inflammation if over-expressed (Hackett et al., 2012; Jaremka, Fagundes, Glaser, et al., 2013; Jaremka, Fagundes, Peng, et al., 2013; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004). By contrast, levels of circulating CRP (a protein whose circulating concentrations rise in response to inflammation or infection and can be linked to HIV disease progression) and fibrinogen (a coagulation factor that increases its plasma concentrations in response to inflammation) were more strongly associated with objective social isolation rather than loneliness (McDade, Hawkley, & Cacioppo, 2006; Mezuk et al., 2016; Shankar, McMunn, Banks, & Steptoe, 2011). These differential findings may reflect the trait versus state aspects of loneliness. For example, the experience of loneliness may be a more longstanding, stable construct than when one experiences objective social isolation. Thus, the more acute-response inflammatory biomarkers, CRP and fibrogen, may increase in response to the more transient distress of objective social isolation, while IL-6 may be more reflective of the chronicity that is usually associated with loneliness.

Research suggests that elevated systemic inflammation is not only a common pathway involved in clinical depression but may put individuals at-risk for further downstream consequences such as hypercoagulability, a process involved in cardiovascular disease (Lu et al., 2019; J. C. Stewart et al., 2020). Biomarkers of inflammation such as sCD14, Il-6, and D-dimer have been shown to be elevated and associated with depressive symptoms among PWH and PWoH (Lu et al., 2019; J. C. Stewart et al., 2020). In PWH, chronic inflammation, which persists even in the context of viral suppression on ART, has been linked to several adverse health outcomes (Hunt, 2012; Zicari et al., 2019) and disease-related (e.g., worse disease progression) outcomes, as well as increased risk of mortality (Kuller et al., 2008; Lau et al., 2006; Lien et al., 1998; Sevigny et al., 2007). There is reason to suspect that loneliness in PWH would be associated with an elevated inflammatory response, given findings that show high social support mitigates the negative effect of D-dimer (a fibrin degradation product and marker of inflammation) on successful aging in PWH (Sun-Suslow et al., 2020). To date, there is only one study that has investigated the associations between inflammation, loneliness, and depression in PWH. However, the authors did not find relationships between inflammation and loneliness in their sample, possibly given that it was primarily consisted of older men with HIV.

It is also important to identify individuals who fall into the subgroup of being depressed and having elevated systemic inflammation given evidence that they may experience reduced or no responsiveness to antidepressant therapies (Miller, Haroon, & Felger, 2017). It is hypothesized that the increase in inflammation observed in those who are lonely represents a "biological scar" that has resulted from early exposure to high levels of stress (Pariante, 2017), and the biological pathways involved in loneliness and chronic stress overlap a great deal. In addition, as mentioned, evidence strongly suggests that loneliness has an influence on

depression. Therefore, individuals who are lonely may also be at higher risk of being part of the patient subgroup that is depressed and has high systemic inflammation. Although there are some links between these biomarkers and loneliness in PWoH, no studies have yet examined the relationships between these biomarkers of systemic inflammation and loneliness in PWH. In addition, there are no studies that have examined the associations between loneliness, biomarkers of systemic inflammation, and depression simultaneously.

Overall Study Objectives

PWH may be at increased risk of loneliness compared to PWoH due to stigma, discrimination, and objective social isolation. Furthermore, depression can be a consequence of loneliness, which is problematic given its high prevalence in PWH. To our knowledge, there are no studies that have directly compared the prevalence of loneliness, its predictors, or it's outcomes between PWH and PWoH, nor are there any longitudinal studies investigating loneliness and depression in PWH. This dissertation aimed to address gaps in the literature related to loneliness in PWH by examining: 1) the prevalence of loneliness and psychosocial factors that may mitigate it, 2) associations between loneliness and systemic inflammatory biomarkers, and 3) cross-sectional and longitudinal impacts of loneliness on depression. **Figure 1** below illustrates the overall conceptual model and multi-study design of this dissertation.

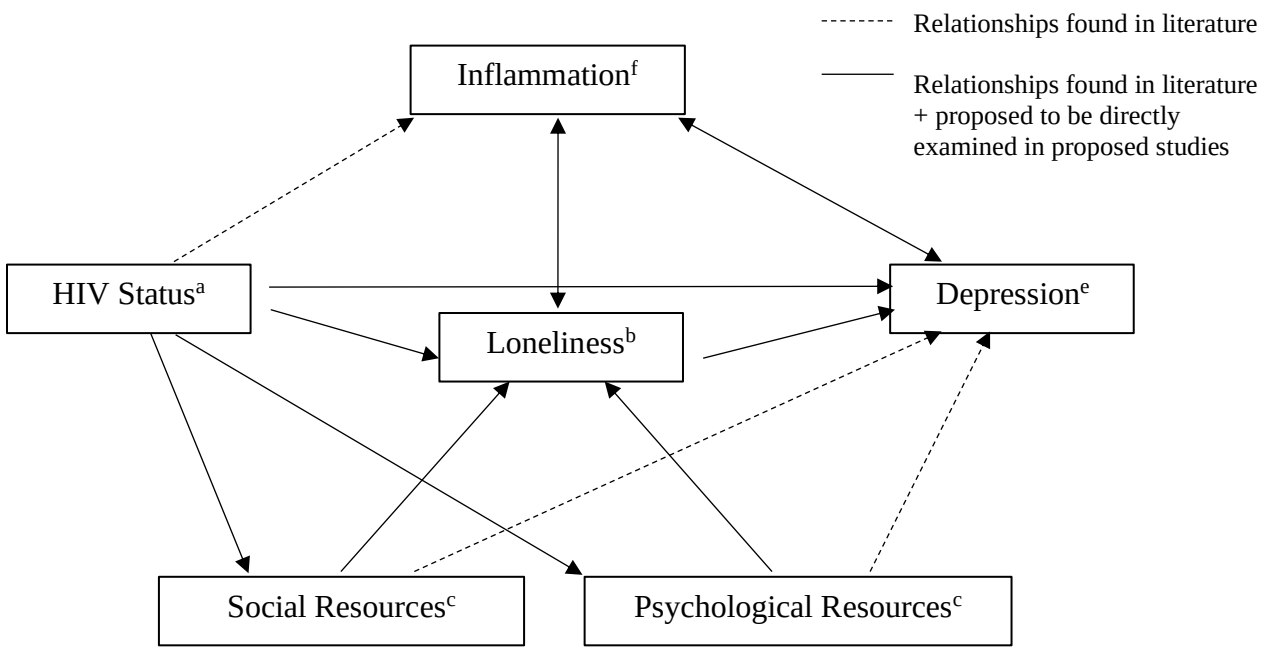

Figure 1. Conceptual model and multiple-study design of the dissertation, examining the hypothesized predictors and consequences of loneliness in PWH, using both cross-sectional and longitudinal methods. [a]HIV: People with HIV (PWH) or people without HIV (PWoH); [b]Loneliness: revised UCLA Loneliness Scale – Version 3 total score; [c]Social Resources: Number of social interactions in the past week (Duke Social Support Scale) and frequency of emotional support (Emotional Support Scale from the MacArthur Healthy Aging Questionnaire); [c]Psychological Resources: resilience (Connor-Davidson Resilience Scale), personal mastery (Personal Mastery Scale), wisdom (Three-Dimensional Wisdom Scale); [e]Depression: Center for Epidemiological Studies Depression Scale; [f]Peripheral plasma biomarkers of chronic inflammation: C-reactive protein (CRP), D-dimer, Interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1), soluble CD14 (sCD14).

Specific Aims and Hypotheses

Study 1 (N = 202). This cross-sectional study included baseline data from 202 community-dwelling adults with and without HIV (PWH, n = 120; PWoH, n = 82) who participated in the NIH-funded study of Multi-Dimensional Successful Aging among Adults living with HIV study (R01 MH099987). The study was conducted at the HIV Neurobehavioral Research Program (HNRP) and Stein Institute for Research on Aging (SIRA) at the University of California San Diego (UC San Diego). Data from participants' first study visit at which the revised UCLA Loneliness Scale-Version 3 (UCLA-3) was completed were included in analyses and considered baseline data. These visits took place between November 2015 and January 2019. The primary aims of this study were to determine the prevalence of clinically relevant loneliness

in people with HIV (PWH) relative to people without HIV (PWoH), and investigate the predictors (i.e., social, and psychological resources) of loneliness and its impact on depression in these groups.

Hypothesis 1a. The proportion of people who self-report moderate-to-high levels of lonely (using validated cutoffs for the UCLA Loneliness Scale), will be significantly higher in PWH than people without HIV (PWoH), independent of other relevant covariates (e.g., demographic characteristics, medical comorbidities). Hypothesis 1b. The presence of social resources (social interactions and emotional support) and psychological resources (resilience, personal mastery, wisdom) will mitigate loneliness in PWH. Hypothesis 1c. Individuals with higher loneliness will report significantly higher depression symptoms, particularly among PWH, after accounting for relevant covariates (e.g., social interactions), given evidence of PWH's increased vulnerability to depression (McIntosh, Seay, Antoni, & Schneiderman, 2013).

Study 2 (N = 82). In this cross-sectional study, a subset of PWH from the Study 1 baseline cohort who had available data across five plasma biomarkers of systemic inflammation (CRP, D-dimer, IL-6, CCL2/MCP-1, and sCD14) and were on suppressive antiretroviral therapies (ART) were examined. The average age of this cohort was 52.90 years old (SD = 8.53). The aim of this study was to determine the relationship between loneliness and biomarkers of systemic inflammation in PWH and investigate the independent and interactive effects of loneliness and inflammation on depression symptoms in PWH.

Hypothesis 2a: In PWH, higher levels of systemic inflammatory biomarkers will be associated with increased loneliness. Hypothesis 2b: In PWH, loneliness will remain a significant predictor of depression symptoms, when simultaneously controlling for biomarkers of systemic inflammation that associated with depression and HIV disease processes and were available for

analysis in the parent study. Hypothesis 2c: There will be a significant interaction between loneliness and biomarkers of systemic inflammation in PWH, such that participants who report higher loneliness and evidence higher inflammation will also report more depression symptoms.

Study 3 (N = 139). This longitudinal study included a subset of n=139 participants (80 PWH and 59 PWoH) from the Study 1 sample who completed a follow-up assessment that occurred at least one year after their comprehensive baseline assessment, and at both visits were administered the revised UCLA Loneliness Scale-Version 3 (UCLA-3) and the Center for Epidemiologic Studies Depression Scale (CES-D). The average interval period in this cohort was between visits was 2.25 years (SD = 1.04) and the average time interval between visits was 14.84 months (SD = 5.82). The aim of this study was to determine the within- and between-person longitudinal effects of loneliness on depression in PWH relative to PWoH.

Hypothesis 3a. At visits when individuals report more loneliness than is their usual, they also will report more concurrent depression symptoms, and this relationship will be stronger in PWH than PWoH. Hypothesis 3b. Higher relative loneliness at one point in time will predict increased depression symptoms at the next visit, and this relationship will be stronger in PWH than PWoH. Hypothesis 3c. The number of average weekly social interactions that a person typically experienced across their study visits will moderate the relationship between their relative loneliness and concurrent depression symptoms, as well as the predictive relationship between relative loneliness and follow-up depression symptoms.

CHAPTER 1.

Prevalence of Loneliness, its Associations with Psychological and Social Resources, and its Impact on Depressive Symptoms among Adults with and without HIV

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Abstract

Background: Approximately 50% of people with HIV (PWH) experience some degree of loneliness (i.e., perceived social isolation) in their lifetime. However, it is unknown whether loneliness disproportionately affects PWH compared with people without HIV (PWoH), what factors may mitigate feelings of loneliness, and to what extent loneliness affects depression in these groups. Setting: 202 community-dwelling adults (mean age [SD]=52.5 [9.73]) were grouped by HIV status: PWH (*n*=120) and PWoH (*n*=82). Methods: Self-report measures captured loneliness (The UCLA Loneliness Scale-Version 3), depressive symptoms (Center for Epidemiological Studies Depression Scale), and other psychological (i.e., resilience, personal mastery, wisdom) and social resources (i.e., social interactions and emotional support). Two stepwise multivariable linear regression models using backwards Akaike information criterion (AIC) selection elucidated the predictors of loneliness and depressive symptoms.
Results: PWH reported significantly higher loneliness than PWoH (*p*=.005). The rates of high loneliness were significantly greater among PWH (41.67%) than among PWoH (29.3%; *p*=.049). Low cognitive wisdom was associated with more loneliness, but only among PWH, while low emotional support was associated with more loneliness only among PWoH. Race/ethnicity, resilience, and personal mastery were significant main effects predicting loneliness. Additionally, loneliness significant variance in depression scores, even after account for relevant covariates. Conclusion: PWH experience more severe loneliness compared to PWoH. In PWH, wisdom served as protective factors against loneliness, suggesting that PWH may rely more on internal rather than external resources to counteract perceived social isolation. Regardless of HIV status, individuals experiencing more loneliness are likely to experience more depressive symptoms.

1. Introduction

Loneliness, the discrepancy between an individual's desired and actual social relations, is based on subjective perceptions of the quality and quantity of social connections (Leigh-Hunt et al., 2017). Those with many social interactions may feel lonelier than those who live in solitude, depending on their satisfaction with their social relations. Unfortunately, loneliness prevalence is difficult to estimate given differences in measurement and sample characteristics. A nationally representative U.S. sample of people without HIV (PWoH) aged 50 and older found loneliness prevalence ranged from 14-17% (Das, 2019). Research is limited regarding the prevalence of loneliness in people with HIV (PWH). Current estimates suggest that nearly half of all PWH experience some amount of loneliness across the lifespan (Harris et al., 2020; Stanton et al., 2015). Furthermore, of the individuals who reported loneliness, approximately 37% attributed feelings of loneliness in connection with their HIV status (Nachega et al., 2012). Whether or not HIV-related stresses (i.e., stigma), or other psychological and social issues that concentrate in PWH contribute to loneliness remains unclear.

Loneliness has been closely linked to factors that are highly prevalent among PWH, including poverty, stigma, unemployment, physical illness, functional impairment, low vitality, and low motivation (Greene, 2018; Harris et al., 2020; Yoo-Jeong et al., 2019). Considering the high rates of substance use among PWH, several studies document strong associations between loneliness and illicit drug use, smoking tobacco, and alcohol consumption (Deren et al., 2019; Hussain et al., 2022; Mannes et al., 2016; Mazonson et al., 2020; Stanton et al., 2015). Research examining psychosocial factors that may increase vulnerability to experiencing loneliness among persons without HIV has focused on personal psychological resources including personal mastery, resilience, and wisdom. In PWoH, higher levels of personal mastery were associated

with lower reports of loneliness (Ejlskov, Wulff, Boggild, Kuh, & Stafford, 2018). In a sample of community-dwelling adults across the lifespan, among psychological traits examined (e.g., resilience, optimism, mental well-being, and wisdom) loneliness was most strongly associated with wisdom, a complex human trait comprised of many components including prosocial behaviors, emotional regulation, and self-reflection (Jeste & Lee, 2019; Lee et al., 2019). Despite the prevalence of psychosocial challenges among PWH, studies have yet to examine the role of positive psychological factors and loneliness in this vulnerable population (Remien & Mellins, 2007).

Social structural factors such as the frequency of emotional support, number of social interactions, and quality of social relations may also underlie feelings of loneliness (S. Cohen, 2004; Shiovitz-Ezra & Parag, 2019). Among a nationally representative sample of PWoH, the number of family and friend relationships, and the frequency of social contact, were negatively associated with loneliness (Shiovitz-Ezra & Parag, 2019). Similarly, in PWH, studies suggest that social network strength, quality of relationships, and social support are strongly associated with loneliness (Greene, 2018; Sun et al., 2009). Considering social isolation and marginalization can be heightened in PWH, understanding the complex relationships between social structural factors and loneliness remains a priority to identify targets for interventions to reduce loneliness (Emlet, 2006; Yoo-Jeong et al., 2019).

The goal of the current study was to compare the prevalence of clinically relevant loneliness between PWH and PWoH, investigate possible predictors of loneliness, and examine the impact of loneliness on depressive symptoms. We hypothesized that the prevalence of loneliness will be higher in PWH than PWoH, and loneliness will remain higher among PWH after adjusting for demographic, psychological, and social variables. We also hypothesized

positive psychological and social resources would attenuate the effect of HIV on loneliness. Finally, we hypothesized that higher loneliness would be associated with higher depressive symptoms, after controlling for relevant covariates, particularly among PWH.

2. Methods

2.1. Participants and Study Design

This cross-sectional study included baseline data collected from 202 community-dwelling adults (20-69 years) with and without HIV (PWH, *n*=120; PWoH, *n*=82) who participated in the NIH-funded study of Multi-Dimensional Successful Aging among Adults living with HIV conducted at the HIV Neurobehavioral Research Program (HNRP) and Stein Institute for Research on Aging (SIRA) at the University of California San Diego (UCSD). UCSD's Human Research Protections Program approved all procedures. All participants provided written, informed consent. Study visits took place between November 2015 and January 2019.

2.2. Inclusion/Exclusion Criteria

Data from participants who had completed a baseline loneliness questionnaire were included in analyses. Exclusion criteria were minimal to enroll representative cohorts of PWH and PWoH and avoid potential selection bias. Exclusion criteria included (1) diagnosis of a psychotic disorder (e.g., schizophrenia) or mood disorder with psychotic features, (2) significant neurological condition (beyond HIV infection) known to impact cognitive functioning (e.g., Alzheimer's disease, stroke, traumatic brain injury), and (3) positive urine toxicology (excluding marijuana).

2.3. Assessment Measures

2.3.1. Loneliness

The revised UCLA Loneliness Scale-Version 3 (UCLA-3) is a 20-item self-report measure that determines the degree to which someone experiences dissatisfaction due to feeling socially disconnected or isolated from others (Russell, 1996). Responses fall on a Likert-type scale from 1=Never to 4=Always, which are summed ranging from 20-80 such that higher total scores reflect greater loneliness. This scale has been used across many populations including PWH (Grov, Golub, Parsons, Brennan, & Karpiak, 2010), and showed excellent internal consistency in our sample (Cronbach's α = 0.94). A score of$\geq$44 is categorized as "high loneliness and/or highly lonely" (36.7% of whole group), a score between 28 and 43 is considered "moderate loneliness and/or moderately lonely" (41.4% of whole group), and a score<28 is considered "low loneliness and/or not lonely" (21.9% of whole group). These cutoffs have been previously published and utilized in studies of healthy adults across the lifespan (J. T. Cacioppo & Patrick, 2008; Lee et al., 2019).

2.3.2. Depressive Symptoms

The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item self-report measure that assesses the frequency of depressive symptoms experienced in the past week (Radloff, 1977). The CES-D has good sensitivity and specificity for MDD vs other psychological disorders. It has been used in research and clinical settings across many populations, including in PWH (Chenneville, Gabbidon, Drake, & Rodriguez, 2019; Lewinsohn, Seeley, Roberts, & Allen, 1997; Marando et al., 2016). Responses range from 0 to 3 (0=Rarely or none of the time [< 1 day]; 1=Some or a little of the time [1-2 days]; 2=Occasionally or a moderate amount of time [3-4 days]; 3=All of the time [5-7 days]) and summed to generate a total score ranging from 0-60, with higher scores reflecting greater degree of depressive

symptoms. The scale had acceptable internal consistency within our sample (Cronbach's α = 0.78).

2.3.3. Psychiatric and Psychosocial Assessment

All participants completed the Composite International Diagnostic Interview (CIDI) version 2.1 (Kessler & Ustun, 2004; Wittchen, 1994), a semi-structured clinical interview to assess for the presence of current and lifetime mood disorders (i.e., Major Depressive Disorder) and lifetime substance abuse or dependence based on the *DSM-IV* criteria (APA, 1994).

To determine the possible influence of positive protective social and/or psychological factors on loneliness, the following psychological and social resources were selected. Psychological resources refer to internal, intraindividual differences associated with positive psychological traits (i.e., resilience, personal mastery, and wisdom).

2.3.3.1. Psychological Resources

2.3.3.1.1. Resilience

The Connor-Davidson Resilience Scale (CDRS) is a widely used measure of resilience and has been utilized across multiple populations including in PWH (Connor & Davidson, 2003; Dulin et al., 2018; D. E. Stewart & Yuen, 2011). The CDRS is a 10-item self-report measure that asks individuals to rate their outlook on life related to different adverse circumstances. Responses range from 1=Not True at All to 5=True Nearly All of the Time. Item responses are summed, and higher scores reflect greater resilience. Internal consistency was excellent in our sample (Cronbach's α = 0.93).

2.3.3.1.2. Personal Mastery

The Personal Mastery Scale (PMS) is a 7-item self-report measuring the degree to which an individual believes their life chances are under their personal control rather than fatalistically

determined, is one of the most widely used measures of personal mastery in health research (Pearlin & Schooler, 1978). Items are rated on a Likert scale ranging from 1=Strongly Agree to 4=Strongly disagree. Total scores range from 7-28 with higher scores reflecting higher personal mastery; the scale had good internal consistency in our sample (Cronbach's α = 0.85).

2.3.3.1.3. Wisdom

The Three-Dimensional Wisdom Scale (3D-WS) is a well-validated 39-item self-report measure in which participants rate the degree to which different statements about themselves are true (Ardelt, 2003). Twenty-four of these items are presented with a 5-point Likert-type scale from 1=Definitely true of myself to 5=Not True of Myself, and 15 items are presented with a 5-point Likert scale from 1=Strongly Agree to 5=Strongly Disagree. Three subscales comprise the 3D-WS (cognitive, affective, and reflective wisdom). Higher scores on the subscales and total scale represent greater wisdom traits. Internal consistency was excellent in our sample (Cronbach's α = 0.91).

2.3.3.2. Social Resources

2.3.3.2.1. Social Interactions

Social interactions, a proxy for objective social isolation, can impact loneliness (Menec, Newall, Mackenzie, Shooshtari, & Nowicki, 2020). The sum of two items from the 4-item Duke Social Support Index (H. G. Koenig et al., 1993) were calculated to measure social interactions ("How many times during the past week did you spend time with someone who does not live with you, that is you went to see them or they came to visit you or you went out together?" and "How many times did you talk to someone [friends, relatives or others] on the telephone in the past week [either they called you, or you called them]?"). Responses are summed, ranging from 0-14, with higher scores indicating more social interactions.

2.3.3.2.2. Emotional Support

The sum of two items from the MacArthur Healthy Aging Questionnaire (Seeman, Berkman, Blazer, & Rowe, 1994), which has been validated in healthy older adults and in PWH (Moore et al., 2018), was calculated to measure emotional support ("How often do your spouse, children, close friends and/or relatives make you feel loved and cared for?" and "How often are your spouse, children, close friends and/or relatives willing to listen when you need to talk about your worries or problems?"). Item response range from 0=Never to 3=Frequently and are summed with higher scores reflecting more perceived emotional support. These items showed good internal consistency in our sample (Cronbach's $\alpha = 0.86$).

2.3.4. Neuromedical Assessment

Participants were screened for HIV at the time of study enrollment. A standard enzyme-linked immunosorbent assay (ELISA) with Western blot was completed for those who self-reported HIV-infection to confirm their diagnosis. Others were screened for HIV using an HIV/HCV finger stick test (Miriad-MedMira, Nova Scotia, Canada). All participants who reported being HIV- tested negative for HIV following confirmatory labs.

2.4. Statistical Analyses

All analyses were conducted with JMP Pro 15 statistical software. First, normality was assessed by evaluating the magnitude of skewness and Kurtosis of study variables. Kline (2011) suggested that the absolute value of skewness greater than 3 and Kurtosis value greater than 10 may indicate a problem with normality. The distribution of loneliness scores was somewhat skewed. However, given that the skewness was 0.34 and Kurtosis was 0.60, which fell within the acceptable range of < 3 and < 10, respectively, the magnitude of skewness in loneliness scores was minimal and did not require data transformation or the use of non-parametric methods in

analyses. Therefore, differences between PWH and PWoH's participant characteristics were examined using ANOVA (for continuous variables) or Chi^2 tests (for categorical variables; Fisher's exact tests were used when data in cells were < 20). Pearson's correlation (r) was used to evaluate bivariate correlations. Additionally, Chi^2 tests were used to compare the proportion of individuals who experienced high loneliness (UCLA-3 total score > 44) between groups. Multicollinearity between psychological and social resource variables was also checked by analyzing bivariate correlations between measures, then by calculating the variance inflation factor (VIF) of these variables when included in a multivariable regression predicting loneliness scores. Bivariate correlations between these measures all fell below the suggested threshold for multicollinearity (r=0.7) suggested by Pallant (2020). Additionally, the VIF for all variables was less then 2.0, which was well below the cutoff of 10 that is typically considered (Hair, Black, Babin, & Anderson, 2014). Taken together, these results confirm that multicollinearity did not exist in this study.

Multiple stepwise linear regression modeling using backwards AIC selection, a data-driven approach, was used to determine the variables that parsimoniously explained the most variance in continuous loneliness scores. In addition to HIV status, candidate covariates were included in the regression if they 1) significantly differed between PWH and PWoH (p<.05), and 2) were significantly related to loneliness in the whole sample (N=202) using Pearson's r (α=0.20). This more inclusive cutoff was used in order to guarantee that all potentially relevant variables related to loneliness did not fail to be included in the model given that traditional levels such as α=0.05 can fail in identifying variables known to be important (Mickey & Greenland, 1989). Additionally, the iterative process of backwards AIC regression ensure that redundant, non-significant covariates are excluded in the final model. Depressive symptoms and lifetime

major depressive disorder were not included in the multivariable regression given that these variables were considered, *a* priori, outcomes of loneliness, rather than predictors. Psychological and social resource variables were also selected, *a* priori, as potential predictors in the stepwise model given literature describing their significant associations with loneliness and their significant bivariate associations with loneliness in our sample. For any significant predictor, more detailed subcomponents were examined in the model when possible (e.g., the cognitive, affective, and reflective dimensions of wisdom). Interactions between predictors and HIV status were included to investigate their potential moderating effects in PWH vs PWoH.

Finally, stepwise multivariable linear regression modeling using backwards AIC selection was used to determine whether loneliness remained a significant predictor of depressive symptoms after controlling for covariates. Predictors in the model included loneliness, HIV status, and the interaction between loneliness and HIV status. Covariates were included if significantly associated with depressive symptom frequency at the bivariate level (α=0.20).

3. Results

3.1. Prevalence of Loneliness in PWoH and PWH

Table 1 presents group comparisons for participant characteristics. Loneliness was significantly higher in PWH compared to PWoH (t=2.87, Cohen's d=0.41, p=.005*)*. Using a categorical approach, 15.0% of PWH and 26.8% of PWoH reported low loneliness, 43.3% of PWH and 43.9% of PWoH reported moderate loneliness, and 41.7% of PWH and 29.3% of PWoH reported high loneliness (see **Figure 2**).

3.2. Bivariate Associations with Loneliness

Within the whole group (N=202), loneliness was significantly higher among non-Hispanic (vs Hispanic) individuals (t=1.99, Cohen's d=0.35, p=.048) and among those with a

current MDD diagnosis (t=2.12, Cohen's d=0.66, p=.04), lifetime MDD diagnosis (t=4.59, Cohen's d=0.66, p<.0001), and lifetime substance use disorder (t=2.58, Cohen's d=0.36, p=.01). In PWH, loneliness was significantly higher among those with current MDD (t=2.35, Cohen's d=0.78, p=.02), lifetime MDD (t=3.56, Cohen's d=0.65, p=.0005), and lifetime substance use diagnosis (t=2.26, Cohen's d=0.43, p=.03), but unrelated to sex/gender, ethnicity, current substance use diagnosis, HIV disease characteristics (e.g., ART status, ART adherence, detectability, acute/early infection) or assessed medical comorbidities (e.g., HCV, diabetes, hypertension, hyperlipidemia). In PWoH, loneliness was unrelated (p>.05) to sex/gender, ethnicity, current or lifetime MDD, current or lifetime substance use disorder, or assessed medical comorbidities. Bivariate correlations between loneliness and other continuous participant characteristics are shown in **Table 2**.

3.3. Multivariable Regression Model with Loneliness as the Outcome Variable

A stepwise, backwards multivariable regression using AIC selection approach was conducted to predict loneliness. Model predictors/covariates included ethnicity, HIV status, and psychological and social resource variables; the specific selection criteria for these variables are outlined above. The initial multivariable model was significant (F(10,172)=26.59, Adjusted R^2=0.58, p<.0001). Given that the total wisdom score was a significant predictor of loneliness, the model was rerun to include the specific subcomponents of wisdom (i.e., cognitive wisdom, affective wisdom, and reflective wisdom) in place of total wisdom score. This second model remained significant (F(11,171)=25.63, Adjusted R^2=.60, p<.0001) and is presented in **Table 3**.

In this final model, significant demographic predictors of loneliness included Hispanic ethnicity such that, after accounting for other factors, non-Hispanic ethnicity was associated with more loneliness (B=3.53, 95% CI=[0.57, 6.49], p=.02). Additionally, people with a race/ethnicity

other than White, Black, or Hispanic experienced more loneliness, after accounting for other variables (*B*=5.66, 95% CI=[0.41, 10.90], *p*=.03). There also were significant interactions between HIV status and cognitive wisdom (*B*=-4.29, 95% CI=[-8.24, -0.34], *p*=.03) and HIV status and emotional support (*B*=7.00, 95% CI=[3.46, 10.55], *p*=.0001), in predicting loneliness. Results found a positive moderating effect of cognitive wisdom on loneliness such that PWH reported more loneliness compared to PWoH when cognitive wisdom was low (*B*=5.84, 95% CI=[1.0, 10.69], *p*=.02). By contrast, high emotional support was negatively associated with loneliness only among PWoH (*B*=6.51, 95% CI=[2.84, 10.18], *p*<.001); in PWH, loneliness did not differ by the amount of emotional support reported. A plot of simple slopes illustrating these interactions are presented in **Figures 3a and 3b**, respectively.

3.4. Multivariable Regression Model with Frequency of Depressive Symptoms as the Outcome Variable

A separate stepwise, backwards multivariable regression using AIC selection was conducted with depression score as the outcome variable, and loneliness and HIV status as predictors. Covariates in this model included psychological and social resource variables (i.e., resilience, personal mastery, wisdom, social interactions, emotional support), and were selected using the criteria described above. The resulting model was significant ($F(6, 176) = 20.88$, Adjusted R^2=39.59, *p*<.0001), with loneliness explaining the largest amount of variance in depression scores (*B*=0.25, 95% CI=[0.15, 0.36], *p*<.0001) followed by HIV status (PWH reported more depressive symptoms than PWoH; *B*=-2.48, 95% CI=[-4.27, -0.68], *p*=.007), and the interaction between HIV status and resilience (*B*=0.32, 95% CI=[0.07, 0.57], *p*=.01). This interaction suggested that PWH who had lower resilience experienced more depressive symptoms, however, among PWoH the degree of resilience did not affect depression scores.

Main effects of personal mastery and emotional support were retained in the model but were not significant. Wisdom and number of social interactions in the past week were not predictive of depressive symptoms in this model.

4. Discussion

Findings from our study illustrate that PWH experience more perceived social isolation compared to PWoH. Notably, nearly 42% of PWH reported loneliness that fell in the high/clinically significant range. By contrast, PWoH reported more normal distributions of low (27.8%), moderate (43.9%), and high (29.3%) loneliness, consistent with large-scale studies conducted in non-HIV populations (Leigh-Hunt et al., 2017; Victor & Yang, 2012). Although the rates of clinically significant loneliness in PWH previously published were lower than those observed in our study (Greene, 2018; Grov et al., 2010), prior studies' samples were limited to older adults with HIV. There is evidence among both HIV (Mazonson et al., 2020) and non-HIV (Beutel et al., 2017; Luhmann & Hawkley, 2016) individuals that older age is associated with *less* loneliness. Therefore, given the larger age range in our sample (20-69 years), our study's higher prevalence estimates may be more generalizable to the PWH population than had been previously determined. Beyond establishing the prevalence of loneliness in PWH compared to PWoH, our study closely examined the influence of psychological and socials resources that had been evaluated in relation to loneliness in the general population but had yet to be investigated among PWH. By doing so, main effects of resilience and personal mastery on loneliness were observed, and noteworthy interactions between HIV status and the cognitive component of wisdom and the frequency of emotional support were found.

The frequency of how often an individual saw or spoke to others in recent days was not predictive of loneliness, lending support to the notion that loneliness is a subjective, perceived

experience and separate from objective, social isolation. Findings from our study also did not demonstrate any relationship between HIV disease-related characteristics and loneliness. Although prior literature found that in a sample of men with HIV, loneliness was associated with a lower CD4 cell number, independent of the stage of HIV disease (Straits-tröster et al., 1994), that work was conducted in the earlier era when highly active antiretroviral therapy was not yet widespread. By contrast, our sample of PWH had well-managed HIV, were virally undetectable, and highly adherent to their ARV medication regimen. However, HIV stigma was not assessed in this study, which is specific to PWH and associated with discrimination and/or trauma such as AIDS survivor syndrome (Land & Linsk, 2013; Nachega et al., 2012; Zeligman, Hagedorn, & Barden, 2017), and could explain some of their loneliness experience.

The effects of resilience, personal mastery, and affective wisdom on loneliness were not significantly different between PWH and PWoH. However, among PWH, low cognitive wisdom (i.e., difficulty recognizing different perspectives, positives/negatives of human nature, and processing ambiguity/uncertainty in life) was associated with higher loneliness, while loneliness was stable across different levels of cognitive wisdom in PWoH. The opposite was true of emotional support; the presence of emotional support did not help mitigate feelings of loneliness in PWH in the same way that it helped PWoH. This novel and unexpected finding may suggest that in PWH, loneliness is more sensitive to internal, psychological resources as opposed to external, social resources.

PWH may be more vulnerable to loneliness if they have less cognitive wisdom because they may be more predisposed to experiencing loneliness on a biological level. Prior literature has established strong evidence for an inverse correlation between loneliness and wisdom, in general, and recent studies have found biological support for this inverse relationship. Greater

gut microbiome diversity has been associated with higher levels of wisdom and lower loneliness (T. T. Nguyen et al., 2021). Given that many PWH experience metabolic disorders that may weaken gut diversity (Lozupone et al., 2013; K. A. Nguyen, Peer, Mills, & Kengne, 2016), and in turn affect gene expression, they may be more susceptible to feelings of loneliness. Additionally, the social threat model of loneliness, which states loneliness predisposes individuals to be hypervigilant towards social threats creating a negative feedback loop during emotionally-taxing situations, has been supported by recent findings: loneliness and wisdom activated different components of the temporoparietal junction, an important neural network involved in the processing and perception of social-affective states (Grennan et al., 2021). Given the elevated rates of stigma and discrimination that PWH may experience compared to the general public, their cognitive-neural networks may predispose them to feeling lonely *and* lessen their ability to engage in cognitive tools that may come from wisdom to combat their subjective feelings of loneliness.

Loneliness can have deleterious effects on physical, cognitive, and mental health outcomes in individuals with and without HIV. In this study, we were interested in evaluating whether loneliness was differentially associated with depressive symptoms in PWH versus PWoH. Though there was not a significant interaction between loneliness and HIV status in predicting depression scores, loneliness explained the most variance in depressive symptoms after controlling for other factors such HIV status and protective factors such as social support. Previous studies found that depression explained a significant proportion of variance in loneliness, above and beyond related covariates in PWH such as HIV-associated stigma, cognitive impairment, past unstable housing, and HIV disease burden (Grov et al., 2010; Yoo-Jeong et al., 2019). However, these studies were limited to white, older adults (>50 years), a gap

that our study filled. Additional research is necessary to further elucidate the association between loneliness and depression overtime.

There are some important limitations in the present study. First, our data are cross-sectional, so we cannot assume directionality or claim that psychological and social resource variables influence loneliness longitudinally, or loneliness influences depression longitudinally. It is entirely possible that a bidirectional relationship may exist between these variables. Second, selection criteria for this study's parent study were initially developed to investigate factors of successful aging in PWH. Therefore, most individuals recruited were over the age of 36. However, given recruitment challenges, the age criterion was expanded to include any adults over 18 years. Thus, although our age range is large (20-69 years), it is skewed towards older adults, which may impact interpretation and generalizability. Furthermore, the construct of loneliness can be operationalized and defined in many ways. For this study, we were interested in prevalence rates and predictors of loneliness. However, there is no gold-standard to measure loneliness prevalence rates. Cutoffs for the UCLA-3 were used in this study, which have been used in previously published studies; however, there is wide variability in how prevalence estimates of loneliness have been reported in the literature. Finally, this research would ideally be replicated in a larger sample of PWH and PWoH, including people at higher ages (i.e., $\geq$70 years), who are followed longitudinally to further elucidate the relationships between psychological and social resources with loneliness, and between loneliness and depression.

Despite these limitations, this study has notable strengths. It is the first to directly compare the prevalence of loneliness between HIV and non-HIV samples, and elucidates the factors that may mitigate loneliness, as well as its putative downstream consequences on depression. Consequently, potential areas for intervention are observed. Current literature

suggests that interventions can be effective in enhancing wisdom and emotional support. Numerous randomized-clinical trials have been conducted to enhance the subcomponents of wisdom such as empathy/compassion, emotional regulation, and spirituality, with about half showing moderate to large effect sizes (Lee et al., 2020). Future studies should specifically examine whether loneliness changes following such interventions.

Chapter 1, “Prevalence of Loneliness, its Associations with Psychological and Social Resources, and its Impact on Depressive Symptoms among Adults with and without HIV,” is coauthored with Hussain, Mariam A.; Kohli, Maulika; Karris, Maile; Iudicello, Jennifer E.; Heaton, Robert K.; Jeste, Dilip V.; Moore, David J. The dissertation author was the primary author of this chapter.

Table 1. Participant Characteristics (N = 202).

	PWoH (n=82)	PWH (n=120)	Effect Size	*p*-value
Demographics Characteristics				
Age (years)	52.82 (7.89)	52.28 (10.84)	d = 0.05	.70
Education (years)	**15.16 (2.23)**	**14.29 (2.58)**	***d* = 0.35**	**.01**
Sex/gender (% male)	**67.07%**	**87.50%**	**OR = 1.69**	**.0007**
Ethnicity	--	--	--	.16
White, non-Hispanic (%)	69.51%	55.83%	OR = 0.31	.05
Hispanic (%)	17.07%	20.83%	OR = 1.28	.59
Black (%)	12.20%	15.83%	OR = 1.35	.54
Other[a] (%)	1.22%	7.50%	OR = 6.57	.05
Psychiatric Characteristics				
Depressive symptoms[b]	**15.34 (5.20)**	**18.75 (8.11)**	***d* = 0.48**	**.0009**
Current Major Depressive Disorder (% yes)	2.94%	8.55%	OR = 3.08	.46
Lifetime Major Depressive Disorder (% yes)	**20.73%**	**54.17%**	**OR = 4.52**	**<.0001**
Current Substance Use Disorder (% yes)	2.94%	8.55%	OR = 3.08	.46
Lifetime Substance Use Disorder (% yes)	**35.37%**	**62.50%**	**OR = 3.05**	**.0001**
Neuromedical Characteristics				
HCV (% yes)	**3.66%**	**17.50%**	**OR = 5.59**	**.003**
Diabetes (% yes)	7.32%	12.50%	OR = 1.81	.35
Hypertension (% yes)	**17.07%**	**46.67%**	**OR = 4.25**	**<.0001**
Hyperlipidemia (% yes)	**20.73%**	**40.83%**	**OR = 2.64**	**.004**
HIV Disease Characteristics				
Estimated duration of HIV disease (years)	--	16.63 [3.08, 25.50]	--	--
Nadir CD4 count	--	215 [56, 419]	--	--
Current CD4+ t-cell count	--	678.5 [480.3, 913.5]	--	--
Taking ART (% currently on ART)	--	95.0%	--	--
Total duration of ART (years)	--	10.48 [2.63, 18.49]	--	--
Years of current ART regimen	--	1.20 [0.53, 2.36]	--	--
ART adherence (% adherent[c])	--	91.18%	--	--
Plasma HIV viral load (% undetectable[d])	--	96.58%	--	--
Acute/early HIV infection (% AEH[e])	--	15.84%	--	--
Psychological Resources				
Resilience[f]	**32.17 (6.61)**	**30.02 (7.41)**	***d* = 0.30**	**.047**
Personal mastery[g]	22.77 (3.56)	22.03 (4.36)	d = 0.18	.21
Wisdom[h]	3.66 (0.48)	3.52 (0.55)	d = 0.26	.07
Wisdom – cognitive	3.67 (0.55)	3.52 (0.66)	d = 0.24	.09
Wisdom – affective	3.47 (0.65)	3.41 (0.61)	d = 0.11	.46
Wisdom – reflective	**3.82 (0.61)**	**3.64 (0.63)**	***d* = 0.30**	**.04**
Social Resources				
Social interactions[i]	7.17 (3.42)	6.58 (3.64)	d = 0.17	.25
Emotional support[j]	**2.63 (0.63)**	**2.35 (0.85)**	***d* = 0.37**	**.01**
Loneliness				
UCLA-3 total score[k]	**35.95 (11.23)**	**40.69 (11.75)**	***d* = 0.41**	**.005**

Note. Bold: $p<.05$. Mean (SD) or Median [IQR]; Effect size=Cohen's d or Odds Ratio (OR); [a]Race/ethnicity other than White, Black, or Hispanic; [b]Center for Epidemiological Studies Depression Scale (CES-D); [c]AIDS Clinical Trials Group (ACTG) Adherence Questionnaire (4-day adherence of ≥90%); [d]plasma viral load ≤50 copies/mL; [e]acute/early infection (i.e., between 0- and 52-weeks duration); [f]Connor-Davidson Resilience Scale (CDRS); [g]Personal Mastery Scale (PMS); [h]Three-Dimensional Wisdom Scale (3D-WS); [i]total number of social interactions in the past week determined using 4-item Duke Social Support Index; [j]frequency of emotional support received using MacArthur Healthy Aging Questionnaire; [k]Revised UCLA Loneliness Scale – Version 3 (UCLA-3).

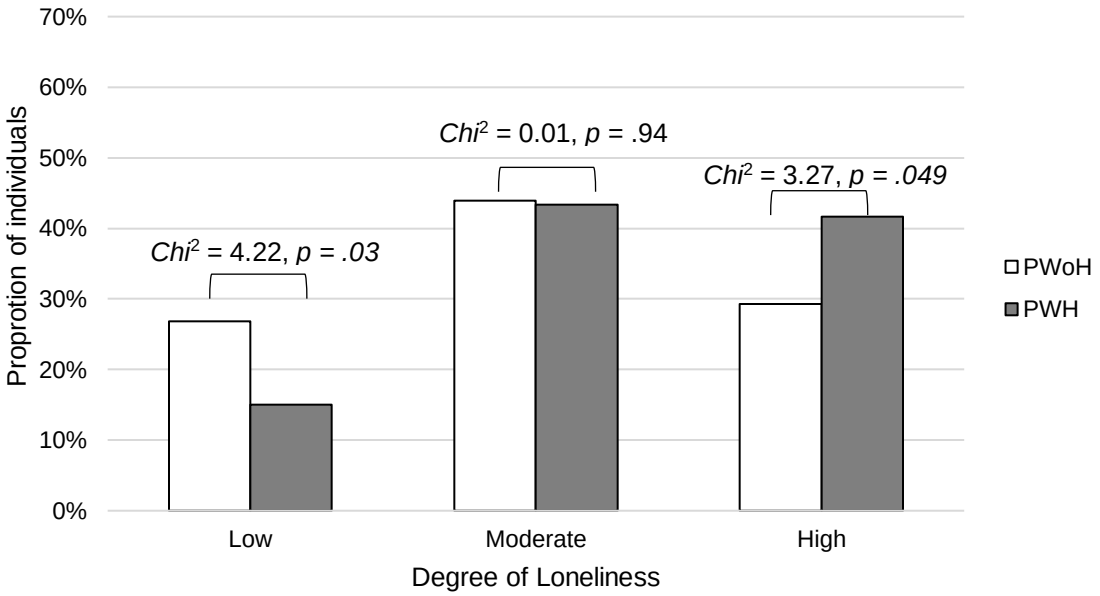

Figure 2. The prevalence of low (UCLA-3 total score < 28), moderate (UCLA-3 total score ≥ 28 and < 44, and high loneliness (UCLA-3 total score ≥ 44) among PWoH and PWH.

Table 2. Bivariate correlations between loneliness scores (UCLA-3[a]) and participant characteristics in the entire sample (*N*=202), and among PWoH (*n*=82) and PWH (*n*=120).

	Entire sample (*N*=202)	PWoH[b] (*n*=82)	PWH[c] (*n*=120)
Demographics Characteristics			
Age (years)	0.05	0.14	0.01
Education (years)	-0.02	0.09	-0.03
Psychiatric Characteristics			
Depressive symptoms[d]	0.56**	0.53**	0.55**
HIV Disease Characteristics			
Estimated duration of HIV disease (years)	--	--	0.04
Nadir CD4 count	--	--	0.12
Current CD4+ t-cell count	--	--	0.16
Total duration of ART (years)	--	--	-0.11
Duration of current[e] ART regimen (years)	--	--	-0.15
Psychological Resources			
Resilience[f]	-0.54**	-0.52**	-0.52**
Personal mastery[g]	-0.57**	-0.50**	-0.59**
Wisdom[h]	-0.48**	-0.40**	-0.51**
Wisdom – cognitive	-0.29**	-0.16	-0.34**
Wisdom – affective	-0.38**	-0.27*	-0.45**
Wisdom – reflective	-0.53**	-0.55**	-0.52**
Social Resources			
Social interactions[i]	-0.35**	-0.44**	-0.28**
Emotional support[j]	-0.56**	-0.70**	-0.48**

Note. Pearson's *r*; Bolded: *p*<.10; **p*<.05; ***p*<.01; [a]Revised UCLA Loneliness Scale–Version 3 (UCLA-3); [b]People without HIV; [c]People with HIV; [d]Center for Epidemiological Studies Depression Scale (CES-D); [e]Among the 95% PWH who are currently on ART; [f]Connor-Davidson Resilience Scale (CDRS); [g]Personal Mastery Scale (PMS); [h]Three-Dimensional Wisdom Scale (3D-WS); [i]total number of social interactions in the past week determined using 4-item Duke Social Support Index; [j]frequency of emotional support received using MacArthur Healthy Aging Questionnaire.

Table 3. Summary of multivariable regression analyses with loneliness as the outcome variable.

Covariate	Risk Direction (More lonely[a])	Bivariate Analyses			Multivariable Analyses (Stepwise Backwards AIC)		
		Statistic	value	*p*	*B*	95% CI	*p*
Age	--	--	--	--	--	--	--
Sex/gender	--	--	--	--	--	--	--
Education	--	--	--	--	--	--	--
Race/ethnicity	--	--	--	--	--	--	--
Hispanic	Non-Hispanic	*t*	1.99	.048	3.53	[0.57, 6.49]	.02
Other	Other	*t*	2.96	.003	5.66	[0.41, 10.90]	.03
HIV status	PWH[b]	*t*	2.87	.005	1.74	[-0.70, 4.18]	.16
Lifetime Substance Use Disorder (SUD)	Yes, lifetime SUD history	*t*	2.58	.011	1.79	[-0.53, 4.12]	.13
Resilience[c]	Less resilience	*r*	-0.55	<.0001	-0.23	[-0.44, -0.03]	.02
Personal Mastery[d]	Less personal mastery	*r*	-0.58	<.0001	-0.95	[-1.30, -0.60]	<.0001
Wisdom – cognitive[e]	Less cognitive wisdom	*r*	-0.29	<.0001	3.85	[0.39, 7.30]	.74
Wisdom – affective[e]	Less affective wisdom	*r*	-0.39	<.0001	-3.34	[-5.46, -1.22]	.002
Wisdom – reflective[e]	Less reflective wisdom	*r*	-0.55	<.0001	--	--	--
Social Interactions[f]	Less social interactions	*r*	-0.33	<.0001	--	--	--
Emotional Support[g]	Less emotional support	*r*	-0.59	<.0001	-10.22	[-13.36, -7.08]	.0004
Wisdom – cognitive[e] x HIV					-4.29	[-8.24, -0.34]	.03
Emotional Support[g] x HIV					7.00	[3.46, 10.55]	.0001
Model Statistics							
F-ratio						**25.63**	
df						**(11, 171)**	
Adjusted R^2						**0.60**	
***p*-value**						**<.0001**	

Note. Variables previously identified in the literature and met the selection criterion (α=0.20) at the bivariate level, were included as candidate covariates in backwards AIC modeling. Light grey shading=variable was not selected by backwards AIC in the final model. [a]Revised UCLA Loneliness Scale–Version 3 (UCLA-3); [b]People with HIV; [c]Connor-Davidson Resilience Scale (CDRS); [d]Personal Mastery Scale (PMS); [e]Three-Dimensional Wisdom Scale (3D-WS); [f]total number of social interactions in the past week determined using 4-item Duke Social Support Index; [g]frequency of emotional support received using MacArthur Healthy Aging Questionnaire.

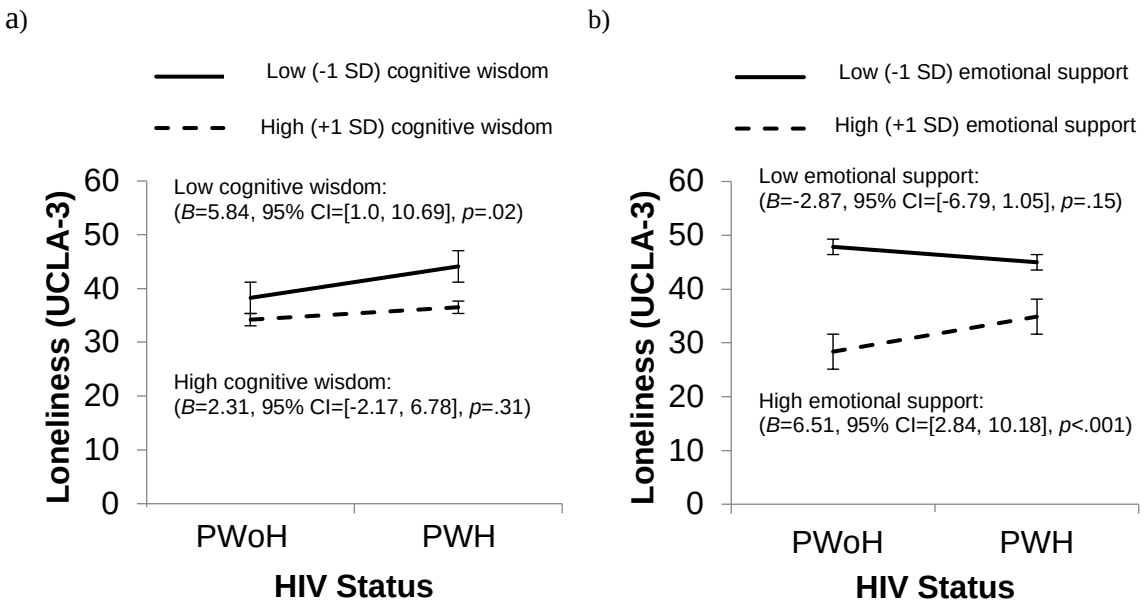

Figure 3. Simple slope plots explaining interactions between a) HIV status and cognitive wisdom on loneliness scores, and b) HIV status and emotional support on loneliness scores.

CHAPTER 2.

Combined Effects of Loneliness and Inflammation on depression in People with HIV

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ABSTRACT

Objective: Loneliness is prevalent in people with HIV (PWH) and associated with adverse health-related consequences, including depression. Chronic inflammation has been linked to depression in PWH, though its association with loneliness is less well established. Simultaneous examination of inflammation, loneliness and depression is needed to clarify these relationships. This study investigated the relationship between loneliness and inflammation, and the effects of loneliness and inflammation on depression in PWH. Methods: 82 PWH who were on suppressive ART (mean age [SD]=53.2 [9.0]) completed the UCLA Loneliness Scale-Version 3 and the Center for Epidemiologic Studies Depression Scale as part of a comprehensive evaluation. Biomarkers of systemic inflammation (CRP, IL-6, CCL2/MCP-1, sCD14) and coagulation (D-dimer) were measured in blood using commercial immunoassays. Results: Multivariable linear regression analyses revealed that higher D-dimer, CCL2/MCP-1, and sCD14 were significant predictors of loneliness (ps<.05) while accounting for relevant covariates. Stepwise multiple linear regression models that included loneliness, biomarkers, and their interactions as predictors of depressive symptoms revealed significant main effects of loneliness and CCL2/MCP-1 levels (ps<.05), and a significant loneliness by D-dimer interaction (p<.05) whereby higher D-dimer was associated with increased depressive symptoms only at higher levels of loneliness. Conclusions: Increased coagulation activity is associated with loneliness, and in the context of loneliness, may increase risk for depression. Increased inflammation was associated with depression suggesting potentially dissociable underlying biological processes. To the extent that these processes are modifiable, such findings could have important implications in the treatment of loneliness and depression in PWH.

1. Introduction

Loneliness, an aversive emotional experience tied to the discrepancy between one's desired and experienced social relations (Perlman & Peplau, 1981), is common among people with HIV (PWH) and is increasingly recognized as an important and understudied health determinant (Grov et al., 2010; J. Holt-Lunstad et al., 2015; Luo et al., 2012). Loneliness (or perceived social isolation) is distinct from objective social isolation (e.g., a lack of contact between an individual and society), or limited social interactions, in that it captures the extent to which an individual feels meaningfully connected to their social world (Hawkley & Cacioppo, 2010). For example, some individuals may feel lonely despite having many social contacts and/or interactions; on the other hand, those who prefer to live solitary lives may not necessarily feel lonely. Studies in the general population have linked loneliness to a host of adverse medical (e.g., cardiovascular disease), psychiatric (e.g., depression, substance use), and neurocognitive (e.g., dementia) consequences (Luo et al., 2012). In older adults, loneliness has also been linked to elevated use of medications such as opioids and benzodiazepines (Vyas, Watt, Yu, Straus, & Kapral, 2021). Additionally, loneliness is a risk factor for mortality (J. Holt-Lunstad et al., 2015; Rico-Uribe et al., 2018) and is a major contributor to the escalating rates of suicides and opioid-related deaths that have led to a reduction in average lifespan in the US over the past two decades (Jeste, Lee, & Cacioppo, 2020).

Loneliness is more common in individuals with chronic illnesses relative to the general population (Pyle & Evans, 2018). In addition to living with a chronic illness, PWH may be even more vulnerable to loneliness due to factors such as stigma, substance use, psychiatric disorders, and lower socioeconomic status (Grov et al., 2010). Studies on loneliness in PWH have found evidence of greater loneliness (Vance, 2006) relative to people without HIV (PWoH). Prevalence

estimates of loneliness in PWH vary across the literature depending on the method of assessment and/or specific operational definition of loneliness used (including different cutoffs on measures of loneliness), as well as differences in sample characteristics (e.g., age, race/ethnicity, psychiatric, and/or substance use characteristics). Studies generally suggest that about 36-58% of PWH report at least one symptom of loneliness (Greene, 2018; Nachega et al., 2012; Rodkjaer et al., 2010). Rates of loneliness have been found to be higher in older PWH (≥50 years old; 46–64%) compared to younger (<50 years) PWH (Mazonson et al., 2020; Yoo-Jeong et al., 2019). Greene (2018) evaluated the prevalence of loneliness in *n*=356 PWH over age 50 using the UCLA 8-item loneliness scale (scores range from 8-32) and found that 58% reported at least one symptom of loneliness, with 24%, 22%, and 12% reporting mild (17-20), moderate (21-24), and severe (>24) loneliness, respectively. In this study (Greene, 2018), lonely PWH reported fewer relationships and were more likely to report depression and substance use (e.g., alcohol, tobacco). Common predictors of loneliness in PWH include social support, network size, and stigma/discrimination, which can be elevated among PWH (Harris et al., 2020). Although factors such as loneliness and social support are closely linked, and both are supported by cognitive theory that relies heavily on perceived, subjective evaluation of social networks (X. Zhang & Dong, 2022), the biological processes between these factors appear to be distinct. For example, aspects of social engagement such as objective social isolation and social support have been associated with lower inflammation, such as lower CRP, while loneliness has been associated with poorer *regulation* of inflammatory processes, such as lower insulin like growth factor-1 (Walker, Ploubidis, & Fancourt, 2019). Importantly, loneliness has been linked to a range of negative health outcomes in PWH, including poorer sleep, less physical activity, increased stress, more risky sexual and drug use behaviors, increased risk of neurocognitive impairment, and

poorer overall quality of life (Bryant et al., 2018; Fekete et al., 2018; Golub et al., 2010; Greene, 2018; Han et al., 2017; Harris et al., 2020; Hussain et al., 2022; Mannes et al., 2016).

Large-scale studies in the general population across the adult lifespan have shown a significant association between loneliness and depression (Erzen & Cikrikci, 2018). This relationship also has been demonstrated in PWH (Fekete et al., 2018; Grov et al., 2010; Rodkjaer et al., 2010). In one study of older PWH, increased loneliness explained an additional 8% of the variance in depression symptoms (R^2=0.42), after accounting for HIV-associated stigma, neurocognitive impairment, fatigue, and age (Grov et al., 2010). Longitudinal research examining the relationship between loneliness and depression in PWH is limited. Studies in the general population have suggested that there are likely bidirectional relationships between loneliness and depression, such that while loneliness often precedes onset of depression, loneliness and depression can exacerbate each other in a cyclical manner (Nuyen et al., 2020). The co-occurrence of loneliness and depression is also problematic and has been associated with increased sexual and drug risk-taking behaviors in PWH (Siconolfi et al., 2013; Su et al., 2018; Wang et al., 2017).

Despite its high prevalence and clinical consequences, little is known about biological processes associated with loneliness in PWH. Chronic inflammation, which persists even in the context of viral suppression on ART, has been linked to several adverse health outcomes in PWH (Deeks, Tracy, & Douek, 2013; Fukui, Piggott, & Erlandson, 2018; Nordell et al., 2014). The biopsychosocial relationships between inflammation and its consequences such as loneliness are complex. Inflammation can cause significant changes in social behavior (Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017). For example, it is suggested that increased inflammation can lead to heightened sensitivity to negative, threatening social experiences (Moieni & Eisenberger,

2018). Inflammation can also be a physiological response to loneliness. While acute loneliness may serve adaptive functions such as pursuit of meaningful social interactions, chronic loneliness may increase perception of social threat and hypervigilance that activates a chronic inflammatory response (J. T. Cacioppo, Hawkley, Norman, & Berntson, 2011), which can have adverse downstream health effects (Hawkley, Burleson, Berntson, & Cacioppo, 2003; Kiecolt-Glaser, Gouin, & Hantsoo, 2010). Consistent with these notions, a recent review and meta-analyses conducted in individuals aged 16 or older from the general population found evidence supporting the link between inflammation and loneliness, though this publication noted limitations with regards to methodological heterogeneity across studies (Smith et al., 2020). Many of the available loneliness studies examined biomarkers of systemic inflammation that have been linked to downstream health-related consequences such as increased cardiovascular risk (Hawkley et al., 2010); these inflammatory processes include cytokines (e.g., interleukin-6 [IL-6]), chemokines (e.g., chemokine (C-C motif) ligand 2/monocyte chemoattractant protein-1 [CCL2/MCP-1]) and acute phase proteins (e.g., C-reactive protein [CRP]); (Hackett et al., 2012; Leschak & Eisenberger, 2019; Nersesian et al., 2018; Smith et al., 2020).

Pro-inflammatory and immune activation markers are elevated in PWH, and chronic inflammation is common even among PWH who are on suppressive ART. Research in PWH has also demonstrated links between inflammation and psychosocial disturbances. For example, Ellis et al. (2021) and Sun-Suslow et al. (2020) found that poorer social support was associated with higher inflammatory biomarkers in plasma and CSF in PWH. Literature in PWoH suggests that the link between social support and inflammation may be mediated through depressive symptoms (Santini, Koyanagi, Tyrovolas, Mason, & Haro, 2015). To our knowledge, only one study has examined the relationship between loneliness (specifically, as opposed to social

isolation or social support) and inflammation in PWH. Derry et al. (2021) examined cross-sectional associations between psychosocial factors and inflammatory markers (IL-6, interferon-gamma [IFN-γ], tumor necrosis factor-alpha [TNF-α], and CRP) in older PWH (aged 54-78; n=143), 93% of whom had a viral load <200 copies/mL; the authors of this study did not find significant associations between loneliness and biomarker levels. Future research is needed to determine possible explanations for the discrepant findings between this study and research in PWoH. The authors suggested that the link between inflammation and loneliness could perhaps be stronger in younger PWH. Another possibility is that, in the context of chronic inflammatory conditions such as HIV, other unmeasured inflammation-related processes may be involved. For example, studies have found associations between greater coagulation activity (e.g., higher levels of fibrinogen and/or D-dimer) and poorer perceived social support in both PWoH (Wirtz, Redwine, Ehlert, & von Kanel, 2009) and PWH (Sun-Suslow et al., 2020). Since D-dimer is associated with similar health-related outcomes as loneliness such as cardiovascular disease (Leigh-Hunt et al., 2017; Valtorta et al., 2016), it is possible that coagulation activity may be another biological process related to loneliness. Thus, in addition to examining the relationship between biomarkers of inflammation and loneliness in PWH, the current study also sought to investigate the relationship between loneliness and D-dimer, a marker of coagulation activation and chronic inflammation, which is elevated and associated with adverse outcomes (e.g., cardiovascular disease, mortality) in PWH (Ford et al., 2010; Kuller et al., 2008).

Inflammation also has been implicated in the pathogenesis of depression in the general population (Kiecolt-Glaser, Derry, & Fagundes, 2015; Miller, Maletic, & Raison, 2009), and in individuals at risk for HIV (Lu et al., 2019). In PWH, a number of studies have found associations between depression and biomarkers of immune activation and inflammation such as

CRP, IL-6, and soluble cluster of differentiation-14 [sCD14] (Lu et al., 2019; Norcini Pala et al., 2016; Rivera-Rivera, Vazquez-Santiago, Albino, Sanchez, & Rivera-Amill, 2016; J. C. Stewart et al., 2020), even in PWH who are virally suppressed (Ellis et al., 2020). Moreover, inflammation-related vascular biomarkers also have been linked to depressive symptoms in PWH such as D-dimer (Norcini Pala et al., 2016; J. C. Stewart et al., 2020).

Despite the above referenced studies, there remains a limited understanding of the complex biopsychosocial relationships between loneliness and inflammation in PWH, as well as the complex biopsychosocial relationships between loneliness, inflammation, and depression. Our study sought to contribute knowledge to this area of research by examining: (1) the relationships between loneliness and biomarkers of systemic inflammation (CRP, IL-6, CCL2/MCP-1, sCD14) and related processes (e.g., coagulation; D-dimer), and (2) the combined influence of loneliness and inflammation on depressive symptoms.

2. Methods

2.1. Participants and Study Design

This cross-sectional study included 82 PWH from the NIMH-funded Multi-Dimensional Successful Aging among Adults living with HIV study, which was conducted at the University of California San Diego (UCSD) HIV Neurobehavioral Research Program (HNRP) and Sam and Rose Stein Institute for Research on Aging (SIRA). IRB approval was obtained from the UCSD Human Research Protections Program, and written consent was obtained from participants after they were informed of the design and purpose of the study, risk and benefits to participation, compensation, data sharing, confidentiality, and participant rights. Visits for the current study took place between November 2015 and December 2018.

2.2. Inclusion/Exclusion Criteria

To enroll a representative cohort of participants, the parent study (i.e., the Multi-Dimensional Successful Aging Among Adults living with HIV study) applied minimal overall exclusion criteria. These were: 1) neurologic condition (not attributable to HIV) known to impact neurobehavioral functioning (e.g., Alzheimer's disease, stroke, traumatic brain injury), 2) psychotic disorders (e.g., schizophrenia), and 3) positive urine toxicology on the day of testing (except for cannabis). Inclusion criteria for the parent study were: 1) aged 36–65 years, 2) fluent in English, and 3) ability to provide informed consent. This study included all PWH from the parent study who completed the UCLA Loneliness Scale - Version 3 and the Center for Epidemiological Studies Depression Scale (CES-D), had complete biomarker data, were currently taking antiretroviral therapy (ART), and were virally suppressed (undetectable plasma HIV RNA viral load [<50 copies/mL]).

2.3. Assessment Measures

2.3.1. Loneliness

Loneliness was measured using the revised UCLA Loneliness Scale – Version 3 (UCLA-3), a self-report measure that assesses the degree to which one perceives themselves to be socially disconnected or isolated from others (Russell, 1996). The UCLA-3 is comprised of 20-items that required a Likert-type response from 1 (Never) to 4 (Always). Example items include, “How often do you feel that people are around you but not with you?” and “How often do you feel that your relationships with others are not meaningful?” Notably, no item explicitly uses the word “lonely.” The UCLA-3 revisions incorporated ten reverse-scored items and simplified the language from previous versions to make it more easily comprehensible to people of all education levels. After reverse-scoring, item responses are summed to provide a total score ranging from 20 to 80, with higher scores reflecting more loneliness. A cut of $\geq$44 on the UCLA-

3 is indicative of high loneliness (Lee et al., 2019). This scale has previously been used to assess loneliness in PWH (Grov et al., 2010), and had excellent internal consistency in our sample (Cronbach's $\alpha = 0.94$).

2.3.2. Depressive Symptoms

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D). This 20-item self-report measure assesses the frequency of depressive symptoms, such as dysphoria, anhedonia, poor appetite, sleep disturbance, difficulty in thinking/concentration, worthlessness, fatigue, or suicidal ideation, that are experienced by the participant over the past week (Radloff, 1977). Participants' responses on each item can range from 0 to 3 (0=Rarely or none of the time [< 1 day in the past week]; 1=Some or a little of the time [1-2 days]; 2=Occasionally or a moderate amount of time [3-4 days]; 3=All of the time [5-7 days]). After reverse-scoring appropriate items, a total score is derived by summing item responses. The total score can range from 0 to 60, with higher scores reflecting a greater frequency of depressive symptoms, and a score of $\geq$16 suggestive of clinically significant depressive symptoms (Lewinsohn et al., 1997). The CES-D has good sensitivity and specificity in identifying Major Depressive Disorder, has been used extensively across many research and clinical populations including PWH (Chenneville et al., 2019; Lewinsohn et al., 1997; Marando et al., 2016), and showed good internal consistency in our sample (Cronbach's $\alpha = 0.80$).

2.3.3. Psychiatric and Psychosocial Assessment

Participants were also administered a comprehensive neurobehavioral evaluation which included collection of demographic data as well as psychiatric, substance use and social characteristics. Psychiatric histories such as current and lifetime Major Depressive Disorder (MDD), as well as current and lifetime histories of substance use disorders, were assessed using

the Composite International Diagnostic Interview (CIDI) version 2.1 (Kessler & Ustun, 2004; Wittchen, 1994), which follows *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria (APA, 1994), consistent with other ongoing research studies at our center.

The 4-item Duke Social Support Index (H. G. Koenig et al., 1993) and the MacArthur Health Aging questionnaire (Seeman et al., 1994) were administered to collect information regarding social interactions and perceived emotional support, respectively. Social interactions, a proxy for measuring objective social isolation, was indexed by summing two items from the Duke Social Support Index that ask participants to indicate how many times in the past week they either spent time with or spoke on the phone with someone who did not live with them. Responses for each item were coded as 0 ("none") to 7 ("seven or more times"; possible range of scores=0-14). Two items from the Macarthur Health Aging questionnaire were used as an index of perceived emotional support. These items asked participants to rate on a 4-point scale ranging from 1 ("Never") to 4 ("Frequently") how often their spouse, children, close friends and/or relatives: 1) make them feel loved and cared for, and 2) are willing to listen when they need to talk about worries and problems. These two items were summed for an index of perceived emotional support (possible range of scores=0-8) and showed good internal consistency in our sample (Cronbach's $\alpha = 0.83$).

2.3.4. Neuromedical Assessment

The neuromedical assessment included a clinical interview to gather a comprehensive medical history (e.g., conditions, medications) as well as a blood draw, breathalyzer and urine drug screen, and self-report questionnaires (e.g., AIDS Clinical Trials Group [ACTG] Adherence Questionnaire [4-day adherence of >90%]); (Chesney et al., 2000). HIV status was determined

by standard enzyme-linked immunosorbent assay (ELISA) and a confirmatory Western blot. HIV RNA was quantified in plasma by reverse transcriptase-polymerase chain reaction using a commercial assay with lower limit of quantification of 50 copies/mL. Hepatitis C Virus (HCV) serostatus was determined by commercial immunoassay.

Plasma levels of CRP, IL-6, CCL2/MCP-1, sCD14, and D-dimer were measured by the parent study using commercial enzyme-linked immunosorbent assay kits. Specifically, CRP was assayed by Lab Corp, IL-6 and CCL2/MCP-1 were run on a Mesoscale Discovery Imager 2400, and sCD14 and D-dimer were measured on a Molecular Devices ELISA microplate reader.

We considered each of these biomarkers of inflammation [CRP, IL-6, CCL2/MCP-1, sCD14] (Kuller et al., 2008; Lau et al., 2006; Lien et al., 1998; Sevigny et al., 2007) and associated processes (e.g., coagulation; D-dimer); (Freiberg et al., 2016; Kuller et al., 2008; Montoya et al., 2019) given their relevance to HIV disease. Additionally, these biomarkers are linked to psychosocial disturbances in PWoH such as social isolation and poor social support (Hackett et al., 2012; Leschak & Eisenberger, 2019; Smith et al., 2020) and PWH (Ellis et al., 2021; Sun-Suslow et al., 2020), as well as their associations with loneliness in people without HIV (M. A. Cole et al., 2007).

2.4. Statical Analyses

Variables of interest were checked for normality and skewness. Biomarkers were log-transformed to better improve fit, and outliers were removed if they were >4 SDs from the mean. UCLA-3 total scores were normally distributed. CES-D total scores were skewed towards the lower range, but still acceptable based on established absolute-value cutoffs for skewness and Kurtosis; 3 and 10, respectively (Kline, 2011). Given that both outcome variables (loneliness and depressive symptoms) were not significantly skewed, multivariable regression were appropriate

for use. However, biomarkers were significantly skewed and therefore transformed, and CRP and D-dimer remained skewed after log transformations. Therefore, non-parametric approaches (e.g., Spearman's ρ) were utilized for bivariate analyses that included biomarkers. Cohen's *d* was calculated to estimate effect size (J. Cohen, 1988). In addition, multicollinearity between our variables were checked first by analyzing the bivariate correlations between measures, then by calculating the variance inflation factor (VIF). Bivariate correlations between measures all fell below the suggested threshold for multicollinearity (r=0.7) suggested by Pallant (2020). Additionally, the VIF for all variables was less then 2.0, which was well below the suggested cutoff of 10 (Hair et al., 2014). Thus, multicollinearity did not exist in this study. All analyses were conducted with JMP Pro 16 statistical software.

First, Spearman's rank-order correlation (ρ) tests were conducted to examine bivariate associations between biomarkers of systemic inflammation and coagulation (CRP, IL-6, sCD14, CCL2/MCP-1, and D-dimer) with loneliness (i.e., UCLA-3 total loneliness score) and depressive symptoms (i.e., CES-D Total Score). Two separate multivariable regressions were then conducted, one with loneliness as the outcome variable and the other with depressive symptoms as the outcome variable and loneliness as a predictor. All biomarkers were considered in multivariable analyses to examine their independent influences, after accounting for the relative variance predicted by other biomarkers on the outcome variables. Other candidate covariates from **Table 4** (i.e., demographic, medical, psychiatric, social, and HIV disease characteristics) were included in multivariable regression models if they demonstrated bivariate trend-level associations (p<.10) with the outcome variable (i.e., loneliness or depressive symptoms). Age was considered *a* priori for inclusion in multivariable analyses predicting loneliness given its association with loneliness in the literature (Dyal & Valente, 2015) and associations with system

inflammatory biomarkers (Fukui et al., 2018). Interactions between loneliness and biomarkers of systemic inflammation were also included in the second model predicting depressive symptoms to evaluate whether loneliness may moderate the relationship between inflammation and depression in PWH. Backwards stepwise regression was conducted for each outcome and a minimal Akaike information criterion; AIC (Akaike, 1974) was used to reduce the model. The AIC method was preferred over the coefficient-based stepwise regression because AIC is a more data-driven approach, which balances goodness of fit and model complexity, while the coefficient-based approach relies more on theoretical framework for the regression model. Given that loneliness, inflammation, and depression literature in PWH is still limited and somewhat inconsistent, the AIC was chosen as the appropriate method to use for our more exploratory aims.

3. Results

3.1. Participant Characteristics

Participant characteristics are presented in **Table 4**. The study sample was 87% male and 59% non-Hispanic White with a mean age of 53.2 years (range 36-69 years) and mean education of 14.5 years. Participants' median estimated duration of HIV disease was 16.3 years (interquartile range [IQR] 4.0, 25.5). All participants were currently on ART and were virally suppressed (plasma HIV viral load $\leq$ 50 copies/mL). Median nadir and current $CD4^+$ T-cell counts were 188.5 (IQR=53.8, 353.0) and 678.0 (IQR=524.5, 911.0), respectively. About 60% of our sample met criteria for lifetime substance use disorder with alcohol use disorder being the most prevalent (40.2%). **Table 4** provides additional participant characteristics such as current and lifetime psychiatric and substance use histories, common comorbid medical conditions, social interaction and support characteristics, total loneliness scores (i.e., Total UCLA-3 Score),

and depressive symptoms (i.e., Total CES-D Score). Approximately 34.2% and 57.3% reported elevated loneliness and depression, respectively. **Table 5** provides the mean and distributions of the biomarkers in the sample.

3.2. Bivariate and Multivariable Analyses Examining Associations between Loneliness and Inflammation

At the bivariate level, loneliness was significantly associated with higher levels of D-dimer (Spearman's ρ=0.26; p=.02), but not with the remaining biomarkers (CRP, IL-6, CCL2/MCP-1, and sCD14; Spearman's ρs range 0.06-0.14; ps>.10). **Table 6** displays the predictors identified as candidates for multivariable modelling. Predictors included all biomarkers (rationale stated above), age given its associations with loneliness and biomarkers in the literature, and variables from **Table 4** that were associated (p<.10) with loneliness at the bivariate level (i.e., race/ethnicity, social interactions and perceived emotional support, nadir $CD4^+$, and lifetime illicit [i.e., other than alcohol or cannabis] substance use disorder). The final model selected by AIC accounted for 49.3% of the variance in loneliness (F(7,74)=10.3, p<.0001; See **Table 6**). D-dimer, sCD14, and CCL2/MCP-1 were significant independent predictors of loneliness in the multivariable model, which also included less frequent emotional support (B=0.45, 95% CI=[0.38, 1.62], p<.001), higher nadir CD+ T-cell count (B=0.35, 95% CI=[0.10, 1.87] p<0.001), and presence of lifetime substance use disorder (B=0.24, 95% CI=[0.036, 2.68], p=0.007). Younger age was associated with loneliness at the trend level (B=-0.24, 95% CI=[-0.36, 0.41], p=0.083). To ensure these findings were not better explained by vascular risk factors (e.g., smoking, hypertension, obesity), which are common in PWH and associated with inflammation and coagulation in the literature, we added these variables to the

model, but their addition did not weaken the association between the significant biomarkers (CCL2/MCP-1, sCD14, and d-dimer) and loneliness.

3.3. Bivariate and Multivariable Analyses Examining the Relationships between Loneliness, Inflammation, and Depressive Symptoms

At the bivariate level, increased frequency of depressive symptoms (i.e., higher Total CESD Scores) was associated with greater loneliness (r=0.53; p<.0001), as well as with higher levels of IL-6 (ρ=0.23; p=0.04) and CCL2/MCP-1 (ρ=0.24; p=.03). To examine biomarkers that impact depression in the context of loneliness, and to test whether loneliness moderates the relationship between depressive symptoms and inflammation, a second stepwise regression was conducted. **Table 6** displays the predictors identified as candidates for multivariable modelling, including loneliness, all biomarkers, and variables from **Table 4** that were associated (p<0.10) with depressive symptoms at the bivariate level (i.e., race/ethnicity, current $CD4^+$ T-cell count, lifetime substance use disorder, and hypertension). The final model selected by AIC accounted for 54.4% of the variance in depressive symptoms (F(8, 73) =10.9, p<0.0001). Loneliness (B=0.31, 95% CI=[0.19, 0.43], p<.0001) and higher CCL2/MCP-1 (B=25.53, 95% CI=[11.58, 39.48], p=.0005) emerged as significant independent predictors of depressive symptoms. A significant interaction loneliness by D-dimer was also found (B=0.59, 95% CI=[0.01, 1.17], p=.0497) whereby a positive relationship between D-dimer and increased frequency of depressive symptoms only emerged at higher levels of loneliness. This finding is depicted graphically in **Figure 4**. Race/ethnicity was the only other covariate associated with depressive symptoms (Black race/ethnicity was associated with a higher frequency of depressive symptoms while Hispanic race/ethnicity and those identifying with a race/ethnicity other than White, Hispanic, or Black was associated with less frequent depressive symptoms).

To ensure these relationships were not better explained by factors associated with inflammation and/or coagulation (e.g., age, acute/early HIV infection, or vascular risk factors such as hyperlipidemia and smoking status), these additional variables were considered alongside age, ethnicity, lifetime substance use disorder, loneliness, and biomarkers of inflammation in a follow-up stepwise regression analysis. Despite accounting for these risk factors, results remained unchanged.

4. Discussion

Loneliness is common among PWH and is associated with depression and other adverse health-related consequences, including non-AIDS-associated comorbidities (e.g., CVD) and increased risk of mortality. However, the biological processes associated with loneliness in PWH are not well understood. Moreover, the biopsychosocial relationships between loneliness, inflammation, and depression in PWH are complex, and research examining these relationships simultaneously in PWH is sparse. Our results suggest that loneliness is associated with increased coagulation activity (D-dimer) and monocyte activation (sCD14, CCL2/MCP-1) in virally suppressed PWH while accounting for demographics (e.g., age, race/ethnicity), and relevant psychosocial covariates (e.g., social interactions, perceived emotional support). Loneliness was, as expected, associated with depressive symptoms, as were higher levels of CCL2/MCP-1, though D-dimer was only associated with more frequent depressive symptoms at higher levels of loneliness. These findings provide insight into the potential biological processes associated with loneliness in virally suppressed PWH that may be to some extent dissociable from those of depressive symptoms. This knowledge may help improve treatment efforts aimed at remediating these highly prevalent conditions and reducing their impact on health-related outcomes in PWH.

Regarding our first aim, to our knowledge, this study is the first to report significant associations between loneliness and biomarkers of systemic inflammation (sCD14, CCL2/MCP-1) and coagulation (D-dimer) in ART-treated and virally suppressed PWH, providing valuable insight into the biological mechanisms by which loneliness may impact health in this population. Increased coagulation activity (as indexed by higher levels of D-dimer) was associated with loneliness in both unadjusted (i.e., bivariate correlations) and adjusted analyses (i.e., stepwise backwards AIC multivariable regression), and biomarkers of monocyte activation and microbial translocation (CCL2/MCP-1, sCD14) were associated with loneliness in adjusted models. Other significant predictors of loneliness included lower emotional support, higher nadir CD4 count, and lifetime substance use disorder. Importantly, these results appear to be independent of relevant comorbidities since we adjusted final models for common cardiovascular risk factors (e.g., smoking status, hypertension, hypercholesterolemia, diabetes) and hepatitis C virus to ensure our findings were not better explained by these factors.

D-dimer is a fibrin degradation product that reflects ongoing activation of the coagulation system. Higher levels of D-dimer are indicative of coagulation imbalance, which can be both a cause and amplifier of the inflammatory response (Funderburg & Lederman, 2014). CCL2/MCP-1 is a chemokine produced constitutively or in response to proinflammatory stimuli that is involved in the recruitment of monocytes, lymphocytes, and other cells to sites of infection and inflammation peripherally and in the CNS (Gu et al., 1997). Soluble CD14 is released from monocytes and macrophages following stimulation by proinflammatory cytokines, bacterial lipopolysaccharide (LPS), and other ligands (Shive, Jiang, Anthony, & Lederman, 2015). Previous studies have linked loneliness to elevated levels of CCL2/MCP-1 in PWoH (Hackett et al., 2012; Hackett, Poole, Hunt, Panagi, & Steptoe, 2019) though to our knowledge no studies

have examined associations between loneliness and D-dimer or sCD14. Nersesian et al. (2018) found an association between levels of fibrinogen, which, with D-dimer can lead to a hypercoagulable state, and loneliness in PWoH. Associations between loneliness and social support, as well as with comorbid substance use disorders, has been reliably demonstrated in the literature (Greene et al., 2018; Stanton et al., 2015). In PWH, studies have linked poorer social support, which is related to but independent of loneliness, with CCL2/MCP-1 in PWH (Ellis et al., 2020), as well as with D-dimer in PWH (Sun-Suslow et al., 2020), and with D-dimer and fibrinogen levels after acute psychosocial stress (Wirtz et al., 2009). Our findings extend these to demonstrate effects of systemic inflammation on loneliness independent of social support, though additional studies are needed to further examine these interrelationships. Importantly, higher levels of D-dimer, CCL2/MCP-1, and sCD14 are observed even in treated and virally suppressed PWH (Mendez-Lagares et al., 2013) and have been linked to CVD (Joven et al., 2006; Kelesidis, Kendall, Yang, Hodis, & Currier, 2012; Longenecker et al., 2014; Zungsontiporn et al., 2016) and increased risk for mortality (Duprez et al., 2012).

As expected, loneliness was associated with higher frequency of depressive symptoms in both adjusted and unadjusted analyses, which is consistent with existing literature in PWH (Grov et al., 2010) and PWoH (Lee et al., 2019). The robustness and strength of the loneliness main effect in explaining variance in depressive symptoms beyond inflammation and immune health was notable given the extensive evidence supporting the role of inflammation in depression (Osimo et al., 2020). Higher levels of monocyte activation marker CCL2/MCP-1 also were independently associated with increased depressive symptoms at the bivariate and multivariable levels, highlighting CCL2/MCP-1 as a biomarker sensitive of depressed mood independent of loneliness. This finding is consistent with studies that have observed higher CCL2/MCP-1 levels

in individuals with major depressive disorder (Rajagopalan et al., 2001) as well as in individuals reporting even mild depressive symptoms (Suarez et al. 2003). Novel findings in the current study also demonstrated that the relationship between D-dimer and depressive symptoms was only present at higher levels of loneliness. This requires replication but provides further support for the specificity of the association between coagulation and loneliness and suggests that if both are elevated this could lead to combined adverse effects on depressive symptoms. Race/ethnicity was another significant predictor of increased depressive symptoms, whereby PWH who self-identified as Black reported greater depressive symptoms relative to those who self-reported as non-Black race/ethnicities. This race/ethnicity effect may reflect the impact of lifetime(s) of racial discrimination and systemic socioeconomic disadvantages, which were not directly measured in the current study, on increased risk for depression. Finally, higher nadir CD+ T-cell count was independently associated with loneliness, which was unexpected based on prior literature (Brouillette et al., 2022). Perhaps those with higher nadir CD+ T-cell counts represent an HIV survivor bias of those who experienced more HIV stigma/discrimination, thereby contributing to more feelings of loneliness. Future studies should investigate the links between elevated psychosocial disturbance with higher nadir CD+ count in more detail.

Our overall findings suggest that activation of inflammatory and/or coagulation pathways may be mechanisms associated with loneliness and depression within virally suppressed PWH. Feelings of loneliness can be both a cause of inflammation (e.g., via dysregulation of neuroendocrine and immune pathways) and a consequence of inflammation. For example, loneliness can be conceptualized as a threat to our social well-being, which activates the body's stress-response (Hawkley & Cacioppo, 2003). In the general population, chronic loneliness and subsequent heightened sensitivity to social threats have been shown to activate similar

neuroendocrine pathways involved in chronic stress, releasing epinephrine, cortisol, and glucocorticoids, which can hinder immune function and amplify peripheral and central inflammation (Hackett et al., 2012). Research in healthy adults and clinical populations have demonstrated that lonelier people are more psychologically reactive to stress than those who are less lonely, and their responses to acute laboratory stressors are characterized by enhanced concentrations of inflammatory biomarkers, including CCL2/MCP-1 (Hackett et al., 2012; Hackett et al., 2019). In addition, reliable increases in D-dimer levels have been observed in response to acute psychosocial stressors across clinical populations (Wirtz et al., 2006; Wirtz et al., 2008), highlighting the role of enhanced stress response in both inflammatory and coagulation pathways that may result from loneliness. Loneliness is also associated with difficulties in cognitive-behavioral processing such as a tendency to engage in negative appraisals (i.e., perceived poorer emotional support) and poorer health behaviors (i.e., substance use disorders), which may have downstream consequences on vascular and immune regulation (J. T. Cacioppo et al., 2000). Moreover, an association between stress-induced D-dimer levels and depression has been observed in PWoH (von Känel, Bellingrath, & Kudielka, 2008), which could help explain the relevance of loneliness in the relationship between D-dimer and depressive symptoms in our study. Given evidence that stress causes changes in gut microbiota and may play a role in gut dysbiosis (Mackos, Maltz, & Bailey, 2017), it also is possible that psychosocial stress associated with loneliness may have similar effects that may explain, in part, the association we observed between elevated sCD14 and loneliness. In addition to enhanced inflammatory responses, loneliness is associated with reduced immune function and antiviral immunity (Jaremka et al., 2013; Leschak & Eisenberger, 2019; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004). Indeed, people who are lonely have been shown to be more susceptible to viral

infections such as the common cold (LeRoy, Murdock, Jaremka, Loya, & Fagundes, 2017), and are more vulnerable to chronic diseases such as metabolic syndrome (Henriksen et al., 2019), heart disease (Valtorta et al., 2016) and even all-cause mortality risk (J. Holt-Lunstad et al., 2015). The dysregulation of immune and inflammatory response systems resulting from loneliness can have further downstream consequences on D-dimer, a measure of coagulation imbalance and a proxy for systemic inflammation within the body.

As noted above, multiple factors contribute to activation of inflammatory and coagulation pathways in PWH such as ongoing viral replication and co-infections (Deeks et al., 2013), which may help explain our loneliness and biomarker findings. Chronic immune activation also is associated with microbial translocation in both acute and chronic HIV infection (Brenchley et al., 2006; Somsouk et al., 2015) and in treated PWH (Cassol et al., 2010). In virally suppressed PWH, chronic monocyte activation and damage to the gut mucosa and associated microbial translocation are considered prominent drivers of persistent inflammation (Deeks et al., 2013; Godfrey et al., 2019). Microbial translocation causes an increase in circulating microbial products such as lipopolysaccharide (LPS) which activates monocytes leading to the production of sCD14 (Sandler & Douek, 2012). Elevated levels of sCD14 and LPS can persist despite ART (Mendez-Lagares et al., 2013; Villanueva-Millan, Perez-Matute, Recio-Fernandez, Lezana Rosales, & Oteo, 2017) and both have been associated with subclinical atherosclerosis (Longenecker et al., 2014). LPS-stimulated monocyte activation also leads to increased tissue factor expression which activates the coagulation cascade on the surface of monocytes (Funderburg et al., 2010). Thus, HIV causes direct and indirect activation of both the adaptive and innate immune systems, leading to a state of chronic low-level inflammation that persists in PWH despite viral suppression on ART. Over time, the combined persistent, chronic low-level

inflammation may lead to other consequences including vascular dysfunction and coagulation imbalance, as well as atherosclerosis, CVD, and other adverse health-related outcomes. In PWH, increased sCD14 and elevated tissue factor expression have been associated with D-dimer levels in PWH (Funderburg et al., 2010). Thus, there may be overlapping etiologies contributing to the associations observed in this study. Future research is needed to explore these bidirectional links and between loneliness and inflammation in PWH and the underlying biological pathways.

To our knowledge, only one other study has examined associations between inflammation and loneliness in PWH (Derry et al., 2021). This study also investigated associations between inflammation and depressive symptoms, though in separate analyses. They did not find significant associations between loneliness and inflammatory biomarkers in their sample of older PWH (aged 54-78). Interestingly, the only overlap in terms of biomarkers between our study and Derry et al. (2021) were IL-6 and CRP, neither of which reached significance in bivariate or multivariable analyses in our study as well. Some studies in PWoH have found positive associations between these biomarkers and loneliness, though the evidence is mixed (Smith et al., 2020). One possible explanation for the lack of associations in the current study, and in Derry et al. (2021), is that IL-6 and CRP may not be as sensitive to loneliness in the context of viral suppression. All or most participants in our studies were virally suppressed (100% $\leq$ 50 copies/mL in the current study and 93% < 200 copies/mL in Derry et al. (2021)). Another possibility is that the associations between some inflammatory processes and loneliness may be stronger in women, a finding that has been demonstrated in the literature in PWoH (Hackett et al., 2012). Given the limited number of females in our study (n=11), we were unable to examine this possibility, but it should be considered for future studies.

By contrast, higher IL-6 levels were associated with *depressive* symptoms in PWH, which is consistent with other studies in PWH (Derry et al., 2021; Ellis et al., 2020) and PWoH (Yuan, Chen, Xia, Dai, & Liu, 2019), though in our study this association did not remain significant in multivariable modelling. One possibility is that this association was influenced more strongly by other factors, such as race/ethnicity, which was also a significant predictor of depressive symptoms (i.e., more frequent depressive symptoms reported by Black PWH relative to other race/ethnicities). Post-hoc bivariate associations conducted to explore this possibility provided preliminary support for an association between higher IL-6 levels and depressive symptoms in Black PWH (ρ=0.58, p=.059) that was not observed in the combined non-Black race/ethnicity groups (ρ=0.14, p>.10). While our sample size of Black PWH in this study is quite small (n=11), this possible association is consistent with findings linking IL-6 to depressive symptoms in a sample of PWH where 50% of participants self-reported as Black (Derry et al., 2021). Future studies are needed to further determine race/ethnicity-specific associations between systemic inflammation and depressive symptoms in virally suppressed PWH. We also did not find associations between CRP and depressive symptoms, which runs contrary to other studies in PWH (Ellis et al., 2020) though the evidence is mixed and other studies have not observed significant associations (Derry et al., 2021; Irwin et al., 2018). Additionally, Poudel-Tandukar, Bertone-Johnson, Palmer, and Poudel (2014) found an association between CRP and depressive symptoms only in PWH with higher levels of inflammation (CRP>3mg/L). Using this threshold, 21.4% of our sample (n=19) had high CRP levels, though post hoc analyses did not reveal any significant associations between the dichotomous CRP variable and either loneliness or depressive symptoms (Cohen's ds=0.38 and 0.30, ps>.10). As with loneliness, other research suggests that the relationship between CRP and depression may be influenced by race/ethnicity

and sex (Morris et al., 2011), which as mentioned above would be an important avenue for future research.

There are limitations to note regarding this study. First, our data were cross-sectional, which precludes making determinations regarding the directionality of associations. As noted in the introduction, there may be bidirectional relationships between loneliness, systemic inflammation, and depression that were unable to be fully examined given the cross-sectional nature of our study. Therefore, longitudinal follow-up studies are necessary to further elucidate the directionality of these findings. Second, our findings were derived from a relatively small sample size, and our sample was mostly male and approximately 58% were White and middle-to-older adults. In the future, efforts to expand the subject pool to include women (to better understand potential sex differences on loneliness, biomarkers, and depression), those across age ranges (given that loneliness may be experienced across the lifespan including in critical periods of young adulthood and higher ends of older age [i.e., >85 years]), and racially/ethnically underrepresented participants to better improve generalizability of findings. Furthermore, our study lacked a comparison group of PWoH. However, the primary aim of this investigation was to examine inflammation as a mechanism underlying loneliness in HIV given that very limited work has been published to-date filling this gap in literature. By contrast, the links between loneliness and inflammation in people without HIV (PWoH) have been much more extensively studied. Also, the biomarker values in our PWH sample were comparable to other values in other published studies (Sun-Suslow et al., 2020) that had a PWoH comparison group, suggesting that our results are consistent and reliable despite the lack of control group. Additionally, biomarkers in this present study were selected based on their association with HIV-disease processes and prior reports of relationships with psychosocial outcomes, but by no means are all-inclusive. Is it

possible that other biomarkers (e.g., microbiome, EEG, cardiovascular injury, fMRI) not examined in this study may have associations with loneliness and/or depression, and further highlights the need to continue to grow this area of research. Finally, HIV-specific variables such as HIV-related stigma/discrimination, which has been associated with elevated loneliness in PWH, was not examined in the current study and would be important to include in future investigations to further explain HIV and loneliness findings such as the positive relationship between loneliness and nadir CD+ T-cell count observed in our study.

Despite these limitations, this study provides unique contributions to the literature that could have significant clinical implications. To our knowledge, this study is the first to demonstrate associations between loneliness and systemic inflammation and coagulation in PWH, and to show that there were both independent and combined influences of these factors on depressive symptoms. Ongoing research examining the efficacy of interventions for loneliness across many populations is promising, including both younger and older adults without HIV, and people with psychotic disorders such as schizophrenia (Masi, Chen, Hawkley, & Cacioppo, 2011; Shah, Nogueras, van Woerden, & Kiparoglou, 2019; Shah, Nogueras, van Woerden, & Kiparoglou, 2021). Given the compounding effect of loneliness and systemic inflammation on depressive symptoms, it may be possible to simultaneously target loneliness through social and cognitive-behavioral interventions, as well as by screening for and reducing elevated levels of loneliness and inflammation, when treating depression in PWH. Pharmacological interventions targeting the reduction of systemic inflammation and/or coagulation (e.g., anti-inflammatory medications, probiotics, (Gori et al., 2011; Villar-Garcia et al., 2015) may be useful as potentially independent treatments for loneliness and/or depression, and/or as adjuncts to non-pharmacological interventions.

Chapter 2, “Combined Effects of Loneliness and Inflammation on depression in People with HIV,” is coauthored with Hussain, Mariam A.; Watson, C. Wei-Ming; Morgan, Erin E.; Heaton, Robert K.; Letendre, Scott L.; Jeste, Dilip V.; Moore, David J.; Iudicello, Jennifer E. The dissertation author was the primary author of this chapter.

Table 4. Participant Characteristics (*N* = 82).

	PWH (*N* = 82)
Demographics	
Age (years)	53.2 (9.0)
Education (years)	14.5 (2.8)
Sex/gender (% male)	86.6%
Race/ethnicity	--
White, non-Hispanic (%)	58.5%
Hispanic (%)	19.5%
Black (%)	13.4%
Other[a] (%)	8.5%
HIV Disease Characteristics	
Estimated duration of HIV disease (years)	16.3 [4.0, 25.5]
AIDS Status (%)	58.5%
Nadir CD4 count	188.5 [53.8, 353.0]
Current CD4+ T-cell count	678.0 [524.5, 911.0]
Taking ART (% currently on ART)	100.0%
Duration of current ART regimen (years)	1.1 [0.4, 2.4]
Plasma HIV viral load (% undetectable[b])	100.0%
Psychiatric Diagnoses	
Current Major Depressive Disorder (% yes)	7.4%
Lifetime Major Depressive Disorder (% yes)	50.0%
Current Substance Abuse Diagnosis (% yes)	7.4%
Lifetime Substance Use Disorder[c] (% yes)	59.8%
Lifetime Alcohol Use Disorder (% yes)	40.2%
Lifetime Cannabis Use Disorder (% yes)	24.4%
Lifetime Other[d] Substance Use Disorder (% yes)	43.9%
Medical Comorbidities	
Obesity (% Body Mass Index ≥30)	28.4%
Hepatitis C Virus (% yes)	15.9%
Diabetes (% yes)	12.2%
Hypertension (% yes)	46.3%
Hyperlipidemia (% yes)	43.9%
Social Resources	
Social Interactions (# in past week)[e]	6.0 [3.0, 9.3]
Perceived Emotional Support (Total)[f]	3.4 (0.9)
Perceived Emotional Support (% Frequent Support)	54.9%
Primary Study Variables	
Loneliness Total (UCLA-3[g] total score)	40.6 (12.0)
Loneliness Elevated[h] (%)	34.2%
Depressive Symptoms Total (CES-D[i] total score)	19.4 (8.3)
Depressive Symptoms Elevated[j] (%)	57.3%

Note. Mean (SD) or Median [IQR]; [a]Race/ethnicity other than White, Black, or Hispanic. [b]plasma HIV RNA viral load ≤50 copies/mL; [c]Substance Use Disorder=DSM-IV lifetime substance abuse and/or dependence diagnosis; [d]Other=illicit substances of abuse (most prevalent=methamphetamine, cocaine, and opioid). [e]Total number of social interactions in the past week determined using items from the 4-item Duke Social Support Index; [f]Frequency of perceived emotional support using items from the MacArthur Healthy Aging Questionnaire; [g]Revised UCLA Loneliness Scale – Version 3 (UCLA-3). [h]UCLA-3 ≥ 44. [i]Center for Epidemiological Studies Depression Scale (CES-D); [j]CES-D≥16.

Table 5. Biomarker distributions.

Plasma Biomarker	Mean (SD)	Median [IQR]
log10(CRP)	0.11 (0.42)	0.08 [-0.22, 0.41]
Log10(D-dimer)	2.71 (0.20)	2.67 [2.58, 2.82]
Log10(IL-6)	-0.15 (0.22)	-0.16 [-0.05, -0.28]
Log10(CCL2/MCP-1)	2.26 (0.10)	2.26 [2.22, 2.32]
Log10(sCD14)	5.88 (0.50)	6.06 [5.75, 6.18]

Note. SD = Standard Deviation; IQR = Interquartile range; CRP = C-reactive protein; IL-6 = Interleukin-6; CCL2/MCP-1 = Chemokine (C-C motif) ligand 2/ monocyte chemoattractant protein-1; sCD14 = soluble cluster of differentiation 14.

Table 6. Summary of bivariate and multivariable analyses when loneliness is the outcome. In MV analyses, the final model was established using backwards stepwise regression using the Akaike information criterion (AIC). Note: For multivariable analyses, light grey shading indicates variables not selected by AIC for inclusion in the final model.

Variable	Risk Direction (Lonelier)	Bivariate Analyses			Multivariable Analyses: Final AIC Model		
		Statistic	value	*p*-value	*B*	95% CI	*p*-value
CRP[a]	--	*ρ*	0.12	0.278	--	--	--
IL-6[a]	--	*ρ*	0.10	0.355	--	--	--
CCL2/MCP-1[a]	--	*ρ*	0.06	0.568	**0.20**	**[0.11, 2.56]**	**0.029**
sCD14	--	*ρ*	0.14	0.211	**0.19**	**[0.09, 1.84]**	**0.033**
D-dimer[a]	**Higher**	***ρ***	**0.26**	**0.017**	**0.32**	**[0.21, 2.0]**	**<0.001**
Age	**Younger**	***ρ***	**-0.12**	**0.294**	-0.24	[-0.36, 0.41]	0.083
Social Interactions	**Fewer**	***ρ***	**0.26**	**0.016**	--	--	--
Emotional Support	**Less often**	***t***	**4.25**	**<0.001**	**0.45**	**[0.38, 1.62]**	**<0.001**
Race/ethnicity					--	--	--
White, non-Hispanic	--	*t*	0.14	0.887	--	--	--
Hispanic	**Non-Hispanic**	***t***	**2.24**	**0.028**	--	--	--
Black	--	*t*	0.82	0.416	--	--	--
Other[b]	**Other[b]**	***t***	**2.43**	**0.018**	--	--	--
Nadir $CD4^+$ T-cell count[c]	**Higher**	***ρ***	**0.30**	**0.005**	**0.35**	**[0.10, 1.87]**	**<0.001**
Lifetime substance use disorder[d]	**Present**	***t***	**2.15**	**0.034**	**0.24**	**[0.06, 2.68]**	**0.007**
Model Statistics							
F-ratio					**10.3**		
df					**(7,74)**		
R^2					**0.49**		
***p*-value**					**<0.001**		

Note. CRP=C-Reactive Protein; IL-6=Interleukin-6; CCL2/MCP-1=Chemokine (C-C motif) ligand 2/monocyte chemoattractant protein-1; sCD14= soluble cluster of differentiation 14. [a]log transformed; [b]Self-reported race/ethnicity as other than White, Black, or Hispanic (e.g., more than one race); [c]square root transformed; [d]Lifetime abuse or dependence on substances other than alcohol or cannabis.

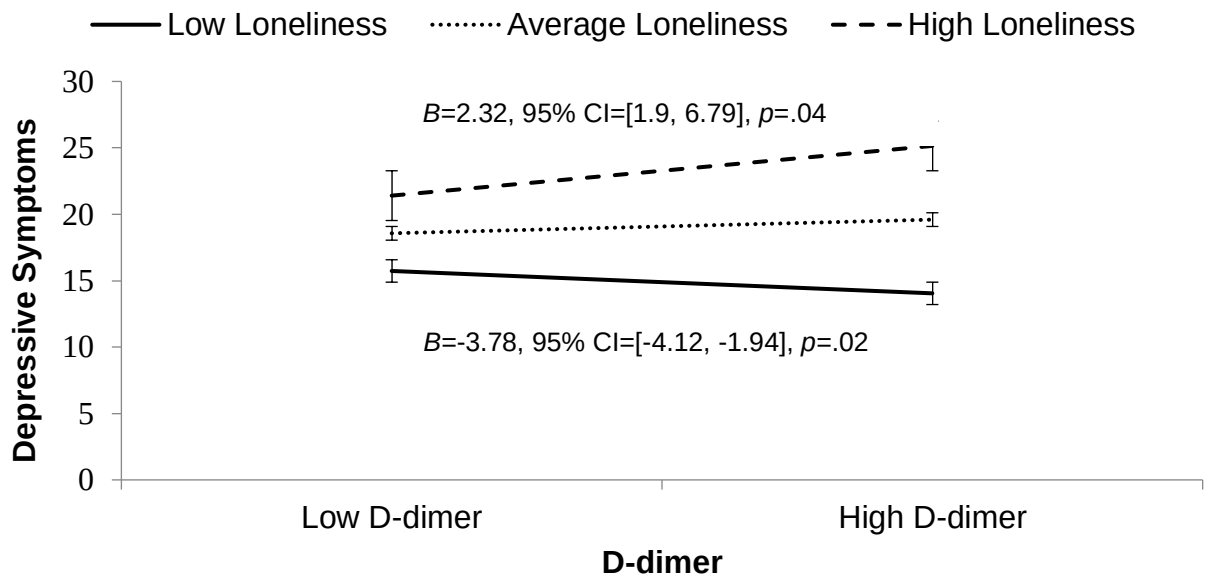

Figure 4. Higher loneliness scores, in conjunction wither high D-dimer values, contributed to a combined effect on depressive symptoms in PWH. ***Note***. Depressive Symptoms = CES-D total score; D-dimer = log10(d-dimer); Loneliness = UCLA-3 total score; Low = -1 SD; High = +1 SD; Error bars represent standard error of measurement.

CHAPTER 3.

Understanding the Longitudinal Impact of Loneliness on Depressive Symptoms in People with and without HIV

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ABSTRACT

Objective: People with HIV (PWH) report higher degrees of loneliness compared to people without HIV (PWoH). In addition to its high prevalence, loneliness is associated with many adverse outcomes. One of the strongest links is loneliness' associations to negative psychological health and well-being, including depression. Although there have been many cross-sectional studies investigating this link, there remains limited understanding about the longitudinal impact of loneliness on depressive symptoms, particularly among PWH. We sought to investigate the impact of individual and group variability over time on the relationship between loneliness depressive symptoms in a sample of PWH and PWoH. Methods: 139 adults (ages ranged from 36-69 at baseline) who completed at least one follow-up annual visit (average years of follow-up = 2.3, *SD* = 1.0; average months between follow-up visits = 14.8, *SD* = 5.8). Participants were grouped by HIV status (PWH, *n* = 80; PWoH, *n* = 59). Multi-level modeling investigated the within-person effect of relative loneliness (i.e., person-mean centered loneliness), and between-person effects of HIV status and average numbers of social interactions on depressive symptoms reported concurrently and at follow-up over time. Results: Higher relative loneliness at each specific time point predicted higher concurrent depressive symptoms (*B* = 3.01, *p* = .001) and higher follow-up depressive symptoms (*B* = 2.30, *p* = .02). HIV status was a significant between-person predictor of concurrent depressive symptoms (*B* = 5.71, *p* < .001), and significantly moderated the relationship between relative loneliness and follow-up depressive symptoms (*B* = 1.89, *p* = .03). However, number of social interactions did not predict concurrent or follow-up depressive symptoms (*p*s > .05). Conclusions: Loneliness is commonly experienced in both PWH and PWoH. Our results suggest that not only is loneliness associated with depression in the present moment but can also exacerbate depressive symptoms over time.

PWH showed a particular likelihood of experiencing more depressive symptoms in the future if they had experienced more loneliness than usual. These results held true regardless of the number of objective social contacts individuals reported; thus, social interactions had no protective effects on depressive symptoms. Findings suggest that individuals, especially PWH, should be carefully assessed for elevated loneliness given its predictive impact on future depressive symptomatology, which can have further downstream consequences on their health and well-being.

1. Introduction

Loneliness is common among both people with HIV (PWH), as well as people without HIV (PWoH). Prevalence estimates can vary widely based on differences in measurement and classification approaches, as well as differences across demographic factors such as age and ethnicity (Julianne Holt-Lunstad, 2018). Global estimates range from about 10-25% (Surkalim et al., 2022). In the United States, significant rates of loneliness in PWoH fell around 20% (as measured by those who endorsed high loneliness (Lee et al., 2019). Among PWH, these estimates are even higher, with about 40% of PWH reporting feeling lonely (Greene et al., 2018; Harris et al., 2020; Rodkjaer et al., 2010; Stanton et al., 2015).

The high prevalence of loneliness across PWoH and PWH can have widespread, negative impacts on overall health, including poorer sleep and motor function, frailty, falls, hypertension, malnutrition, and increased risk of morbidity and mortality (Ganesalingam, 2019; Griffin et al., 2019). Loneliness is also associated with nearly two-times greater likelihood of depression diagnosis, and greater likelihood of suicidal ideation, after controlling for confounding factors such as demographics and psychological distress (Beutel et al., 2017), as well as increased rates of cognitive decline in older adults (J. T. Cacioppo & Hawkley, 2009; Lara, Caballero, et al., 2019; Montoliu, Hidalgo, & Salvador, 2019; Tilvis et al., 2004; Wilson et al., 2007). Beyond the individual impact of loneliness on health and well-being, there is evidence for more widespread public health and economic impacts. Increased economic burden due to loneliness-associated stress/sick absences, reduced productivity and quality of work, and higher staff turnover has been identified (Jeffrey et al., 2017), as well as higher healthcare utilization (J. Zhang et al., 2018). Among PWH, the impact of loneliness on physical, mental, and cognitive health outcomes has been less extensively studied, though existing findings show similar negative impacts on sleep

(Fekete et al., 2018), more risky sexual activities (Bryant et al., 2018; Golub et al., 2010; Munoz-Laboy et al., 2009), increased drug use behaviors (Greene et al., 2018; Hussain et al., 2022; Mannes et al., 2016; Stanton et al., 2015), poorer quality of life and more functional impairments (Greene et al., 2018).

The impact of loneliness on health outcomes has also been studied longitudinally. Strong, consistent, longitudinal evidence has linked chronic loneliness to poorer cardiovascular health among PWoH (Friedler et al., 2015; Hawkley et al., 2010; Thurston & Kubzansky, 2009; Valtorta et al., 2016). The longitudinal impact of loneliness on reduced physical activity (Hawkley et al., 2009), metabolic syndrome (Henriksen et al., 2019; Shiovitz-Ezra & Parag, 2019), frailty (Ganesalingam, 2019), and cognitive decline/dementia (Abell et al., 2019; Lara, Martin-Maria, et al., 2019; Sundstrom et al., 2019; Wilson et al., 2007). Consequently, loneliness also has a combined impact on further consequences including increased risk of early mortality (Christensen et al., 2020; Rico-Uribe et al., 2018). Additionally, loneliness has been closely linked to depressive symptoms and Major Depressive Disorder (MDD) across the lifespan (J. T. Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006).

The relationship with depression is one of the most robust findings in the loneliness literature. In PWoH, studies have demonstrated that loneliness predicts worsening of depression symptoms across the lifespan, from mid-adolescent children (L. J. Koenig & Abrams, 1999) to ethnically diverse healthy older (50-68 years) adults Cacioppo, Hawkley, & Thisted, 2010), even after controlling for baseline depressive symptoms. A recent systematic review of ten studies examining the longitudinal associations between loneliness and depression in older PWoH was evaluated and found that was a consistent temporal association relationship between loneliness and the development, maintenance, or exacerbation of depression at follow-up (Van As,

Imbimbo, Franceschi, Menesini, & Nocentini, 2021). Authors suggested that difficulty in maintaining relationship with older age may explain this relationship between loneliness and depression. However, there is evidence that loneliness, but not objective social isolation, was a significant predictor of depression incidence in a large cohort of community-dwelling older adults ($\geq$ 65 years old) after a three-year period (B. H. Green et al., 1992). Literature suggests that loneliness and social isolation can both impact health in well-being, but in different ways, highlighting the importance of understanding the specific mechanism by which they impact long-term health outcomes.

Although there is likely a bidirectional relationship between loneliness and depression, most longitudinal studies have suggested that loneliness has more predictive influence on depressive influence than vice-versa. For example, in a study of 5,000 community-dwelling older adults ($\geq$ 50 years), there was evidence of a bidirectional relationship between loneliness and incidence of mood disorder. However, while loneliness was a significant predictor of both Generalized Anxiety Disorder (GAD) and MDD, only GAD (not MDD) significantly predicted loneliness scores at two-year follow-up (Domenech-Abella, Mundo, Haro, & Rubio-Valera, 2019), suggesting that there is stronger directionality of loneliness influencing depression outcomes than depression influencing loneliness outcomes. Among older adults (60-90 years) with depression, loneliness was also associated with poorer MDD remission despite treatment after two years, illustrating the adverse impact that loneliness can have on recovering from clinical depression as well (Holvast et al., 2015). Furthermore, loneliness was found to worsen depressive symptoms over time as well, as measured by scores on the Patient Health Questionnaire-9 (PHQ-9; Creese et al., 2021).

Despite strong evidence suggesting a casual role of loneliness in the development, persistence, and worsening of depression symptoms, there remain gaps in the literature. First, most longitudinal studies of loneliness and depression focus on PWoH, particularly those who are older adults. Though older adults are at risk for experiencing increased late-life depression, literature suggests that loneliness has a non-linear trajectory across the lifespan, such that ages in the late-20s, mid-50s, and late-80s were associated with higher levels of loneliness relative to other ages (Lee et al., 2019). Additionally, research investigating the relationship between loneliness and depression in PWH is limited to cross-sectional studies and lacks comparisons with PWoH. Most studies investigating depression and loneliness in PWH are cross-sectional and focus on older (> 50 years) white males. However, there is not yet clear how loneliness and depression in PWH influences each other over time (e.g., does loneliness predict depression, or does depression predict loneliness in PWH?).

The current longitudinal study sought to investigate the potential impact of loneliness on depressive symptoms over time in PWH compared to PWoH. Our goals were three-fold: to determine 1) whether levels of loneliness and depression were associated concurrently and consistently over time, 2) whether participants who reported more loneliness than usual also reported more depressive symptoms (both concurrently and over time), and 3) whether these relationships differed by HIV status. We hypothesized that when participants reported more loneliness than usual (i.e., higher relative loneliness), they would report more concurrent depressive symptoms. We also hypothesized that higher relative loneliness would predict more depressive symptoms at follow-up. Finally, we predicted that PWH would show stronger associations between loneliness and depressive symptoms over time than PWoH.

2. Methods

2.1. Participants and Study Design

Subjects in this study had participated in a parent study that evaluated successful cognitive aging in adults with (PWH) and without HIV (PWoH). From this parent study, we included 139 community-dwelling adults who completed a baseline assessment of loneliness and depressive symptoms and at least one follow-up visit with loneliness and depressive symptoms data (PWH, n = 80; PWoH, n = 59). Follow-up visits were completed at least 12-months apart. The average length of participation in the study was 2.25 years (SD = 1.04), the average number of follow-up visits was 1.68, and the average time interval between visits was 14.84 months (SD = 5.82). The study was active for approximately 4 years. Comprehensive follow-up visits were conducted every two years from baseline, with a brief follow-up visit completed between each comprehensive follow-up visit. Assessments for the comprehensive visit included a blood draw, comprehensive neuropsychological assessment, and administration of psychosocial questionnaires and structured medical, substance use, and emotional history interviews. The brief visit only included the psychosocial questionnaires and structured medical, substance use, and emotional history interviews. Participants were compensated $90 for baseline and comprehensive follow-up visits, and $50 for brief follow-up visits. All study procedures were approved by the UC San Diego Institutional Review Board, and all participants provided written, informed consent.

2.2. Inclusion/Exclusion Criteria

Parent study inclusion criteria included being 36 years or older at the time of study enrollment. The current study inclusion criteria also required having completed at least two study visits with loneliness and depressive symptom data. Parent study exclusion criteria included having a diagnosis of a significant psychotic disorder (e.g., schizophrenia or mood disorder with

psychotic features), the presence of a significant neurological condition (beyond HIV infection) known to impact cognitive functioning (e.g., Alzheimer's disease, stroke, traumatic brain injury), and positive urine toxicology (excluding marijuana) on the day of the assessment.

2.3. Assessment Measures

2.3.1. Loneliness

Loneliness was assessed via self-report using the revised UCLA Loneliness Scale - Version 3 (UCLA-3), a 20-item self-report measure that determines the degree to which someone feels socially disconnected or isolated from others (Russell, 1996). This scale is well- validated in older adult populations but has also been used in a variety of other populations including PWH (Grov et al., 2010). No items use the word "lonely" to capture this construct; rather, items are phrased as, for example, "How often do you feel that people are around you but not with you?" and "How often do you feel that your relationships with others are not meaningful?". Participants were asked to respond using a Likert-type scale from 1 (Never) to 4 (Always). Items are summed, with total scores ranging from 20 to 80, such that higher total scores reflect more loneliness. Internal consistency in our sample was excellent (Cronbach's $\alpha = 0.95$). We will examine loneliness as both a continuous outcome (i.e., Total Loneliness Score") and as a categorical variable for characterization purposes, whereby a Total Loneliness Score of ≥ 44 is categorized as "high loneliness and/or highly lonely", a score between 28 and 43 is considered "moderate loneliness and/or moderately lonely", and a score < 28 is considered "low loneliness and/or not lonely". These cutoffs have been previously published and utilized in studies of healthy adults across the lifespan (Cacioppo & Patrick, 2008; Lee et al., 2019).

2.3.2. Depressive Symptoms

Depressive symptoms were assessed via self-report using the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item self-report measure that assesses the frequency of depression symptoms (e.g., dysphoria, anhedonia, appetite, sleep, thinking/concentration, worthlessness, fatigue, suicidal ideation) experienced in the past week (Radloff, 1977). The CES-D has good sensitivity and specificity to assessing Major Depressive Disorder and has been extensively used in research and clinical settings across many populations, including in PWH (Chenneville, Gabbidon, Drake, & Rodriguez, 2019; Lewinsohn, Seeley, Roberts, & Allen, 1997; Marando et al., 2016). Responses for each item on the CES-D range from 0 to 3 (0 = Rarely or none of the time [< 1 day]; 1 = Some or a little of the time [1-2 days]; 2 = Occasionally or a moderate amount of time [3-4 days]; 3 = All of the time [5-7 days]). Item responses are summed to generate a total score ranging from 0 to 60, with higher scores reflecting greater degree of depression symptoms. Internal consistency in our sample was acceptable (Cronbach's $\alpha = 0.77$).

2.3.3. Psychiatric and Psychosocial Assessment

All participants completed the Composite International Diagnostic Interview (CIDI) version 2.1 (Kessler & Ustun, 2004; Wittchen, 1994), a semi-structured clinical interview to assess for the presence of current and lifetime mood disorders (i.e., Major Depressive Disorder) and substance abuse or dependence based on *DSM-IV criteria* (APA, 1994).

Social interactions have been evaluated as a proxy for measuring objective social isolation, which can impact loneliness (Menec et al., 2020); therefore, it was considered an *a* priori covariate. We assessed for social interactions quantitatively using two items from the 4-item Duke Social Support Index (H. G. Koenig et al., 1993); "How many times during the past week did you spend time with someone who does not live with you, that is you went to see them

or they came to visit you or you went out together?" and "How many times did you talk to someone [friends, relatives or others] on the telephone in the past week [either they called you, or you called them]?". Responses for each item ranged from 0 (None) to 7 (seven or more times) were summed and used as a proxy for the total number of social interactions that occurred in the past week. For the multi-level modeling analyses, the number of one's social interactions reported across study visits was averaged and analyzed as a between-person variable representative of the degree of social engagement that a person typically experiences.

2.3.4. Neuromedical Assessment

Demographic information (age, education, sex, race, ethnicity, employment) were collected by self-report. HIV disease status was assessed via self-report and confirmed during study enrollment. For those who self-reported HIV-infection, a standard enzyme-linked immunosorbent assay (ELISA) with Western blot was completed to confirm their diagnosis. Others were screened to be HIV-uninfected using an HIV/HCV finger stick test (Miriad-MedMira, Nova Scotia, Canada). Of the participants who reported that they were HIV- at screening, none screened positive for HIV following lab testing.

In PHW, additional baseline information was collected to characterize their HIV disease and treatment. These data included self-reported estimated duration of HIV disease (determined by time since first positive HIV test), nadir CD4+ T-cell count, and detailed antiretroviral therapy (ART) history and adherence was assessed using the AIDS Clinical Trials Group [ACTG] Adherence Questionnaire ('adherent' was defined as ART adherence $\geq$ 90% of the time; Chesney et al., 2000). Current CD4+ T-cell counts were collected by lab assessment. Plasma HIV viral load was measured using one of three different assays: the Abbott RealTime HIV-1 test, Abbott Laboratories, Illinois, USA (used in 46.4% of the PWH sample), Hologic Aptima®

HIV-1 Quant Assay (used in 4.8% of the PWH sample), COBAS Ampliprep/COBAS TaqMan HIV-1 Test v2.0 (used in 48.8% of the PWH sample). Each test had a different lower limit of quantitation (LLQ), such that HIV viral load was characterized as undetectable if the LLQ was less than, or equal to, the corresponding LLQ cutoff for each test: 40 copies/mL, 30 copies/mL, and 20 copies/mL, respectively.

2.4. Statistical Analyses

Baseline group differences between PWH and PWoH were examined using analysis of variance or Wilcoxon tests for continuous variables, and χ^2 tests for categorical variables. Multi-level modeling was used to study the longitudinal relationship between loneliness and depression, with depressive symptoms as the primary outcome variable and loneliness scores as the primary predictor variable.

Participant characteristics from **Table 7** were selected for inclusion as covariates in the multi-level models if they differed by HIV status at baseline and were associated with depressive symptoms at baseline ($p < .05$) as determined by bivariate correlations and ANOVA. History of Major Depressive Disorder was excluded from covariate consideration to avoid over-correction given our primary outcome of interest (i.e., CES-D total score). Using this approach, the variables selected as covariates included sex/gender and lifetime substance use disorder. Among PWH, HIV disease characteristics such as estimated duration of HIV infection, CD4 count, and total duration on ART were unrelated to loneliness scores ($p > .05$).

Multi-level modeling investigated the impact of within-person fluctuations between study visits (e.g., relative loneliness, or person-mean centered loneliness [i.e., the difference between an individual's loneliness score at a particular study visit compared to their average loneliness score across visits]) and time since baseline on concurrent and longitudinal depressive

symptoms, as well as the influence of between-person effects (i.e., HIV status, average social interactions across visits) on current and longitudinal depressive symptoms. Within-person effects reflect the effect of visit-to-visit variations in loneliness within an individual and estimates the influence of higher relative loneliness on depressive symptoms at a specific time-point. Between-person effects capture the impact of participant variables that are conceptualized as relatively stable characteristics (i.e., HIV status) on depressive symptoms. **Figure 5** displays a conceptual design depicting the longitudinal effects being modeled (i.e., within-person and between-person effects) using multi-level modeling.

Two multi-level models were examined to investigate whether 1) the level of loneliness reported was concurrently associated with depressive symptoms at each visit, and 2) whether participants who reported higher loneliness than usual at a particular visit (i.e., greater loneliness relative to their person-mean centered loneliness) predicted higher depressive symptoms concurrently (i.e., at the same visit) and longitudinally (i.e., at the next visit). Thus, concurrent depressive symptoms (i.e., CES-D total scores reported at the same visit as the loneliness scores being considered) will serve as the outcome variable for model 1, while follow-up depressive symptoms (i.e., CES-D total scores reported at the next follow-up visit relative to the loneliness scores being considered) served as the outcome variable for model 2. Random intercepts were specified, and unstandardized model estimates and 95% confidence intervals are reported.

In addition to the covariates defined above, HIV status and the average number of social interactions across visits, as well as their cross-level interactions with person-mean centered loneliness, were included in the models to determine whether the concurrent and longitudinal relationships between loneliness and depressive symptoms are stronger (i.e., have steeper slopes) in PWH compared to PWoH, or stronger among those who typically experience greater social

engagement. A three-way interaction between person-mean centered loneliness, HIV status, and average social interactions was not evaluated given low power to detect this effect.

3. Results

3.1. Baseline Participant Characteristics

Baseline participant characteristics are presented in **Table 7**. PWH and PWoH were comparable for mean age (55.1 years, SD = 8.2 vs 52.8 years, SD = 7.8, respectively; Cohen's *d* = 0.29, *p* = .13), education level (Cohen's *d* = 0.32, *p* = .09), and race/ethnicity (*p* = .16). Nearly all PWH in our study identified as male compared to 64.4% of the PWoH cohort (OR = 1.71, *p* = .003). Current rates of Major Depressive Disorder (MDD) and substance use disorder (SUD) were low in both groups (i.e., <10%) and did not differ across groups (*p*s > .10), although lifetime MDD and SUD diagnoses were elevated in PWH relative to PWoH (OR = 2.76, *p* = .003; OR = 2.89, *p* = .007, respectively). Most PWH (95%) were currently taking antiretroviral therapy, with a median duration of current regimen of one year (IQR = 0.5, 2.4). Of those on ART, 91.2% reporting being adherent; these participants also had undetectable HIV RNA in plasma. **Table 8** summarizes the number of participants in each group at each visit, and their respective number of follow-up visits. Although PWoH had somewhat fewer follow-up visits than PWH, HIV status did not predict the length of study follow-up (*p* > .05), suggesting that the assumption of data missing completely at random was not violated.

3.2. Baseline Loneliness

On average, PWH endorsed statistically higher levels of baseline loneliness compared to PWoH (Cohen's *d* = 0.51, *p* = .003; see **Table 7**). When using a categorical approach, it was observed nearly half of PWH (45.5%) endorsed experiencing high degrees of loneliness at baseline compared to only a quarter of PWoH (25.4%); OR = 2.40, *p* = .02). Among PWH, HIV

disease characteristics such as estimated duration of HIV infection, CD4 count, and total duration on ART were unrelated to loneliness scores ($p > .05$).

3.3. Within-Person Effects

3.3.1. Loneliness Effect on Concurrent Depressive Symptoms

Model 1 of the multi-level modeling approach examined the relationship between relative loneliness and concurrent depressive symptoms. Loneliness scores were positively associated with depressive symptoms at each study visit ($B = 3.01$, 95% CI = [2.46, 3.56], $p = .001$). In other words, at the within-person level, multi-level modeling found that at visits when a participant reported loneliness scores that were higher than their person-mean centered loneliness scores (i.e., higher relative loneliness), they also reported higher depressive symptoms compared to visits when they did not report higher relative loneliness. These results held even after accounting for covariates such as sex/gender, lifetime substance use disorder, and time (months) between visit (ps > .05). **Table 9** summarizes these findings.

3.3.2. Loneliness Effect on Depressive Symptoms at the Next Follow-up

Model 2 of the multi-level modeling examined the relationship between relative loneliness and depressive symptoms reported at the next follow-up visit. Results of the multi-level model found that there was a main effect of higher relative loneliness on follow-up depressive symptoms, indicating that individuals who reported higher relative loneliness at a study visit were more likely to report higher depressive symptoms at the next follow-up study visit ($B = 2.30$, 95% CI = [1.43, 3.17], $p = .02$). Again, these within-person results held even after adjusting for time between visits, and time-invariant covariates sex/gender and lifetime history of substance use disorder (ps > .05). **Table 10** summarizes these findings.

3.4. Between-Person Effects and Cross-Level Interactions

3.4.1. HIV Effect on the Relationship between Loneliness and Depressive Symptoms.

At the between-person level, HIV status was a primary predictor of interest. The cross-level interaction between HIV (a between-person effect) and visit-specific relative loneliness (a within-person effect) on concurrent and longitudinal depressive symptoms was also examined using two separate models. In model 1, with concurrent depressive symptoms as the outcome of interest, the cross-level interaction between HIV status and relative loneliness was trending towards significance (B = 1.30, 95% CI = [0.76, 1.84], p = .06). Although this effect did not reach statistical significance ($p < .05$), there was a significant main effect of HIV status on concurrent depressive symptoms (B = 5.71, 95% CI = [5.29, 6.13], $p < .001$). These results indicated that PWH reported higher depressive symptoms at each study visit relative to PWoH; however, the relationship between relative loneliness and current depressive symptoms was trending, but not significantly stronger among PWH compared to PWoH. In model 2, with follow-up depressive symptoms as the outcome of interest, the cross-level interaction between HIV status and relative loneliness was significant (B = 1.89, 95% CI = [1.53, 2.25], p = .03). This finding indicated that the relationship between relative loneliness and future depressive symptoms was moderated by HIV status such that the relationship was stronger (i.e., steeper sloped) in PWH compared to PWoH.

3.4.2. Social Interaction Effect on the Relationship between Loneliness and Depressive Symptoms.

The average number of social interactions a person experienced across visits was considered an a priori, between-person covariate. Its main effect on depressive symptoms and potential moderating effect on the relationship between relative loneliness and depressive symptoms were investigated. In both models (with concurrent depressive symptoms and follow-

up depressive symptoms as the outcome variables), the cross-level interaction between average social interactions and relative loneliness and the main effect of average social interactions on depressive symptoms were not significant (*p*s > .05). Thus, the degree of social engagement that a person typically experienced did not impact current or longitudinal depressive symptoms and was removed from the models.

4. Discussion

Our study sought to investigate the longitudinal impact of loneliness on self-reported depressive symptoms over time and compare these experiences between PWH and PWoH. When an individual experienced more loneliness compared to their typical level, depressive symptoms at that same time-point was elevated. Although this relationship was not significantly higher in PWH compared to PWoH, results were trending in that direction. Longitudinally, loneliness also significantly predicted the number of depressive symptoms reported at the next follow-up, and this relationship was significantly stronger among PWH compared to PWoH. Together, these findings suggest a dynamic, predictive, and robust relationship between loneliness and depression over time. Additionally, this relationship was unaffected by other factors such as sex/gender, lifetime history of substance use disorder, or whether a person engaged in more or less social interactions compared to others.

Although previous studies have investigated the longitudinal impact of loneliness on depression in PWoH, only cross-sectional studies have examined loneliness and depression in PWH. Thus, findings from the current study have not been established previously. Our study used a methodological approach (multilevel modeling) that was able to examine both inter- and intra-individual differences over time, which provided additional variance to examine the nuances of relationships over time. Findings expand those in the current literature to demonstrate

that PWH are more likely to report elevated depressive symptoms if/when they experience higher loneliness than their usual. Though this was a novel finding, our results fit into the larger framework that has already been established. Prior studies generally lend support for the predictive power of loneliness on depression in the general population. Across different age and racial/ethnic groups, loneliness has been predictive of increased depressive symptoms over several years (Koenig & Abrams, 1999; Cacioppo, Hawkley, & Thisted, 2010), even after controlling for baseline depression symptoms. Furthermore, a meta-analysis of studies investigating the link between loneliness and depression found that these effects were robust, and unaffected by potential publication bias such as type of publication, study sampling group, or publication year (Erzen & Cikrikci, 2018). Some studies have suggested a bidirectional relationship between loneliness and depression across time, with slightly stronger support for depression preceding loneliness (Hsueh, Chen, Hsiao, & Lin, 2019). Although we did not specifically test bidirectionality in our current study, our findings support the directionality that has typically been reported in the literature (i.e., loneliness being more likely to cause depression than vice versa).

There are a few potential mechanisms that could explain the predictive impact of loneliness on depression. First, research suggests that loneliness and depression, although interrelated and somewhat overlapping in terms of symptoms (e.g., poorer sense of belongingness, and sadness; Hagerty, Williams, Coyne, & Early, 1996), they remain distinct constructs. In loneliness, appraisals are limited to those pertaining to social aspects in one's life, while appraisals in depression are more global and encompass many multiple domains (van Winkel et al., 2017). Consequently, loneliness likely contributes to the affective (e.g., negative feelings of rejection, worthlessness, isolation), cognitive (e.g., negative self-conceptions, bias

towards negative social cues, poorer self-efficacy), and behavioral (e.g., inhibited sociability, poor social skills, and social effectiveness) subcomponents of depression. Additionally, the effects of loneliness on the quality of social interactions persists even after controlling for depression (L. C. Hawkley et al., 2003). Functional neuroimaging also demonstrates that the neural networks during active and resting state periods differ based on whether individuals experienced loneliness and/or depression. During a task of inhibitory control, loneliness was positively associated with greater prefrontal-anterior cingulate-parietal connectivity across individuals with and without MDD. Furthermore, those with MDD and higher loneliness showed weaker activation of the parietal and cerebellar regions during this task and overall reduced parietal-anterior cingulate connectivity during a resting state period, compared to those with MDD and lower loneliness (Shao et al., 2019). Finally, evidence suggests that loneliness, especially chronic loneliness, activates chronic stress responses and inflammatory pathways (Leschak & Eisenberger, 2019).

Inflammation has also been implicated in the pathogenesis of depression, which may explain how the presence of ongoing or elevated loneliness leads to increased depressive symptoms overtime (McDade, Hawkley, & Cacioppo, 2006; Mezuk et al., 2016; Theeke et al., 2016). PWH may be especially at risk for depression due to the additive impact of having compromised immune functioning following HIV infection and related comorbidities. In the current study, HIV disease characteristics were not significantly associated with loneliness. However, literature suggests that depressive symptoms in PWH are associated with elevated sCD14 and associated with other biomarkers of systemic inflammation such as IL-6 and D-dimer, even in virally suppressed PWH (Stewart et al., 2020). Therefore, future research examining changes in biomarkers of systemic and neuroinflammation as they relate to the

relationship of loneliness and depression over time may provide insight into the directionality between the two and identify more specific biological mechanisms that may be involved.

Additionally, PWH may experience HIV-related distress such as stigma and discrimination, leading to feelings of loneliness and increased vulnerability to depression. Cross-sectionally, HIV-related stigma remained significantly associated with loneliness after controlling for disease burden and demographic variables (Yoo-Jeong et al., 2019). Of the more than 2000 global adult participants who completed the AIDS Treatment for Life Survey, 37% reported feeling loneliness and/or socially isolated because of their HIV status (Nachega et al., 2012), suggesting a strong impact of HIV-related stigma on loneliness that PWoH may not have had to endure. Although our study did not directly examine the role of HIV stigma and discrimination in explaining the long-term relationship between loneliness and depression, is an important avenue for future direction.

Social interactions (as measured by the 2-item Duke Social Support Index), which was considered a covariate in analyses, did not mitigate the predictive impact of loneliness on depressive symptoms, nor did it have a direct impact on reducing depressive symptoms concurrently or overtime. Notably, the amount of baseline weekly social interactions did not significantly differ between PWH and PWoH in our sample. In addition, evidence suggests that loneliness rather than objective social isolation has the most significant impact on depression outcomes. In a large cohort of community-dwelling older adults ($\geq$ 65 years old) loneliness, not objective social isolation, was a significant predictor of depression incidence after a three-year period (B. H. Green et al., 1992). Thus, the impact of *perceived* social isolation (i.e., loneliness), as opposed to objective social isolation highlights its subjective, experiential nature. The influence of loneliness vs social interactions on depressive symptoms, may speak to the

overlapping affective and cognitive features between loneliness and depression. Additionally, it highlights the importance of studying how one *interprets* and *experiences* social isolation (e.g., quality over quantity of social interactions) when studying its impact on depression.

The results of our longitudinal study have important clinical relevance in the identification and treatment of those at risk for experiencing greater loneliness and subsequently higher depressive symptoms. Prior literature has described the additive impact of loneliness and depression, particularly among PWH, on negative health outcomes. In PWoH, these combined factors are associated with earlier mortality (Holwerda et al., 2016). In PWH, the combined influence of loneliness and depression has been associated with more risk-taking behaviors such as risky sexual behaviors and substance use (Siconolfi et al., 2013; Su et al., 2018; Wang et al., 2017). Both loneliness and depressive symptoms also mediated the relationship between HIV-related stigma and medication adherence, as well as HIV-related stigma and sleep quality, suggesting independent effects between these constructs and important areas for future direction. Literature also suggests interconnected mechanisms between loneliness and depression in HIV, such that internalized stigma has predicted higher loneliness, which was associated with more depressive symptoms, poorer medication adherence, and sleep quality in PWH (Fekete et al., 2018; Turan et al., 2016). Our study adds to these cross-sectional findings by establishing the direct, long-term effects of loneliness on depression, not only at one specific point in time, but across time over many months. Given that this predictive relationship was strongest in PWH compared to PWoH, our findings highlight the need for close follow-up of PWH's feelings of social connectedness and social support by clinicians and recommendations for interventions that could reduce loneliness through social recreation intervention, enhancing social support, improving social cognition through social skills training, addressing maladaptive social cognition

through cognitive behavioral therapy (S. Cacioppo, Grippo, London, Goossens, & Cacioppo, 2015).

The current study has many strengths including longitudinal sample with multiple follow-up visits, robust statistical methods, presence of an HIV- comparison group, and novel findings that have important clinical relevance for a population that is vulnerable to experiencing depression. However, there are some limitations of note. First, our study did not collect potentially relevant variables such as relationship status, living situation (alone vs. with others) and rates of perceived stigma and discrimination, which could lend for further explanation of our findings. In addition, the social interaction variable may not have captured the nuanced types of social connection individuals may experience (e.g., at home, at work, through texting and social media). Second, the UCLA-3 questionnaire also does not specify the time period in which a person should respond (e.g., in the past week), making it difficult to assess change in loneliness. Furthermore, the exclusionary criteria of our parent study limited the presence of higher rates of those with current Major Depressive Disorder and substance use disorder, which could add important variability to our sample and findings and extend generalizability of our findings to those with active psychiatric disorders. Additionally, those with HIV who engaged in our longitudinal study may be more clinically stable, and thus not fully representative, of the larger clinical population of PWH. This could have limited the observed within-person, as well as between-person variability in understanding the longitudinal impact of loneliness on depression in the larger HIV population. Future studies could build upon our work by investigating the longitudinal impact of chronic loneliness burden on the incidence of clinical or sub-clinical disorders such as Major Depressive Disorder and dysthymia, and examine the influence of

loneliness over time on inflammation, similar to how the relationship between depression and inflammation over time has been investigated (Saloner et al., 2021).

Despite these limitations, to our knowledge, this study is the first to examine the longitudinal impact of loneliness on depressive symptoms in HIV and compare this relationship to non-HIV counterparts using multi-level modeling, which allowed for more nuanced analysis of both within- and between-person factors. There is evidence for short- and long-term effects of elevated loneliness on self-reported depressive symptoms across time. Findings also identify PWH as being particularly vulnerable to these long-term effects. Additionally, intervention studies targeting the reduction of loneliness through cognitive-behavioral strategies or meaningful community/social engagement, and the impact of interventions to reduce loneliness on reducing depressive symptoms over time could be highly beneficial.

Chapter 3, "Understanding the Longitudinal Impact of Loneliness on Depressive Symptoms in People with and without HIV," is coauthored with Hussain, Mariam A.; Umlauf, Anya; Iudicello, Jennifer E.; Morgan, Erin E.; Heaton, Robert K.; Jeste, Dilip V.; Moore, David J. The dissertation author was the primary author of this chapter.

Table 7. Participant Characteristics (*N* = 139).

	PWH (*n* = 80)	PWoH (*n* = 59)	Effect size	*p*-value
Demographics Characteristics				
Age (years)	55.1 (8.2)	52.8 (7.8)	*d* = 0.29	.13
Education (years)	14.5 (2.6)	15.3 (2.3)	*d* = 0.32	.09
Sex/gender (% male)	**90.0%**	**64.4%**	**OR = 1.71**	**.003**
Race/ethnicity	--	--	--	.16
White, non-Hispanic (%)	69.5%	55.8%	OR = 1.13	.05
Hispanic (%)	17.1%	20.8%	OR = 0.88	.59
Black (%)	12.2%	15.8%	OR = 0.61	.54
Other[a] (%)	1.2%	7.5%	OR = 0.37	.05
HIV Disease Characteristics				
Estimated duration of HIV disease (years)	16.6 [3.1, 25.5]	--	--	--
Nadir CD4 count	215 [56, 419]	--	--	--
Current CD4+ t-cell count	678.5 [480.3, 913.5]	--	--	--
Taking ART (% currently on ART)	95.0%	--	--	--
Total duration of ART (years)	10.5 [2.6, 18.5]	--	--	--
Duration of current ART regimen (years)	1.2 [0.5, 2.4]	--	--	--
ART adherence (% adherent[c])	91.2%	--	--	--
Plasma HIV viral load (% undetectable[d])	96.6%	--	--	--
Psychiatric Characteristics				
Depressive symptoms[b]	**19.1 (8.0)**	**14.7 (4.9)**	***d* = 0.64**	**.0003**
Current Major Depressive Disorder (% yes)	8.6%	2.9%	OR = 1.59	.46
Lifetime Major Depressive Disorder (% yes)	**54.0%**	**25.4%**	**OR = 2.76**	**.003**
Current Substance Use Disorder (% yes)	8.6%	2.9%	OR = 1.59	.46
Lifetime Substance Use Disorder (% yes)	**62.0%**	**35.6%**	**OR = 2.89**	**.007**
Loneliness (UCLA-3[e] total score)				
UCLA-3[e] total score	**40.9 (12.5)**	**35.0 (10.0)**	***d* = 0.51**	**.003**
Low Loneliness (UCLA-3 < 28)	20.0%	27.1%	OR = 0.67	.42
Moderate-to-High Loneliness (UCLA-3 $\geq$ 28)	80.0%	72.9%	OR = 1.49	.42
Moderate Loneliness (44 < UCLA-3 $\geq$28)	35.0%	47.5%	OR = 0.60	.14
High Loneliness (UCLA-3 $\geq$ 44)	**45.0%**	**25.4%**	**OR = 2.40**	**.02**
Social interactions[d]	6.6 (3.6)	7.2 (3.4)	*d* = 0.18	.25

Note. Bold: $p<.05$. Mean (SD) or Median [IQR]; Effect size=Cohen's *d* or Odds Ratio; [a]Race/ethnicity other than White, Black, or Hispanic; [b]Center for Epidemiological Studies Depression Scale (CES-D); [c]AIDS Clinical Trials Group (ACTG) Adherence Questionnaire (4-day adherence of $\geq$90%); [d]plasma viral load $\leq$50 copies/mL; [e]Revised UCLA Loneliness Scale – Version 3 (UCLA-3); [f]total number of social interactions in the past week determined using 4-item Duke Social Support Index

Table 8. Follow-up visits between groups.

	PWH (*n* = 80)	PWoH (*n* = 59)
Number of visits		
1 (baseline visit)	80	59
2 (1 follow-up visit)	21	40
3 (2 follow-up visits)	29	18
4 (3 follow-up visits)	25	1
5 (4 follow-up visits)	5	0

Note. HIV status did not predict the length of study follow-up ($p > 0.05$), suggesting that the assumption of data missing completely at random was not violated.

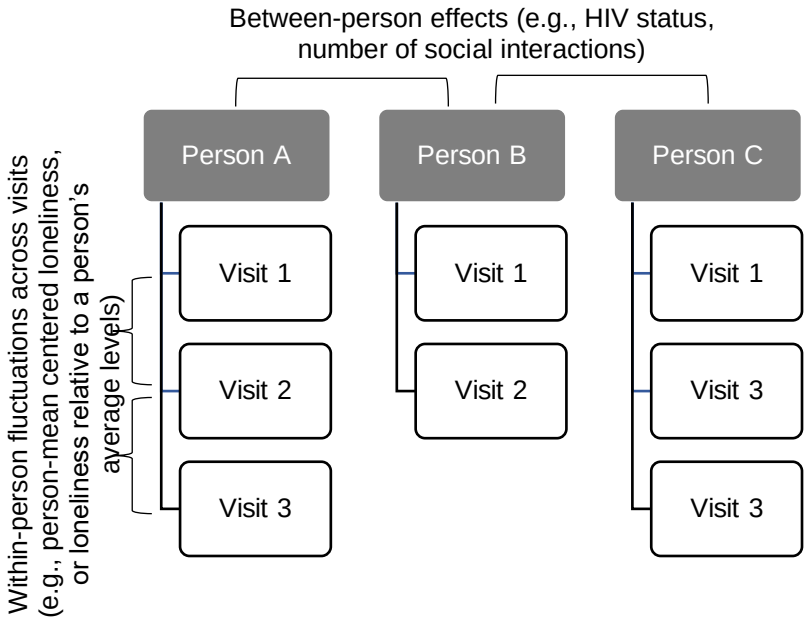

Figure 5. Conceptual design depicting the longitudinal effects being modeled using multi-level modeling.

Table 9. Effects of relative loneliness and HIV status on concurrent depressive symptoms in PWH and PWoH.

	B	*SE*	*p*-value
Within-person effects			
Relative loneliness[a]	3.01	0.55	.001
Time between visits (months)	0.18	0.13	.81
Between-person effects			
HIV status [PWoH]	5.71	0.42	<.001
Sex/gender [male]	1.14	0.79	.13
Lifetime history of substance use disorder [-]	0.84	0.37	.44
Cross-level interaction			
Relative loneliness x HIV status	1.30	0.54	.06

Note. [a]person-mean centered loneliness (the difference between an individual's loneliness score at a particular study visit compared to their average loneliness score across visits).

Table 10. Effects of relative loneliness and HIV status on follow-up depressive symptoms in PWH and PWoH.

	B	*SE*	*p*-value
Within-person effects			
Relative loneliness[a]	2.30	0.87	.02
Time between visits (months)	0.15	0.24	.52
Between-person effects			
HIV status [PWoH]	4.13	0.36	<.001
Sex/gender [male]	0.26	0.63	.11
Lifetime history of substance use disorder [-]	0.98	0.32	.35
Cross-level interaction			
Relative loneliness x HIV status	1.89	0.36	.03

Note. [a]person-mean centered loneliness (the difference between an individual's loneliness score at a particular study visit compared to their average loneliness score across visits).

Discussion

The overall goal of this staple dissertation was to expand the current literature on loneliness in people with HIV (PWH) and provide novel contributions that would have important clinical and therapeutic implications. Three separate studies were designed to: 1) evaluate the prevalence and risk factors of loneliness in people with HIV (PWH) relative to age-matched people without HIV (PWoH); 2) provide insight into the biological mechanisms underlying loneliness in PWH; and 3) evaluate the relationship between present and persistent loneliness and depression, another highly prevalent condition with important clinical consequences in HIV. Loneliness has been linked with several adverse health outcomes across many populations. Our findings reveal important insights regarding loneliness' clinical impact on depression in HIV, and potential avenues for loneliness intervention in PWH.

Review of Study Design

The studies included in this dissertation utilized data that were collected from the NIH-funded Multi-Dimensional Successful Aging among Adults living with HIV study conducted at the HIV Neurobehavioral Research Program (HNRP) and Stein Institute for Research on Aging (SIRA) at the University of California San Diego (UC San Diego). Study 1 included baseline data from 202 community-dwelling adults with and without HIV (PWH, n = 120; PWoH, n = 82) who had completed the revised UCLA Loneliness Scale-Version 3 (UCLA-3). Study 2 included a subset of those PWH from Study 1 who also had biomarker data that were collected during their study visit (n = 82), to investigate the relationships between loneliness, depression, and inflammation in PWH. Study 3 included a subset of Study 1 participants (PWH [n = 80] and PWoH [n = 59]) with follow-up data to investigate longitudinal associations between loneliness and depression. The revised UCLA Loneliness Scale was used to assess loneliness in our

samples across all studies. This measure has been used extensively in various populations including PWH (Grov et al., 2010). Cutoffs associated with low, moderate, and high loneliness have also been used in previously established (Lee et al., 2019) and used for characterization purposes to identify potentially problematic levels of loneliness.

In Study 1 (N = 202), the prevalence rates of loneliness among PWH and PWoH was established. Consistent with our hypothesis, PWH reported significantly more feelings of loneliness compared to their PWoH counterparts. The difference between groups was largest on rates of high loneliness, which suggests potentially problematic levels of loneliness; 41.7% of PWH endorsed the highest level of loneliness symptoms compared to 29.3% of PWoH. Consistent with our exploratory hypothesis, positive psychological resources (i.e., resilience, personal mastery, and wisdom) were negatively associated with loneliness in both groups. However, findings were mixed when psychological and social resources were more closely examined. Notably, we found that PWH, compared to PWoH, were more likely to experience loneliness if they endorsed less cognitive wisdom traits. However, regardless of the level of emotional support a person with HIV reported, it did not alleviate feelings of loneliness. Results suggested that PWH may have more difficulty in effectively engaging in cognitive tools involved in wisdom and/or perceived emotional support to manage their subjective feelings of perceived social isolation. Finally, loneliness remained significantly associated with depressive symptoms even when positive psychological and social resources were present, illustrating loneliness' robust association with clinical psychiatric outcomes (depressive symptoms).

In Study 2 (N = 82), the biological processes that potentially underlie loneliness, as well as the relationship between loneliness and depression in PWH was studied on a biological level by examining the independent and combined effects of loneliness and systemic inflammation on

depressive symptoms. This was of particular interest given the reliable link between chronic inflammation and depression in PWH (Lu et al., 2019; Norcini Pala et al., 2016; Rivera-Rivera et al., 2016). However, research linking loneliness and inflammation in PWH was very limited; therefore, our hypotheses were exploratory. Results showed that increased coagulation activity (as indexed by higher levels of D-dimer) was associated with loneliness. D-dimer, a coagulation factor, was also associated with depressive symptoms when loneliness was high, suggesting independent and combined effects of inflammation and loneliness on clinical psychiatric outcomes (depressive symptoms). These findings were observed on both unadjusted models and models adjusted for participant demographics related to depressive symptoms (i.e., ethnicity), as well as potential confounds such as lifetime substance use disorder and perceived emotional support, highlighting the robustness of these effects. The close link between loneliness and coagulation factors in HIV, which are both elevated even in virally suppressed PWH, is consistent with previous literature linking D-dimer with other aspects of social connection (i.e., social support) in HIV (Ellis et al., 2020; Sun-Suslow et al., 2020). The current study's findings extend this literature to highlight the negative impact of social threat (i.e., loneliness or perceived social isolation) on the activation of coagulation factors, which can have further downstream consequences on systemic inflammation throughout the body.

In Study 3 (N = 139), the relationship between loneliness and depression was explored longitudinally to reveal the short- and long-term influence of loneliness on depressive symptoms reported in PWH and PWoH. Consistent with our hypothesis, increased or decreased levels of loneliness, relative to a person's typical experience of loneliness, significantly predicted current and future depressive symptoms reported by that individual. Furthermore, this relationship was stronger in PWH compared to PWoH, even after adjusting for time intervals. However, our

measure of social interaction was not a significant factor in explaining this relationship. Notably, this measure of social interaction was limited and did not consider more modern means of social connection such as mobile texting, social media, etc. Through this longitudinal analysis, the unique and predictive contribution of loneliness, as opposed to apparent objective social isolation, on depressive symptoms was confirmed. Of clinical significance, our findings suggest that loneliness may be a risk factor for worsening depressive symptoms in the future, especially in PWH compared to PWoH. One possibility for these findings may be the propensity of people who are lonely to engage in negative appraisals about the social aspect of one's life. By consistently engaging in this cognitive approach, people who are lonely may move from state loneliness to trait loneliness and begin engaging in more negative appraisals throughout other domains (e.g., affective health), further exacerbating feelings of depression. Additionally, depressive symptoms may also develop overtime as a consequence of the chronic low-level inflammation that accompanies feelings of loneliness/social threat.

Collectively, these three studies shed light on potentially important aspects of the degree to which PWH experience loneliness in their lives. By modeling loneliness and its relationship with depression, which is elevated and of clinical importance in PWH, through both cross-sectional and longitudinal methods, insights have been gleaned regarding its underlying processes and clinical impact. The following themes emerged as a result of the findings across studies: (1) loneliness is a relatively common experience across both populations, but PWH are particularly at risk of experiencing high levels of perceived social isolation, (2) loneliness is subjective and contingent upon an individual's ability to cognitively interpret their experience and/or resources, especially in PWH, and (3) although loneliness and depression share some

common features, they remain dissociable constructs (explained through underlying biological mechanism), with loneliness having a dynamic influence on future depressive symptoms.

Loneliness in People with HIV

Loneliness has been an area of high interest given its associations with several downstream consequences in the general population. For example, answering "yes" to the *single* question of, "Do you often feel lonely?" is associated with increased risk of all-cause dementia (Sundstrom et al., 2019), and feelings of loneliness are related to increased mortality risk (Luo et al., 2012). However, loneliness has been less well studied in more vulnerable populations such as PWH. Furthermore, current prevalence estimates of loneliness in PWH are difficult to interpret since many studies are small and did not include PWoH as a comparison cohort. Thus, the first and foremost objective of this dissertation was to establish the prevalence of this construct in PWH and compare its rates to a sample of PWoH who had similar demographic characteristics. Our overall hypothesis, that PWH would experience more loneliness than PWoH, was confirmed. Although PWH and PWoH had similar rates of moderate-to-high loneliness, PWH were more likely to report the *highest* amounts of loneliness. This is of significant clinical importance, since even mild loneliness has been linked to more serious outcomes such as depression, cardiovascular risk, dementia, and all-cause mortality (Christensen et al., 2020; Hawkley et al., 2010; Henriksen et al., 2019; Sundstrom et al., 2019; Vingeliene, Hiyoshi, Lentjes, Fall, & Montgomery, 2019). This also raises particular concerns given that PWH are already susceptible to more clinical conditions such as metabolic syndromes, HIV-associated neurocognitive disorders, and compromised immune functioning (Bonfanti et al., 2007; Heaton et al., 2010; Heaton et al., 2015; Williams, Ipser, Stein, Joska, & Naude, 2020). Previous work has established lower rates of loneliness in both PWH and PWoH (Beutel et al., 2017; Grov et

al., 2010; Harris et al., 2020; Qualter et al., 2015; Surkalim et al., 2022). However, few studies of PWH have utilized the specific categorical approach used in our study, though it has been used in previously published studies (Lee et al., 2019). By demonstrating that PWH were at greater risk of experiencing high degrees of loneliness, this raises immediate concerns regarding the contribution and impact of loneliness on clinical outcomes in an already vulnerable population, which was further investigated in Study 2 and Study 3.

Risk and protective factors of loneliness were examined across all three studies. There were no HIV disease characteristics that were associated with loneliness in PWH. However, other aspects specific to HIV were not assessed such as HIV-related stigma and discrimination. These areas have been suggested as factors that likely contribute to the experience of loneliness in PWH (Harris et al., 2020; Nachega et al., 2012). Other clinical variables such as history of depression and substance use disorders may contribute to the higher prevalence of loneliness in PWH compared to PWoH. The higher prevalence of these clinical disorders in PWH has been previously established (Carrico, 2011; Deren et al., 2019; Nanni, Caruso, Mitchell, Meggiolaro, & Grassi, 2015; Rueda et al., 2016), although the associations between depressive disorders and substance use disorders with loneliness among PWH was novel. Study 1 also found particularly interesting associations highlighting the importance of positive psychiatric factors in PWH, which is novel and important in understanding protective factors against loneliness in PWH. Wisdom, or more specifically, cognitive wisdom, defined as the ability to understand life and perceive reality as it is without any major distortions, was associated with less loneliness, especially in PWH. By contrast, perceived emotional support, which was less available in PWH than PWoH, was associated with reduced feelings of loneliness in PWoH, but not in PWH. The later finding was unexpected, but perhaps suggests that PWH may engage in different

interpretation or appraisals of their social-emotional supports. Taken together, results indicate that PWH may have more difficulty in effectively engaging in cognitive tools (i.e., cognitive wisdom and perceived emotional support) to combat social isolation and/or social threat, which predisposes them to experiencing more loneliness. Finally, not all demographic factors such as race/ethnicity were consistently associated with loneliness across studies, suggesting that study cohort effects may influence the rates of loneliness. These mixed race/ethnicity findings are consistent with the literature, and differences in study cohorts' demographics have been implicated in the one of the reasons loneliness prevalence rates may be so varied across studies in the literature.

Insight into the Biological Mechanisms Underlying Loneliness in PWH

In recent years, the literature examining the immune and neurobiology of loneliness have expanded our understanding of the previously observed links between loneliness and disease outcomes such as cardiovascular disease and metabolic syndromes. Three major pathways of pathogenesis related to loneliness in the general population, and its influence on clinical outcomes have been proposed: poor health behaviors, heightened stress response, and inadequate physiological repairing activity (Hackett et al., 2012). Results from our investigation, especially Study 2, suggest that loneliness is associated with dysregulation in the body's ability to carry out reparative processes in PWH, as well as activation of a heightened chronic stress response that likely compounds this immune dysregulation. However, work specifically examining these factors within PWH is limited and would benefit from further follow-up.

Findings from Study 2 suggested that D-dimer, a biomarker involved in coagulation process associated with systemic inflammation, and sCD14, which impacts D-dimer, were inflammatory biomarkers that were elevated in association with loneliness in this sample of

PWH. By contrast, MCP-1/CCL-2, a pro-inflammatory chemokine, was elevated in association with depressive symptoms in PWH. These findings suggest that although loneliness may have an indirect impact on immune activation, the underlying mechanism responsible for inflammation in the body is likely the stress circuitry that is chronically activated in those experiencing loneliness. Literature suggests that when this stress circuitry is activated, a number of physiological processes are impacted, including glycemic control, lipid metabolism, and increased vascular coagulation, which in turn produces downstream inflammatory consequences (Hackett et al., 2012; Hawkley & Cacioppo, 2003, 2010). The link between loneliness and activation of a stress response is supported by the theory of social threat and hypervigilance (Hawkley & Cacioppo, 2010). This theory proposes that individuals who experience chronic loneliness have increased perceptions and hypervigilance of social threat resulting from prolonged deficits in social and emotional connection with others. This link between psychosocial disturbances and activation of the coagulation system, specifically D-dimer, has been previously established in PWH and supports our findings (Sun-Suslow et al., 2020). Prior findings in the literature also suggest that by improving social support, coagulation/D-dimer processes may be improved (Wirtz et al., 2006; Wirtz et al., 2008; Wirtz et al., 2009).

Loneliness and Its Impact on Depression in HIV

Findings in Studies 1, 2 and 3 confirmed positive associations between loneliness and depressive symptoms in PWH. This association was observed in cross-sectional analyses, even after positive psychological and social resources were considered, and is supported by the existing literature base. The strength of the association between loneliness and depression was stronger than with any other factor, suggesting that there is a very strong influence between these variables. Thus, if loneliness can be reduced, depressive symptoms may likely be reduced as

well. Our findings also confirmed that loneliness and depression were distinct constructs as evidenced by different underlying biological processes that were elevated in relation to each respective variable. In particular, higher loneliness was associated with altered coagulation, as indexed by higher plasma D-dimer levels, which have been independently associated with poorer cardiovascular health and mortality. Depression was linked with pro-inflammatory processes, which has been previously established in the literature. There may also be overlapping contributions related to the coagulation pathways that underlie loneliness. First, loneliness has been implicated in activating the same pathways involved in chronic stress. Second, the combined persistent, chronic low-level inflammation stemming from chronic stress may lead to other consequences including vascular dysfunction and coagulation imbalance. By contrast, depression appears to directly impact the activation of inflammation through increasing chemokine processes. The differential processes linked to loneliness and depression are supported by previous work that have linked these biomarkers with different clinical outcomes such as cardiovascular disease and clinical depression, respectively (Hawkley et al., 2003; Hawkley & Cacioppo, 2003; Hawkley et al., 2010; Henriksen et al., 2019; Lu et al., 2019; Miller et al., 2009; Yoo-Jeong et al., 2019; Yuan et al., 2019).

Dynamic modeling of longitudinal data provided novel insights into the relationship between loneliness and depressive symptoms not only at the same point in time, but also related to the ongoing influence of loneliness on depression, which lends supports to predictive directionality between loneliness and depression. Although prior research has supported the link between loneliness and depression over time in PWoH (Beller & Wagner, 2018; J. T. Cacioppo et al., 2006; Domenech-Abella, Mundo, Haro, & Rubio-Valera, 2019; Jaremka et al., 2013; Richard et al., 2017; Van As et al., 2021), such work had not yet been examined in PWH. Our

study identified HIV status as a risk factor for the development of increased depressive symptoms at follow-up when loneliness was higher than usual. Based on findings from Study 1, it can be hypothesized that PWH may lack the ability to engage effectively with cognitive resources (e.g., wisdom) to combat the feelings of loneliness from developing into more severe clinical symptoms of depression at a later point. Results from our studies consistently found that absolute numbers of social interactions outside the home did not moderate the relationship between loneliness and depression, cross-sectionally or longitudinally; however, our measure of social interactions may have been limited and precluded us from capturing varied aspects of the types of social engagement a person may engage with (e.g., social media). The literature examining objective social isolation and perceiving social isolation (i.e., loneliness) is somewhat mixed (Beller & Wagner, 2018; Domenech-Abella et al., 2019; Lee et al., 2019; Walker et al., 2019; Yu, Steptoe, Chen, & Jia, 2020), potentially due to differences in the measurement of social engagement/connection across studies. Our studies lend support to the case that although these constructs can be related, they remain distinct and essentially unrelated in our samples. Of note, our *a* priori approach modeled depression as an outcome of loneliness; however, studies have also examined and found effects in the opposite direction (Hsueh, Chen, Hsiao, & Lin, 2019; McHugh Power et al., 2020). However, neither of these studies considered social support or social connectedness, which may have affected results given that depression can impact behaviors such as social withdrawal or disengagement, which in turn may increase feelings of perceived social isolation. It is likely that loneliness and depression have bidirectional influences, although our current study did not specifically evaluate this bidirectionality.

Overall Limitations

Despite novel contributions to the literature, limitations exist within these studies. First, the data for all three studies were observational, retrospective, and overlapping given that they were gathered from one larger study without the specific goals of examining loneliness in HIV. Unfortunately, data pertaining to aspects of loneliness that may have been relevant in PWH and PWoH such as stigma, discrimination, partner status, and living situation were not collected. The inclusion of these variables will be important to the further exploration and assessment of the mechanisms influencing loneliness in HIV and depression. Second, two of the three studies involved cross-sectional data (Study 1 and Study 2), and Study 3 involved observational longitudinal analyses; therefore, interpretations of causality cannot be confidently drawn from these findings. As previously stated, the bidirectionality of the relationships between loneliness and depression was not evaluated but should be a target for future research in PWH. Third, much of the data used for these analyses were based upon subjective self-report, which may be prone to reporting biases (under- or over-reporting). However, given that the nature of loneliness is inherently subjective, as are other clinical aspects that were evaluated such as depressive symptoms, the subjectivity of our data may be deemed unavoidable. Fourth, the sample sizes for Studies 2 and 3 were reduced as not every participant had biomarker or longitudinal data. Consequently, the reduced samples may have limited our generalizability. Further studies regarding the relationship between loneliness and demographic characteristics such as race/ethnicity in PWH should also be further investigated. Although some questions remain unanswered due to these limitations, they also help guide directions for future research.

Conclusion

The results from this multi-study dissertation reveal the importance of assessing loneliness in PWH and suggest indirect and direct pathways in which loneliness can have

negative consequences in this population, particularly on psychiatric outcomes such as depression. **Figure 6** below provides a conceptual framework in which the results of these three studies fit into the larger understanding and literature base of how loneliness may exacerbate clinic, psychiatric outcomes. Taken together, the model and findings from this dissertation illustrates that loneliness can act through a variety of mechanism including behavioral, cognitive, and biological processes to exacerbate and increase distress to a level of clinical significance.

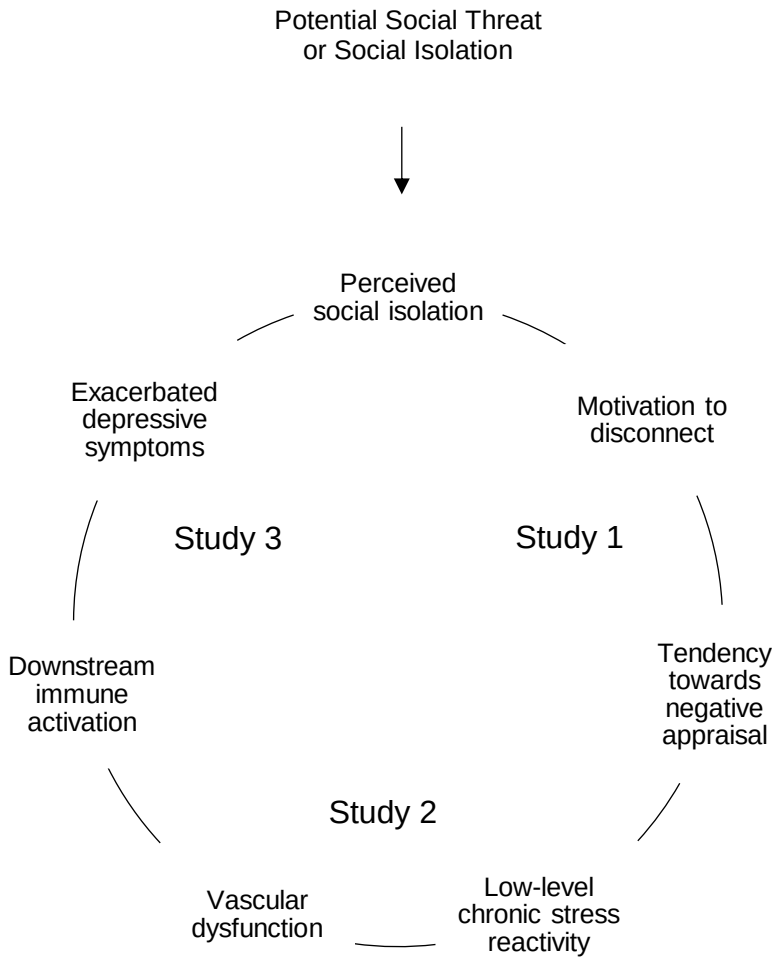

Figure 6. Conceptual framework illustrating how the three studies in this dissertation fit into the larger framework, and expand our current understanding, of loneliness, biological processes, and clinical psychiatric outcomes.

Research suggests that when an individual experiences objective social isolation or perceives a social threatening situation, they may experience subjective feelings of distress that is related to a mismatch between their desired and actual social experience. Because of this encounter, an individual may either have a motivation to increase their social connection to reduce their emotional distress or may perceive the social landscape as dangerous and have an increased hypervigilance to future social situations. The latter approach can result in further social disengagement as individuals will seek to protect themselves from potentially socially painful situations in the future. This maladaptive behavior coping mechanism results in confirmatory bias, as well as attentional and memory biases of their experience in social environments. Through this behavioral confirmation process, individuals experience more negative affect and tend to engage in negative appraisals of themselves and others during social situations. Study 1 findings from this dissertation extend this literature to illustrate that PWH may be even more affected by this maladaptive cognitive coping as evidenced by the moderating influence of wisdom on loneliness in PWH (and not in PWoH), and the lower perceived emotional support reported among PWH despite reporting the same number of social interactions as their non-HIV counterparts.

Because of these maladaptive cognitive-behavioral mechanisms, as well as the hypervigilance towards future social encounters, individuals begin to experience low-level chronic stress reactivity. This stress reactivity and subsequent neuroendocrine activation can lead to altered gene expression (Brown et al., 2020). For example, during this chronic stress reactivity, the body releases the hormones epinephrine and cortisol, which affects genes that code for the body's inflammatory response (Hawkley & Cacioppo, 2003). Therefore, downstream inflammatory pathways may be both up- and down-regulated. For example, the

block of genes that code for type-1 interfere, which directs the immune system to kill viruses and are involved in fending off against viral infections, have been shown to be suppressed during acute periods of loneliness (S. W. Cole et al., 2007). The activation of the neuroendocrine stress-response system can also be accompanied by vascular dysregulation. Consistent with the literature (Hackett et al., 2012), our findings from Study 2 found that D-dimer, a coagulation factor that is elevated during vascular and immune dysregulation, was closely linked to loneliness in our sample of PWH. Ultimately, this process likely contributes to further downstream immune activation that has been linked to exacerbations of depressive symptoms in PWH and PWoH (Kiecolt-Glaser et al., 2015; Lu et al., 2019; Miller et al., 2009; Norcini Pala et al., 2016; Pariante, 2017).

Neuroimaging findings also support evidence of biological processes on a neural level that may be involved in loneliness. Functional imaging studies have found that particular brain regions are reduced in individuals identifying as highly lonely. In particular, the ventral striatum, which is involved in reward processing, as well as the dorsomedial prefrontal cortex, which is involved in cognitive control processes, show reduced activation (Lam et al., 2021). Thus, individuals who are lonely may experience less reward from social encounters and may have difficulty engaging in cognitive tools to interpret social situations accurately or in non-threatening ways. Unfortunately, there have not yet been any loneliness and neuroimaging studies in PWH to investigate these neural processes further in HIV. However, the results of Study 1, which illustrated lonely PWH may potentially have difficulty engaging in cognitive resources compared to lonely PWoH, as well as prior neuropsychological studies that have found disruptions in frontal-subcortical circuitry in HIV (Castellon, Hinkin, & Myers, 2000; M. A.

Cole et al., 2007), lends support to a neural basis for why PWH may be more vulnerable to loneliness compared to their HIV- counterparts.

Together, the above behavioral, cognitive, neuroendocrine, vascular, immune, and neural mechanism underlying loneliness work likely work in confluence to maintain and perpetuate depressive symptoms over time, especially in PWH. Findings from Study 3 of this dissertation confirmed that not only was loneliness associated with depressive symptoms in the present, but it was also predictive of exacerbations of future depressive symptoms when loneliness was previously elevated. It is likely that the cognitive-behavioral and biological processes found to be associated with loneliness in Studies 1 and 2 help to perpetuate the long-term effects of loneliness on depressive symptoms overtime.

Future Directions and Treatment Targets

The three studies from this dissertation illustrated a high prevalence of loneliness in PWH, robust short- and long-term effects of loneliness on immune activation and depression, respectively, and identified factors that may mitigate the consequences of loneliness in this potentially vulnerable population. Although these three studies investigated and gleaned insights into various aspects of understanding the contributors and impact of loneliness in HIV (i.e., wisdom, emotional support, stress-reactivity, coagulation-induced inflammation, and depression), there remain several unaddressed questions for future exploration. By understanding the role of loneliness in the development of these clinical outcomes, as well as the processes that underlie them, specific targets for future directions and intervention can also be suggested.

First, given the role of behavioral confirmation processes, to what extent can cognitive-behavioral interventions or social skills training help to adjust an individual's tendency to engage in maladaptive appraisals and perpetuate social isolation? Furthermore, can enhancement of

difference components of wisdom, especially those that may specifically increase cognitive wisdom, be a valuable treatment target to reducing loneliness in PWH? These components may include enhancing prosocial behaviors, building emotion regulation skills, and engaging in self-reflection so that individuals can better engage in accepting uncertainty and ambiguity, appreciate diversity of perspectives, and improve decisiveness.

For example, traditional approaches such as improving social cognition through social skills training, and addressing maladaptive social cognition through cognitive behavioral therapy may be as valuable for PWH, or even more so, in reducing feelings of loneliness (S. Cacioppo et al., 2015). Additionally, as mentioned above, wisdom has been shown to be inversely linked to loneliness in PWoH, and is comprised of modifiable factors such as empathy, compassion, mindfulness, and emotional regulation. This may be a novel target intervention to help reduce loneliness in PWH. Treatment goals such as improving cognitive aspects of wisdom, as well as the *quality* of perceived emotional support received by PWH, are also suggested by our findings. By reducing loneliness through these targets, immune responses generated by the stress reactivity experienced by PWH potentially might be reduced, which could have positive downstream effects in reducing the risk of depression or poorer cardiovascular health in the long-term.

At the biological level, would reducing the neuroendocrine stress-response when individuals feel lonely through exogenous administration of endocrine steroids or precursors prevent further downstream vascular and immune dysregulation observed in loneliness? Can reducing inflammation directly following a social threatening or perceived socially isolating situation decrease subsequent negative, depressed affect? Some of these questions have begun to be investigated in PWoH to varying degrees of success (S. Cacioppo & Cacioppo, 2015; Elheja

et al., 2021); however, it will be important to continue evaluating these future directions in PWH given their vulnerability to biological- and psychiatric-health consequences.

The extent to which digital interventions may help facilitate better quality of social relationships, and improvements in cognitive wisdom in PWH is another novel area for therapeutic intervention. This is especially important in recent years given the impact of a world-wide pandemic that resulted in loss of social connection for many individuals. Some recent intervention approaches using digital technologies such as videoconferencing, social activities via social websites, and text-messaging groups have been examined in older PWoH (Shah et al., 2021). Although these techniques did not help reduce loneliness in older PWoH, the studies' samples were limited to those residing in residential and nursing facilities. It is possible that PWH and others who are more functionally independent would show more responsiveness and better efficacy from these types of digital interventions. Additionally, social recreation intervention and enhancement of social support through digital means may be possible through online adaptation of a friendship enrichment program or participation in virtual self-help groups. Finally, our findings may in fact help guide the focus of these interventions in PWH, and other potentially vulnerable populations, in targeting specific areas. For example, using technology to increase one's ability to engage with internal, cognitive resources such as empathy, compassion, and wisdom to better relate with others with more positive prosocial behaviors may be more beneficial than simply increasing the number of social interactions – in other words, focusing on improving the *quality* of the interactions and how they are interpreted rather than simply increasing the *number* of encounters that a person experiences.

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