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Title PTSD and its Associations with STIs – from Infection and Treatment to Morbidity and Mortality – among Veterans who Deployed to Iraq and Afghanistan

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Degree Doctor of Philosophy

Program Epidemiology

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PTSD and its Associations with STIs – from Infection and Treatment to Morbidity and Mortality – among Veterans who Deployed to Iraq and Afghanistan

By

Kartavya J. Vyas
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MPH, University of California Los Angeles, 2017

Chair: **Jodie L. Guest, PhD, MPH**
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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor in Philosophy
in Epidemiology
2023

Abstract

PTSD and its Associations with STIs – from Infection and Treatment to Morbidity and Mortality – among Veterans who Deployed to Iraq and Afghanistan

One-quarter of the 2.5 million Veterans who deployed to Iraq and Afghanistan post-9/11 are thought to have posttraumatic stress disorder (PTSD); many of whom may go on to develop other medical conditions of concern, including sexually transmitted infections (STIs). We aim to address a knowledge gap in the extant scientific literature for wartime Veterans and to help inform the care of all those with PTSD more broadly; of particular interest are Veterans with HIV (VWH).

In **Aim 1 – Infection**, Joinpoint regression models and marginal structural models were fitted to examine trends in PTSD and STI diagnoses, estimate the associations between PTSD and STI incidence, measure effect modification by number of deployments and combat exposure, and explore how these associations varied over time in a prospective cohort of all Veterans who deployed to Iraq and Afghanistan and received care in the VA between 7 October 2001 and 31 December 2022 (n=1,570,654). We found PTSD increased the rates of all STIs examined – chlamydia, genital HSV, gonorrhea, HBV, HCV, HIV, HPV, and syphilis.

In **Aim 2 – Treatment**, marginal structural models were fitted to estimate the associations between PTSD and HIV treatment non-adherence, modifications, and adverse outcomes; measure effect modification by number of deployments and combat exposure; and explore how these associations varied over time in a prospective cohort of all VWH on treatment who deployed to Iraq and Afghanistan and received care in the VA between 7 October 2001 and 31 December 2022 (n=3,206). We found PTSD increased the risk of HIV treatment non-adherence and the rate of HIV treatment modifications but was not associated with adverse outcomes.

In **Aim 3 – Morbidity and Mortality**, marginal structural models were fitted to estimate the associations between PTSD and 10 age-related comorbidities, multimorbidity, and all-cause mortality; measure effect modification by number of deployments and combat exposure; and explore how these associations varied over time in a prospective cohort of all VWH on treatment who deployed to Iraq and Afghanistan and received care in the VA between 7 October 2001 and 31 December 2022 (n=3,206). We found PTSD increased the risks of AIDS, arthritis, CKD, COPD, CVD, and multimorbidity but was not associated with asthma, cancer, CeVD, DM, liver disease, or mortality.

Individuals with PTSD have higher risks of STIs, treatment non-adherence, and some comorbid conditions. Results underscore the need for routine PTSD screening so that providers can better identify patients at increased risk of adverse outcomes and possibly mitigate these risks by referring them to risk reduction counseling or treatment advocacy programs.

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Acknowledgements

I want to thank my family, all those who currently serve or who have ever served in the military, all members of my dissertation committee, my past mentors, the clinical and research staff at the Infectious Disease Clinic in the Atlanta Veterans Affairs Medical Center, and all faculty and staff at the Rollins School of Public Health.

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Chapter 1: Introduction

The invisible yet palpable wounds of war, including traumatic stress following combat exposure, can have debilitating effects on perceived risk and self-care.[1] It was not until after the Vietnam War that post-traumatic stress disorder (PTSD) was added to the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), but before that, it was colloquially referred to as "soldier's heart" (Civil War), "shell shock" (World War I), and "combat fatigue" (World War II, Korean War).[2] Concurrently, increasing rates of sexually transmitted infections (STIs) were observed in military personnel, particularly after returning from combat deployment.[3] More recently, during Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) post-9/11, the incidence rate of PTSD among military personnel increased substantially (Figure 0a),[4,5] perhaps a harbinger for the escalation in incidence rates for human immunodeficiency virus (HIV) and other STIs that soon followed (Figures 0b-c).[6-8] The coincident nature of these two epidemics among wartime Veterans does not imply causality, but the scarcity of data in the extant scientific literature implores that their relationship be examined. The objective of the current work is to describe the association between combat-related PTSD and the full gamut of STI experience, from behavior to infection and from treatment to morbidity and mortality, in an understudied population – wartime veterans.

Nearly 80% of the 19.5 million veterans alive today are wartime veterans, 3.4 million of whom served during OEF/OIF/OND.[9] Of those who deployed in support of OEF/OIF/OND, 57%, 27%, and 16% deployed one, two, and three or more times, respectively[10]; and approximately 64% reported any combat exposure, of whom 49% witnessed someone who was wounded or killed, 49% felt in danger of being killed, and 17% discharged their weapon.[11] As a result of the cumulative effect of these and other stressors, one-third of all OEF/OIF/OND veterans reported mental health symptoms and 12-20% screened positive for PTSD.[12-14] Combat exposure has been shown to confer a three-fold increased risk for PTSD.[15] The severity of the traumatic exposure and PTSD symptomatology are positively associated with increased risk-taking behaviors, including high-risk sexual behaviors and heightened risks for an STI diagnosis and medication nonadherence[16-19]; this presumably results in elevated risks for treatment failure, faster disease progression, age-related multimorbidity, and premature mortality.[20]

Wartime veterans may return not only with physical wounds but also psychological trauma, which is inherently intangible, inextricable, and intractable; yet, this trauma manifests behaviorally as impulsivity and an impaired perception of risk[16,17] and can result in adverse health outcomes, including STIs[16] and HIV treatment failure.[21] Traumatic stress may also accelerate biological aging, resulting in earlier-onset age-related comorbidities and premature mortality.[22,23] The proposed work will help elucidate the association between combat-related PTSD and HIV/STI epidemiology and outcomes in this understudied population.

The overarching goal of the current work is to describe the association between combat-related PTSD and the full gamut of HIV/STI experience, from behavior to infection and from treatment to morbidity and mortality, in OEF/OIF/OND veterans. The current work is novel, may underscore the need to better screen for and treat PTSD earlier during military service, and may help inform policy-makers on the long-term effects of combat. Results may also advocate for a trauma-informed model of HIV care, in which trauma and PTSD symptoms are routinely screened for and measured, respectively, and integrated in medical decision-making.

Specific aims

Aim 1 – Infection

Objectives of aim 1 are to (1) examine the trends in the incidences of PTSD and STIs, (2) estimate the association between PTSD and STI incidence, (3) measure effect modification by number of deployments and combat exposure, and (4) explore how these effects vary over time among all OEF/OIF/OND Veterans who receive care in the VA.

Aim 2 – Treatment

Objectives of aim 2 are to (1) estimate the overall associations between PTSD and ART non-adherence, modifications, and treatment failure (virologic, immunologic, and clinical); (2) measure effect modification by number of deployments and combat exposure; and (3) examine how these associations vary over time among all OEF/OIF/OND VWH on ART who receive care in the VA.

Aim 3 – Morbidity and mortality

Objectives of aim 3 are to (1) estimate the associations between PTSD and 10 age-related comorbidities, multimorbidity, and all-cause mortality; (2) measure effect modification by number of deployments and combat exposure; and (3) examine how these vary over time among all OEF/OIF/OND VWH on ART who receive healthcare in the VA.

Systematic literature review

A search of the published literature in PubMed was conducted separately for each aim; the article selection process, including search terms, Boolean operators, and exclusion criteria are described in Figures 1, 2, and 3. Titles and abstracts were initially screened for eligibility; thereafter, the full text of articles identified in the initial screening was read. Inclusion criteria included: peer-reviewed articles, published in 2000-2022, written in English, and exposure defined as PTSD. Data (study design, outcomes, years of data collection, sample size, setting and population, assessments used, results, and limitations) were collected on precoded spreadsheets and are described in Tables 1-3. A compilation of STI incidence data in active-duty military personnel were pulled and depicted in Figures 4a-c.

Figure 1. Article selection process for reviewing aim 1 – infection.

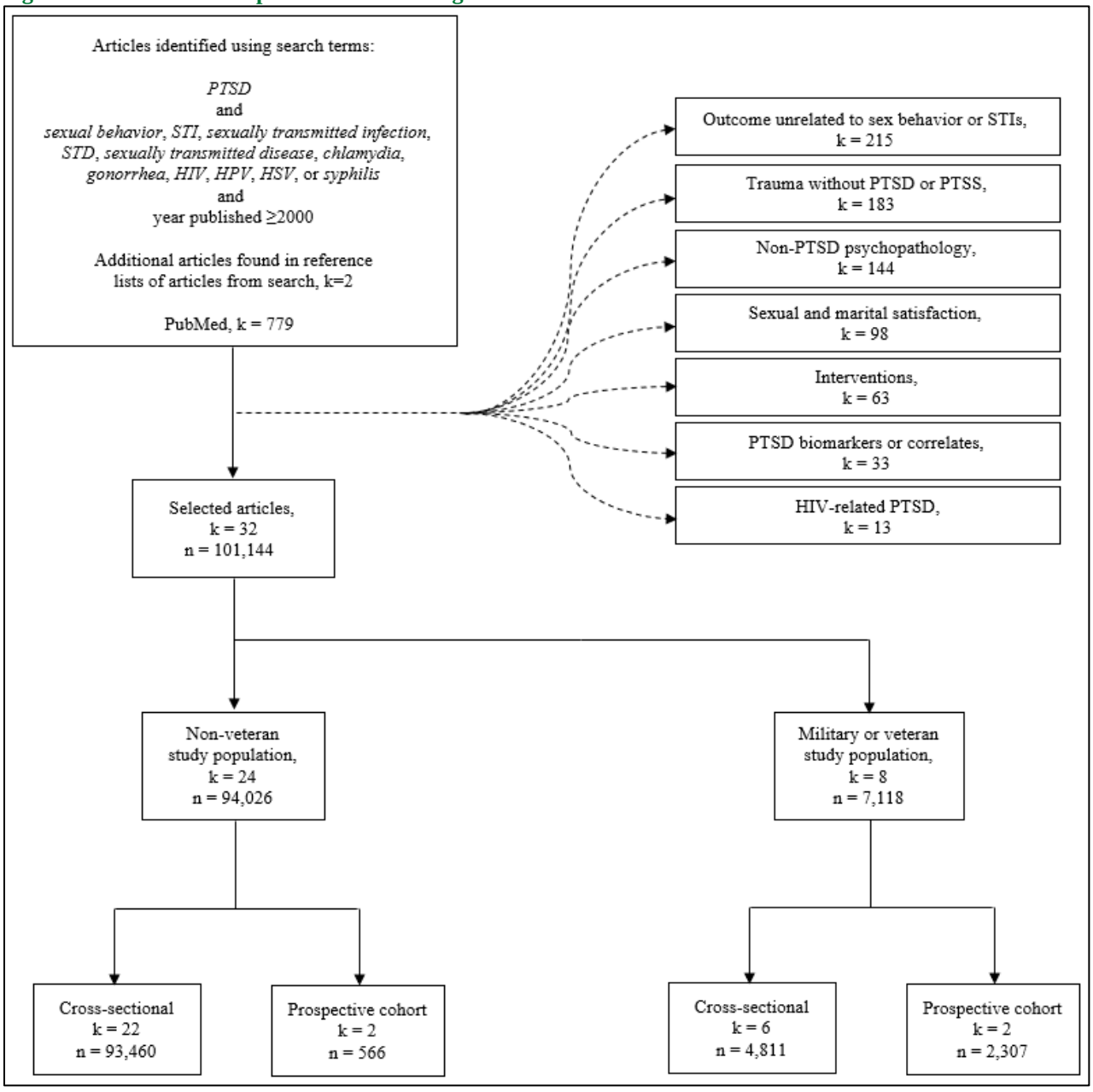


Table 1. Summary of published studies related to aim 1 – infection (n=32).

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
Adler, 2011	Prospective cohort	PTSD positive screen on PCL	Self-reported risk for an STI 4 months post-deployment	2,298	Active-duty U.S. soldiers after combat deployment	PTSD was associated with a higher odds for an STI (aOR = 1.6 [1.2, 2.0])	Self-reported measures; time-gap between exposure and outcome was minimal; loss-to-followup
Alvarez, 2009	Cross-sectional	PTSD positive screen on PC-PTSD scale	Self-reported lifetime history of chlamydia	3,521	Women 18-44 years of age in California	≥4 trauma events was associated with chlamydia (aOR = 5.7 [3.3, 9.6])	Study design; unmeasured confounders; self-reported measures; short-term exposure
Anastario, 2011	Cross-sectional	PTSD positive screen by Breslau tool	Self-reported HRSBs by RBA and CDQ	351	Active-duty soldiers in Belize Defense Force	PTSD was associated with a higher odds for an STI (aOR = 2.5 p1.1-5.7])	Study design; possible selection bias; limited generalizability; social desirability bias
Batchelder, 2017	Cross-sectional	PTSD positive screen on DTS	Self-reported condomless sex in past 3 months	288	HIV-negative MSM in Boston and Miami	Substance abuse, self-esteem, and distress tolerance moderated the association of interest	Study design; restricted trauma symptoms; PrEP not addressed; limited generalizability
Beidas, 2012	Prospective cohort	Clinician-diagnosed PTSD	Self-reported HRSBs on ARBA	119	Young, male MSM 16-20 years of age	PTSD moderated effect of distress on unprotected anal sex acts (ERR=0.03)	Broad categorization of race; small sample size; did not assess drug use; self-reported measures
Black, 2016	Prospective cohort	PTSD positive screen on PCL	Self-reported HRSBs using *ad hoc* items	9	Veterans applying for service-connected benefits for PTSD	Negative affect and externalizing behaviors associated with HRSBs	Small sample size; spurious multiple comparison results; short duration of followup
Bowleg, 2014	Cross-sectional	PTSD positive screen on PSS	Self-reported HRSBs on NSHS	526	Sexually-active Black heterosexual men	PTSD was associated with greater sexual risk for HIV ($\beta = 0.11$, $p=0.02$)	Study design; social desirability bias; selection bias due to low response; limited generatability
Brown, 2010	Cross-sectional	PTSD positive screen on C-DISC	Self-reported HRSBs on ARBA	840	Adolescents 13-18 years of age receiving mental health treatment	PTSD not associated with sex, ≥2 partners, STI, or unprotected sex	Study design; not all disorders assessed; misclassification bias; limited generalizability
Brown, 2017	Cross-sectional	Clinician-diagnosed PTSD	Self-reported history of STIs in the past year	34,391	Nationally representative sample of U.S. adults	PTSD was associated with a higher prevalence of STI (PR = 2.4 [1.8, 3.1])	Study design; low prevalence of STIs; self-reported measures; did not consider effect modification
Cavanaugh, 2010	Cross-sectional	PTSD positive screen on PDS	Self-reported HSRBs in the past 6 months	136	Sexually-active, low-income, adult women experiencing IPV	PTSD was associated with a higher odds of a HRSB (aOR = 4.0 [1.3, 11.9])	Study design; PTSD due to other trauma excluded; small sample size; self-reported measures
Choi, 2017	Cross-sectional	PTSD positive screen on DTS	Self-reported HRSBs using *ad hoc* items	296	HIV-negative MSM in Boston and Miami	Five of 17 PTSD symptoms had non-zero associated with sexual risk	Study design; self-reported measures; effects of PTSD clusters may reflect scale factors
Decker, 2020	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs defined by USPSTF	29	Male OEF/OIF veterans with combat-related PTSD from Connecticut	Qualitative interviews revealed six themes of their lived experiences	Study design; missing data; limited generalizability; did not assess interpersonal goals

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
El-Bassel, 2011	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs using *ad hoc* items	241	Low-income inner-city women receiving care in an emergency department	PTSD associated with a higher odds of sex with a risky partner (aOR = 2.3 [1.1, 4.8])	Study design; excluded psychiatric admissions; unmeasured confounders; limited present-day generalizability
Hahn, 2021	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs using CARE	88	Female college students who have a history of childhood sexual abuse	PTSD was associated with HRSBs ($\rho = 0.31$)	Study design; expected not actual HRSBs; limited generalizability; PTSD not anchored to sex abuse
Harbertson, 2013	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs using *ad hoc* items	1,307	Male, active-duty soldiers from Rwanda Defense Forces	PTSD was associated with reporting STI symptoms (aOR = 2.8 [1.3, 5.8])	Study design; small number with HIV; missing data; culturally different; limited generalizability
Holmes, 2005	Cross-sectional	PTSD positive screen on PDS	Self-reported number of LSPs	298	Philadelphia County representative sample of men 18-39 years of age	PTSD was associated with a higher rate of LSPs (aIDR = 1.19, p = 0.04)	Study design; small sample size; self-reported measures; assumes absence of current symptoms indicates no history of PTSD
Houston, 2012	Cross-sectional	PTSD positive screen on PCL	Self-reported and laboratory-confirmed STIs	190	Single women living in New York City shelters	No significant relationship between PTSD and STIs	Study design; inappropriate sampling procedure; limited generalizability
Hutton, 2001	Cross-sectional	PTSD positive screen using SCID	Self-reported HRSBs by adapted RBA	177	Women prisoners at the Maryland Correctional Institution for Women	PTSD was associated with 71% and 56% increased anal sex and prostitution	Study design; self-selection bias; self-reported measures of HRSBs; recall bias
Koegler, 2017	Cross-sectional	PTSD positive screen on HTQ	Self-reports of lifetime history of any STI	753	Adults 16 years of age and older from 10 villages in rural DRC	PTSD was associated with a higher odds of any STI (aOR = 1.9 [1.2, 3.1])	Study design; unmeasured confounders; disparate time frames; self-reported measures
Marshall, 2013	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs from the BRFSS	2,259	Enlisted Ohio Army National Guard soldiers	PTSD alone was not, but comorbid depression was associated with HRSBs (aOR = 2.8 [1.1, 7.1])	Study design; measures not designed to assess HIV risk; could not evaluate more antecedent components
Mota, 2019	Cross-sectional	PTSD positive screen using AUDADIS	Self-reported HRSBs from the NESARC	36,909	Nationally representative sample of U.S. adults	PTSD was associated with STIs (aOR = 1.5) and sex with an IDU (aOR = 1.7)	Study design; misclassification bias of exposure; self-reported measures; limited generalizability
Overstreet, 2015	Cross-sectional	PTSD positive screen on PDS	Self-reported HRSBs using *ad hoc* items	186	Sexually-active, low-income, adult women experiencing IPV	Significant indirect effect of IPV on HRSBs by way of PTSD ($\beta = 0.004$)	Study design; did not assess co-occurrence of IPV or stalking; only addresses current partner
Pearson, 2015	Cross-sectional	PTSD positive screen using PSS-I	Self-reported HRSBs using *ad hoc* items	129	Sexually-active young American Indian/Alaska Native women	PTSD associated with a higher number of partners ($\beta = 0.26$, $p < 0.10$)	Study design; self-reported measures; underreported binge drinking; limited generalizability
Pengpid, 2013	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs using *ad hoc* items	268	Women who received a domestic violence order in Vhembe, South Africa	PTSD associated with STI (aOR = 3.2), unprotected sex (aOR = 4.7)	Study design; self-reported measures; childhood abuse not assessed; limited generalizability

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
Reisner, 2011	Cross-sectional	PTSD positive screen using AUDADIS	Self-reported HIV infection in past year	13,274	Nationally representative sample of U.S. adults	PTSD partially mediated effect of early stressors and HIV (aOR = 1.1 [1.0, 1.3])	Study design; misclassification bias; disparate timeframes of covariates; self-report measures
Reisner, 2009	Cross-sectional	PTSD positive screen using SPAN	Self-reported HRSBs using *ad hoc* items	189	Adult MSM from a community health center in Massachusetts	PTSD was associated with unprotected anal sex (aOR = 2.7 [1.2, 6.2])	Study design; self-reported measures; inconsistent measures; poorly designed survey items
Rosenberg, 2001	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs by adapted RAB	275	Adults with a mental illness from outpatient health care facilities	HSRBs were marginally associated with PTSD cluster B symptoms	Study design; self-reported measures; small sample size; non-representative sample
Strom, 2012	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs using *ad hoc* items	395	Veterans receiving out-patient mental healthcare at a Mid-Western VAMC	PTSD was associated with higher HRSB scale score ($F[1,351] = 13.6$, $p<0.001$)	Study design; self-reported measures; no measure of trauma exposure; survey never validated
Tavarez, 2011	Cross-sectional	PTSD positive screen by Breslau tool	Self-reported HRSBs using *ad hoc* items	470	Active-duty military personnel in the Dominican Republic	PTSD was associated with unprotected sex, and sex multiple partners and CSW	Study design; social desirability bias; limited generalizability; unmeasured confounders
Weine, 2012	Cross-sectional	PTSD positive screen on PC-PTSD scale	Self-reported HRSBs using CHAMP scale	400	Tajik male migrants from bazaars and construction sites in Moscow	PTSD was not associated with HRSBs in univariate or multivariate analyses	Study design; cultural bias of survey items; childhood trauma unexplored; non-generalizable
Weiss, 2013	Cross-sectional	PTSD positive screen on PCL	Self-reported HRSBs on TCU HVHP scale	85	Adult patients from a residential SUD treatment facility in Mississippi	PTSD was associated with HRSBs, particularly hyper-arousal symptom cluster	Study design; self-reported measures; non-generalizable; findings diverge from literature
Weiss, 2019	Prospective cohort	PTSD positive screen on PCL	Self-reported HRSBs using SRS scale	447	Young adult women from communities in southern and midwestern U.S.	PTSD was moderately associated with HRSBs ($\rho = 0.10$-0.14, $p < 0.05$)	Study design; selection bias; non-generalizable; small sample size; self-reported measures

aIDR, adjusted incidence density ratio; aOR, adjusted odds ratio; AUDADIS, Alcohol Use Disorder and Associated Disabilities Interview Schedule; BRFSS, Behavioral Risk Factor Surveillance System; CARE, Cognitive Appraisals of Risky Events; C-DISC, Computerized Diagnostic Interview for Children; CDQ, Client Diagnostic Questionnaire; CHAMP, Chicago HIV Prevention and Adolescent Mental Health Project; CSW, commercial sex worker; DRC, Democratic Republic of the Congo; DTS, Davidson Trauma Scale; ERR, event rate ratio; HIV, human immunodeficiency virus; HRSB, high-risk sexual behavior; HTQ, Harvard Trauma Questionnaire; IDU, injection drug use; IPV, intimate partner violence; LSP, lifetime sexual partners; MSM, men who have sex with men; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NSHS, National Sexual Health Survey; PCL, PTSD Checklist; PC-PTSD, Primary Care PTSD Screen; PDS, Posttraumatic Stress Diagnostic Scale; PR, prevalence ratio; PSS, PTSD Scale – Self-Report; PSS-I, Posttraumatic Symptom Severity Interview; PTSD, post-traumatic stress disorder; RAB, Risk Assessment Battery; RBA, Risk Behavior Assessment; SCID, Structured Clinical Interview; SPAN, Startle, Physiologic Arousal, Anxiety, and Numbness, derived from DTS; SRS, Sexual Risk Survey; STI, sexually transmitted infection; SUD, substance use disorder; TCU HVHP, Texan Christian University HIV/AIDS Risk Assessment; USPSTF, U.S. Preventive Services Task Force; VAMC, Veterans Affairs Medical Center.

Figure 2. Article selection process for reviewing aim 2 – treatment.

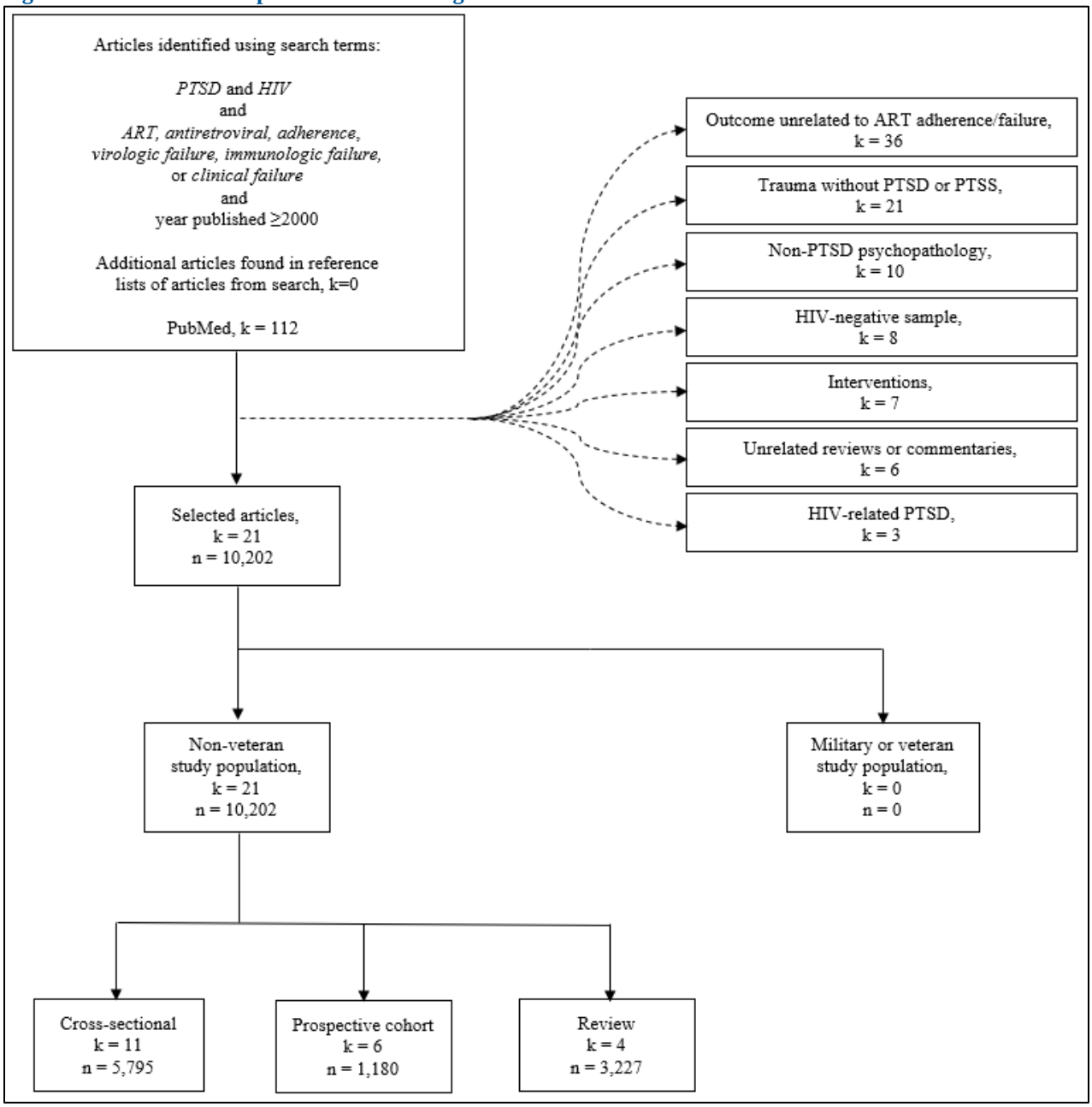


Table 2. Summary of published studies related to aim 2 – treatment (n=21).

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
Blashill, 2011	Review	PTSD positive on screen and diagnosis	HIV viral load, CD4 cell count, ART adherence	435	U.S. adults with HIV, including a study after Hurricane Katrina	PTSD associated with a detectable viral load, low CD4 count, non-adherence	Inferences based on a small number of publications and limited to only two years
Boarts, 2009	Prospective cohort	PTSD positive screen on PDS	Self-reported ART adherence on ACTG scale	84	Adults with HIV at a service organization or from a hospital clinic	PTSD was associated with lower ART adherence; increased over time	Small sample size, short duration followup; selection bias; limited generalizability
Boarts, 2006(	Prospective cohort	PTSD positive screen on PDS	HIV viral load, CD4 cell count, ART adherence	84	Adults with HIV at a service organization or from a hospital clinic	PTSD associated with a detectable viral load, low CD4 count, non-adherence	Small sample size, short duration followup; selection bias; limited generalizability
Delahanty, 2004	Cross-sectional	PTSD positive screen on IES	ART adherence on ACTG scale, CD4 cell count	110	Adults with HIV from a service organization in a Midwestern city	PTSD was associated with ART non-adherence but higher CD4 cell counts	Study design; self-reported measures, including lab values; selection bias; recall bias
Ebrahimza, 2019	Cross-sectional	PTSD positive screen on M-PTSD	Self-reported ART adherence on ACTG scale	220	Adults with HIV from HCTs in Fars Province and Shiraz, Iran	PTSD predicted 53% of ART adherence and 4% of CD4 cell count variance	Study design; self-reported measures except CD4 cell count; cultural bias of instruments
Glynn, 2021	Cross-sectional	PTSD positive screen on PC-PTSD scale	Self-reported ART adherence Wilson scale	1,237	Adults with HIV from a public tertiary care hospital in Miami	PTSD, while controlling for trauma, was associated with worse adherence	Study design; cultural bias in instruments; dose-response not evaluated; self-reported measures
Harkness, 2018	Prospective cohort	PTSD positive screen using SPAN	HIV viral load, CD4 cell count, ART adherence	390	Adult MSM with HIV who are patients at Fenway Health	PTSD associated with a detectable viral load, low CD4 count, non-adherence	Secondary analysis of two prior intervention studies; self-reported measures; non-generalizable
Hilerio, 2005	Cross-sectional	PTSD positive screen on TSI	Self-reported ART adherence *ad hoc* items	15	Women with HIV, not pregnant, from a study center in Puerto Rico	Arousal, depression, avoidance, dissociation associated with adherence	Study design; very small sample size; limited generalizability; should include qualitative data
Hou, 2020	Review	Self-reported PTSD positive screen tools	Self-reported ART adherence and pill counts	2,489	U.S. adults with HIV; 3 studies of high-quality by AHRQ standards	Pooled odds ratio of non-adherence to ART was 1.2 (1.0-1.4, p = 0.02)	Most articles did not assess potential moderations; more complicated modeling required
Keuroglian, 2011	Cross-sectional	Dissociative experiences on DES	Self-reported ART adherence on ACTG scale	43	Adults with HIV from community-based clinics in San Francisco Bay	PTSD associated with non-adherence (OR = 1.1), moderated by dissociation	Study design; self-reported measures; small sample size; limited generalizability
Machtinger, 2012	Cross-sectional	Past trauma using two *ad hoc* items	Self-reported ART adherence and failure	113	Self-identified females with HIV from two clinics in San Francisco	Past trauma was associated with ART failure (aOR = 4.3) but not non-adherence	Exploratory study design; lacked validated self-reported measures; unmeasured confounders
Negi, 2018	Cross-sectional	PTSD positive screen on PCL	Self-reported ART adherence on ACTG scale	305	Adults with HIV from 14 districts in Nepal affected by earthquake	PTSD associated with ART non-adherence (aOR = 2.9) but not failure	Study design; short duration of adherence measurement; event itself may have impacted access
Nel, 2011	Review	Self-reported PTSD positive screen tools	Self-reported ART adherence on screen tools	303	U.S. African-American and Caucasian, and Swedish adults with HIV	PTSD negatively and positively associated with adherence in two studies	Inferences based on a small number of publications; limited generalizability; information bias

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
Peterson, 2012	Prospective cohort	PTSD positive screen on IES	HIV viral load, CD4 cell count, time on ART	252	Adult Gambians with HIV from a genito-urinary medicine clinic	PTSD was not associated with viral load, CD4 count, or time on ART	Patients with urgent needs not enrolled; random interruptions in survey availability; screen tools
Roux, 2018	Cross-sectional	PTSD positive screen using CIDI-SF	Self-reported ART VTI on screen tool	3,022	Adults with HIV from 73 French hospitals that delivery HIV care	PTSD was independently associated with VTI (aOR = 1.6 [1.1-2.5])	Study design; self-reported measures; ART adherence not assessed; limited generalizability
Schonesson, 2007	Cross-sectional	PTSD positive screen on IES	HIV viral load, CD4 cell count, ART adherence	193	Adults with HIV without a diagnosed psychiatric disorder in Sweden	PTSD was associated with poor adherence to schedule (aOR = 0.4 [0.2-0.8])	Study design; exclusion criteria limits generalizability; selection bias; social desirability bias
Sherr, 2011	Review	Self-reported PTSD positive screen tools	Self-reported ART adherence on screen tools	635*	Adults with HIV from a variety of sources and a number of countries	Studies reported increased (2/6), decreased (3/6), no effect (1/6) on adherence	Exclusion of non-peer-reviewed journals; lack of studies from non-Western countries
Sledjeski, 2005	Cross-sectional	PTSD positive screen on IES	ART adherence on ACTG scale, CD4 cell count	69	Adults with HIV from a service organization in a Midwestern city	PTSD associated with ART (OR = 27.6 [2.0-381.8]) adherence, high CD4 count	Study design; high exposure population; self-reported measures; recall bias
Vranceanu, 2008	Prospective cohort	PTSD positive screen using SPAN	ART adherence using MEMS Smart Caps	156	Adults with HIV from five Boston-area hospitals willing to use pill counter	PTSD not associated with adherence except with comorbid depression	PTSD assessed using self-reported measures and based on a general traumatic event
Wagner, 2012	Prospective cohort	PTSD positive screen on PDS	ART adherence using MEMS Smart Caps	214	African-American adults with HIV in Los Angeles	PDS score, re-experience subscale were associated with adherence, not PTSD	Non-representative sampling; self-reported measure to assess PTSD; limited generalizability
Whetten, 2013	Cross-sectional	PTSD positive screen on PCL	Self-reported ART adherence on ACTG scale	468	Adults with HIV from hospital-based clinics and HCTs in Tanzania	Mean PCL scores greater in non-adherent (14.9) than adherent (10.5) patients	Study design; self-reported measures; conservative cutoffs for ART adherence; recall bias

ACTG, AIDS Clinical Trials Group; AHRQ, Agency for Healthcare Research and Quality; aOR, adjusted odds ratio; ART, antiretroviral therapy; CIDI-SF, Composite International Diagnostic Interview Short Form; DES, Dissociative Experiences Scale; DTS, Davidson Trauma Scale; HCT, HIV counseling and testing center; HIV, human immunodeficiency virus; IES, Impact of Event Scale; LGBT, lesbian, gay, bisexual, and transgender; MEMS, Medication Event Monitoring System; M-PTSD, Mississippi PTSD Questionnaire; OR, odds ratio; PCL, PTSD Checklist; PC-PTSD, Primary Care PTSD Screen; PDS, Posttraumatic Stress Diagnostic Scale; PTSD, posttraumatic stress disorder; SPAN, Startle, Physiologic Arousal, Anxiety, and Numbness, derived from DTS; TSI, Trauma Symptom Inventory; VTI, voluntary treatment interruption.
*Review includes literature already included; therefore the additional contribution to the total sample size is 0.

Figure 3a. Article selection process for reviewing aim 3 – morbidity and mortality.

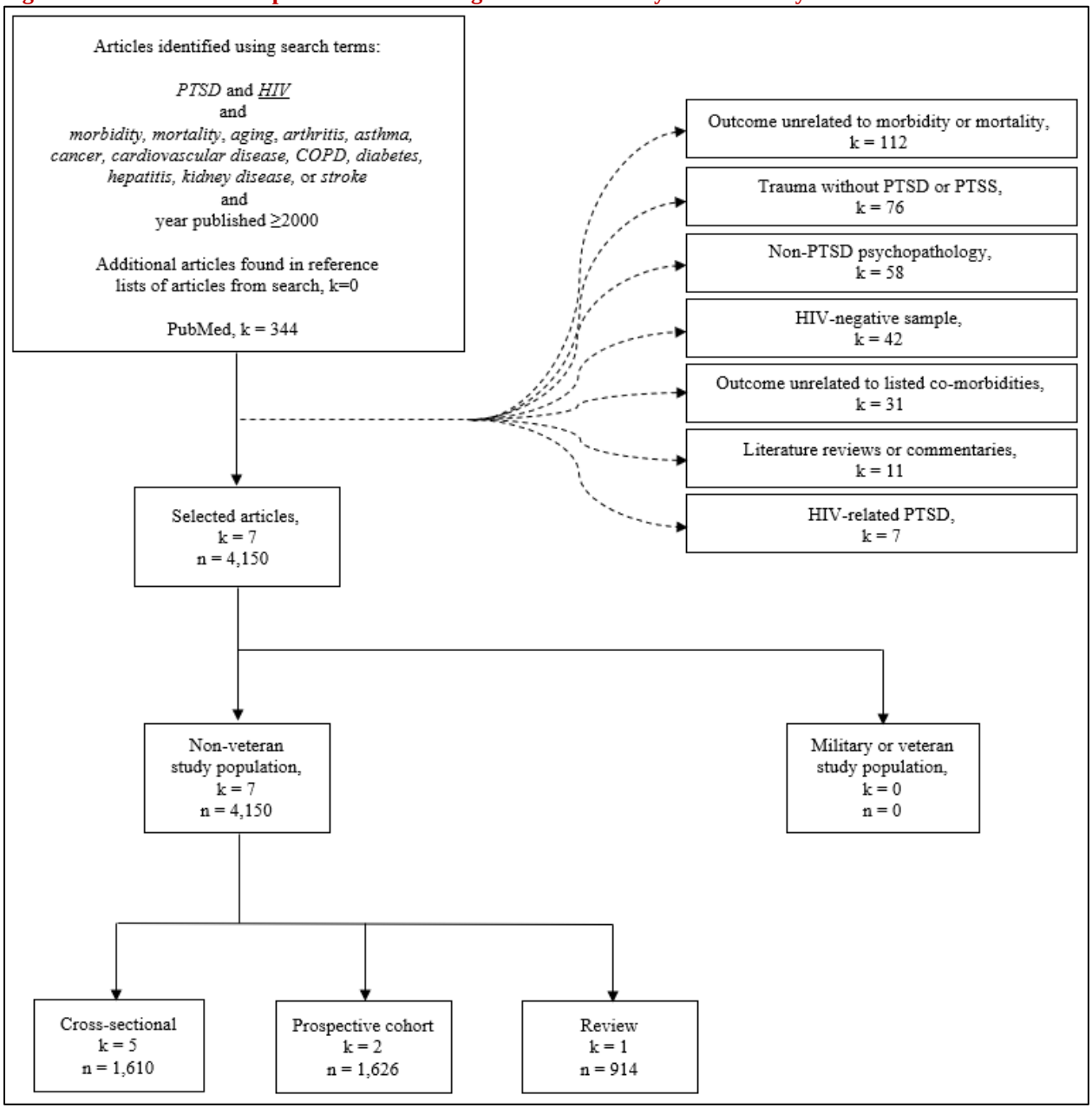


Table 3a. Summary of published studies related to aim 3 – morbidity and mortality (n=7).

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
Brezing, 2015	Review	Self-reported PTSD positive screen tools	Self-reported ART adherence on screen tools	914	Adult outpatients with HIV, including MSM newly diagnosed	One-third of MSM newly diagnosed had PTSD, this predicted morbidity	Inferences based on a small number of publications; limited generalizability; information bias
Leserman, 2005	Cross-sectional	PTSD positive screen on PCL	Self-reported physical function on SF-36	611	Adults with HIV from 8 ID clinics throughout the Southeastern U.S.	PTSD explained 12-27% variance in health function beyond demographics	Study design; self-reported measures; uncontrolled, unmeasured confounders
Levy, 2020	Prospective cohort	PTSD positive screen on PCL	Subclinical carotid athero-sclerosis by US	700	Women with HIV 25-60 years of age from large metropolitan cities	PTSD was not associated with atherosclerosis (aOR = 0.8 [0.3-2.0])	Small sample size; exposure assessed infrequently; lack of data; low outcome prevalence
Nightingale, 2011	Cross-sectional	PTSD positive screen on IES	Current chronic conditions from medical records	118	Adults with HIV from an urban medical center receiving outpatient care	Trauma associated with HIV-related symptoms and coronary artery diseases	Study design; unmeasured confounders; recall bias; small sample size; inappropriate tools
Pantalone, 2012	Cross-sectional	PTSD positive screen on PSS	Laboratory-confirmed HCV coinfection	171	Adult MSM with HIV from 2 HIV clinics in Seattle for underserved	PCL scores associated with HCV coinfection (0.4 [0.6] vs. 0.6 [0.8])	Study design; non-representative sampling; non-generalizable; self-reported measures
Pence, 2012	Prospective cohort	PTSD positive screen on PCL	Self-reported physical function on SF-8	926	Four Tanzanian cohorts: HIV, incident HIV, new negative, community	PTSD symptoms not associated with function (β = -0.07 [-0.15-0.02])	Self-reported measures; recall and social desirability biases; selection bias, excluded those not in care
Sinayobye, 2015	Cross-sectional	PTSD positive screen on HTQ	Self-reported history, exam of shingles	710	Rwandan females ≥15 years of age with HIV who are ART naïve	PTSD was associated with shingles in past 6 months (aOR = 1.7 [1.0-2.9])	Study design; self-reported measures, including outcome; directionality; recall bias

ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTQ, Harvard Trauma Questionnaire; IES, Impact of Event Scale; MSM, men who have sex with men; PCL, PTSD Checklist; PSS, PTSD Scale – Self-Report; PTSD, posttraumatic stress disorder; SF, RAND Short Form Survey; US, ultrasound.

Figure 3b. Article selection process for reviewing aim 3 – morbidity and mortality.

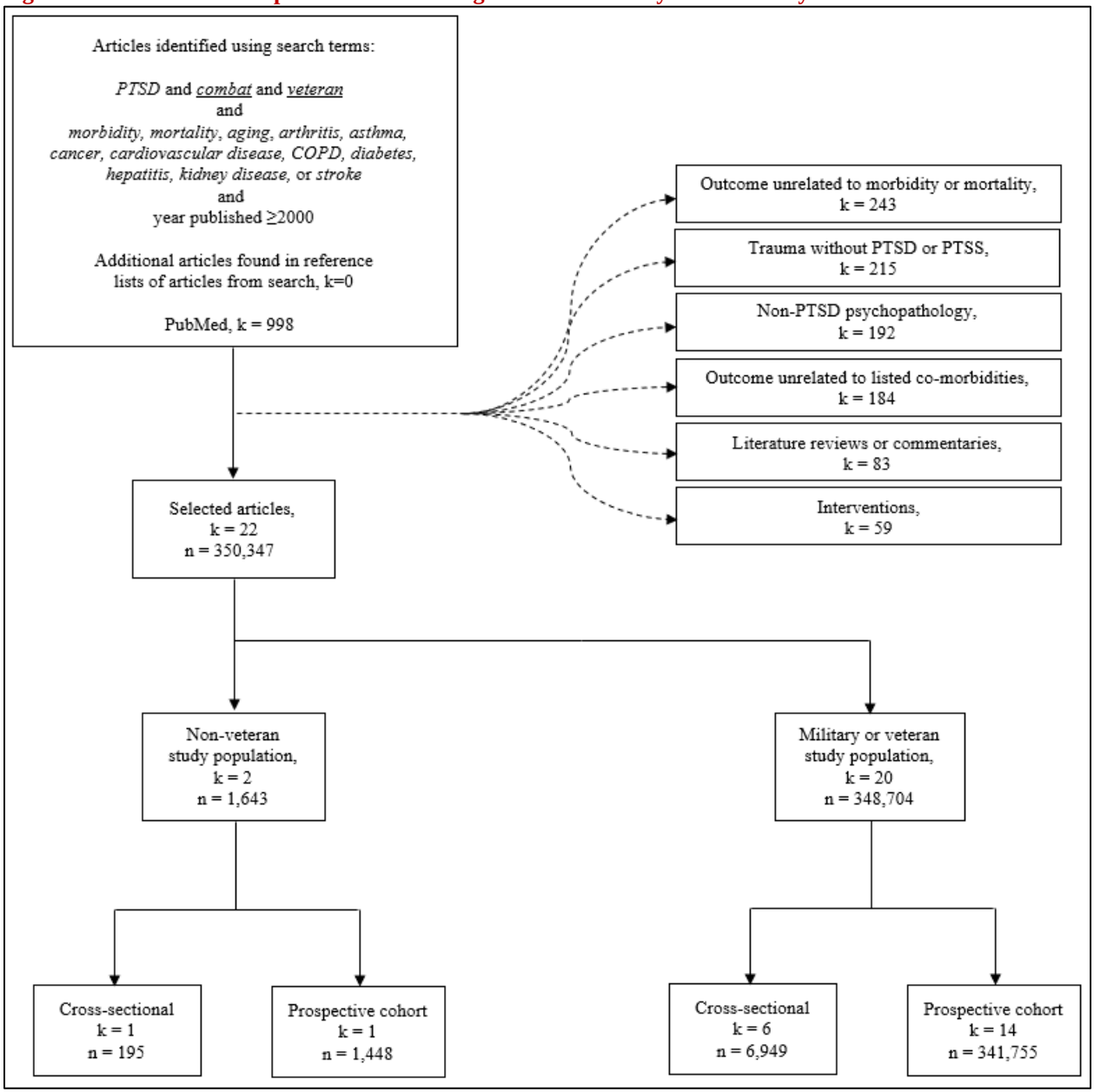


Table 3b. Summary of published studies related to aim 3 – morbidity and mortality (n=22).

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
Abouzeid, 2011	Cross-sectional	PTSD positive screen using CIDI-SF	Probable cases of hypertension by clinician	1,381	Male veterans from Australia who had deployed to Gulf War	PTSD was associated with probable hypertension (aOR = 2.3 [1.0-5.1])	Study design; other psychiatric disorders assessed in CIDI not included, including severity
Blakey, 2021	Cross-sectional	EA positive screen using BEAQ	Self-reported medical health outcomes	454	Nationally representative sample of Gulf War-era deployed veterans	EA associated with all conditions assessed, but asthma and COPD	Study design, no comparison group; self-reported measures, diagnoses; EA misclassification
Bookwalter, 2020	Prospective cohort	Diagnosis and self-reported PTSD on PCL	Diagnoses of autoimmune diseases in EMR	120,572	Active-duty military personnel from all services, components	PTSD associated with autoimmune disorders (aOR = 1.6 [1.3-2.0])	Did not review EMR to confirm diagnoses; Berkson's bias; self-reported measures; short followup
Boscarino, 2006	Prospective cohort	PTSD positive screen using DIS-III	All-cause and cause-specific mortality	15,288	Nationally representative sample of Vietnam War-era U.S. Army soldiers	PTSD was associated with all-cause and external cause mortality (HR > 2.0)	Misclassification of exposure, outcome; death certificates underreport some conditions;
Boyko, 2010	Prospective cohort	Diagnosis and self-reported PTSD on PCL	Self-reported type-2 diabetes mellitus	44,754	Active-duty military personnel from all services, components	PTSD was associated with type-2 diabetes mellitus (aOR = 2.1 [1.3-3.3])	Self-reported exposure, outcome; selection bias, low participation rate; social desirability bias
Bramsen, 2007	Prospective cohort	PTSD positive screen using SRIP	All-cause mortality from vital records	1,448	World War II survivors from general population in 9 Dutch cities	PTSD was associated with all-cause mortality (aHR = 1.5 [1.0-2.3])	Selection bias, restricted survivors until 1992, low participation rate; self-reported measures
Crawford, 2009	Prospective cohort	Diagnosis of PTSD in EMR	Cause-specific mortality from NDI	79,551	Vietnam War veterans 40-59 years of age who sought mental healthcare	7-year all-cause mortality rate = 11.3%, double rate of general U.S. population	Did not evaluate misclassification bias; unmeasured confounders; limited generalizability
Crum, 2014	Prospective cohort	PTSD positive screen on PCL	Diagnosis and self-reported CHD	60,025	Active-duty military personnel from all services, components	PTSD not associated with self-reported CHD and diagnosis of CHD	Unmeasured confounders; misclassification bias; residual confounding; short followup
Howard, 2018	Prospective cohort	Diagnosis of PTSD in EMR	Diagnosis of HTN in EMR	3,846	U.S. OEF/OIF/OND military service members who had been injured	aHR of HTN positively associated with number of PTSD diagnoses	Unmeasured confounders; biased estimates towards the null due to sensitivity of ICD; short followup
Kimbrell, 2011	Prospective cohort	Diagnosis of PTSD in EMR	All-cause mortality from vital records	10,255	U.S. veterans ≥65 years of age who have had ≥2 VA visits for healthcare	PTSD was associated with all-cause mortality (aHR = 1.1 [1.0-1.2])	Misclassification bias; role of ethnicity unclear; selection bias; time-varying PTSD not assessed
Kulenovic, 2008	Cross-sectional	Diagnosis of PTSD in EMR	10-year risk of CAD based on lab algorithm	100	Male combat veterans 40-50 years of age, with reference BMI, no meds	10-year arteriosclerosis (7% vs. 4%) and CAD risks (19% vs. 10%%)	Study design; non-representative sampling; non-uniform diet before lab draws; misclassification bias
O'Toole, 2008	Prospective cohort	PTSD positive screen using SCID	Self-reported health function using ABS	593	Representative sample of Australian Vietnam War veterans who deployed	PTSD associated with all recent and chronic illness conditions assessed	Did not account for multiple comparisons; self-reported measures; recall bias
O'Toole, 2009	Prospective cohort	PTSD positive screen using SCID	Self-reported health function using ABS	450	Representative sample of Australian Vietnam War veterans in records	PTSD was associated with ulcers, substance abuse, and many mental disorders	Self-reported measures; selection bias; limited generalizability; misclassification bias

First author, year (reference no.)	Study design	Exposure(s)	Outcome(s)	Sample size	Setting and population	Result(s)	Limitations
O'Toole, 2010	Prospective cohort	PTSD positive screen using SCID	Self-reported health function using ABS	1,000	Representative sample of Australian Vietnam War veterans in records	PTSD was not associated with all-cause mortality; statistics not reported	Selection bias; unmeasured confounding; small sample size; chemical exposures not assessed
Schlenger, 2015	Prospective cohort	PTSD based on multiple screen and interviews	Mortality from NDI, SSDI, and death certificates	1,632	Nationally representative sample of Vietnam War-era and theater veterans	High probability of PTSD associated with mortality (aHR = 2.3 [1.3-3.8])	Lack of civilian comparison group; time-varying confounding; low prevalence of outcome
Schnurr, 2000	Cross-sectional	PTSD positive screen on PCL	Self-reported health function and illnesses	363	Random sample of male Army and Navy veterans exposed to mustard gas	PTSD associated with many illnesses assessed, but HTN, DM, stroke	Study design; recall and social desirability biases; self-reported measures; non-generalizable
Schnurr, 2000	Prospective cohort	PTSD positive screen using M-PTSD	Diagnosed chronic illnesses from EMR	605	Older male military veterans from the Boston Normative Aging Study	PTSD was associated with arterial CVD, lower GI, skin, and muscular disease	Selection bias due to healthy warrior effect; small sample size; limited generalizability
Sheffler, 2016	Prospective cohort	PTSD positive screen using CIDI-SF	Self-reported chronic illness on *ad hoc* items	727	Male Vietnam War-era veterans 40-65 old, some exposed to combat	Combat associated with many illnesses; PTSD associated with headaches	Small subset of larger cohort used; misclassification bias; women excluded; limited generalizability
Solter, 2002	Cross-sectional	Diagnosis of PTSD in EMR	Concentrations of serum lipids	195	Adults from an inpatient psychiatric treatment facility in Croatia	PTSD was associated with higher serum lipids, risks for arteriosclerosis, CHD	Non-generalizable to women as men had higher prevalence of outcome; did not assess stress
Spitzer, 2009	Cross-sectional	PTSD positive screen using SCID	Self-reported history of medical illness	3,171	Representative sample of adults 20-79 years of age in Northeastern Germany	PTSD was associated with angina pectoris, heart failure, bronchitis, asthma	Limited generalizability; study design; high outcome prevalence; self-reported measures
Thomas, 2017	Cross-sectional	PTSD positive screen on PCL	Self-reported history of medical illness	1,480	Nationally representative sample of U.S. veterans from the NHRVS	PTSD was associated with suicide, stroke, chronic pain; associated with age	Advancing age masked the true effect; study design; selection bias due to healthy warrior effect
Zohar, 2014	Prospective cohort	Diagnosis of PTSD in EMR	Mortality from vital registries	2,457	Israeli veterans with PTSD referred for psychiatric treatment	PTSD not associated with increased but decreased mortality, matched for jobs	Misclassification bias, suicide not teased out; exposure chart review; unmeasured confounders

ABS, Australian Bureau of Statistics National Health Survey; aHR, adjusted hazard ratio; BEAQ, Brief Experiential Avoidance Questionnaire; CAD, coronary artery disease; CHD, coronary heart disease; CIDI-SF, Composite International Diagnostic Interview Short Form; COPD, chronic obstructive pulmonary disorder; CVD, cardiovascular; DIS-III, Diagnostic Interview Schedule – Version III; DM, diabetes mellitus; EA, experiential avoidance; EMR, electronic medical records; GI, gastrointestinal; HTN, hypertension; ICD, International Classification of Diseases; M-PTSD, Mississippi PTSD Questionnaire; NDI, National Death Index; NHRVS, National Health and Resilience in Veterans Study; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; SCID, Structured Clinical Interview; SRIP, Self-Rating Inventory for PTSD; SSDI, Social Security Death Index.

Figure 4a. Incidence rate of PTSD diagnoses among active-dute military personnel.

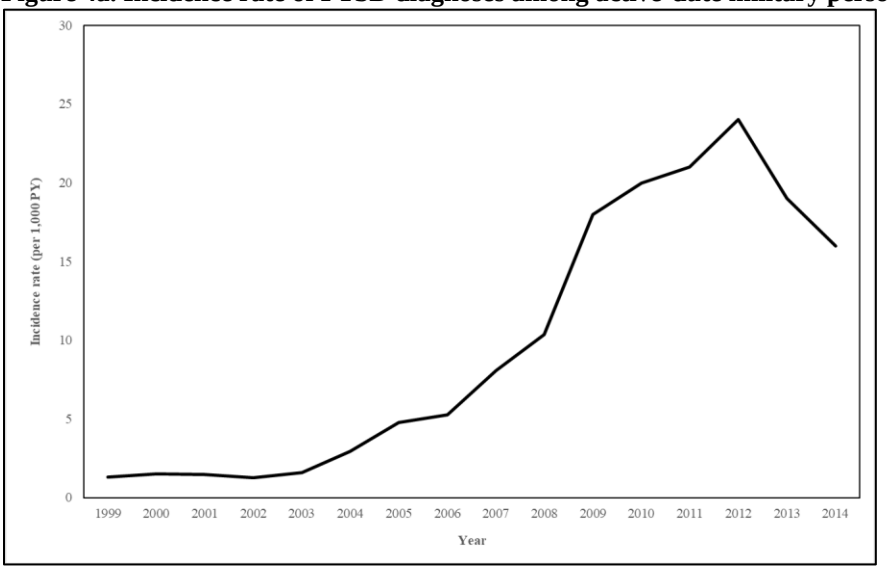


Figure 4b. Incidence rate of HIV diagnoses among active-duty military personnel.

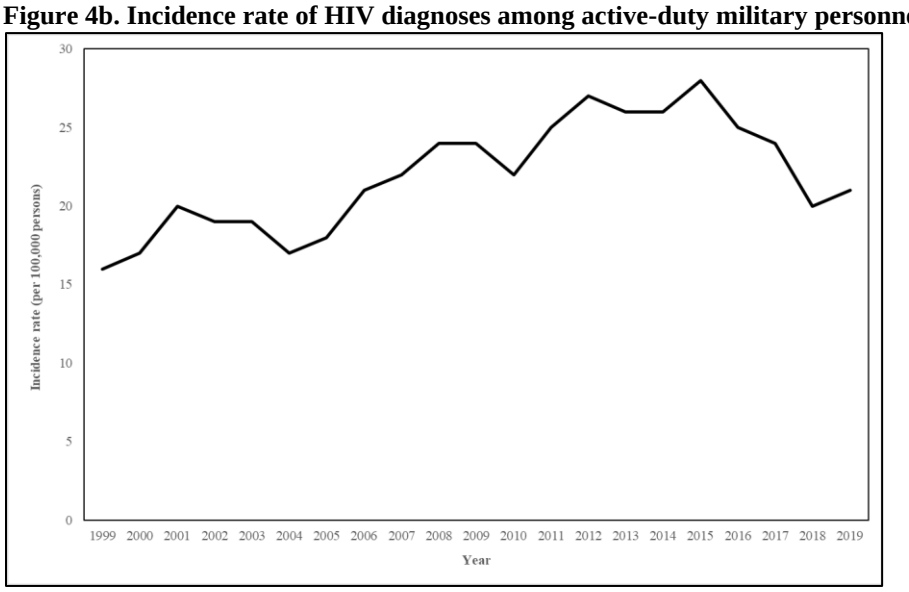
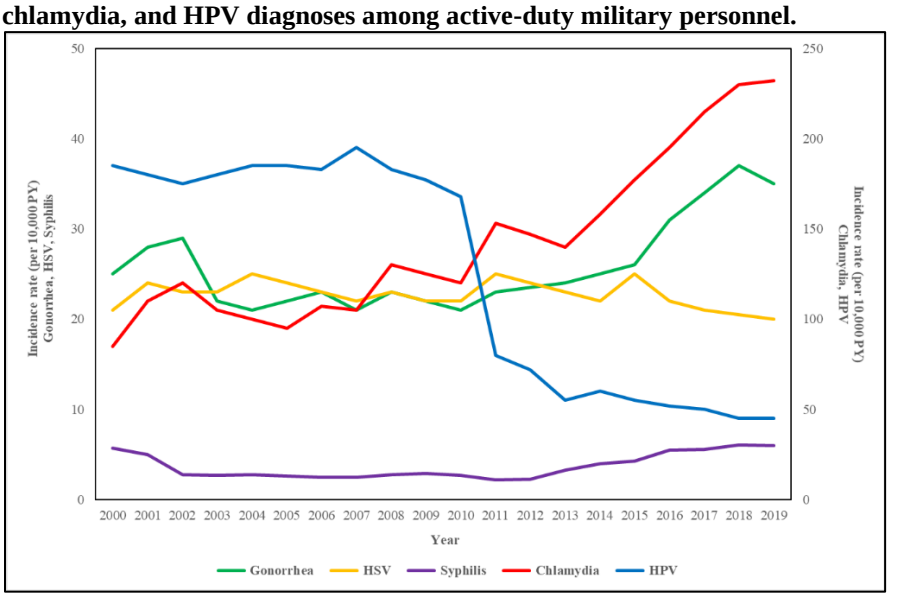


Figure 4c. Incidence rates of gonorrhea, HSV, syphilis, chlamydia, and HPV diagnoses among active-duty military personnel.



Background

Aim 1 – Infection

PTSD symptomatology can be grouped into four clusters: (1) avoidance, (2) hyperarousal, (3) negative cognitions or mood, and (4) re-experiencing.[1] It is thought that these symptoms may interfere with information processing and risk perception, such that those with PTSD engage in high-risk sexual behaviors (HRSB) that increases one's risk for an STI.[2] Of the four clusters, avoidance and hyperarousal symptoms are thought to be particularly relevant. Avoidance may result in not being fully present to risks during sex, difficulty maintaining monogamous relationships, or seeking riskier sexual encounters to counter numbing symptoms.[3]

> "During sexual intercourse, …I'm able to let go of everything,
> I don't have to think about anything, just to live in the moment."
> – Male OEF/OIF/OND veteran with PTSD after recent HRSB[1]

Hyperarousal may contribute to inaccurate appraisals of safety vs. risk, an inability to negotiate safe sex, and a need for sexual stimulation due to physiological and emotional dysregulation.[3]

> "If I have any sort of feelings toward the person then [after sex] it's still relatively on a high."
> – Male OEF/OIF/OND veteran with PTSD after recent HRSB[1]

In studies of civilian populations, PTSD has been associated with greater composite scores of HRSBs.[4-10] In one such study of low-income women, PTSD was associated with a four-fold increased risk for HRSBs (aOR = 4.0 [1.3-11.9]).[8] More specifically, other studies have shown that PTSD is associated with a greater number of sexual partners,[11-13] sex not protected by condoms,[14-18] having multiple partners,[3] sex with a risky partner or commercial sex worker (CSW),[3,7,12] sex under the influence of drugs or alcohol,[11,16] and HIV infection and other incident STIs.[2,15,19-22] For example, in two studies of women who had experienced intimate partner violence and of men who have sex with men (MSM), PTSD was associated with never having used condoms (aOR = 4.7 [1.7-12.7]) and condomless sex in the past year (aOR = 2.7 [1.2-6.2]), respectively.[17,18] In another study of low-income inner-city women, PTSD was associated with multiple sex partners (aOR = 3.1 [1.6-6.2]), sex with risky partners (aOR = 2.3 [1.1, 4.8]), and violence related to condom use (aOR = 3.7 [1.9, 7.0]).[3] Still other studies have shown PTSD to be associated with increased risks for any STI (aOR = 1.9 [1.2-3.1]) and HIV (aOR = 5.8 [4.8-7.0]).[21,22] There also seems to be a dose-response: each additional traumatic event has been shown to confer an elevated risk for HIV (aOR = 1.3 [1.2-1.5]) and chlamydia (aOR = 2.35 [1.6-3.4]).[19,22]

In studies of Military and Veteran populations, similar to civilian populations, PTSD has been associated with greater composite scores of HRSBs.[23-25] In one such study of OEF/OIF active-duty soldiers, PTSD was associated with a 57% increased risk of engaging in HRSBs four months post-deployment.[23] More specifically, other studies have shown that PTSD is associated with a greater number of sexual partners,[26-28] sex not protected by condoms,[27] having multiple partners, sex with a risky partner or CSW,[28] and HIV infection and other incident STIs.[28,29] For example, in a study of active-duty military personnel in the Dominican Republic, PTSD was associated with condomless sex (aOR = 2.4 [1.4-4.1]), having multiple partners (aOR = 2.6 [1.6-4.4]), and having sex with a CSW (aOR = 2.3 [1.2-4.4]) in the past 12 months. In two other studies of active-duty military personnel in Rwanda and Belize, PTSD was associated with increased risks for any STI (aOR = 2.8 [1.3-5.8]) and HIV (aOR = 2.5 [1.1-5.7]), respectively.[28,29] Interestingly, compared to veterans of past wars, a higher proportion of OEF/OIF/OND veterans endorsed having had condomless sex (57% vs. 42%), sex with

someone they had just met (45% vs. 33%), sex in public (35% vs. 17%), and sex with more than one person in the same day (19% vs. 15%) – a reflection of the fact that they reported greater PTSD symptom severity than veterans of past wars.[24]

Aim 2 – Treatment

The efficacy of antiretroviral therapy (ART) requires moderately high levels of adherence; such that, nonadherence rates of even 10-15% can dramatically impact its effect.[30] Optimal effectiveness of ART requires not only adherence to dose instructions, but also to dose schedules and dietary instructions.[31] In addition to the complexity of ART regimens, individuals with HIV are more likely to have been diagnosed with PTSD, which is characterized by an impairment in multi-cognitive domains that may further affect ART non-adherence.[30] Suboptimal ART adherence may then result in negative health outcomes, including lower CD4 cell counts, higher HIV viral loads, poorer quality of life, multi-resistant strains requiring second-line antiretrovirals (ARV), and mortality.[32] The causal mechanisms underlying the association between PTSD and ART non-adherence are poorly understood. Of the four PTSD symptom clusters, it is thought that avoidance may be the most likely to affect adherence; such that, ARVs may bring back memories of traumatic events, causing voluntary treatment interruptions (VTI), or that it may affect self-efficacy and self-control due to a sense of futility.[33] Alternatively, this association may be mediated by depression and substance abuse; whereby depressive symptoms (e.g., loss of interest and motivation, memory deficits, disrupted sleep) and the effects of substance abuse (e.g., impaired functioning, elevated distress) may adversely affect ART adherence.[34] Estimates of the associations between PTSD and ART adherence and treatment failure are based on civilian populations only; no known studies have examined this in military or Veteran populations.

The preponderance of evidence suggests that PTSD negatively affects ART adherence.[31-45] A recent meta-analysis of 12 such studies comprising 2,489 participants reported that, collectively, PTSD is associated with a 19% increased risk for ART non-adherence (pooled OR = 1.2 [1.0-1.4]), although there was significant heterogeneity.[33] For example, in a study of persons with HIV who had been impacted by a massive earthquake in Nepal and another of patients from community-based clinics in San Francisco, those with PTSD were 80% (aOR = 0.2 [0.0-0.9]) and 8% (aOR = 0.9 [0.9-1.00]) less likely to be completely adherent to ART in the past four days, respectively.[42,44] In a study of patients with HIV from French hospitals and another from community-based clinics in Sweden, PTSD was associated with an increased risk for VTI (aOR = 1.6 [1.1-2.5]) and suboptimal adherence to dose instructions (aOR = 1.5 [0.6-3.7]), respectively.[31,45] A dose-response has also been observed: each additional lifetime traumatic exposure is estimated to confer an 11% increased risk for ART non-adherence.[46] In contrast, evidence substantiating the association between PTSD and treatment failure – including virologic, immunologic, and clinical failure – are inconclusive and few and far between.

PTSD has been shown to be associated with lower CD4+ T-cell counts and detectable HIV viral loads,[37] but not necessarily ART failure. For example, in a study of women and female-identified transgender women with HIV, recent (not lifetime) trauma was associated with a four-fold increased risk of having a detectable HIV viral load (aOR = 4.3 [1.1-16.6]).[43] In another study of persons with HIV who had been impacted by a massive earthquake in Nepal, PTSD was not associated with a composite measure of treatment failure (aOR = 0.9 [0.2-3.2]), which included a CD4 count <250 cells/mL, a HIV viral load >5,000 copies/mL, and an AIDS-defining condition.[44] However, no study has examined this phenomenon using CDC or WHO definitions of treatment failure, which requires longitudinal, consecutive markers of HIV progression.[47,48]

Aim 3 – Morbidity and mortality

The cumulative negative effect of trauma exposure, mediated by PTSD, is thought to elevate one's biological and psychological vulnerability to stress, increase the likelihood of perceiving this stress as traumatic, and deplete stores of psychological and physical resources to cope with said stress; thus resulting in increased risks for pre-mature mortality and a myriad of co-morbidities.[49] The causal mechanisms underlying the associations between PTSD and morbidity and mortality are poorly understood, particularly among persons with HIV and in the context of combat exposure. Assuming this association is not confounded by exposure to biochemical agents during deployment or substance abuse, some have postulated that PTSD induces a greater susceptibility to co-morbidities through attentional processes (e.g., altered symptom perception) and psychological alterations (e.g., poor coping) that shape health behaviors and self-care, as well as through biological alterations (e.g., systematic dysregulation of metabolic, inflammatory, and cardiovascular biomarkers).[50,51] Because little knowledge of these phenomena exist in the scientific literature with respect to populations with HIV, an additional search was performed for Military and Veteran populations without HIV.

In populations with HIV, PTSD has been associated with a number of co-morbidities, including chronic pain,[49] coronary artery disease,[49] hepatitis C virus (HCV) infection,[52] renal disease,[49] shingles,[53] and subclinical carotid atherosclerosis.[54] In one such study of Rwandan women with HIV who had experienced rape during the 1994 genocide, PTSD was associated with a 72% increased risk for shingles in the past six months (aOR = 1.7 [1.0-2.9]). Moreover, PTSD has also been associated with poorer functional health and healthcare utilization.[55,56] For example, in a study of adult patients with HIV in the Southeast, PTSD was associated with spending ≥5 days in bed due to illness (aOR = 1.7 [1.3-2.1]), an emergency room visit (aOR = 1.5 [1.2-1.9]), and hospital admission (aOR = 1.4 [1.1-1.7]) during the past nine months.[56] No studies have examined the association between PTSD and mortality among persons with HIV.

In Military and Veteran populations without HIV, PTSD has been associated with all-cause and external-cause mortality[51,57-62], as well as a number of co-morbidities, including arthritis,[50,63-65] autoimmune disease,[66] asthma,[50,63,65,67] cancer,[64,68] chronic pain,[50,69] coronary artery disease,[67,68,70-73] endocrine disorder (type 2 diabetes mellitus[50,64,70,74]),[63] headache,[50] hypertension,[63,70,75,76] liver disease,[67] gastrointestinal disorder,[63-65,68,73] musculoskeletal disorder,[63,73] ophthalmologic disorder,[68] pulmonary disease,[50,65,67,68] sexual dysfunction,[68] skin disorder,[63,68,73] stroke,[69] and urologic disease.[68] For example, in a study of World War II Veterans who had been exposed to mustard gas, PTSD was associated with a three-, four-, and five-fold increased risk for urologic disease (aOR = 2.8 [1.7-4.6]), ophthalmologic disorder (aOR = 4.1 [2.1-8.1]), and pulmonary disease (aOR = 5.4 [3.1-9.2]), respectively.[68] Interestingly, this association seems to be modified by level of combat exposure; as shown in a cohort study of active-duty Military service members in which the risk for autoimmune disease increased among those with PTSD if they had also been exposed to combat (aOR = 1.5 [1.1-2.1] vs. 1.7 [1.2-2.4]).[66] The association between PTSD and all-cause mortality is well-documented but there is considerable variation, from an aHR = 1.1 (1.0-1.2) among Purple Heart recipients to an aHR = 18.3 (10.4-32.1) among Vietnam War-era veterans.[51,60] In regard to cause-specific mortality, PTSD was associated with a two-fold increased risk for external-cause mortality (aHR = 2.3 [1.5-3.5]; e.g., homicide, suicide, drug overdose).[57] No other causes of death have been examined. Notably, there appears to be a dose-response: each additional year of service, deployment, and decrease in rank is associated with an increased risk for all-cause mortality,[61] particularly for those who had been wounded, been permanently disabled, or seen someone else die during deployment.[58]

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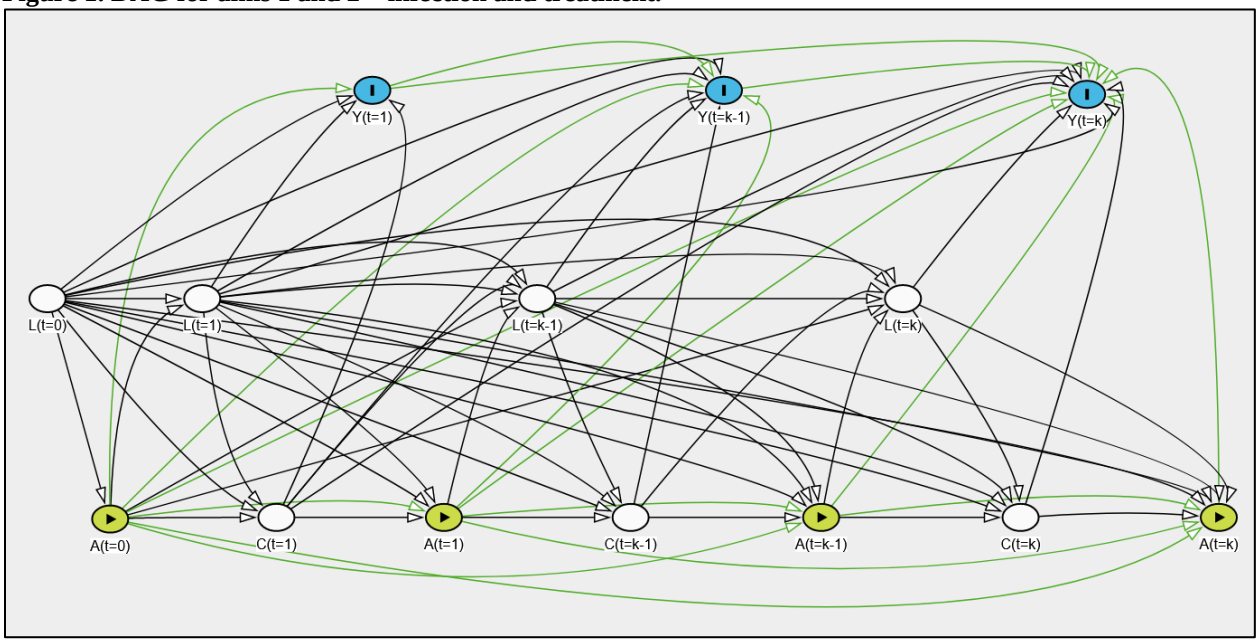
Chapter 2: Overview of methods

Multiple imputation

To address missing data, the distribution of the observed data was used to estimate multiple values that reflect the uncertainty around the true value; it was an iterative form of stochastic imputation.[1] The process created several different plausible imputed datasets and appropriately combined results obtained from each, and consisted of the following stages: (1) imputation, in which missing data were filled in with estimated values and a complete dataset was created, this was repeated *m* times; (2) analysis, in which each of the *m* completed datasets were analyzed using a statistical method of interest; and (3) pooling, in which the resultant parameter estimates were combined for inference.[1]

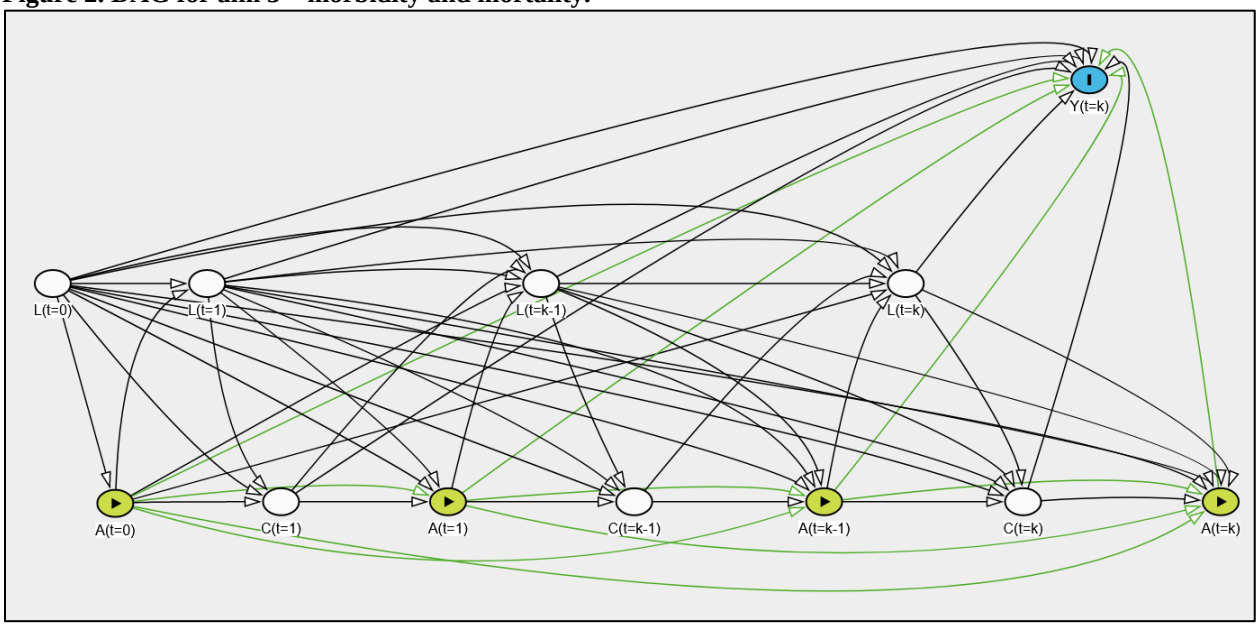
Directed acyclic graphs

Figure 1. DAG for aims 1 and 2 – infection and treatment.



PTSD, posttraumatic stress disorder. k represents the number of times during which any one of the time-dependent variables, including the exposure and confounders, change. A(t=0), A(t=1), A(t=k-1), A(t=k) represent the PTSD status at baseline and each subsequent time during which there is a change in the time-dependent variables. L(t=0) denotes baseline time-independent confounders. L(t=1), L(t=k-1), L(t=k) represent measured time-dependent confounders. L(t=1), L(t=k-1), L(t=k) represent measured time-dependent confounders. C(t=1), C(t=k-1), C(t=k) reflect loss-to-followup before 31 December 2020. Y(t=1), Y(t=k-1), Y(t=k) indicate the outcome. If all possible confounding paths are blocked, the green arrows into Y represent the remaining causal paths.

Figure 2. DAG for aim 3 – morbidity and mortality.



PTSD, posttraumatic stress disorder. k represents the number of times during which any one of the time-dependent variables, including the exposure and confounders, change. A(t=0), A(t=1), A(t=k-1), A(t=k) represent the PTSD status at baseline and each subsequent time during which there is a change in the time-dependent variables. L(t=0) denotes baseline time-independent confounders. L(t=1), L(t=k-1), L(t=k) represent measured time-dependent confounders. L(t=1), L(t=k-1), L(t=k) represent measured time-dependent confounders. C(t=1), C(t=k-1), C(t=k) reflect loss-to-followup before 31 December 2020. Y(t=1), Y(t=k-1), Y(t=k) indicate the outcome. If all possible confounding paths are blocked, the green arrows into Y represent the remaining causal paths.

Marginal structural models

All of the analyses performed were susceptible to time-varying confounding and/or selection bias, for which MSMs are one of several options that can be used to adjust for this bias and obtain a valid estimate of the association of interest.[2] MSMs relate exposure and censoring history, up to time *t*, to the corresponding counterfactual outcome at time *t*.[3] The parameters of MSMs are estimated using inverse probability weighting (IPW), which calculates weights based on the inverse of the predicted joint probabilities of a patient's exposure and censoring history, conditional on their observed set of covariates.[3] The reweighted pseudo-population is then a representative sample of the overall study population, in which all patients are observed during the entire study period and all measured covariates are balanced across exposure groups.[3] After time-dependent confounding was addressed, a standard regression model was fitted to account for time-independent confounding and effect modification.[3]

Inverse probability treatment weights – Time-dependent confounding was addressed using IPTW, which adjusts for imbalances in the characteristics of the exposed and unexposed patients.[2] It was fit by building a predictive model for becoming exposed given past exposure and the history of time-dependent confounders at each time-point and then obtaining a single weight per patient by multiplying the current weight with that of the weights from previous time-points[2]; these were then used to construct stabilized weights for each participant at each time-point during followup:

$$sw_i{}^T(t) = \prod_{k=0}^{int(t)} \frac{pr(A[k] = a_i[k] | \bar{A}[k-1] = \bar{a}_i[k-1], V = v_i)]}{pr\left(A[k] = a_i[k] \middle| \bar{A}[k-1] = \bar{a}_i[k-1], \bar{L}(k) = \bar{l}_i[k]\right)}$$

Where: A(k) = exposure status at time t=k
$\bar{A}(k)$ = [A(u); $0 \leq u \leq t=k$], exposure history; defined as 0 at t=k-1
$\bar{L}(k)$ = [A(u); $0 \leq u \leq t=k$], history of time-dependent confounders
V, vector of time-independent confounders at baseline

Informally, the denominator represents the probability that a patient had his own exposure status at time t=k, given the patient's exposure history and history of time-dependent and time-independent confounders.[2] Also informally, the numerator represents the probability that the patient had his own exposure status at time t=k, conditional on the patient's exposure history and time-independent confounders, but not further adjusting for the patient's history of time-dependent confounders.[2]

Estimation of IPTWs – The numerator and denominator must be estimated for each patient and time-point. Because patients diagnosed with PTSD were assumed to have PTSD thereafter, time to PTSD diagnosis was regarded as a failure time variable and was modeled using pooled logistic regression whereby each unit-increment in person-time was treated as an observation, allowing for time-dependent intercepts[2]:

$$pr([A] = 0 | \bar{A}(k-1) = 0, \bar{L}[k]) = \alpha_0(k) + \alpha_1 L(k) + \alpha_2 V$$

$$\hat{\alpha} = (\hat{\alpha}_0[k], \hat{\alpha}_1, \hat{\alpha}_2)$$

$$\hat{\bar{p}}_i(k) = expit(\hat{\alpha}_0[k] + \hat{\alpha}_1 L_i[k] + \hat{\alpha}_2 V_i)$$

Where: A(k) = exposure status at time t=k
$\bar{A}(k)$ = [A(u); $0 \leq u \leq t=k$], exposure history; defined as 0 at t=k-1
$\bar{L}(k)$ = [A(u); $0 \leq u \leq t=k$], history of time-dependent confounders
V, vector of time-independent confounders at baseline
$\hat{\alpha}$ = parameter estimates from fitted model
$\hat{\bar{p}}_i$ = estimated predicted values from fitted model

It was only necessary to fit the model for patients alive and uncensored at each unit-increment in person-time who have yet to be diagnosed with PTSD. The estimated predicted values represented the probability of a particular patient not being diagnosed with PTSD at time t=k, given that the patient had not been diagnosed with PTSD at time t=k-1.[2] The estimate of the IPTW denominator for a particular patient at a specific time-point was[2]:

$$\bar{\hat{p}}_i(k) = \prod_{u=0}^{k} \hat{p}_i(u)$$

If patient had not been diagnosed with PTSD at time $t \leq k$

$$\bar{\hat{p}}_i(k) = (1 - \hat{p}_i[t]) \prod_{u=0}^{t-1} \hat{p}_i(u)$$

If patient had been diagnosed with PTSD at time $t \leq k$

In calculating $\bar{\hat{p}}_i(k)$, it was assumed that a PTSD diagnosis cannot be reversed. To calculate the IPTW numerator, the same logistic model described above was fitted except without including the time-dependent confounders, L(k).[2] For IPTW estimates to be consistent, it was necessary that the denominator be consistently estimated, which required that the intercept at each time-point be held constant or assuming that the intercept at each time-point was a smooth function that can be estimated by smoothing techniques.[2]

Inverse probability of censoring weights – To account for attrition bias due to loss-to-followup, IPCWs were calculated using similar methods. Here, weights were the inverse probability of not being loss-to-followup. IPCWs do not eliminate censoring in the pseudo-population, it makes loss-to-followup a random phenomenon with respect to covariates: patients with complete records and who have similar characteristics to those who were censored were weighted to represent those lost-to-followup[2,3]:

$$sw_i{}^{C}(t) = \prod_{k=0}^{t} \frac{\Pr(C[k] = 0 | \bar{C}[k-1] = 0, \bar{A}[k-1] = \bar{a}_i[k-1], V = v_i)]}{\Pr\left(C[k] = 0 \middle| \bar{C}[k-1] = 0, \bar{A}[k-1] = \bar{a}_i[k-1], \bar{L}(k-1) = \bar{l}_i[k-1]\right)}$$

Where: C(k) = patient is right-censored at time t=k
$\bar{C}(k)$ = [C(u); $0 \leq u \leq t=k$], defined as 0 at t=k-1
A(k) = exposure status at time t=k
$\bar{A}(k)$ = [A(u); $0 \leq u \leq t=k$], exposure history; defined as 0 at t=k-1
$\bar{L}(k)$ = [A(u); $0 \leq u \leq t=k$], history of time-dependent confounders
V, vector of time-independent confounders at baseline

Informally, IPCWs are the ratio of a patient's probability of remaining uncensored up to time t, calculated as if there had been no time-dependent determinants of censoring except past exposure history, divided by the patient's conditional probability of remaining uncensored up to time t.[2]

Estimation of IPCWs – The numerator and denominator must be estimated for each patient and time-point. Because patients uncensored at a specific time-point were assumed to be uncensored at earlier time-points, time to censorship was regarded as a failure time variable that can be modeled using pooled logistic regression whereby

each unit-increment in person-time was treated as an observation, allowing for time-dependent intercepts[2]:

$$\mathrm{pr}([\mathrm{C}] = 0|\mathrm{C}(\mathrm{k}-1), \bar{\mathrm{L}}[\mathrm{k}]) = \alpha_0(\mathrm{k}) + \alpha_1\mathrm{A}(\mathrm{k}-1) + \alpha_2\mathrm{L}(\mathrm{k}) + \alpha_3\mathrm{V}$$

$$\hat{\alpha} = (\hat{\alpha}_0[\mathrm{k}], \hat{\alpha}_1, \hat{\alpha}_2, \hat{\alpha}_3)$$

$$\bar{\hat{\mathrm{p}}}_{\mathrm{i}}(\mathrm{k}) = \mathrm{expit}(\hat{\alpha}_0[\mathrm{k}] + \hat{\alpha}_1\mathrm{A}_{\mathrm{i}}(\mathrm{k}-1) + \hat{\alpha}_2\mathrm{L}_{\mathrm{i}}[\mathrm{k}] + \hat{\alpha}_3\mathrm{V}_{\mathrm{i}})$$

Where: C(k) = patient is right-censored at time t=k
$\bar{\mathrm{C}}$(k) = [C(u); 0 ≤ u ≤t=k], defined as 0 at t=k-1
A(k) = exposure status at time t=k
$\bar{\mathrm{A}}$(k) = [A(u); 0 ≤ u ≤t=k], exposure history; defined as 0 at t=k-1
$\bar{\mathrm{L}}$(k) = [A(u); 0 ≤ u ≤t=k], history of time-dependent confounders
V, vector of time-independent confounders at baseline
$\hat{\alpha}$ = parameter estimates from fitted model
$\bar{\hat{\mathrm{p}}}_{\mathrm{i}}$ = estimated predicted values from fitted model

It was only necessary to fit the model for patients alive and uncensored at each unit-increment in person-time who have yet to be censored. The estimated predicted values represented the probability of a particular patient remaining in the study at time t=k, given that the patient has remained in the study at time t=k-1.[2] The estimate of the IPCW denominator for a particular patient at a specific time-point was[2]:

$$\bar{\hat{\mathrm{p}}}_{\mathrm{i}}(\mathrm{k}) = \prod_{\mathrm{u}=0}^{\mathrm{k}} \hat{\mathrm{p}}_{\mathrm{i}}(\mathrm{u})$$

If patient had not remained uncensored at time t ≤ k

$$\bar{\hat{\mathrm{p}}}_{\mathrm{i}}(\mathrm{k}) = (1 - \hat{\mathrm{p}}_{\mathrm{i}}[t]) \prod_{\mathrm{u}=0}^{\mathrm{t}-1} \hat{\mathrm{p}}_{\mathrm{i}}(\mathrm{u})$$

If patient remained uncensored at time t ≤ k

In calculating $\bar{\hat{\mathrm{p}}}_{\mathrm{i}}$(k), it was assumed that censorship cannot be reversed. To calculate the IPCW numerator, the same logistic model described above is fitted except without including the time-dependent confounders, L(k).[2] For IPCW estimates to be consistent, it was necessary that the denominator be consistently estimated, which required that the intercept at each time-point be held constant or assuming that the intercept at each time-point was a smooth function that can be estimated using smoothing techniques.[2]

Estimation of final weights – Multiplying both IPTWs and IPCWs produces weights that account for both time-dependent confounding and selection bias due to attrition; weighting by their product produced a consistent estimate of the causal effect under the assumption of no residual confounding or other biases.[2] At a few illustrative time-

points, all analyses using MSMs included summary statistics on the center and dispersion of the four estimated probabilities, IPTW and IPCW numerators and denominators, as well as the distribution of the final weights.[2]

Robust variance estimators – Use of IPW induces within-subject correlation, invalidating the standard error estimates outputted by standard logistic programs.[2] To address this issue, the above weighted logistic model was fitted using generalizing estimating equations (GEE) with independent correlation matrices that output robust variance estimators, allowing for correlated observations and thus producing conservative confidence intervals (CI).[2]

Assumptions – The validity of analyses using MSMs depend on a number of assumptions: (1) conditional exchangeability (i.e., no unmeasured confounders, noninformative censoring); (2) positivity (i.e., conditional probability of exposure and uncensorship is greater than zero); (3) no model misspecification (i.e., correct weights and regression models); and (4) all missing data are missing at random (MAR).[2,3]

Interaction assessment

To determine whether the associations between PTSD and the outcomes of interest are modified by number of deployments and combat exposure, a chunk test was performed.[4]

$$H_0: \delta_1 = \delta_2 = \delta_3 = \delta_4 = 0$$
$$H_A: \text{at least one } \delta \neq 0$$
$$\text{LRT} \sim \chi^2_{df=4} \text{ under } H_0$$

If it is statistically significant, backwards elimination will be conducted to determine whether any of the product terms can be dropped.[4] If there is ≥1 product term with $p < \alpha$, the least significant term will be dropped and the model re-run; this will be iteratively performed until all product terms reach statistical significance or have been removed.[4]

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EMORY | ROLLINS SCHOOL OF PUBLIC HEALTH

Date: 27 October 2023

To: Frederick P. Rivara, MD, MPH
Editor-in-Chief, ***JAMA Network Open***

Subject: Manuscript Submission

Dear Editors,

Enclosed you will find our paper entitled, "Posttraumatic Stress Disorder and its Associations with Sexually Transmitted Infections among Veterans." We kindly ask that you consider our manuscript for publication in your special issue on the effects of war on health and healthcare delivery, access, and equity.

Our study includes all Veterans who deployed to Iraq and Afghanistan and who receive care in the Department of Veterans Affairs. We aimed to estimate the overall and time-varying associations between PTSD and STI incidence, and measure effect modification by number of deployments and combat exposure. We found PTSD increased the risk of all STIs examined – namely chlamydia, genital HSV, gonorrhea, HBV, HCV, HIV, HPV, and syphilis – and that these associations did not diminish with time. Results may help policy-makers anticipate the potential negative health consequences of war for Veterans and possibly even displaced citizens in war-torn nations, and how to best attenuate those risks by supporting preventive measures. Results may also enable providers to better understand which STIs are of greatest concern, identify those patients at elevated risks, mitigate these risks by referring patients to risk reduction counseling, and inform other medical decisions and treatments for those with PTSD.

We believe that this manuscript is appropriate for your journal and will be of interest to your readers. This work is original, has not been published elsewhere, and is not under concurrent consideration elsewhere. Thank you for your consideration of this manuscript.

Very respectfully,

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Abstract

Importance: One-quarter of all Veterans who deployed to Iraq and Afghanistan developed posttraumatic stress disorder (PTSD). No known studies have examined the long-term associations between PTSD and sexually transmitted infections (STI), especially the roles of multiple deployments and combat exposure.

Objectives: We sought to examine trends in incidences of PTSD and STIs, estimate the associations between PTSD and STI incidence, measure effect modification by number of deployments and combat exposure, and explore time-varying associations.

Design: This was a population-based prospective cohort study. Joinpoint regression models, marginal structural Poisson models, and marginal structural shared frailty models were fitted to examine trends, estimate overall associations, measure effect modification, and explore how these associations varied over time.

Setting: U.S. Department of Veterans Affairs (VA).

Participants: All Iraq and Afghanistan Veterans enrolled in the VA between 7 October 2001 and 31 December 2022 were included; 2% died, 18% were lost-to-follow-up, and 80% survived the study period.

Exposure: Time-dependent, clinician-diagnosed PTSD.

Main outcomes: Time-dependent, clinician-diagnosed (ICD-based) or laboratory-confirmed STIs – namely chlamydia, genital herpes simplex virus (HSV), gonorrhea, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), human papillomavirus (HPV), and syphilis.

Results: A total of 1,570,654 OEF/OIF/OND Veterans were included, contributing 15,535,454 person-years. Overall, incidences in PTSD, HCV, and HPV significantly decreased, but those of chlamydia, HIV, and syphilis significantly increased throughout the study period. PTSD was associated with increased rates (adjusted incidence rate ratio, 95% CI) of HPV by 3% (1.03 [1.00, 1.05]), HIV by 8% (1.08 [1.02, 1.15]), HBV by 9% (1.09 [1.01, 1.18]), genital HSV by 9% (1.09 [1.07, 1.11]), syphilis by 11% (1.11 [1.05, 1.17]), chlamydia by 20% (1.20 [1.17, 1.24]), gonorrhea by 21% (1.21 [1.13, 1.31]), and HCV by 69% (1.69 [1.62, 1.77]). These associations increased throughout the study period and remained statistically significant. Multiple deployments and combat exposure demonstrated varying interactions with PTSD depending on the STI examined.

Conclusion and relevance: PTSD was associated with increased rates of all STIs examined, and these associations did not diminish with time. Results may help guide preventive efforts and other medical decisions and treatment for those with PTSD.

Key Points

Question

Is posttraumatic stress disorder (PTSD) associated with sexually transmitted infections (STI) among Veterans?

Findings

In this prospective cohort study of 1,570,654 Veterans who deployed to Iraq and Afghanistan, PTSD significantly increased the rates of all STIs examined – human papillomavirus (HPV) by 3%, human immunodeficiency virus (HIV) by 8%, hepatitis B virus (HBV) by 9%, genital herpes simplex virus (HSV) by 9%, syphilis by 11%, chlamydia by 20%, gonorrhea by 21%, and hepatitis C virus (HCV) by 69%.

Meaning

Individuals with PTSD have an elevated risk of STIs.

Introduction

Of the 2.5 million U.S. Veterans who deployed to Iraq and Afghanistan during Operations Enduring Freedom, Iraqi Freedom, and/or New Dawn (OEF/OIF/OND) post-9/11, nearly one-quarter are thought to have developed PTSD.[1–5] In particular, symptoms of avoidance and hyperarousal can interfere with information processing, resulting in high-risk sexual behaviors that may increase the incidence of sexually transmitted infections (STI).[6] For example, avoidance may result in not being fully aware of risks during sex, seeking riskier sexual encounters to counter numbing symptoms, and difficulty maintaining monogamous relationships.[7] Hyperarousal may contribute to inaccurate appraisals of safety vs. risk, an inability to negotiate safe sex, and a need for sexual (often excessive) stimulation due to physiological and emotional dysregulation.[7] PTSD has been shown to be associated with a four-fold increased prevalence of high-risk sexual behaviors,[8] including sex without condoms,[9–13] having multiple partners,[7] sex with a commercial sex worker,[7,14,15] and sex under the influence of drugs or alcohol,[11,16] resulting in an elevated incidence of STIs.[6,10,17–20]

Each additional traumatic stressor has been shown to increase the risk of STIs, suggesting there may be a dose-response.[17,20] One possible traumatic stressor among OEF/OIF/OND era Veterans may have been the increased operational tempo, particularly the intense and repeated deployments that was characteristic during their wartime military service. It is estimated that 57%, 27%, and 16% of all OEF/OIF/OND Veterans deployed one, two, and three or more times, respectively.[21] Another potential traumatic stressor includes combat exposure. Sixty-four percent of all OEF/OIF/OND Veterans reported some form of combat exposure, of whom 49% witnessed someone who was wounded or killed, 49% felt in danger of being killed, and 17% discharged their weapon.[22] Each additional fire-fight has shown to linearly increase the risk of PTSD, from 5% among those with no exposure to 19% among those who experienced ≥5 fire-fights.[23] Further, combat exposure during deployment has been shown to increase the risk of PTSD three-fold compared to non-deployment.[24] However, in either military or Veteran populations, no known studies have examined the long-term association of PTSD and STI incidence, especially the roles of multiple deployments and combat exposure.

The objective of this current work was to address this knowledge gap for wartime Veterans and to inform the care of those with PTSD more broadly – by (1) examining trends in the incidences of PTSD and STIs, (2) estimating the association between PTSD and STI incidence, (3) measuring effect modification by number of deployments and combat exposure, and (4) exploring how these associations vary over time among all OEF/OIF/OND Veterans enrolled in the Department of Veterans Affairs (VA). Expanded knowledge may help policymakers anticipate the potential long-term negative health consequences of war for Veterans, the risk profiles of those most vulnerable, and how to best attenuate those risks by supporting and implementing preventive measures.[25] It may also enable providers to better understand which STIs are of greatest concern, identify those patients at an elevated risk of an STIs, mitigate these risks by referring patients to risk reduction counseling, and inform other medical decisions and treatments for those with PTSD.[25,26]

Methods

Study population

All U.S. Veterans who have ever (1) been deployed in support of OEF (7 October 2001 – 28 December 2014), OIF (20 March 2003 – 31 August 2010), and/or OND (1 September 2010 – 15 December 2011), and (2) received healthcare at the VA were included in this study. Patients entered the study at the date of VA enrollment and were right censored (1) at death, if recorded; (2) at the date of their last encounter if they had not visited the VA after 31 December 2020 (considered lost-to-follow-up [LTFU]); or (3) 31 December 2022 if the date of their last encounter occurred after 31 December 2020.

Data sources

Datasets were generated and analyzed within the VA Informatics and Computing Infrastructure (VINCI), a secure, central analytic platform that hosts suites of databases integrated from select national VA data sources, including those used here – namely, the Corporate Data Warehouse (CDW), the Department of Defense (DoD)-VA Informatics and Computing Infrastructure (DaVINCI), and the U.S. Veterans Eligibility Trends and Statistics (USVETS) databases.[27] CDW is a repository of over 20 million unique patient-level electronic health records (EHR) aggregated from across the VA's national healthcare delivery system.[28] DaVINCI is built on existing data infrastructures – the Health Services Data Warehouse (HSDW) and the Military Health System Data Repository (MDR) on the DoD side and VINCI, which largely draws from the CDW, on the VA side – and provides a consolidated view of EHR for over 4 million unique Veterans during and after their military service.[29] The final data source was USVETS, which combines data from the VA, DoD, and commercial sources and contains data such as utilization of VA services and benefits, military history, geography, demographics, and socioeconomic factors for nearly 40 million Veterans.[30]

Definitions

The National Cancer Institute Comorbidity Index and the Centers for Medicare and Medicaid Services Chronic Condition Warehouse coding algorithms (using International

Classification of Diseases, Ninth and Tenth Revisions [ICD-9 and -10] codes) were used to define each mental health disorder of interest, including the exposure (PTSD)[31] and mental health history (anxiety disorder, depressive disorder, high-risk sexual behavior, military sexual trauma [MST], substance use disorder [SUD], and traumatic brain injury [TBI]; Supplemental Table 1).[32–34] The Armed Forces Health Surveillance Division coding algorithm was used to define each STI outcome of interest, including chlamydia, genital herpes simplex virus (HSV), gonorrhea, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodefiency virus (HIV), human papillomavirus (HPV), and syphilis (Supplemental Table 1).[35] Incident cases of chlamydia and gonorrhea were defined by a case-defining diagnosis (ICD-9 and -10 codes) or a positive lab test (any specimen source or test type); recurrent cases must have occurred >30 days after the previous diagnosis.[35] Incident cases of HBV and HCV were defined as a case-defining diagnosis (ICD-9 and -10 codes) or positive lab test (any specimen or test type).[35] Incident cases of HIV were defined by a case-defining diagnosis (ICD-9 and -10 codes) or positive screening and confirmatory tests.[35] Incident cases of genital HSV and HPV were defined by a case-defining diagnosis (ICD-9 and -10 codes) or a positive lab test (HSV: genital specimen source, antibody tests excluded; HPV: any specimen source or test type).[35] Incident cases of syphilis were defined by a case-defining diagnosis (ICD-9 and -10 codes) or a positive polymerase chain reaction or treponemal lab test.[35] Combat exposure was defined as having met the combat Veteran VA eligibility requirements.[36]

Descriptive analyses

Descriptive analyses were performed to characterize and compare patients who were and were not ever diagnosed with PTSD by socio-demographics (age at military separation, sex, race/ethnicity, marital status, educational attainment, and household income), military history (branch, component, rank/grade, length of service, occupation, number of deployments, combat exposure, in-theater injuries, and discharge character), and mental health history. Frequencies of each STI outcome of interest were also compared between patients who were and were not ever diagnosed with PTSD. Fisher's exact tests or chi-square tests for categorical data and Mann-Whitney-Wilcoxon tests for continuous data were performed as appropriate.

Trend analyses

Crude incidence rates (cIR) and 95% confidence intervals (CI) were calculated annually for incident PTSD diagnoses, each STI outcome of interest, and any STIs that had occurred in the study period. Joinpoint regression models, which are piecewise linear regression models, were fitted to estimate annual percent changes (APC) during periods when significant changes in rates were observed, which was inferred using a Monte Carlo permutation procedure.[37]

Inferential analyses

Marginal structural models (MSM) were fitted for each STI outcome of interest with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at military separation, sex, race/ethnicity, marital status, educational attainment, household income, MST, and TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, and SUD).[38] To adjust for both time-dependent confounding and informative

censoring, inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCW) were estimated by weighted pooled logistic regression models and used to calculate the final stabilized weights.[38] Final stabilized weights for each outcome of interest were aggregated by one-year increments and their distribution were examined.

Specifically, marginal structural Poisson models were fitted to estimate adjusted incidence rates (aIR) and incidence rate ratios (aIRR) for the association between PTSD and STI incidence.[39] The generalized estimating equations (GEE) procedure was performed to account for within-patient correlation of recurrent events (chlamydia and gonorrhea). Further, marginal structural shared frailty models[40] – which includes a random effect called the frailty to account for within-subject correlation of recurrent events – were fitted to estimate adjusted risk differences (aRD) of the association between PTSD and each STI outcome of interest over time, under the hypothetical of always versus never exposed.[38] All analyses were performed under three scenarios: (1) no effect modification, (2) effect modification by number of deployments, and (3) effect modification by combat exposure. Wald tests were used to assess for interaction. Bootstrapping procedures were applied to calculate 95% CIs. Multiple imputation was performed for each STI outcome of interest to address missingness among all time-independent confounders (except MST and TBI) using the Markov chain Monte Carlo approach.

Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC), Joinpoint Trend Analysis 5.0 (NCI, Bethesda, MD),[37] and the %MSM SAS macro (CAUSALab, Harvard University, Boston, MA) was employed to calculate all stabilized weights and was modified to fit marginal structural shared frailty models.[38] Probability values <0.05 were considered statistically significant. All work was conducted in accordance with the Declaration of Helsinki. The study was approved by the Emory University Institutional Review Board and the Atlanta VA Medical Center Research and Development Committee. A waiver of consent was obtained for this work.

Results

A total of 1,570,654 OEF/OIF/OND Veterans enrolled in the VA between 7 October 2001 and 31 December 2022, contributing a total of 15,535,454 person-years (PY, mean [standard deviation, SD] = 10.0 [5.2] PY). Patients with PTSD (n=666,065, 42.4%) contributed 7,356,788 PY (mean [SD] = 11.5 [4.6] PY); whereas those without PTSD (n=904,589, 57.6%) contributed 8,178,666 PY (mean [SD] = 8.9 [5.3] PY). In total, 31,825 died (2.0%), 285,010 (18.1%) were LTFU, and 1,253,819 (79.8%) survived past the study period.

Characteristics

Most patients were male (87.2%), White (75.2%), married (52.9%), high school educated (64.6%), and had an annual household income of USD $40,000-74,999 (38.5%); the median (interquartile range [IQR]) age at military separation was 30.2 (15.5) years (Table 1). Regarding their military history, most patients served in the Army (54.7%) and on active-duty (70.2%), were ranked as enlisted E5-E9 (51.3%), worked in service/supply (56.3%), deployed only once (75.7%), were unexposed to combat (75.0%), never sustained combat (95.6%) or noncombat (66.2%) injuries, and were honorably discharged (99.9%); the median (IQR) length of service was 9.4 (16.5) years. Patients with PTSD were significantly different across all factors examined, including sociodemographics, military history, mental health history, and frequency of STIs compared to those without PTSD, except for gonorrheal infections.

Trends

Incidences, along with their joinpoints, of PTSD and each STI outcome of interest are depicted over time in Figure 1. Incidences decreased (APC, in order of magnitude) for PTSD by 8.1% in 2005-2022, chlamydia by 12.1% in 2018-2022, HCV by 12.2% in 2014-2022, gonorrhea by 15.8% in 2012-2015, any STI by 16.0% in 2014-2017, genital HSV by 19.5% in 2014-2017, and HPV by 38.1% in 2014-2017. Further, incidences increased (APC, in order of magnitude) for genital HSV by 3.6% in 2002-2014, HIV by 3.6% in 2003-2022, any STI by 3.7% in 2002-2014, chlamydia by 7.5% in 2002-2018, HPV by 7.8% in 2002-2014 and 8.6% in 2017-2022, syphilis by 9.3% in 2003-2022, and gonorrhea by 24.7% in 2015-2018.

Overall associations

PTSD significantly increased the overall rates (aIRR [95% CI], in order of magnitude) for all STI outcomes of interest – specifically, HPV by 3% (1.03 [1.00, 1.05]), HIV by 8% (1.08 [1.02, 1.15]), HBV by 9% (1.09 [1.01, 1.18]), genital HSV by 9% (1.09 [1.07, 1.11]), any STI by 10% (1.10 [1.09, 1.12]), syphilis by 11% (1.11 [1.05, 1.17]), chlamydia by 20% (1.20 [1.17, 1.24]), gonorrhea by 21% (1.21 [1.13, 1.31]), and HCV by 69% (1.69 [1.62, 1.77]) (Table 2, Figure 2). These associations of PTSD on the incidence of each STI outcome of interest increased throughout the study period and remained statistically significant (Figure 3).

Effect modification

Multiple deployments increased the association (aIRR [95% CI]) between PTSD and the incidence of chlamydia (1.33 [1.29, 1.37] vs. 1.22 [1.18, 1.26], p=0.014), but decreased the association with HCV incidence (1.59 [1.50, 1.68] vs. 1.86 [1.76, 1.97, p=0.006), compared to one deployment (Table 2, Figure 2). Further, combat exposure decreased the associations (aIRR [95% CI]) between PTSD and the incidences of chlamydia (1.13 [1.10, 1.17] vs. 1.22 [1.19, 1.26], p=0.032), genital HSV (1.00 [0.97, 1.03] vs. 1.11 [1.08, 1.14], p<0.001), HCV (1.45 [1.38, 1.52] vs. 1.75 [1.67, 1.83], p=0.001), and any STI (1.02 [1.00, 1.03] vs. 1.12 [1.10, 1.13], p<0.001), but increased the association with HPV incidence (1.13 [1.10, 1.16] vs. 1.01 [0.98, 1.04], p<0.001), compared to no combat exposure. Crude estimates and the distribution of final stabilized weights over time are described in Supplemental Table 2 and depicted in Supplemental Figure 1, respectively.

Discussion

Our data show that those with a PTSD diagnosis have increased STI incidence. This analysis represents one of the more comprehensive and robust analyses to estimate the association of PTSD and STI incidence in any population, even among Veterans. Results show that the incidence of PTSD diagnoses has declined over time in this population. However, renewed concern should be directed at recent increases in the incidences of gonorrhea, HIV, HPV, and syphilis. Results also suggest PTSD increased the rates (in order of increasing magnitude) of HPV, HIV, HBV, genital HSV, any STI, syphilis, chlamydia, gonorrhea, and HCV. Moreover, multiple deployments and combat exposure acted antagonistically or synergistically with PTSD, if at all,

depending on the STI examined. Finally, these associations between PTSD and STI incidence increased during the study period and remained statistically significant.

Ten known studies have examined the associations between PTSD and STIs[6,10,12,13,17–19,41–43]; only two were performed in military or Veteran populations[41,43] (none in the U.S.). For example, in a cross-sectional study of 351 active-duty Belizean soldiers, PTSD was associated with 2.5-fold increased risk for an STI; however, both PTSD and STIs were self-reported and temporality could not be established.[41] In another cross-sectional study of 1,307 active-duty Rwandan soldiers, PTSD was associated with a 2.8-fold increased risk for STI symptoms; however, here too both PTSD and STI symptoms were self-reported and temporality could not be established.[43] Due to their study designs and analytical methods, these studies were limited in their causal inference and were variably contradicting. Building on this prior work, this current study has shown that PTSD was associated with (and predicted) STI incidence and that these associations were moderately strong.

Because PTSD normally develops within the first few months after an index traumatic event (although a delayed onset of ≥6 months does occur in 20-30% of cases),[44] it is not surprising that the incidence of PTSD diagnoses parallels that of the troop surges and withdrawals during OEF/OIF/OND. Interestingly, however, compared to Veterans of past wars, a higher proportion of OEF/OIF/OND Veterans have reported engaging in high-risk sexual behaviors, suggesting there may be cohort effects or differences in reporting.[45] While temporal declines in genital HSV, gonorrhea, HCV, HPV, and all STIs in 2014-2017 appear largely inexplicable (given the low HPV vaccination rate in the VA[46]), but these do coincide with the 2014 enactment of the Veterans Choice Act, which may have obscured STIs diagnosed by non-VA providers.[47] Whereas differences in the effects of PTSD on each STI examined may be wholly or partly explained by differences in their transmissibility (except HPV, which has an unusually attenuated effect size).[48] In regard to effect modification, the potentially unexpected results may be due to the healthy warrior effect, as service members who either self-select or are chosen for multiple deployments or combat roles are likely healthier, more resilient, and may be less prone to high-risk sexual behaviors and STIs later in life; or, possibly the healthy survivor effect wherein those who develop PTSD may be affected earlier and therefore may deploy less frequently.[49–51]

A major strength of this current work was its robust analysis to estimate the causal effects of PTSD on STI incidence. MSMs related the exposure and censoring history, up to time *t*, to the corresponding counterfactual outcome at time *t*.[52] Resultant estimates are consistent with causal effects under the assumption of no residual confounding or other biases; however, because this assumption is likely unfounded, we only infer associations and not causal effects here.[38,52] Other strengths of this study include its complete enumeration and enrollment of a nationally representative population; use of large repositories of patient-level EHR and military service records[27]; and limited LTFU[53]. Limitations of this study include possible misclassification of the exposure and effect modifiers; possible selection bias in trend analyses due to informative censoring; possible selection bias due to the healthy warrior effect[49–51]; that the assumptions of MSMs – exchangeability, consistency, positivity, and accuracy of the weight-generating model – were presumed true[54]; and that the true index traumatic stressor could not be ascertained. Bias analyses may be able to examine the extent to which misclassification and selection bias affected results, if at all. For the MSMs, only the positivity assumption was assessed, the other three cannot be verified given the observational data. Not knowing the true index traumatic stressor does not invalidate these findings.

As Tolstoy writes in *War and Peace*, "…war is always pernicious even when successful."[55] Success in war should extend past the battlefield and include the life-long health and well-being of

all those who survive it. Veterans return from war with invisible wounds that result in long-term downstream effects, including high-risk sexual behaviors and STIs. Today, with the wars in Ukraine and Israel, it is now more important than ever to understand how trauma can have long-lasting effects on health, including the tens of thousands of civilians who become displaced in its wake. Results may help policy-makers anticipate the potential negative health consequences of war for Veterans and possibly even displaced citizens in war-torn nations, and how to best attenuate those risks by supporting preventive measures.[25] Results may also enable providers to better understand which STIs are of greatest concern, identify those patients at elevated risks, mitigate these risks by referring patients to risk reduction counseling, and inform other medical decisions and treatments for those with PTSD.[25,26]

Conflicts of interest and source of funding

No funding was received to assist with the preparation of this manuscript. KJV, BKA, RHL, and JLG have no relevant financial or non-financial interests to disclose. VCM received support from the Emory CFAR (P30AI050409). VCM has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Eli Lilly, Bayer, Gilead Sciences, Merck, and ViiV. PSS received funding from the NIH and CDC. PSS has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Gilead, Merck, and ViiV.

The views expressed are those of the authors and do not reflect the official views of the Uniformed Services University of the Health Sciences, the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc, the National Institutes of Health or the Department of Health and Human Services, the Department of Defense, the Defense Health Agency, the Departments of the Army, Navy or Air Force, the Department of Veterans Affairs, and U.S. Government. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

Author contributions

All authors contributed to the content of the manuscript and concurred with the decision to submit it for publication. KJV contributed to the conception and design of the study, acquisition of the data, statistical analysis, interpretation, and drafting the manuscript. BKA, VCM, PSS, and JLG contributed to the conception and design of the study, interpretation, drafting and critical revision of the manuscript, and supervision. KJV had full access to all data in the study and takes full responsibility for the integrity of the data and the accuracy of the analysis.

Acknowledgements

We thank all those who currently serve or have ever served in the U.S. military. We also thank Dr. Robert H. Lyles (Department of Biostatistics, Rollins School of Public Health, Emory University) for his review and critical revision of the manuscript.

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Table 1. Characteristics of OEF/OIF/OND Veterans by PTSD diagnosis (2001-2022).

	N=1,570,654[1] n (%)[2]	PTSD n=666,065 (42.4%) n (%)[2]	No PTSD n=904,589 (57.6%) n (%)[2]	P-value[3]
Sociodemographics				
Age at military separation (years), median (IQR)	30.2 (15.5)	29.0 (13.9)	31.4 (16.4)	<0.001
Sex, male[4]	1,369,852 (87.2)	582,830 (87.5)	787,022 (87.0)	<0.001
Race/ethnicity[4,5]				<0.001
Black	260,399 (19.1)	127,205 (21.0)	133,194 (17.6)	
White	1,024,317 (75.2)	444,956 (73.5)	579,361 (76.5)	
Other	78,314 (5.8)	33,154 (5.5)	45,160 (6.0)	
Marital status[4,5]				<0.001
Married	780,009 (52.9)	344,104 (52.8)	435,905 (52.9)	
Never married	398,293 (27.0)	153,763 (23.6)	244,530 (29.7)	
Divorced/separated/widowed	297,052 (20.1)	154,124 (23.6)	142,928 (17.4)	
Educational attainment[4-6]				<0.001
High school	768,321 (64.6)	334,745 (67.2)	433,576 (62.7)	
Vocational/technical	9,121 (0.8)	4,102 (0.8)	5,019 (0.7)	
College/university	412,702 (34.7)	159,581 (32.0)	253,121 (36.6)	
Household income (USD, annual)[4,5]				<0.001
<20,000	150,833 (9.9)	71,259 (11.1)	79,574 (9.1)	
20,000-39,999	291,425 (19.2)	134,802 (20.9)	156,623 (17.9)	
40,000-74,999	584,462 (38.5)	248,711 (38.6)	335,751 (38.4)	
≥75,000	492,457 (32.4)	190,030 (29.5)	302,427 (34.6)	
Military history[7]				
Branch[4,8]				<0.001
Air Force	256,382 (15.6)	63,816 (9.1)	192,566 (20.4)	
Army	900,834 (54.7)	451,269 (64.2)	449,565 (47.6)	
Coast Guard	4,375 (0.3)	1,352 (0.2)	3,023 (0.3)	
Marines	243,752 (14.8)	118,376 (16.8)	125,376 (13.3)	
Navy	242,954 (14.7)	68,239 (9.7)	174,715 (18.5)	
Component[4,8]				<0.001
Active-duty	1,275,421 (70.2)	542,210 (70.6)	733,211 (69.9)	
Guard	306,838 (16.9)	132,308 (17.2)	174,530 (16.6)	
Reserve	234,597 (12.9)	93,391 (12.2)	141,206 (13.5)	
Rank/grade[4]				<0.001
Enlisted, E1-E4	557,305 (38.0)	276,001 (44.8)	281,304 (33.1)	
Enlisted, E5-E9	753,086 (51.3)	303,734 (49.3)	449,352 (52.9)	
Officer, O1-O9	156,341 (10.7)	36,977 (6.0)	119,364 (14.0)	
Length of service (years), median (IQR)	9.4 (16.5)	8.2 (15.8)	10.7 (17.3)	<0.001
Occupation[8]				<0.001
Infantry	169,631 (10.8)	89,919 (13.5)	78,699 (8.7)	
Service/supply	884,278 (56.3)	387,650 (58.2)	496,619 (54.9)	
All others	364,392 (23.2)	117,894 (17.7)	245,144 (27.1)	
Non-qualified/undesignated	152,353 (9.7)	70,603 (10.6)	84,127 (9.3)	
Number of deployments[4]				<0.001
1	1,189,565 (75.7)	480,751 (72.2)	708,814 (78.4)	
2	267,214 (17.0)	130,782 (19.6)	136,432 (15.1)	
≥3	113,875 (7.3)	54,532 (8.2)	59,343 (6.6)	
Combat exposure[9]	235,365 (15.0)	113,755 (17.1)	121,610 (13.4)	<0.001
In-theater injuries[4]				<0.001
Combat	68,916 (11.5)	47,642 (16.1)	21,274 (7.0)	
Noncombat	530,604 (88.5)	247,545 (83.9)	283,059 (93.0)	
Discharge character[4]				<0.001
Dishonorable	1,427 (0.1)	785 (0.1)	642 (0.1)	
Honorable	1,526,726 (99.9)	651,248 (99.9)	875,478 (99.9)	
Mental health history				
Anxiety	647,276 (41.2)	408,218 (61.3)	239,058 (26.4)	<0.001
Depression	413,094 (26.3)	297,250 (44.6)	115,844 (12.8)	<0.001
High-risk sexual behavior	8,880 (0.6)	5,266 (0.8)	3,534 (0.4)	<0.001
Military sexual trauma[4]	75,254 (5.4)	52,958 (8.1)	22,296 (3.0)	<0.001
Substance use disorder	597,309 (38.0)	376,594 (56.5)	220,715 (24.4)	<0.001
Traumatic brain injury	15,097 (1.0)	12,092 (1.8)	3,005 (0.3)	<0.001
Sexually transmitted infections[10]				
Chlamydia[11]	22,937 (1.5)	9,515 (1.4)	13,422 (1.5)	0.004
Genital HSV	33,958 (2.2)	13,961 (2.1)	19,997 (2.2)	<0.001
Gonorrhea[11]	5,080 (0.3)	2,107 (0.3)	2,973 (0.3)	0.179
HBV	2,864 (0.2)	1,360 (0.2)	1,504 (0.2)	<0.001
HCV	9,253 (0.6)	2,621 (0.4)	6,632 (0.7)	<0.001
HIV	3,949 (0.3)	1,902 (0.3)	2,047 (0.2)	<0.001
HPV	30,888 (2.0)	13,387 (2.0)	17,501 (1.9)	0.001
Syphilis[11]	5,126 (0.3)	2,102 (0.3)	3,024 (0.3)	0.042

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IQR, interquartile range; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; USD, United States dollar; VA, United States Department of Veterans Affairs. [1]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, and censored on 31 December 2022. [2]Percentages may not add to 100% due to rounding up to the nearest tenth. [3]Fisher's exact and χ^2 tests for categorical data; Mann-Whitney-Wilcoxon tests for continuous data. [4]Missing [PTSD, no PTSD]: sex (n=0 [0.0%]; n=6 [0.0%]), race/ethnicity (n=60,750 [9.1%]; n=146,874 [16.2%]), marital status (n=14,074 [2.1%]; n=81,226 [9.0%]), education (n=167,637 [25.2%]; n=212,873 [23.5%]), household income (n=21,263 [3.2%]; n=30,214 [3.3%]), branch (n=3,937 [0.6%]; n=8,896 [1.0%]), component (n=4,246 [0.6%]; n=9,403 [1.0%]), rank (n=49,460 [7.4%]; n=54,462 [6.0%]), discharge character (n=14,139 [2.1%]; n=28,388 [3.1%]), military sexual trauma (n=8,041 [1.2%]; n=155,387 [17.2%]). [5]Last updated on 31 December 2019. [6]College/university includes graduate school. [7]Last updated at military separation. [8]Not mutually exclusive categories. [9]Meets combat Veteran eligibility requirements. [10]Update: Sexually transmitted infections, active component, U.S. Armed Forces, 2011-2019. *MSMR*. 2020;27(3):2-11. [11]Initial (not recurrent) infections tabulated.

Table 2. Adjusted associations between PTSD and STIs among OEF/OIF/OND Veterans (2001-2022, n=1,570,654).

	PTSD	No PTSD		
STIs[1]	**Adjusted IR[2,3] (95% CI), per 10,000 PY**	**Adjusted IR[2,3] (95% CI), per 10,000 PY**	**Adjusted IRR[2,3] (95% CI)**	**P-value**
Chlamydia	5.81 (5.69, 5.93)	4.82 (4.73, 4.91)	1.20 (1.17, 1.24)	<0.001
Number of deployments				0.014
1	6.05 (5.89, 6.21)	4.96 (4.83, 5.09)	1.22 (1.18, 1.26)	<0.001
≥2	5.38 (5.17, 5.60)	4.06 (3.88, 4.24)	1.33 (1.29, 1.37)	<0.001
Combat exposure[4]				0.032
No	5.89 (5.76, 6.02)	4.83 (4.73, 4.93)	1.22 (1.19, 1.26)	<0.001
Yes	5.38 (5.12, 5.66)	4.78 (4.55, 5.02)	1.13 (1.10, 1.17)	<0.001
Genital HSV	8.33 (8.19, 8.47)	7.64 (7.52, 7.75)	1.09 (1.07, 1.11)	<0.001
Number of deployments				0.951
1	8.54 (8.36, 8.72)	7.61 (7.45, 7.77)	1.12 (1.09, 1.15)	<0.001
≥2	8.47 (8.20, 8.74)	7.53 (7.29, 7.78)	1.12 (1.09, 1.16)	<0.001
Combat exposure[4]				<0.001
No	8.23 (8.08, 8.38)	7.42 (7.30, 7.55)	1.11 (1.08, 1.14)	<0.001
Yes	8.84 (8.50, 9.19)	8.84 (8.51, 9.17)	1.00 (0.97, 1.03)	0.926
Gonorrhea	0.76 (0.72, 0.81)	0.63 (0.59, 0.66)	1.21 (1.13, 1.31)	<0.001
Number of deployments				0.735
1	0.83 (0.77, 0.89)	0.65 (0.61, 0.70)	1.27 (1.15, 1.40)	<0.001
≥2	0.70 (0.63, 0.78)	0.53 (0.47, 0.60)	1.32 (1.20, 1.46)	<0.001
Combat exposure[4]				0.097
No	0.75 (0.70, 0.80)	0.60 (0.57, 0.64)	1.25 (1.15, 1.36)	<0.001
Yes	0.83 (0.73, 0.94)	0.78 (0.69, 0.88)	1.06 (0.98, 1.15)	0.354
HBV	0.71 (0.68, 0.75)	0.65 (0.62, 0.69)	1.09 (1.01, 1.18)	0.024
Number of deployments				0.597
1	0.69 (0.64, 0.74)	0.66 (0.61, 0.72)	1.04 (0.95, 1.15)	0.395
≥2	0.69 (0.62, 0.76)	0.63 (0.56, 0.70)	1.10 (1.00, 1.22)	0.044
Combat exposure[4]				0.192
No	0.68 (0.64, 0.72)	0.64 (0.60, 0.68)	1.07 (0.98, 1.16)	0.129
Yes	0.90 (0.80, 1.01)	0.74 (0.65, 0.85)	1.22 (1.12, 1.32)	<0.001
HCV	2.74 (2.67, 2.82)	1.62 (1.57, 1.68)	1.69 (1.62, 1.77)	<0.001
Number of deployments				0.006
1	3.24 (3.13, 3.36)	1.74 (1.67, 1.82)	1.86 (1.76, 1.97)	<0.001
≥2	2.24 (2.10, 2.39)	1.41 (1.30, 1.52)	1.59 (1.50, 1.68)	<0.001
Combat exposure[4]				0.001
No	2.74 (2.66, 2.83)	1.57 (1.52, 1.63)	1.75 (1.67, 1.83)	<0.001
Yes	2.76 (2.57, 2.95)	1.91 (1.76, 2.08)	1.45 (1.38, 1.52)	<0.001
HIV	1.28 (1.21, 1.36)	1.18 (1.13, 1.24)	1.08 (1.02, 1.15)	0.009
Number of deployments				0.530
1	1.32 (1.23, 1.43)	1.14 (1.07, 1.22)	1.16 (1.07, 1.25)	<0.001
≥2	1.13 (1.01, 1.26)	1.02 (0.93, 1.13)	1.11 (1.02, 1.20)	0.003
Combat exposure[4]				0.072
No	1.24 (1.16, 1.33)	1.18 (1.12, 1.24)	1.06 (0.99, 1.13)	0.101
Yes	1.47 (1.32, 1.64)	1.22 (1.09, 1.37)	1.20 (1.12, 1.28)	<0.001
HPV	7.11 (7.00, 7.22)	6.92 (6.80, 7.05)	1.03 (1.00, 1.05)	0.026
Number of deployments				0.072
1	7.64 (7.48, 7.79)	7.45 (7.28, 7.62)	1.03 (1.00, 1.06)	0.096
≥2	5.97 (5.76, 6.19)	6.15 (5.92, 6.39)	0.97 (0.94, 1.00)	0.048
Combat exposure[4]				<0.001
No	6.98 (6.86, 7.10)	6.92 (6.79, 7.06)	1.01 (0.98, 1.04)	0.502
Yes	7.82 (7.53, 8.13)	6.94 (6.63, 7.26)	1.13 (1.10, 1.16)	<0.001
Syphilis	1.28 (1.22, 1.33)	1.15 (1.11, 1.20)	1.11 (1.05, 1.17)	<0.001
Number of deployments				0.984
1	1.32 (1.25, 1.39)	1.12 (1.06, 1.18)	1.18 (1.09, 1.27)	<0.001
≥2	1.23 (1.13, 1.34)	1.05 (0.96, 1.14)	1.17 (1.08, 1.26)	<0.001
Combat exposure[4]				0.284
No	1.27 (1.22, 1.33)	1.13 (1.09, 1.18)	1.12 (1.06, 1.19)	<0.001
Yes	1.29 (1.16, 1.43)	1.25 (1.13, 1.37)	1.03 (0.97, 1.09)	0.892
All STIs	24.85 (24.62, 25.08)	22.54 (22.34, 22.74)	1.10 (1.09, 1.12)	<0.001
Number of deployments				0.294
1	26.19 (25.88, 26.51)	23.19 (22.92, 23.47)	1.13 (1.11, 1.15)	<0.001
≥2	23.40 (22.96, 23.85)	20.38 (19.99, 20.78)	1.15 (1.13, 1.17)	<0.001
Combat exposure[4]				<0.001
No	24.79 (24.53, 25.05)	22.16 (21.95, 22.38)	1.12 (1.10, 1.13)	<0.001
Yes	25.18 (24.62, 25.77)	24.68 (24.14, 25.22)	1.02 (1.00, 1.03)	0.032

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; IR, incidence rate; IRR, incidence rate ratio; MST, military sexual trauma; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; PY, person-year; STI, sexually transmitted infection; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs. [1]Update: Sexually transmitted infections, active component, U.S. Armed Forces, 2011-2019. *MSMR*. 2020;27(3):2-11. [2]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, and censored on 31 December 2022. [3]Marginal structural Poisson models with generalized estimating equations, as appropriate, with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at military separation, sex, race/ethnicity, marital status, education, income, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. [4]Meets VA combat Veteran eligibility requirements.

Supplemental Table 1. Diagnostic codes used to define variables of interest.

Variables	ICD-9 codes	ICD-10 codes
Anxiety disorder[1]	300.00, 300.02, 300.09	F41.1, F41.3, F41.8, F41.9
Chlamydia[2]	099.41, 099.5	A56
Depressive disorder[1]	296.3	F33.1 – F33.9
Genital herpes simplex virus[2]	054.1	A60
Gonorrhea[2]	098	A54
Hepatitis B virus[2]	070.20, 070.22, 070.30, 070.32	B18.0, B18.1, B19.10
Hepatitis C virus[2]	070.41, 070.44, 070.51, 070.54, 070.70, 070.71	B18.2, B19.20
High-risk sexual behavior[1]	V69.2	Z72.51 – Z72.53
Human immunodeficiency virus[2]	042, V08	B20, Z21
Human papillomavirus[2]	078.11, 079.4, 795.05, 795.09, 795.15, 796.75, 796.79	A63.0, R85.81, R85.82, R87.81, R87.810, R87.811, R87.82, R87.820, R87.821, B97.7
Posttraumatic stress disorder[1]	309.81	F43.12
Substance use disorder[1]	291, 292, 303 – 305	F10 – F19, F55
Syphilis[2]	091 – 096, 097.0, 097.1, 097.9	A51 (excluding A51.31), A52, A53.0, A53.9
Traumatic brain injury[1]	800.0 – 801.9, 803.0 – 804.9, 805.1 – 805.5, 805.9, 851.0 – 854.1, 959.01	S02.0, S02.1, S02.8, S02.91, S04.02 – S04.04, S06.0, S06.1 –S06.9, S07.1, T74.4

CMS, Centers for Medicare and Medicaid Services; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; NCI, National Cancer Institute. [1]NCI Comorbidity Index and CMS Chronic Condition Warehouse. [2]Update: Sexually transmitted infections, active component, U.S. Armed Forces, 2011-2019. *MSMR*. 2020;27(3):2-11.

Supplemental Table 2. Crude associations between PTSD and STIs among OEF/OIF/OND Veterans (2001-2022, n=1,570,654).

	PTSD	No PTSD		
STIs[1]	**Crude IR[2,3] (95% CI), per 10,000 PY**	**Crude IR[2,3] (95% CI), per 10,000 PY**	**Crude IRR[2,3] (95% CI)**	**P-value**
Chlamydia	6.19 (6.07, 6.32)	4.48 (4.40, 4.56)	1.38 (1.35, 1.42)	<0.001
Number of deployments				0.031
1	6.47 (6.31, 6.64)	4.65 (4.53, 4.77)	1.39 (1.35, 1.44)	<0.001
≥2	5.75 (5.53, 5.99)	3.84 (3.68, 4.01)	1.50 (1.46, 1.55)	<0.001
Combat exposure[4]				0.035
No	6.26 (6.13, 6.40)	4.47 (4.38, 4.57)	1.40 (1.36, 1.44)	<0.001
Yes	5.84 (5.56, 6.15)	4.51 (4.30, 4.74)	1.29 (1.25, 1.33)	<0.001
Genital HSV	8.87 (8.72, 9.02)	7.01 (6.91, 7.12)	1.27 (1.24, 1.29)	<0.001
Number of deployments				0.686
1	9.13 (8.94, 9.32)	7.05 (6.91, 7.19)	1.30 (1.26, 1.33)	<0.001
≥2	9.02 (8.74, 9.32)	7.04 (6.82, 7.27)	1.28 (1.24, 1.31)	<0.001
Combat exposure[4]				<0.001
No	8.75 (8.59, 8.91)	6.80 (6.69, 6.92)	1.29 (1.26, 1.32)	<0.001
Yes	9.47 (9.11, 9.85)	8.21 (7.91, 8.51)	1.15 (1.12, 1.18)	<0.001
Gonorrhea	0.83 (0.79, 0.88)	0.57 (0.54, 0.60)	1.45 (1.35, 1.56)	<0.001
Number of deployments				0.887
1	0.92 (0.86, 0.98)	0.60 (0.57, 0.65)	1.52 (1.38, 1.67)	<0.001
≥2	0.76 (0.68, 0.85)	0.49 (0.44, 0.55)	1.55 (1.41, 1.70)	<0.001
Combat exposure[4]				0.063
No	0.82 (0.77, 0.87)	0.55 (0.52, 0.58)	1.50 (1.38, 1.62)	<0.001
Yes	0.90 (0.79, 1.02)	0.72 (0.64, 0.81)	1.25 (1.12, 1.39)	<0.001
HBV	0.70 (0.66, 0.74)	0.65 (0.61, 0.68)	1.08 (1.00, 1.16)	0.043
Number of deployments				0.403
1	0.71 (0.66, 0.77)	0.63 (0.59, 0.68)	1.12 (1.02, 1.24)	0.020
≥2	0.67 (0.59, 0.75)	0.64 (0.57, 0.71)	1.05 (0.96, 1.16)	0.693
Combat exposure[4]				0.162
No	0.68 (0.63, 0.72)	0.61 (0.58, 0.65)	1.10 (1.02, 1.20)	0.020
Yes	0.80 (0.70, 0.92)	0.83 (0.74, 0.93)	0.96 (0.89, 1.04)	0.784
HCV	2.92 (2.84, 3.00)	1.48 (1.43, 1.53)	1.97 (1.89, 2.06)	<0.001
Number of deployments				0.004
1	3.45 (3.33, 3.57)	1.61 (1.54, 1.68)	2.15 (2.03, 2.26)	<0.001
≥2	2.36 (2.22, 2.52)	1.30 (1.20, 1.40)	1.82 (1.72, 1.91)	<0.001
Combat exposure[4]				<0.001
No	2.92 (2.83, 3.01)	1.43 (1.38, 1.48)	2.04 (1.94, 2.14)	<0.001
Yes	2.93 (2.73, 3.14)	1.75 (1.62, 1.90)	1.67 (1.59, 1.75)	<0.001
HIV	1.33 (1.27, 1.40)	1.00 (0.96, 1.04)	1.33 (1.25, 1.41)	<0.001
Number of deployments				0.358
1	1.39 (1.30, 1.47)	0.98 (0.93, 1.03)	1.42 (1.31, 1.53)	<0.001
≥2	1.21 (1.10, 1.33)	0.92 (0.84, 1.00)	1.32 (1.22, 1.42)	<0.001
Combat exposure[4]				0.055
No	1.28 (1.21, 1.35)	0.99 (0.95, 1.03)	1.29 (1.21, 1.38)	<0.001
Yes	1.60 (1.44, 1.78)	1.07 (0.97, 1.18)	1.50 (1.35, 1.63)	<0.001
HPV	7.43 (7.30, 7.56)	6.51 (6.41, 6.61)	1.14 (1.11, 1.17)	<0.001
Number of deployments				0.206
1	8.03 (7.85, 8.21)	7.06 (6.92, 7.20)	1.14 (1.10, 1.17)	<0.001
≥2	6.58 (6.34, 6.84)	5.57 (5.38, 5.77)	1.18 (1.14, 1.21)	<0.001
Combat exposure[4]				<0.001
No	7.42 (7.28, 7.57)	6.38 (6.27, 6.49)	1.16 (1.13, 1.19)	<0.001
Yes	7.45 (7.13, 7.79)	7.26 (6.99, 7.54)	1.03 (1.00, 1.06)	0.012
Syphilis	1.37 (1.32, 1.43)	1.06 (1.02, 1.10)	1.29 (1.22, 1.37)	<0.001
Number of deployments				0.779
1	1.42 (1.35, 1.50)	1.03 (0.98, 1.09)	1.38 (1.28, 1.48)	<0.001
≥2	1.32 (1.22, 1.43)	0.98 (0.90, 1.06)	1.35 (1.25, 1.45)	<0.001
Combat exposure[4]				0.284
No	1.37 (1.31, 1.43)	1.04 (1.00, 1.09)	1.31 (1.23, 1.39)	<0.001
Yes	1.39 (1.26, 1.54)	1.15 (1.05, 1.26)	1.21 (1.14, 1.28)	<0.001
All STIs	26.39 (26.14, 26.64)	20.73 (20.55, 20.91)	1.27 (1.26, 1.29)	<0.001
Number of deployments				0.751
1	27.93 (27.60, 28.27)	21.56 (21.31, 21.81)	1.30 (1.28, 1.32)	<0.001
≥2	24.87 (24.40, 25.35)	19.10 (18.74, 19.47)	1.30 (1.28, 1.33)	<0.001
Combat exposure[4]				<0.001
No	26.29 (26.02, 26.57)	20.34 (20.14, 20.53)	1.29 (1.28, 1.31)	<0.001
Yes	26.93 (26.32, 27.55)	23.02 (22.53, 23.52)	1.17 (1.16, 1.19)	<0.001

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IPCW, inverse probability of censoring weighting; IR, incidence rate; IRR, incidence rate ratio; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; PY, person-year; STI, sexually transmitted infection; VA, United States Department of Veterans Affairs. [1]Update: Sexually transmitted infections, active component, U.S. Armed Forces, 2011-2019. *MSMR*. 2020;27(3):2-11. [2]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, and censored on 31 December 2022. [3]Marginal structural Poisson models with generalized estimating equations, as appropriate, with a time-dependent exposure (PTSD), adjusted for informative censoring by IPCW. [4]Meets VA combat Veteran eligibility requirements.

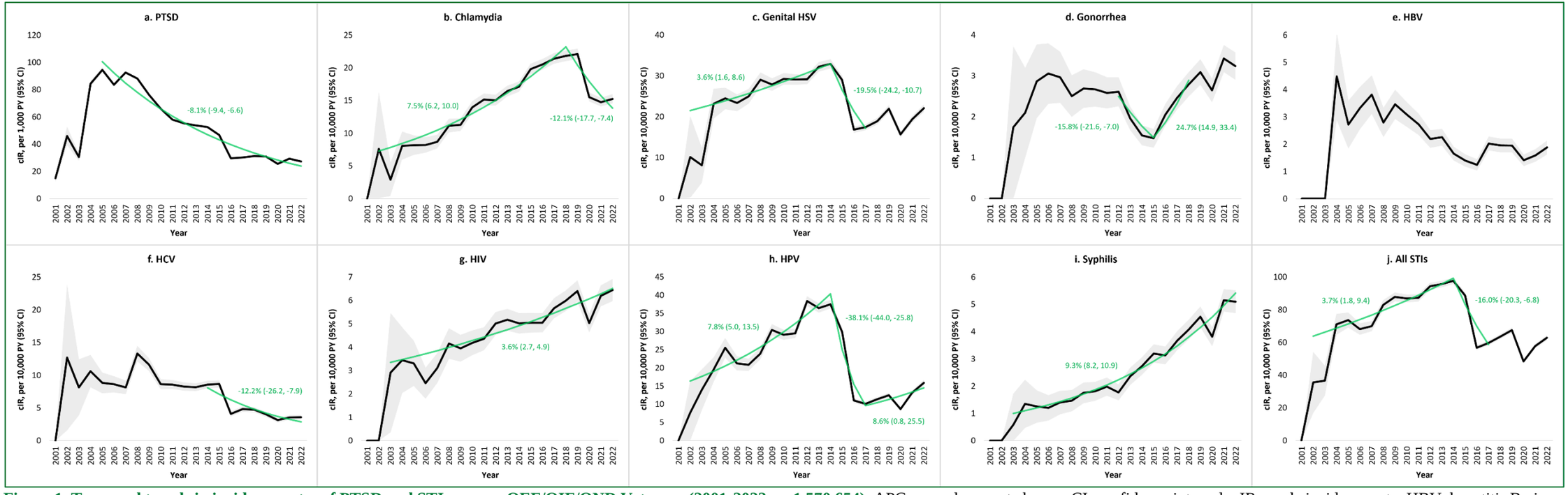


Figure 1. Temporal trends in incidence rates of PTSD and STIs among OEF/OIF/OND Veterans (2001-2022, n=1,570,654). APC, annual percent change; CI, confidence interval; cIR, crude incidence rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; PY, person-year; STI, sexually transmitted infection; VA, United States Department of Veterans Affairs. Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, and censored on 31 December 2022. Joinpoint regression models were fitted to estimate APCs during periods when significant changes in rates were observed, as denoted by the green lines. STIs coding algorithm from Update: Sexually transmitted infections, active component, U.S. Armed Forces, 2011-2019. *MSMR*. 2020;27(3):2-11.

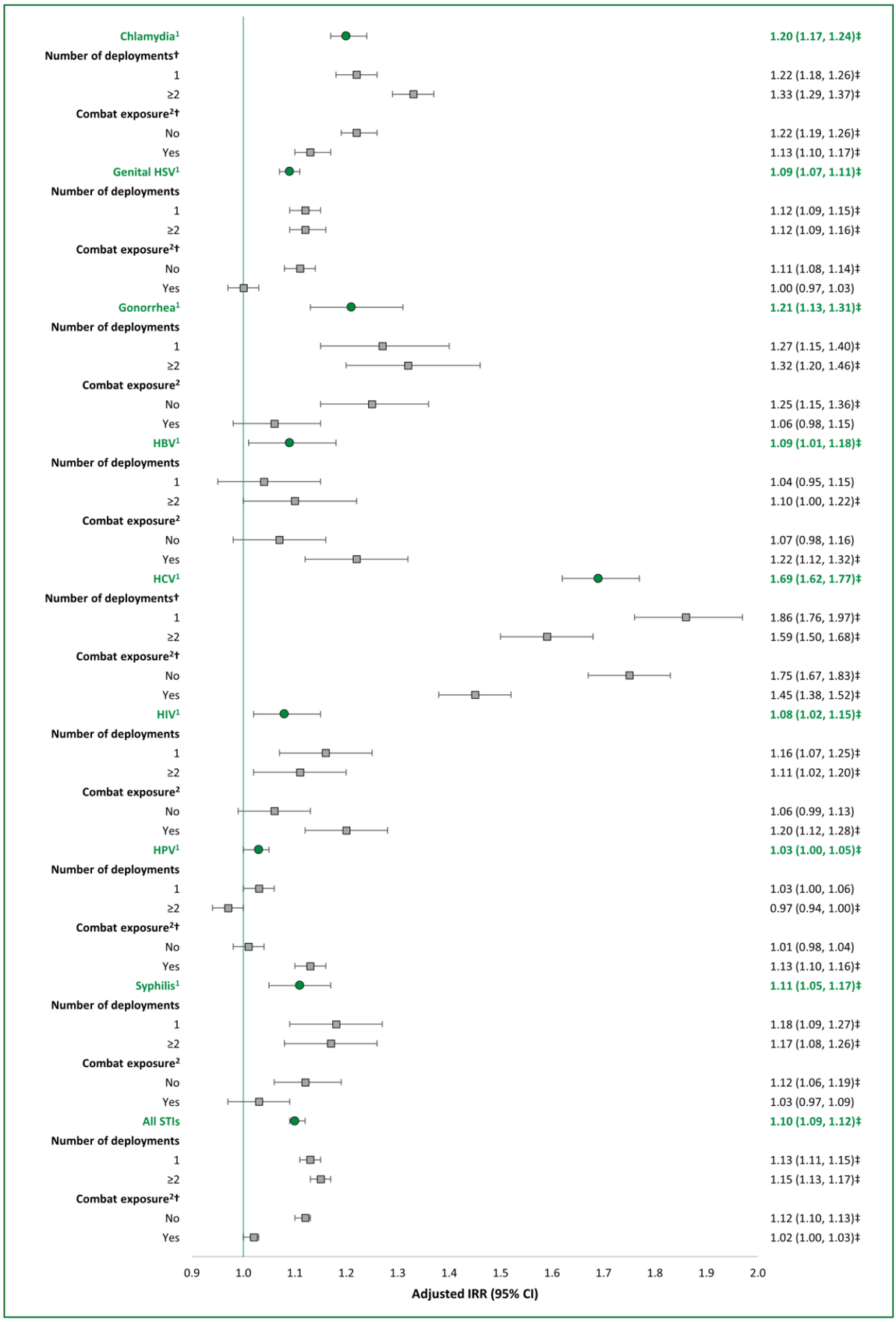


Figure 2. Adjusted associations between PTSD and STIs among OEF/OIF/OND Veterans (2001-2022, n=1,570,654). CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; MST, military sexual trauma; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; STI, sexually transmitted infection; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs. Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, and censored on 31 December 2022. Marginal structural Poisson models with generalized estimating equations, as appropriate, with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at military separation, sex, race/ethnicity, marital status, education, income, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. [1]Update: Sexually transmitted infections, active component, U.S. Armed Forces, 2011-2019. *MSMR*. 2020;27(3):2-11. [2]Meets VA combat Veteran eligibility requirements. †Wald test for interaction statistically significant at α=0.05. ‡Adjusted IRR statistically significant at α=0.05.

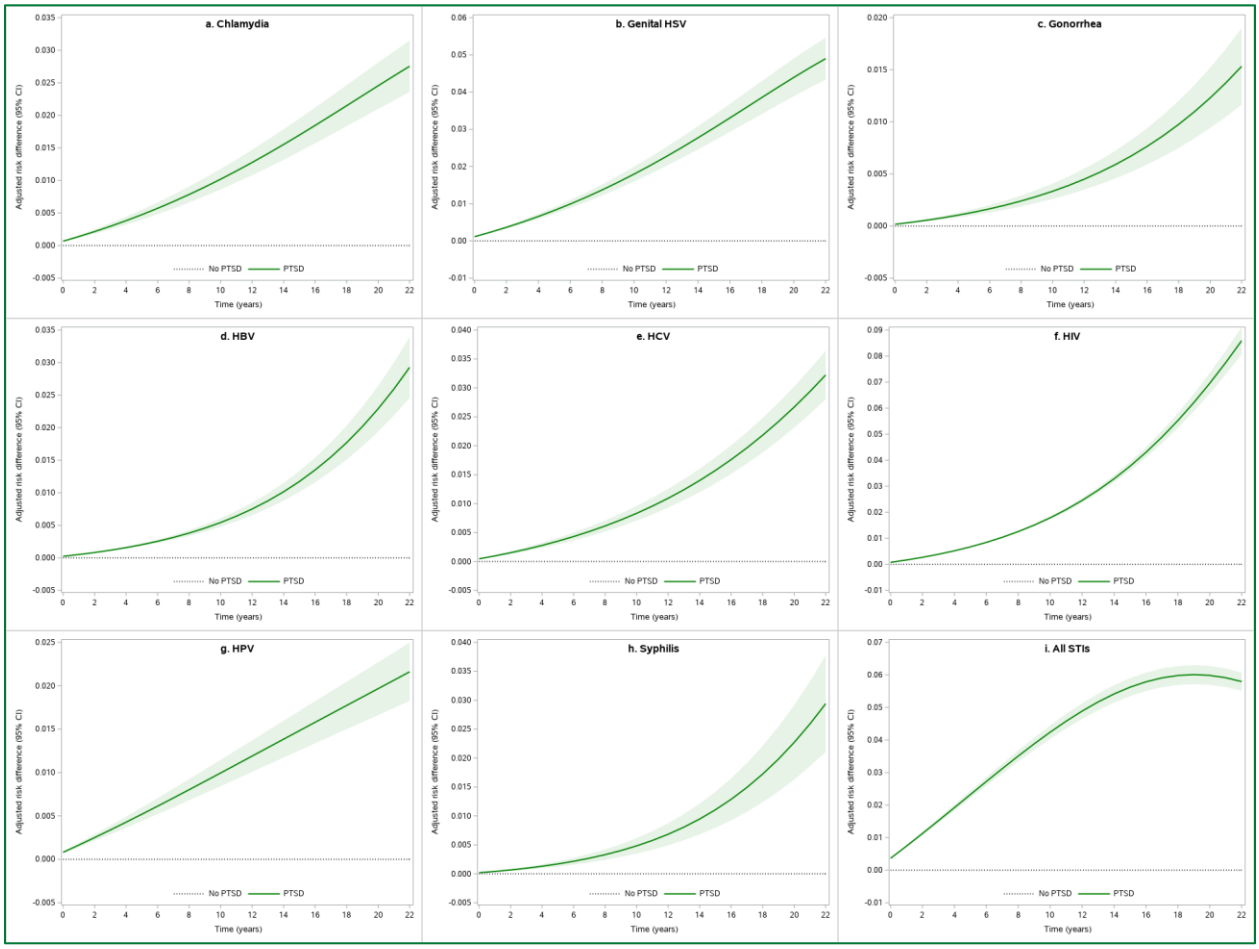
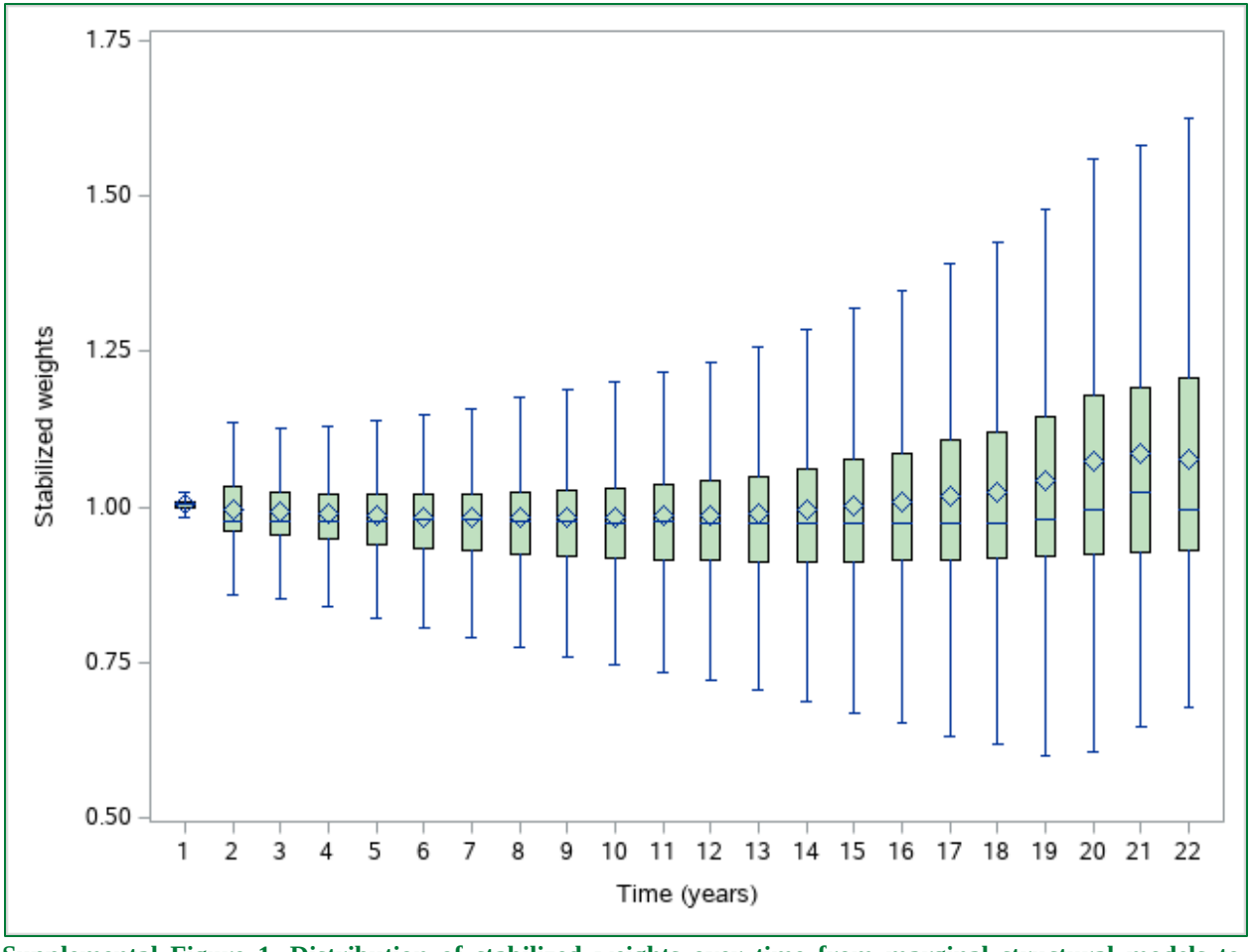


Figure 3. Adjusted risk differences for STIs between those diagnosed with and without PTSD among OEF/OIF/OND Veterans (2001-2022, n=1,570,654). Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, and censored on 31 December 2022. Reference group defined as those without PTSD. Marginal structural Poisson models with generalized estimating equations, as appropriate, with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at military separation, sex, race/ethnicity, marital status, education, income, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. STI definitions from Update: Sexually transmitted infections, active component, U.S. Armed Forces, 2011-2019. *MSMR*. 2020;27(3):2-11. CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; MST, military sexual trauma; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; STI, sexually transmitted infection; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs.



Supplemental Figure 1. Distribution of stabilized weights over time from marginal structural models to estimate the effects of PTSD on STIs among OEF/OIF/OND Veterans (2001-2022, n=1,570,654). Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, and censored on 31 December 2022. Marginal structural Poisson models with generalized estimating equations, as appropriate, with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at military separation, sex, race/ethnicity, marital status, education, income, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; MST, military sexual trauma; Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; STI, sexually transmitted infection; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs.

Chapter 4: PTSD and its associations with ART among Veterans with HIV

EMORY | ROLLINS SCHOOL OF PUBLIC HEALTH

Date: 9 October 2023

To: Jay A. Levy, MD
Editor-in-Chief, ***AIDS***

Subject: Manuscript Submission

Dear Editors,

Enclosed you will find our paper entitled, "Posttraumatic Stress Disorder and its Associations with Antiretroviral Therapy among Veterans with HIV." We kindly ask that you consider our manuscript for publication in your journal.

Our study includes all Veterans with HIV who deployed to Iraq and Afghanistan and who receive care in the Department of Veterans Affairs. We aimed to estimate the overall and time-varying associations between PTSD and ART non-adherence, modifications, and treatment failure, and measure effect modification by number of deployments and combat exposure. We found PTSD increased the risk of ART non-adherence and the rate of ART modifications, and that these associations seemed most pronounced within the first decade post-PTSD-diagnosis. It is important that all providers recognize the role PTSD may play in ART non-adherence and its downstream effects on treatment failure and clinical decline. Due to the syndemic nature of HIV and PTSD, it is recommended that providers who work with people with HIV adopt a trauma-informed model of HIV care, refer patients to treatment advocacy programs and services when indicated, and screen Veterans for PTSD so that their trauma history can help guide medical decisions and treatment.

We believe that this manuscript is appropriate for your journal and will be of interest to your readers. This work is original, has not been published elsewhere, and is not under concurrent consideration elsewhere. Thank you for your consideration of this manuscript.

Very respectfully,

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Abstract

Objectives: Posttraumatic stress disorder (PTSD) may affect antiretroviral therapy (ART) response and clinical outcomes for Veterans with HIV (VWH) receiving care in the Department of Veterans Affairs (VA). Objectives are to (1) estimate the associations between PTSD and ART non-adherence, modifications, and failure; (2) measure effect modification by number of deployments and combat exposure; and (3) examine how these associations vary over time.

Design: In this prospective cohort study of all VWH on ART who deployed to Iraq and Afghanistan and receive care in the VA (n=3,206), patients entered at ART initiation and were censored in December 2022, totaling 22,261 person-years of follow-up.

Methods: Marginal structural log-binomial and Poisson models were fitted with a time-dependent exposure, adjusted for time-independent and time-dependent confounding and informative censoring, to estimate the associations between PTSD and ART non-adherence, modifications, and failure. Marginal structural shared frailty models were fitted to examine time-varying associations.

Results: PTSD increased the risk (adjusted risk ratio, 95% CI) of ART non-adherence by 6% (1.06 [1.00, 1.13]) and the rate (adjusted incidence rate ratio, 95% CI) of ART modifications by 38% (1.38 [1.19, 1.58]). Multiple deployments amplified the association with ART non-adherence by 14%; combat exposure did not modify any association examined. The association with ART modifications increased during the first decade post-PTSD-diagnosis but subsequently stabilized.

Conclusions: PTSD increased ART non-adherence and ART modifications. Providers should screen for PTSD so that it can help guide medical decisions and treatment; particular attention should be paid to Veterans with multiple combat deployments.

Introduction

With the advent of combination antiretroviral therapy (ART), HIV disease has become more manageable and chronic, improving the life expectancy and quality of life for all people with HIV (PWH).[1] However, no matter how forgiving newer regimens may be, ART still requires moderately high levels of adherence; such that, non-adherence rates of even 10-15% can dramatically impact its efficacy.[2] Mental health has been shown to play a pivotal role in ART adherence, and posttraumatic stress disorder (PTSD) has been shown to be among the strongest and most consistent predictors of non-adherence.[3-5] Ninety-five percent of PWH report at least one severe traumatic stressor,[6, 7] and more than half meet the criteria for PTSD.[4, 6, 8] PTSD symptoms including avoidant behaviors, intrusive thoughts, and general hyperarousal can place demands on an individual's cognitive capacity, thus affecting their ability to remember medication instructions, dosing schedules, and dietary requirements– all important facets for optimal ART efficacy.[3, 9] Alternatively, symptoms of depression (e.g., loss of interest and motivation, memory deficits, disrupted sleep) and substance use (e.g., impaired functioning, elevated stress) may also negatively affect ART adherence[3, 4]; however, PTSD has been shown to predict non-adherence independent of depression and substance use.[5] Some evidence suggests there may also be a dose-response: each traumatic stressor has been shown to increase the risk for ART non-adherence by 11%.[10]

Suboptimal ART adherence may result in other downstream adverse effects, including diminished viral suppression, poorer immunologic functioning, greater clinical decline, increased viral mutations, and therefore emergence of viral resistance, thus perhaps necessitating the need for modifications to the ART regimen.[10-16] Here too, there appears to be a dose-response: each traumatic stressor has been shown to increase the risk for virologic failure four-fold.[17] Although the scientific body of evidence on PTSD and its association with ART non-adherence is fairly robust (yet sometimes conflicting),[2-5, 9, 11, 17-31] these studies are often limited in their causal inference due to their study designs and analytical methods. Moreover, few known studies have examined PTSD and its association with one or more definitions of treatment failure,[5, 18, 22, 26, 28] and none have examined its association with ART modifications; studies examining these associations among active duty military or Veterans with HIV (VWH), populations in which PTSD is highly prevalent are also lacking. The recent wars in Iraq and Afghanistan – Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) – offer a unique opportunity to examine the associations between PTSD and ART in VWH.

One-quarter of all those who deployed in support of OEF/OIF/OND meet the criteria for PTSD.[32-34] One possible index traumatic stressor may have been the increased operational tempo, particularly intense and repeated deployments, that was characteristic during the time. It is estimated that 57%, 27%, and 16% of all OEF/OIF/OND Veterans deployed one, two, and three or more times, respectively.[35] Another possible index traumatic stressor may have been combat exposure. Sixty-four percent of all OEF/OIF/OND Veterans reported any combat exposure, of whom 49% witnessed someone who was wounded or killed, 49% felt in danger of being killed, and 17% discharged their weapon.[36] Combat exposure during deployment has been shown to increase the risk for PTSD three-fold compared to non-deployment.[37] Given the evidence of traumatic stressors,[10, 17] it is hypothesized that multiple deployments and combat exposure modifies the association between PTSD and ART in VWH.

The objective of this current work is to fill in this knowledge gap for VWH and to inform the care of PWH more broadly – by (1) estimating the overall associations between PTSD and

ART non-adherence, modifications, and treatment failure (virologic, immunologic, and clinical); (2) measuring effect modification by number of deployments and combat exposure; and (3) examining how these associations vary over time among all OEF/OIF/OND VWH on ART who receive care in the Department of Veterans Affairs (VA). Expanded knowledge may help policymakers anticipate the potential long-term negative health consequences of war for VWH, the risk profiles of those most vulnerable, and how to best attenuate those risks by supporting preventive measures.[38] It may also enable providers to better identify those patients at highest risk for ART non-adherence; mitigate this risk by referring patients to treatment advocacy programs and services; modify ART regimens to improve adherence, reduce viral resistance, and prevent treatment failure; and inform other medical decisions and treatment among PWH.[39]

Methods

Study population

All U.S. Veterans who have ever (1) been deployed in support of OEF (7 October 2001 – 28 December 2014), OIF (20 March 2003 – 31 August 2010), and/or OND (1 September 2010 – 15 December 2011); (2) received care at the VA; (3) been diagnosed with HIV; and (4) initiated ART prior to 31 December 2020 were included in this study. Patients entered the study at ART initiation and were censored (1) at death, if recorded; (2) at the date of their last ART refill if they had not had a refill after 31 December 2020 (considered lost-to-follow-up [LTFU]); or (3) 31 December 2022 if the date of their last ART refill occurred after 31 December 2020.

Data sources

Datasets were generated and analyzed within the VA Informatics and Computing Infrastructure (VINCI), a secure, central analytic platform that hosts suites of databases integrated from select national VA data sources, including those used here – namely, the Corporate Data Warehouse (CDW), the Department of Defense (DoD)-VA Informatics and Computing Infrastructure (DaVINCI), and the U.S. Veterans Eligibility Trends and Statistics (USVETS) databases.[40] CDW is a repository of over 20 million unique patient-level electronic health records (EHR) aggregated from across the VA's national healthcare delivery system.[41] DaVINCI is built on existing data infrastructures – the Health Services Data Warehouse (HSDW) and the Military Health System Data Repository (MDR) on the DoD side and VINCI, which largely draws from the CDW, on the VA side – and provides a consolidated view of EHR for over 4 million unique Veterans during and after their military service.[42] The final data source was USVETS, which combines data from the VA, DoD, and commercial sources and contains data such as utilization of VA services and benefits, military history, geography, demographics, and socioeconomic factors for nearly 40 million Veterans.[43]

Definitions

International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and -10) codes were used to define the study population (HIV),[44] exposure (PTSD),[45] and mental health history (anxiety disorder, depressive disorder, high-risk sexual behavior, military sexual trauma [MST], substance use disorder [SUD], and traumatic brain injury [TBI]). ART non-adherence was

operationalized using the proportion of days covered (PDC) metric, which was calculated annually as the number of nonzero cabinet supply days divided by the number of days of observation.[46] The PDC metric was then dichotomized at 90%, the threshold necessary for ART efficacy.[47] ART modifications were defined as the removal, addition, or switch of an antiretroviral (ARV) class from the previous ART regimen; within class substitutions were not counted.[13] Treatment failure was defined using World Health Organization (WHO)[48] and Department of Health and Human Services (DHHS)[49] guidelines. Virologic failure was defined as an HIV viral load ≥200 copies/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART.[48, 49] Immunologic failure was defined as a CD4 count less than at baseline (≤6 months after HIV diagnosis) or CD4 counts ≤100 cells/μL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART.[48] Clinical failure was defined as a new or recurrent AIDS-defining illness (ADI) after ≥6 months on ART.[48, 50] The National Cancer Institute (NCI) Comorbidity Index and the Centers for Medicare and Medicaid Services (CMS) Chronic Condition Warehouse coding algorithms were used to define each mental health disorder (Supplemental Table 1a),[51-53] and Centers for Disease Control and Prevention (CDC) coding algorithms were used to define each ADI (Supplemental Table 1b).[49, 50] Combat exposure was defined as having met the combat Veteran VA eligibility requirements.[54]

Descriptive analyses

Descriptive analyses were performed to characterize and compare patients who were and were not ever diagnosed with PTSD by socio-demographics (age at HIV diagnosis, sex, race/ethnicity, marital status, educational attainment, and household income), military history (branch, component, rank/grade, length of service, occupation, number of deployments, combat exposure, in-theater injuries, and discharge character), HIV clinical history (ART era of initiation, time to ART initiation, first [≤6 months after HIV diagnosis], nadir, and last [≤6 months before censorship] CD4 counts; and first [≤6 months after HIV diagnosis] and last [≤6 months before censorship] HIV viral loads), and mental health history. Frequencies of specific ADIs and ART modifications were also compared between patients who were and were not ever diagnosed with PTSD. Fisher's exact tests or chi-square tests for categorical data and Mann-Whitney-Wilcoxon tests for continuous data were performed as appropriate.

Inferential analyses

Marginal structural models (MSM) were fitted for each outcome of interest with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, sex, race/ethnicity, marital status, educational attainment, household income, MST, TBI, and ART era of initiation) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, and SUD).[55] To adjust for both time-dependent confounding and informative censoring, inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCW) were estimated by weighted pooled logistic regression models and used to calculate the final stabilized weights.[55] Final stabilized weights for each outcome of interest were aggregated by one-year increments and their distributions were examined.

Models were fitted to their appropriate distributions based on how the outcomes of interest were measured, and the generalized estimating equations (GEE) procedure was performed to account for within-subject correlation of recurrent events. Specifically, marginal structural log-

binomial[56] and Poisson[57] models with GEE were fitted to estimate adjusted risk ratios (aRR) for the overall association between PTSD and ART non-adherence, and to estimate adjusted incidence rate ratios (aIRR) for the overall associations between PTSD and ART modifications and treatment failure, respectively. Further, marginal structural shared frailty models[58] – which includes a random effect, called the frailty, to account for within-subject correlation of recurrent events – were fitted to estimate adjusted risk differences (aRD) of the association between PTSD and each outcome of interest (except ART non-adherence) over time, under the hypothetical of always versus never exposed.[55] All analyses were performed under three scenarios: (1) no effect modification, (2) effect modification by number of deployments, and (3) effect modification by combat exposure. Wald tests were used to assess for interaction. Multiple imputation was performed for each outcome of interest to address missingness among all time-independent confounders (except MST, TBI, and ART era of initiation) using the Markov Chain Monte Carlo (MCMC) approach.

Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC), and the %MSM SAS macro (CAUSALab, Harvard University, Boston, MA) was employed to calculate all stabilized weights and was modified to fit marginal structural shared frailty models.[55] Probability values <0.05 were considered statistically significant. All work was conducted in accordance with the Declaration of Helsinki. The study was approved by the Emory University Institutional Review Board and the Atlanta VA Medical Center Research and Development Committee. A waiver of consent was obtained for this analysis.

Results

Of the 1,570,654 OEF/OIF/OND Veterans enrolled in the VA, 3,949 (0.3%) were diagnosed with HIV prior to 31 December 2020; of whom, 3,206 (81.2%) had initiated ART, contributing a total of 22,261 person-years (PY, mean [standard deviation, SD] = 6.9 [3.8] PY). Patients with PTSD (n=1,351, 42.1%) contributed 9,370 PY (mean [SD] = 6.9 [3.7] PY); whereas those without PTSD (n=1,855, 57.9%) contributed 12,891 PY (mean [SD] = 6.9 [3.9] PY). Of the 3,206 patients in the analytic sample, 138 died (4.3%), 229 (7.1%) were LTFU, and 2,839 (88.6%) survived past the study period.

Characteristics

Most patients were male (97.4%), Black (50.4%), never married (51.1%), high school educated (70.0%), and had an annual household income of USD $40,000-74,999 (36.7%); the median (interquartile range [IQR]) age at HIV diagnosis was 31.7 (9.5) years (Table 1). Regarding their military history, most patients served in the Army (50.0%) and on active-duty (78.3%), were ranked as enlisted E5-E9 (53.8%), worked in service/supply (56.3%), deployed only once (78.6%), were unexposed to combat (76.8%), never sustained combat (97.3%) or noncombat (75.9%) injuries, and were honorably discharged (97.0%); the median (IQR) length of service was 6.6 (7.8) years. Patients with PTSD were significantly different only by age at HIV diagnosis and marital status in their sociodemographics, and only by time to ART initiation, nadir CD4 count, and first HIV viral load in their HIV clinical history compared to those without PTSD. However, patients with PTSD were significantly different across all factors of military history assessed and all mental health disorders examined compared to those without PTSD.

ART non-adherence

PTSD significantly increased the overall risk (aRR [95% CI]) of ART non-adherence by 6% (1.06 [1.00, 1.13]; 44.3% [42.2, 46.5] vs. 41.7% [40.4, 43.0]). Number of deployments, but not combat exposure, significantly modified this association; whereby the overall association between PTSD and ART non-adherence increased 14% among those who had deployed ≥2 times compared to those who had only deployed once (1.19 [1.06, 1.34] vs. 1.05 [0.98, 1.12]; Table 2, Figure 1).

ART modifications

PTSD significantly increased the overall rate (aIRR [95% CI]) of ART modifications by 38% (1.38 [1.19, 1.58]; 12.0 [10.6, 13.4] vs. 8.7 [7.7, 10.0] per 1,000 PY). Neither number of deployments nor combat exposure significantly modified this association (Table 2, Figure 1). Patients with PTSD were significantly more likely to have had attachment inhibitors and pharmacokinetic enhancers removed; CCR5 antagonists or protease inhibitors (PI) added and removed; and were less likely to have had non-nucleoside reverse transcriptase inhibitors (NNRTI) added to their ART regimens than patients without PTSD (Supplemental Table 2). This association between PTSD and ART modifications gradually increased during the first decade post-PTSD-diagnosis but subsequently stabilized and remained statistically significant (Figure 2a).

Treatment failure

PTSD increased the overall rates (aIRR [95% CI]) of virologic failure by 14% (1.14 [0.87, 1.49]; 5.2 [4.1, 6.5] vs. 4.6 [3.8, 5.4] per 1,000 PY), immunologic failure by 5% (1.05 [0.49, 2.26]; 0.7 [0.3, 1.2] vs. 0.6 [0.4, 1.0] per 1,000 PY), and clinical failure by 89% (1.89 [0.88, 4.06]; 3.0 [2.2, 4.0] vs. 1.6 [1.1, 3.2] per 1,000 PY), but none of these were statistically significant. Moreover, neither number of deployments nor combat exposure modified these associations (Table 2, Figure 1). Regarding specific ADIs, patients with PTSD were significantly more likely to have been diagnosed with candidiasis (esophageal), cryptococcosis (extrapulmonary), lymphoma (immunoblastic), mycobacterium avium complex or mycobacterium kansaii (disseminated or extrapulmonary), mycobacterium tuberculosis (any site, pulmonary or extrapulmonary), and progressive multifocal leukoencephalopathy than those without PTSD. However, patients with PTSD were significantly less likely to have been diagnosed with Kaposi's sarcoma, *Pneumocystis jirovecii* pneumonia, or toxoplasmosis (brain) than those without PTSD (Supplemental Table 1b). These associations between PTSD and treatment failure gradually increased throughout the observation period but were never statistically significant (Figures 2b-d). Crude effect estimates and distributions of final stabilized weights over time from MSMs for each outcome of interest are described in Supplemental Table 3 and depicted in Supplemental Figure 1, respectively.

Discussion

The work presented represents one of the more comprehensive and robust analyses to estimate the associations between PTSD and ART in PWH. Results suggest PTSD significantly increased the risk of ART non-adherence and the rate of ART modifications but may have had more of an attenuated effect on treatment failure. Moreover, increased number of deployments

amplified the association between PTSD and ART non-adherence but not on ART modifications or treatment failure; combat exposure did not modify any of the associations examined. Finally, this association between PTSD and ART modifications appeared to gradually increase during the first decade post-PTSD-diagnosis but subsequently stabilized and remained statistically significant; while the associations with treatment failure increased throughout the study period but were never statistically significant.

Many of the associations observed in this study may be wholly or partly explained by the attentional and psychological alterations induced by or otherwise associated with PTSD, particularly, memory deficits and avoidance.[3, 9] PTSD may compound the memory deficits already associated with HIV infection, leading to regular ART interruptions.[9] Further, ART itself can bring back memories of HIV-associated trauma, their beliefs of illness, and their fears of death.[9] Further, PTSD has been shown to negatively affect trauma coping self-efficacy and self-control, leading to a sense of futility, impaired risk perception, and disengagement in care.[38] Biological alterations associated with PTSD may also play a role, including sympathetic overactivity, endocrinological irregularities, and modified immunologic pathways.[59] Taken together, these imbalances in various systems, both psychological and biological, produce abnormalities through a cascade of downstream mechanisms that all play crucial roles in the maintenance of homeostasis and health.[60] Such systemic imbalances may lead to difficulties in adhering to complex ART medication instructions, dosing schedules, and dietary requirements, or even increased drug intolerance and toxicity, which may all result in viral resistance, treatment failure, and the need to modify ART regimens.[9, 28]

Seventeen known studies have examined the associations between PTSD and ART for PWH.[2-5, 9, 11, 17-31] A recent meta-analysis of 12 such studies comprising 2,489 participants reported that, collectively, PTSD was associated with a 19% increased risk for ART non-adherence, although there was significant heterogeneity.[9] Due to their study designs and analytical methods, many of these studies were limited in their causal inference and can variably contradict. For example, all of these studies use self-reported measures for the exposure and some outcomes; twelve have small sample sizes[2-5, 17, 19, 20, 23, 24, 26, 28, 30]; eleven are cross-sectional studies[2, 17, 19-21, 23-25, 27, 28, 31]; none examine ART modifications; none use standard definitions of treatment failure[48, 49]; and none accounted for time-varying confounding, informative censoring, or within-patient correlation of recurrent events.

Of particular interest were the sometimes antagonistic and synergistic effects of number of deployments and combat exposure, either attenuating or amplifying the associations with PTSD depending on the outcome examined. Results from this study suggests that multiple deployments strengthened the association between PTSD and ART non-adherence, ART modifications, virologic failure, and immunologic failure, but diminished the association with clinical failure (although only modification for ART non-adherence was statistically significant). Combat exposure did not modify any of the associations examined, except attenuating the association between PTSD and clinical failure; however, this too was statistically insignificant. These potentially unexpected results, particularly for the association between PTSD and clinical failure, may be due to the healthy warrior effect, as service members who either self-select or are chosen for multiple deployments or combat roles are likely healthier, more resilient, and may be less prone to clinical decline later in life.[61-63]

A major strength of this current work was its robust analysis to estimate the causal effects of PTSD on ART in PWH. MSMs related the exposure and censoring history, up to time *t*, to the corresponding counterfactual outcome at time *t*.[64] IPTW and IPCW were employed to control

for time-dependent confounding and selection bias due to informative censoring, respectively.[65] The reweighted pseudo-population was then a representative sample of the overall study population, in which all covariates were balanced across exposure groups and LTFU was a random phenomenon with respect to covariates.[65] GEE and random effects were employed to account for within-subject correlation of recurrent events.[57, 58] Resultant estimates are consistent with causal effects under the assumption of no residual confounding or other biases.[64, 65] Other strengths of this study include its complete enumeration and enrollment of a nationally representative population; use of large repositories of patient-level EHR and military service records[40]; objective measures for all variables assessed, including the use of standardized coding algorithms to define the outcomes of interest[51-53]; limited LTFU[66]; and possible generalizability to other older Veteran and non-Veteran populations. Limitations of this study include possible misclassification of the exposure and effect modifiers; possible selection bias due to the healthy warrior effect[61-63]; that the assumptions of MSCM – exchangeability, consistency, positivity, and accuracy of the weight-generating model – were presumed true[67]; and that the true index traumatic stressor could not be ascertained. Bias analyses may be able to examine the extent to which misclassification and selection bias affected results, if at all; for MSMs, only positivity was assessed, the other three cannot be verified given the observational data; and not knowing the true index traumatic stressor does not invalidate these findings.

As HIV disease shifts to one that is more manageable and chronic, it is important that all providers recognize the role PTSD may play in ART non-adherence and its downstream effects on treatment failure and clinical decline. Due to the syndemic nature of HIV and PTSD, it is recommended that providers who work with PWH adopt a trauma-informed model of HIV care,[68] refer patients to treatment advocacy programs and services when indicated,[39] and screen Veterans for PTSD so that their unique trauma history can help guide medical decisions and treatment.[69]

Author contributions

All authors contributed to the content of the manuscript and concurred with the decision to submit it for publication. KJV contributed to the conception and design of the study, acquisition of the data, statistical analysis, interpretation, and drafting the manuscript. VCM, BKA, PSS, and JLG contributed to the conception and design of the study, interpretation, drafting and critical revision of the manuscript, and supervision. KJV and VCM had full access to all data in the study, and KJV takes full responsibility for the integrity of the data and the accuracy of the analysis.

Declaration of interests

No funding was received to assist with the preparation of this manuscript. KJV, BKA, and JLG have no relevant financial or non-financial interests to disclose. VCM received support from the Emory CFAR and NIH/NIAID. VCM has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Eli Lilly, Bayer, Gilead Sciences, Merck, and ViiV. PSS received funding from the NIH and CDC. PSS has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Gilead, Merck, and ViiV.

The views expressed are those of the authors and do not reflect the official views of the Uniformed Services University of the Health Sciences, the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc, the National Institutes of Health or the Department of

Health and Human Services, the Department of Defense, the Defense Health Agency, the Departments of the Army, Navy or Air Force, the Department of Veterans Affairs, and U.S. Government. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

Data sharing

The datasets in the current study were stored and analyzed on secure VA servers. Although the data are not publicly available, they may be shared with investigators with appropriate VA credentials. All work was conducted in accordance with the Declaration of Helsinki. The study was approved by the Emory University Institutional Review Board and the Atlanta VA Medical Center Research and Development Committee.

Acknowledgements

We thank all those who currently serve or have ever served in the U.S. military. We also thank Dr. Robert H. Lyles (Department of Biostatistics, Rollins School of Public Health, Emory University) for his review and critical revision of the manuscript. This is an unfunded study and therefore at no point were sponsors involved.

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Table 1. Characteristics of OEF/OIF/OND Veterans with HIV on ART by PTSD diagnosis (2001-2022).

	N=3,206[1] n (%)[2]	PTSD n=1,351 n (%)[2]	No PTSD n=1,855 n (%)[2]	P-value[3]
Sociodemographics				
Age at HIV diagnosis (years), median (IQR)	31.7 (9.5)	31.5 (9.3)	32.3 (9.6)	0.024
Sex, male	3,123 (97.4)	1,310 (97.0)	1,813 (97.7)	0.175
Race/ethnicity[5]				0.288
Black	1,493 (50.4)	609 (48.9)	884 (51.5)	
White	1,328 (44.8)	572 (45.9)	756 (44.1)	
Other	141 (4.8)	65 (5.2)	76 (4.4)	
Marital status[4,5]				<0.001
Married	651 (21.2)	312 (24.3)	339 (19.0)	
Never married	1,570 (51.1)	577 (44.9)	993 (55.6)	
Divorced/separated/widowed	851 (27.7)	397 (30.9)	454 (25.4)	
Educational attainment[4-6]				0.429
High school	1,629 (70.0)	690 (71.4)	939 (69.0)	
Vocational/technical	558 (24.0)	219 (22.7)	339 (24.9)	
College/university	140 (6.0)	57 (5.9)	83 (6.1)	
Household income (USD, annual)[4,5]				0.182
<20,000	537 (17.2)	214 (16.2)	323 (17.9)	
20,000-39,999	763 (24.4)	341 (25.9)	422 (23.4)	
40,000-74,999	1,146 (36.7)	492 (37.3)	654 (36.2)	
≥75,000	679 (21.7)	271 (20.6)	408 (22.6)	
Military history[7]				
Branch[4,8]				<0.001
Air Force	452 (14.1)	153 (11.3)	299 (16.1)	
Army	1,606 (50.0)	811 (60.0)	795 (42.7)	
Coast Guard	6 (0.2)	2 (0.1)	4 (0.2)	
Marines	377 (11.7)	179 (13.2)	198 (10.6)	
Navy	771 (24.0)	207 (15.3)	564 (30.3)	
Component[4,8]				0.007
Active-duty	2,710 (78.3)	1,107 (76.3)	1,603 (79.7)	
Guard	398 (11.5)	196 (13.5)	202 (10.0)	
Reserve	354 (10.2)	148 (10.2)	206 (10.2)	
Rank/grade[4]				0.007
Enlisted, E1-E4	910 (39.7)	366 (37.9)	544 (40.9)	
Enlisted, E5-E9	1,234 (53.8)	495 (51.3)	739 (55.6)	
Officer, O1-O9	151 (6.6)	104 (10.8)	47 (3.5)	
Length of service (years), median (IQR)[4]	6.6 (7.8)	6.3 (7.3)	6.9 (8.0)	0.019
Occupation[4,8]				<0.001
Infantry	400 (10.8)	212 (13.5)	188 (8.7)	
Service/supply	2,094 (56.3)	912 (58.2)	1,182 (54.9)	
All others	862 (23.2)	278 (17.7)	584 (27.1)	
Non-qualified/undesignated	363 (9.8)	165 (10.5)	198 (9.2)	
Number of deployments[4]				0.003
1	2,442 (78.6)	984 (75.8)	1,458 (80.7)	
2	490 (15.8)	227 (17.5)	263 (14.6)	
≥3	174 (5.6)	88 (6.8)	86 (4.8)	
Combat exposure[9]	743 (23.2)	337 (24.9)	406 (21.9)	0.043
In-theater injuries (ever)[4]				
Combat	87 (2.7)	53 (3.9)	34 (1.8)	<0.001
Noncombat	772 (24.1)	390 (28.9)	382 (20.6)	<0.001
Discharge character[4]				0.003
Dishonorable	89 (3.0)	51 (4.0)	38 (2.2)	
Honorable	2,921 (97.0)	1,215 (96.0)	1,706 (97.8)	
HIV clinical history				
ART era of initiation				0.275
Early (≤2006)	108 (3.4)	40 (3.0)	68 (3.7)	
Late (>2006)	3,098 (96.6)	1,311 (97.0)	1,787 (57.7)	
Time to ART initiation (months), median (IQR)	1.0 (0.1, 4.4)	1.1 (0.2, 5.2)	0.9 (0.1, 3.8)	<0.001
First CD4 count (cells/mL), median (IQR)[4]	569 (351)	555 (309)	585 (366)	0.172
Nadir CD4 count (cells/mL), median (IQR)[4]	407 (308)	379 (296)	425 (313)	<0.001
Last CD4 count (cells/mL), median (IQR)[4]	676 (386)	670 (369)	681 (397)	0.255
First HIV viral load (copies/mL), median (IQR)[4]	6,440 (56,950)	8,363 (64,950)	4,671 (50,563)	0.003
Last HIV viral load (copies/mL), median (IQR)[4]	50 (30)	50 (30)	50 (30)	0.690
Mental health history				
Anxiety	1,382 (43.1)	772 (57.1)	610 (32.9)	<0.001
Depression	1,063 (33.2)	632 (46.8)	431 (23.2)	<0.001
High-risk sexual behavior	246 (7.8)	121 (9.0)	125 (6.7)	0.020
Military sexual trauma	351 (11.0)	223 (16.5)	128 (7.0)	<0.001
Substance use disorder	1,584 (49.4)	863 (63.9)	721 (38.9)	<0.001
Traumatic brain injury	28 (0.9)	21 (1.6)	7 (0.4)	<0.001

ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; USD, United States dollar; VA, United States Department of Veterans Affairs.[1]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, who were diagnosed with HIV and initiated on ART before 31 December 2020, and censored on 31 December 2022. [2]Percentages may not add to 100% due to rounding up to the nearest tenth. [3]Fisher's exact and χ^2 tests for categorical data; Mann-Whitney-Wilcoxon tests for continuous data. [4]Missing [PTSD, no PTSD]: race/ethnicity (n=105, n=139), marital status (n=65, n=48), education (n=385, n=494), household income (n=33, n=48), branch (n=53, n=50), component (n=53, n=69), rank (n=386, n=50), length of service (n=54, n=53), number of deployments (n=52, n=48), in-theater injuries (n=52, n=48), discharge character (n=85, n=111), first CD4 count(n=165, n=295), nadir CD4 count (n=174, n=311), last CD4 count (n=164, n=300), first HIV viral load (n=58, n=127), last HIV viral load (n=58, n=127), military sexual trauma (n=3, n=13). [5]Last updated on 31 December 2019. [6]College/university includes graduate school. [7]Last updated at military separation. [8]Not mutually exclusive categories. [9]Meets combat Veteran eligibility requirements.

Table 2. Adjusted effect estimates for ART non-adherence, regimen modifications, and treatment failure due to PTSD among OEF/OIF/OND Veterans with HIV on ART, estimated by marginal structural models (2001-2022, n=3,206).

	PTSD	No PTSD		
	Adjusted risk[1,2] (95% CI), %	Adjusted risk[1,2] (95% CI), %	Adjusted RR[1,2] (95% CI)	P-value
ART non-adherence[3]	44.31 (42.23, 46.50)	41.65 (40.36, 42.98)	1.06 (1.00, 1.13)	0.034
Number of deployments				0.017
1	44.07 (41.73, 46.54)	42.09 (40.61, 43.62)	1.05 (0.98, 1.12)	0.166
≥2	50.16 (44.85, 56.11)	40.12 (37.47, 42.95)	1.19 (1.06, 1.34)	0.003
Combat exposure[4]				0.482
No	44.36 (41.90, 46.96)	41.22 (39.77, 42.71)	1.08 (1.01, 1.15)	0.032
Yes	44.19 (40.39, 48.35)	43.01 (40.25, 45.95)	1.07 (0.97, 1.18)	0.158
	Adjusted IR[1,2] (95% CI), per 1,000 PY	**Adjusted IR[1,2] (95% CI), per 1,000 PY**	**Adjusted IRR[1,2] (95% CI)**	**P-value**
ART regimen modifications[5]	11.95 (10.64, 13.44)	8.69 (7.66, 9.87)	1.38 (1.19, 1.58)	<0.001
Number of deployments				0.081
1	11.53 (10.02, 13.26)	8.97 (7.77, 10.36)	1.29 (1.10, 1.51)	0.002
≥2	13.77 (11.71, 16.20)	7.73 (5.60, 10.69)	1.54 (1.24, 1.91)	<0.001
Combat exposure[4]				0.519
No	11.87 (10.24, 13.75)	8.84 (7.57, 10.32)	1.34 (1.13, 1.59)	<0.001
Yes	12.25 (10.74, 13.98)	8.32 (6.73, 10.28)	1.39 (1.13, 1.70)	0.002
Virologic failure[6]	5.18 (4.14, 6.49)	4.55 (3.82, 5.42)	1.14 (0.87, 1.49)	0.344
Number of deployments				0.475
1	4.93 (3.80, 6.39)	4.34 (3.57, 5.29)	1.14 (0.83, 1.55)	0.425
≥2	7.19 (4.38, 11.81)	4.95 (3.19, 7.69)	1.66 (0.97, 2.82)	0.064
Combat exposure[4]				0.555
No	5.32 (4.09, 6.92)	4.87 (4.00, 5.92)	1.09 (0.81, 1.48)	0.567
Yes	4.89 (3.16, 7.56)	3.67 (2.50, 5.38)	1.00 (0.62, 1.62)	0.986
Immunologic failure[7]	0.65 (0.34, 1.22)	0.61 (0.39, 0.98)	1.05 (0.49, 2.26)	0.890
Number of deployments				0.793
1	0.62 (0.29, 1.35)	0.58 (0.36, 0.96)	1.07 (0.43, 2.64)	0.885
≥2	1.04 (0.40, 2.72)	0.77 (0.19, 3.10)	1.79 (0.61, 5.25)	0.292
Combat exposure[4]				0.839
No	0.70 (0.33, 1.50)	0.68 (0.43, 1.09)	1.02 (0.43, 2.44)	0.958
Yes	0.53 (0.19, 1.48)	0.42 (0.09, 1.87)	0.77 (0.25, 2.40)	0.651
Clinical failure[8]	2.96 (2.17, 4.03)	1.57 (1.12, 3.22)	1.89 (0.88, 4.06)	0.104
Number of deployments				0.485
1	2.86 (2.00, 4.09)	1.65 (1.21, 3.36)	1.73 (0.68, 4.37)	0.249
≥2	3.46 (1.68, 7.08)	5.41 (1.78, 7.15)	0.64 (0.26, 1.61)	0.347
Combat exposure[4]				0.274
No	3.17 (2.20, 4.54)	1.55 (1.14, 4.04)	2.04 (0.92, 4.53)	0.079
Yes	2.44 (1.35, 4.40)	3.64 (2.15, 5.91)	0.67 (0.27, 1.68)	0.398

ADI, AIDS-defining illness; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; ARV, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; IR, incidence rate; IRR, incidence rate ratio; mL, milliliter; MST, military sexual trauma; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PDC, proportion of days covered; PTSD, posttraumatic stress disorder; PY, person-year; RR, risk ratio; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs. [1]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, diagnosed with HIV and initiated on ART before 31 December 2020, and censored on 31 December 2022. [2]Marginal structural log-binomial and Poisson models with generalized estimating equations, as appropriate, with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, ART era of initiation, sex, race/ethnicity, marital status, education, income, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. [3]PDC ≤90%, calculated annually since ART initiation. [4]Meets VA combat Veteran eligibility requirements. [5]Removal, addition, or switch of an ARV class from the previous ART regimen. [6]HIV viral load ≥200 copies/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. [7]CD4 count ≤ first CD4 count (≤6 months after HIV diagnosis) or CD4 counts ≤100 cells/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. [8]New or recurrent ADI after ≥6 months on ART.

Supplemental Table 1a. Diagnostic codes used to define covariates of interest.

Covariates	ICD-9 codes[1]	ICD-10 codes[1]
Anxiety disorder	300.00, 300.02, 300.09	F41.1, F41.3, F41.8, F41.9
Depressive disorder	296.3	F33.1 – F33.9
High-risk sexual behavior	V69.2	Z72.51 – Z72.53
Human immunodeficiency virus	042, V08	B20, Z21
Posttraumatic stress disorder	309.81	F43.12
Substance use disorder	291, 292, 303 – 305	F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F55
Traumatic brain injury	800.0 – 801.9, 803.0 – 804.9, 805.1 – 805.5, 805.9, 851.0 – 854.1, 959.01	S02.0, S02.1, S02.8, S02.91, S04.02 – S04.04, S06.0, S06.1 –S06.9, S07.1, T74.4

CMS, Centers for Medicare and Medicaid Services; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; NCI, National Cancer Institute. [1]ICD-9 and ICD-10 codes from NCI Comorbidity Index and CMS Chronic Condition Warehouse.

Supplemental Table 1b. Diagnostic codes and frequencies for AIDS-defining illnesses among OEF/OIF/OND Veterans with HIV on ART by PTSD diagnosis (2001-2022).

			PTSD n = 1,351	No PTSD n = 1,855	
AIDS-defining illnesses	ICD-9 codes[1-3]	ICD-10 codes[1-3]	n (%)[4]	n (%)[4]	P-value[5]
Candidiasis, bronchi, trachea, or lungs	112.4	B37.1	0 (0.0)	0 (0.0)	1.000
Candidiasis, esophageal	112.84	B37.81	23 (1.7)	12 (0.9)	0.006
Cervical cancer, invasive	180	C53	0 (0.0)	0 (0.0)	1.000
Coccidioidomycosis, disseminated or extrapulmonary	114.1 – 114.3	B38.3, B38.4, B38.89	24 (1.8)	21 (1.6)	0.131
Cryptococcosis, extrapulmonary	117.5	B45.0, B45.7, B45.9	14 (1.0)	1 (0.1)	<0.001
Cryptosporidiosis, chronic intestinal	007.4	A07.2	2 (0.1)	3 (0.2)	1.000
Cytomegalovirus disease	078.5	B25.9	13 (1.0)	31 (2.3)	0.093
Histoplasmosis, disseminated or extrapulmonary	115.01 – 115.04	B39.4, H32	0 (0.0)	0 (0.0)	1.000
Human T-cell lymphotropic virus, type II	079.52	B97.34	0 (0.0)	0 (0.0)	1.000
Isosporiasis, chronic intestinal	007.2	A07.3	0 (0.0)	0 (0.0)	1.000
Kaposi's sarcoma	176	C46	79 (5.8)	214 (15.8)	<0.001
Lymphoma, Burkitt's	200.2	C83.7	14 (1.0)	29 (2.1)	0.217
Lymphoma, immunoblastic	202.8	C85.8	19 (1.4)	1 (0.1)	<0.001
Mycobacterium avium complex or mycobacterium kansaii, disseminated or extrapulmonary	031.1 – 031.9, excluding 031.0	A31.1, A31.2, A31.8, A31.9	70 (5.2)	18 (1.3)	<0.001
Mycobacterium tuberculosis, any site, pulmonary or extrapulmonary	010 – 018	A16 – A19	7 (0.5)	2 (0.1)	0.041
Other specific rickettsioses, including bacillary angiomatosis	083.8	A79.81, A79.89	0 (0.0)	0 (0.0)	1.000
Pneumocystis carinii pneumonia	136.3	B59	1 (0.1)	10 (0.7)	0.031
Pneumonia in cytomegalic inclusion disease	484.1	B25.0	0 (0.0)	1 (0.1)	1.000
Progressive multifocal leukoencephalopathy	046.3	A81.2	47 (3.5)	22 (1.6)	<0.001
Salmonella septicemia, recurrent	003.1	A02.1	0 (0.0)	0 (0.0)	1.000
Severe herpes simplex virus chronic ulcer, or bronchitis, pneumonitis, or esophagitis	054.71	B00.81	0 (0.0)	1 (0.1)	1.000
Toxoplasmosis, brain	130.0	B58.2, G02	1 (0.1)	12 (0.9)	0.011
TOTAL			378 (28.0)	314 (23.2)	<0.001

ART, antiretroviral therapy; HIV, human immunodeficiency virus; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder. [1]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, who were diagnosed with HIV and initiated on ART before 31 December 2020, and censored on 31 December 2022. [2]Nurutdinova D, Chrusciel T, Zeringue A, et al. Mental health disorders and the risk of AIDS-defining illness and death in HIV-infected veterans. *AIDS*. 2012;26(2):229-234. [3]An asterisk (*) indicates that any subsequent digit/character is included. [4]Percentages may not add to 100% due to rounding up to the nearest tenth. [5]Fisher's exact tests.

Supplemental Table 2. ART regimen modifications among OEF/OIF/OND Veterans with HIV by PTSD diagnosis (2001-2022).

HIV ARV classes[1]	PTSD n = 1,351[2] Rx = 38,656[3] Rx (%)[4]	No PTSD n = 1,855[2] Rx = 69,216[3] Rx (%)[4]	P-value[5]
Attachment inhibitors			
Additions	3 (0.01)	0 (0.00)	0.086
Removals	9 (0.02)	0 (0.00)	<0.001
CCR5 antagonists			
Additions	37 (0.10)	38 (0.05)	0.020
Removals	27 (0.07)	25 (0.04)	0.023
Fusion inhibitors			
Additions	0 (0.00)	0 (0.00)	1.000
Removals	1 (0.00)	0 (0.00)	0.768
Integrase strand transfer inhibitors			
Additions	858 (2.22)	1,440 (2.08)	0.135
Removals	886 (2.29)	1,684 (2.43)	0.151
Non-nucleoside reverse transcriptase inhibitors			
Additions	523 (1.35)	1,082 (1.56)	0.007
Removals	536 (1.39)	988 (1.43)	0.605
Nucleoside reverse transcriptase inhibitors			
Additions	736 (1.90)	1,223 (1.77)	0.111
Removals	661 (1.71)	1,279 (1.85)	0.107
Pharmacokinetic enhancers			
Additions	571 (1.48)	933 (1.35)	0.088
Removals	547 (1.42)	874 (1.26)	0.038
Protease inhibitors			
Additions	553 (1.43)	790 (1.14)	<0.001
Removals	553 (1.43)	736 (1.06)	<0.001

ART, antiretroviral therapy; ARV, antiretroviral; HIV, human immunodeficiency virus; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; VA, United States Department of Veterans Affairs. [1]Removal, addition, or switch of an ARV class from previous ART regimen. [2]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, diagnosed with HIV and initiated on ART before 31 December 2020, and censored on 31 December 2022. [3]Number of ART refills. [4]Percentages may not add to 100% due to rounding up to the nearest tenth. [5]Fisher's exact tests.

Supplemental Table 3. Crude effect estimates for ART non-adherence, regimen modifications, and treatment failure due to PTSD among OEF/OIF/OND Veterans with HIV on ART, estimated by marginal structural models (2001-2022, n=3,206).

	PTSD	No PTSD		
	Crude risk[1,2] (95% CI), %	**Crude risk[1,2] (95% CI), %**	**Crude RR[1,2] (95% CI)**	**P-value**
ART non-adherence[3]	44.26 (42.79, 45.87)	40.53 (39.41, 41.69)	1.09 (1.05, 1.14)	<0.001
Number of deployments				0.145
1	43.99 (42.31, 45.74)	40.60 (39.35, 41.90)	1.08 (1.03, 1.14)	0.002
≥2	47.70 (44.21, 51.47)	40.47 (37.73, 43.41)	1.17 (1.08, 1.28)	<0.001
Combat exposure[4]				0.352
No	44.43 (42.73, 46.20)	40.19 (38.93, 41.48)	1.11 (1.05, 1.16)	<0.001
Yes	43.84 (41.02, 46.86)	41.60 (39.21, 44.14)	1.09 (1.01, 1.17)	0.021
	Crude IR[1,2] (95% CI), per 1,000 PY	**Crude IR[1,2] (95% CI), Per 1,000 PY**	**Crude IRR[1,2] (95% CI)**	**P-value**
ART regimen modifications[5]	13.47 (12.72, 14.27)	9.17 (8.23, 10.22)	1.47 (1.30, 1.66)	<0.001
Number of deployments				0.080
1	13.33 (12.50, 14.21)	9.61 (8.52, 10.85)	1.39 (1.21, 1.59)	<0.001
≥2	13.78 (11.90, 15.95)	7.39 (5.65, 9.67)	1.43 (1.19, 1.73)	<0.001
Combat exposure[4]				0.902
No	13.68 (12.80, 14.62)	9.29 (8.13, 10.61)	1.47 (1.26, 1.72)	<0.001
Yes	12.88 (11.50, 14.41)	8.88 (7.42, 10.62)	1.39 (1.16, 1.65)	<0.001
Virologic failure[6]	5.55 (4.48, 6.87)	4.66 (3.94, 5.50)	1.19 (0.92, 1.54)	0.181
Number of deployments				0.754
1	5.37 (4.17, 6.90)	4.46 (3.70, 5.38)	1.20 (0.89, 1.63)	0.234
≥2	6.95 (4.48, 10.78)	5.23 (3.36, 8.14)	1.56 (0.97, 2.51)	0.068
Combat exposure[4]				0.968
No	5.91 (4.60, 7.59)	4.90 (4.08, 5.90)	1.20 (0.90, 1.60)	0.204
Yes	4.74 (3.17, 7.09)	3.99 (2.72, 5.84)	0.97 (0.62, 1.50)	0.878
Immunologic failure[7]	0.74 (0.39, 1.41)	0.65 (0.41, 1.02)	1.15 (0.54, 2.47)	0.721
Number of deployments				0.908
1	0.76 (0.35, 1.63)	0.61 (0.38, 0.96)	1.24 (0.51, 3.03)	0.632
≥2	0.90 (0.35, 2.30)	0.80 (0.19, 3.39)	1.48 (0.52, 4.21)	0.467
Combat exposure[4]				0.963
No	0.82 (0.38, 1.77)	0.71 (0.46, 1.10)	1.15 (0.49, 2.72)	0.753
Yes	0.57 (0.22, 1.49)	0.48 (0.11, 2.06)	0.80 (0.28, 2.31)	0.682
Clinical failure[8]	3.37 (2.47, 4.59)	2.99 (2.22, 4.02)	1.13 (0.73, 1.73)	0.588
Number of deployments				0.445
1	3.26 (2.28, 4.66)	3.16 (2.30, 4.36)	1.03 (0.64, 1.66)	0.907
≥2	3.94 (1.92, 8.07)	2.38 (1.00, 5.65)	1.24 (0.57, 2.73)	0.586
Combat exposure[4]				0.292
No	3.61 (2.51, 5.18)	2.80 (1.94, 4.03)	1.29 (0.77, 2.15)	0.334
Yes	2.78 (1.54, 5.02)	3.56 (2.15, 5.91)	0.99 (0.50, 1.99)	0.984

ADI, AIDS-defining illness; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; ARV, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; IR, incidence rate; IRR, incidence rate ratio; mL, milliliter; MST, military sexual trauma; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PDC, proportion of days covered; PTSD, posttraumatic stress disorder; PY, person-year; RR, risk ratio; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs. [1]Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, diagnosed with HIV and initiated on ART before 31 December 2020, and censored on 31 December 2022. [2]Log-binomial and Poisson models with generalized estimating equations, as appropriate. [3]PDC ≤90%, calculated annually since ART initiation. [4]Meets VA combat Veteran eligibility requirements. [5]Removal, addition, or switch of an ARV class from the previous ART regimen. [6]HIV viral load ≥200 copies/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. [7]CD4 count ≤ first CD4 count (≤6 months after HIV diagnosis) or CD4 counts ≤100 cells/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. [8]New or recurrent ADI after ≥6 months on ART.

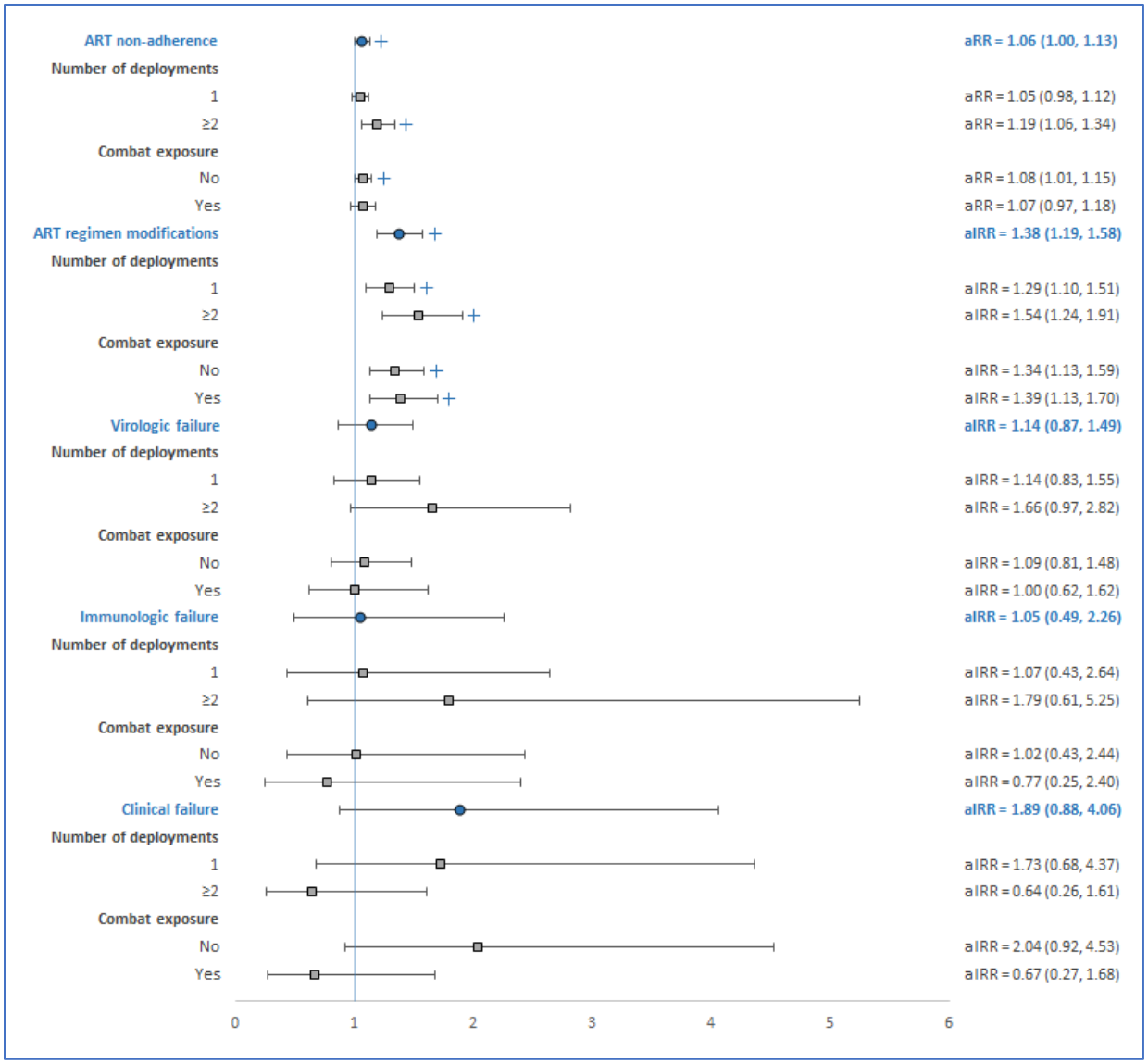


Figure 1. Adjusted effect estimates for ART non-adherence, regimen modifications, and treatment failure due to PTSD among OEF/OIF/OND Veterans with HIV on ART, estimated by marginal structural models (2001-2022, n=3,206). Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, diagnosed with HIV and initiated on ART before 31 December 2020, and censored on 31 December 2022. Marginal structural log-binomial and Poisson models with generalized estimating equations, as appropriate, with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, ART era of initiation, sex, race/ethnicity, marital status, education, income, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. [1]PDC ≤90%, calculated annually since ART initiation. "Positive" marker denotes effect estimates are statistically significant at α=0.05. [2]Removal, addition, or switch of an ARV class from the previous ART regimen. [3]HIV viral load ≥200 copies/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. [4]CD4 count ≤ first CD4 count (≤6 months after HIV diagnosis) or CD4 counts ≤100 cells/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. [5]New or recurrent ADI after ≥6 months on ART. ADI, AIDS-defining illness; AIDS, acquired immunodeficiency syndrome; aIRR, adjusted incidence rate ratio; aRR, adjusted risk ratio; ART, antiretroviral therapy; ARV, antiretroviral; HIV, human immunodeficiency virus; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; mL, milliliter; MST, military sexual trauma; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PDC, proportion of days covered; PTSD, posttraumatic stress disorder; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs.

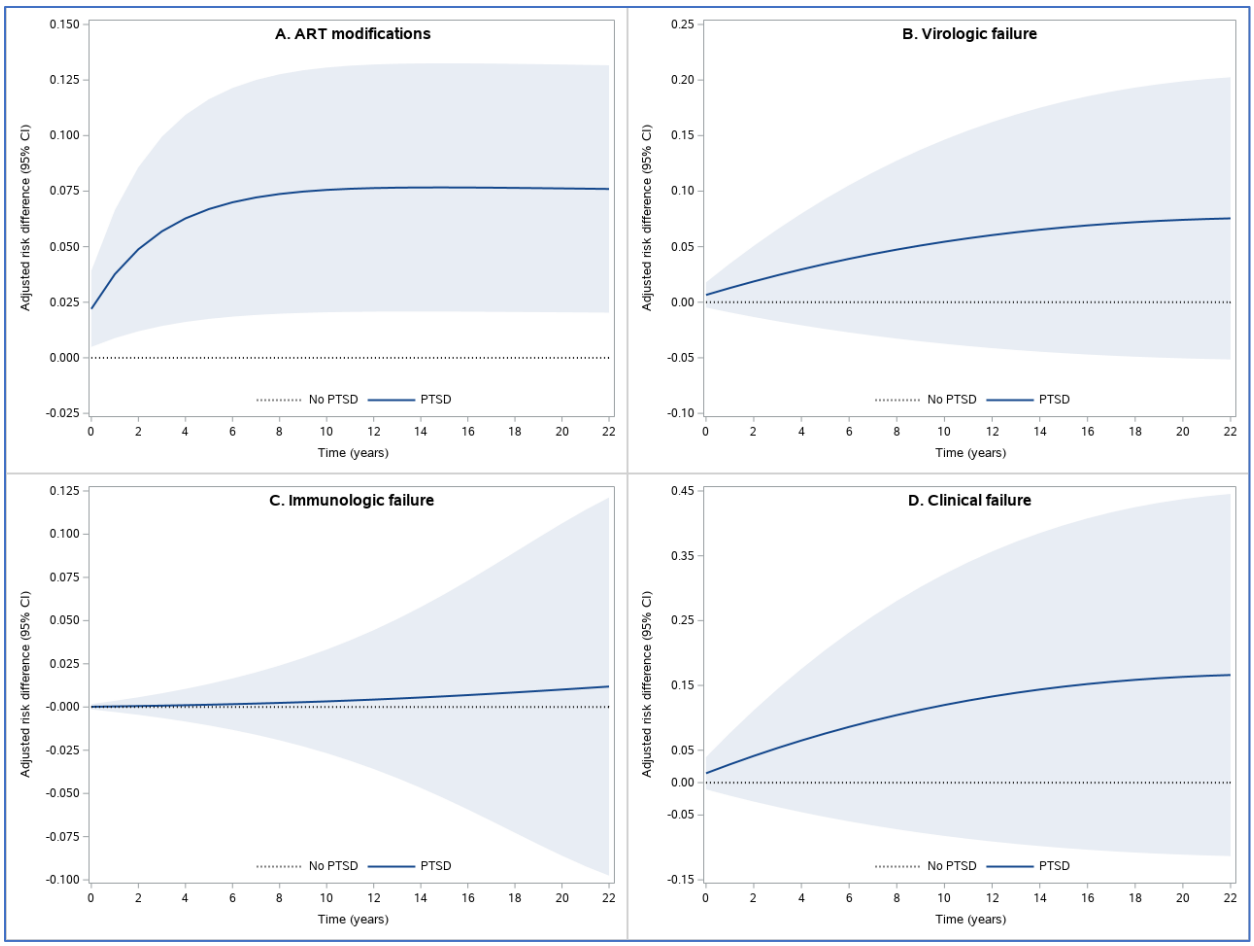
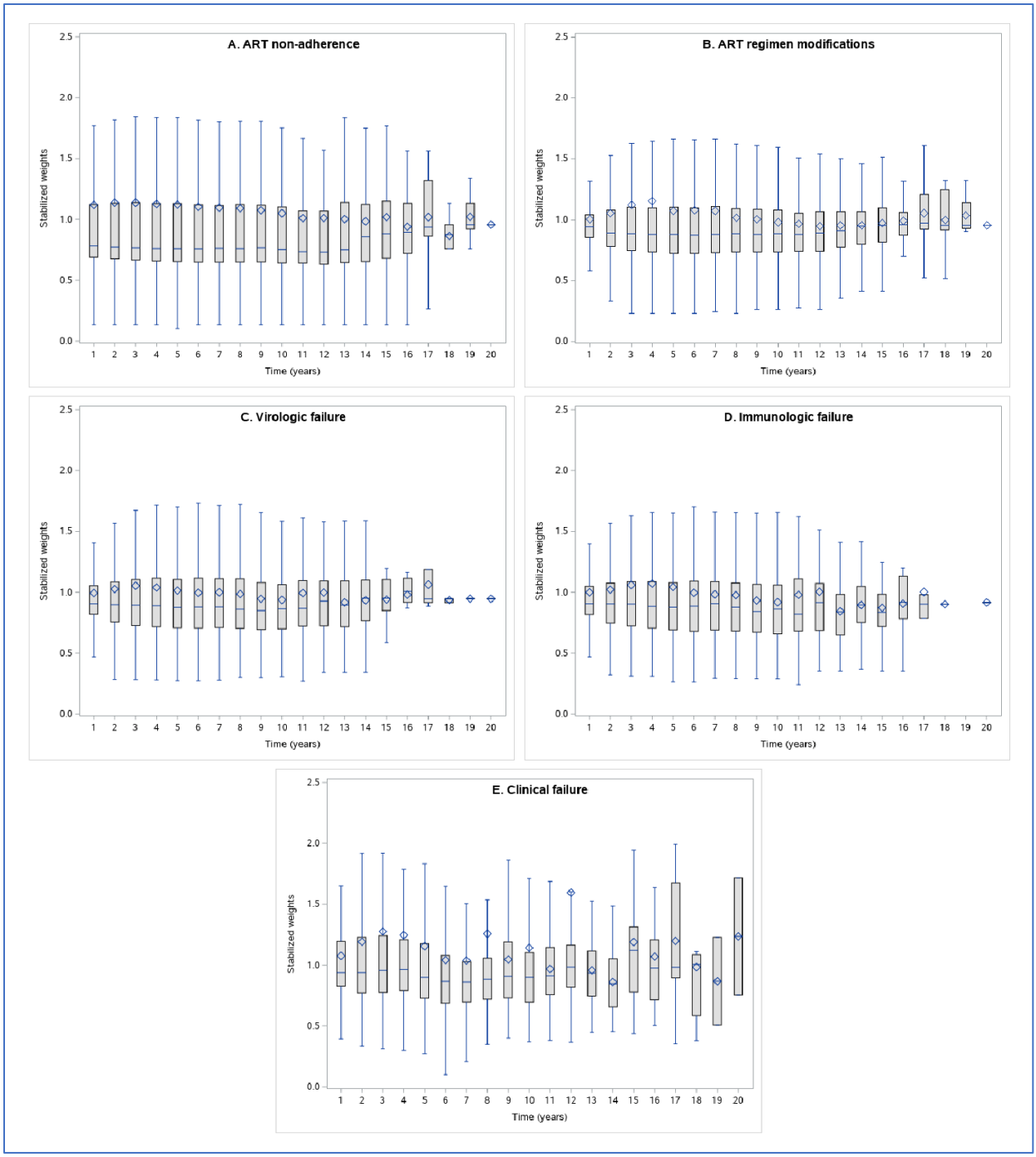


Figure 2. Adjusted risk differences for ART modifications and treatment failure between those diagnosed with and without PTSD among OEF/OIF/OND Veterans with HIV on ART, estimated by marginal structural models (2001-2022, n=3,206). Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, diagnosed with HIV and initiated on ART before 31 December 2020, and censored on 31 December 2022. Reference group defined as those without PTSD. Marginal structural shared frailty models with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, ART era of initiation, sex, race/ethnicity, marital status, education, income, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. ART modifications defined as the removal, addition, or switch of an ARV class from the previous ART regimen. Virologic failure defined as an HIV viral load ≥200 copies/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. Immunologic failure defined as a CD4 count ≤ first CD4 count (≤6 months after HIV diagnosis) or CD4 counts ≤100 cells/mL for two consecutive measurements, with ≥3 months between and after ≥6 months on ART. Clinical failure defined as a new or recurrent ADI after ≥6 months on ART. ADI, AIDS-defining illness; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; ARV, antiretroviral; HIV, human immunodeficiency virus; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; mL, milliliter; MST, military sexual trauma; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs.



Supplemental Figure 1. Distributions of stabilized weights over time from marginal structural models to estimate the effects of PTSD on ART non-adherence, regimen modifications, and treatment failure among OEF/OIF/OND Veterans with HIV on ART (2001-2022). Includes all OEF/OIF/OND Veterans who enrolled in the VA between 7 October 2001 and 31 December 2020, who were diagnosed with HIV and initiated on ART before 31 December 2020, and followed until 31 December 2022. Marginal structural log-binomial and Poisson models with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, ART era of initiation, race/ethnicity, sex, education, income, marital status, MST, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. HIV, human immunodeficiency virus; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; VA, United States Department of Veterans Affairs.

Chapter 5: PTSD and its associations with morbidity and mortality among Veterans with HIV

EMORY | ROLLINS SCHOOL OF PUBLIC HEALTH

Date: 9 October 2023

To: Peter Hayward, MSc
Editor-in-Chief, ***Lancet HIV***

Subject: Manuscript Submission

Dear Editors,

Enclosed you will find our paper entitled, "Posttraumatic Stress Disorder and its Associations with Morbidity and Mortality among Veterans with HIV." We kindly ask that you consider our manuscript for publication in your journal.

Our study includes all Veterans with HIV who served in Iraq and Afghanistan and who received care in the Department of Veterans Affairs. We aimed to estimate the overall and time-varying effects of PTSD on a myriad of chronic medical conditions and premature mortality, and measure effect modification by number of deployments and combat exposure. We found PTSD increased the risks for AIDS, arthritis, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, and multimorbidity, and that these associations seemed most pronounced within the first decade post-diagnosis. Due to the syndemic nature of HIV and PTSD, it is recommended that providers who work with people with HIV adopt a trauma-informed model of HIV care, and that providers screen Veterans for PTSD so that their trauma history can help guide medical decisions and treatment.

We believe that this manuscript is appropriate for your journal and will be of interest to your readers. This work is original, has not been published elsewhere, and is not under concurrent consideration elsewhere. Thank you for your consideration of this manuscript.

Very respectfully,

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Abstract

Background: Behavioral and physiological changes related to posttraumatic stress disorder (PTSD) have been shown to be associated with morbidity and mortality; however, associations among people with HIV (PWH) remain obscure. Objectives of this work were to (1) estimate associations between PTSD and morbidity and mortality; (2) measure effect modification by number of deployments and combat exposure; and (3) examine how these associations vary over time among Veterans with HIV (VWH) receiving antiretroviral therapy who deployed to Iraq and Afghanistan and are enrolled in the Department of Veterans Affairs.

Methods: Patients entered the study at HIV diagnosis beginning on 7 October 2001 and were censored on 31 December 2022. Marginal structural Cox models were fitted with a time-dependent exposure, adjusted for time-independent and -dependent confounding and informative censoring. Adjusted hazard ratios (aHR) and risk differences were calculated to estimate overall and time-varying associations, respectively.

Findings: A total of 3,206 VWH were included, contributing 20,121 person-years of follow-up. PTSD increased the risks (aHR [95% CI]) for AIDS by 11% (1·11 [1·00, 1·23]), chronic kidney disease by 21% (1·21 [1·02, 1·43]), chronic obstructive pulmonary disease by 46% (1·46 [1·10, 1·92]), multimorbidity by 49% (1·49 [1·24, 1·81]), cardiovascular disease by 57% (1·57 [1·25, 1·97]), and arthritis two-fold (1·95 [1·76, 2·15]). PTSD did not affect asthma, cancer, cerebrovascular disease, diabetes mellitus, liver disease, or all-cause mortality. Combat exposure attenuated the association between PTSD and AIDS. Multiple deployments did not modify any of the associations examined. Associations seemed most pronounced within the first decade post-PTSD-diagnosis.

Interpretation: As HIV disease shifts to one that is more manageable and chronic, it is important that providers recognize the role PTSD may play in morbidity and mortality. Results may help providers better address behavioral risk factors, focus diagnostic and therapeutic efforts, and improve overall care for PWH.

Research in context

Evidence before this study

A systematic review of articles published in 2000-2022 and indexed in PubMed was conducted with the following terms: (1) posttraumatic stress disorder or PTSD; (2) human immunodeficiency virus or HIV; and (3) morbidity, mortality, aging, arthritis, asthma, cancer, cardiovascular disease, chronic obstructive pulmonary disease or COPD, diabetes, hepatitis, kidney disease, or stroke. Of the 344 articles found, only seven (n=4,150) studied the associations between PTSD and morbidity and mortality among people with HIV (PWH); only one was performed in a military or Veteran population, and six were cross-sectional in study design. The evidence suggests PTSD may be associated with arthritis, coronary artery disease, hepatitis C virus coinfection, neurocognitive impairment, and shingles. Surprisingly, no known studies have examined the association between PTSD and AIDS or multimorbidity among PWH, nor is there sufficient evidence conducted in military or Veteran populations who are at high risk for PTSD.

Added value of this study

The work presented represents one of the more comprehensive and robust analyses to estimate the associations between PTSD and morbidity and mortality among PWH. Results suggest PTSD increased the risks (in order of increasing magnitude) for AIDS, chronic kidney disease (CKD), COPD, multimorbidity, cardiovascular disease (CVD), and arthritis. And combat exposure attenuated the association between PTSD and AIDS, while multiple deployments did not modify any association examined. Finally, these associations seemed most pronounced within the first decade post-PTSD-diagnosis, followed by gradual waning yet still elevated risks.

Implications of all the available evidence

PTSD has the potential to cause long-term negative health consequences for PWH; particular attention should be directed towards the first decade post-diagnosis. Due to the syndemic nature of HIV and PTSD, it is recommended that providers who work with PWH adopt a trauma-informed model of HIV care, and that providers screen Veterans for PTSD so that their trauma history can help guide medical decisions and treatment and improve their overall care.

Introduction

Ninety-five percent of people with HIV (PWH) report at least one severe traumatic stressor, and more than half meet the criteria for posttraumatic stress disorder (PTSD).[1] It is thought that the behavioral and physiological changes associated with PTSD may prevent the development of effective coping mechanisms to stress, leading to negative health behaviors, and may accelerate biological aging through activation of the neurobiological response cascade, including increases in systemic inflammation and immune dysfunction, resulting in a myriad of early-onset age-related diseases.[2] The scientific body of evidence on PTSD and its associations with morbidity and mortality is vast; however, the PTSD-related literature on PWH is limited.[2-8] HIV infection itself has been shown to be independently associated with accelerated biological aging and how PWH cope with psychological stress is likely distinct and unique to this population, therefore their risks

for comorbid chronic medical conditions may be different.[2,9-11] With the advent of combination antiretroviral therapy (ART) and the shift of HIV disease to one that is more manageable and chronic, addressing age-related comorbidities has become an essential component of overall care for PWH.[2] A population that may benefit from further investigation of this kind is the 3.6 million U.S. Veterans who served during Operations Enduring Freedom, Iraqi Freedom, and/or New Dawn (OEF/OIF/OND) post-9/11, nearly 4,000 of whom are Veterans with HIV (VWH) enrolled in the Department of Veterans Affairs (VA).

Colloquially referred to as "soldier's heart" (Civil War), "shell shock" (World War I), and "combat fatigue" (World War II, Korean War),[12] PTSD is a prevalent disorder among military service members and Veterans, affecting nearly one-quarter of all those who deployed in support of OEF/OIF/OND.[12-14] One possible index traumatic stressor may have been the increased operational tempo, particularly intense and repeated deployments, that was characteristic during the time. It is estimated that 57%, 27%, and 16% of all OEF/OIF/OND Veterans deployed one, two, and three or more times, respectively.[15] Another possible index traumatic stressor may have been combat exposure. Sixty-four percent of all OEF/OIF/OND Veterans reported any combat exposure, of whom 49% witnessed someone who was wounded or killed, 49% felt in danger of being killed, and 17% discharged their weapon.[16] Combat exposure during deployment has been shown to increase the risk for PTSD three-fold compared to non-deployment.[17] In either military or Veteran populations with HIV, no known studies have examined the associations between PTSD and morbidity and mortality, let alone the roles of deployment and combat exposure.

The objective of this current work is to fill in this knowledge gap for VWH and to inform care of PWH more broadly – to (1) estimate the associations between PTSD and 10 age-related comorbidities, multimorbidity, and all-cause mortality; (2) assess whether these are modified by number of deployments and combat exposure; and (3) examine how these vary over time among all OEF/OIF/OND VWH on ART who receive healthcare in the VA. Expanded knowledge may help policymakers anticipate the potential long-term negative health consequences of war for VWH, the risk profiles of those most vulnerable, and how to best attenuate those risks by supporting preventive measures. It may also enable providers to better address behavioral risk factors, focus diagnostic and therapeutic efforts, and improve overall care for PWH.

Methods

Study population

All U.S. Veterans who have ever (1) been deployed in support of OEF (7 October 2001 – 28 December 2014), OIF (20 March 2003 – 31 August 2010), and/or OND (1 September 2010 – 15 December 2011); (2) received healthcare at the VA; (3) been diagnosed with HIV; and (4) initiated ART prior to 31 December 2020 were included in this study. Patients entered the study at HIV diagnosis and were censored (1) at death, if recorded; (2) at their last VA healthcare visit if they had not been seen after 31 December 2020 (considered lost-to-follow-up [LTFU]); or (3) 31 December 2022 if they survived past the study period.

Data sources

Datasets were generated and analyzed within the VA Informatics and Computing Infrastructure (VINCI), a secure, central analytic platform that hosts suites of databases integrated

from select national VA data sources, including those used here – namely, the Corporate Data Warehouse (CDW), the Department of Defense (DoD)-VA Informatics and Computing Infrastructure (DaVINCI), and the U.S. Veterans Eligibility Trends and Statistics (USVETS) databases. CDW is a repository of over 20 million unique patient-level electronic health records (EHR) aggregated from across the VA's national healthcare delivery system. DaVINCI is built on existing data infrastructures – the Health Services Data Warehouse (HSDW) and the Military Health System Data Repository (MDR) on the DoD side and VINCI, which largely draws from the CDW, on the VA side – and provides a consolidated view of EHR for over 4 million unique Veterans during and after their military service. The final data source was USVETS, which combines data from the VA, DoD, and commercial sources and contains data such as utilization of VA services and benefits, military history, geography, demographics, and socioeconomic factors for nearly 40 million Veterans.

Definitions

International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and -10) codes were used to define the study population (HIV), exposure (PTSD), mental health history (anxiety disorder, depressive disorder, high-risk sexual behavior, military sexual trauma [MST], substance use disorder [SUD], and traumatic brain injury [TBI]), and all incident age-related comorbidities of interest (AIDS, arthritis, asthma, cancer, cardiovascular disease [CVD], cerebrovascular disease [CeVD], chronic kidney disease [CKD], chronic obstructive pulmonary disease [COPD], diabetes mellitus [DM], liver disease, and multimorbidity [co-occurrence of ≥2 age-related comorbidities]). The National Cancer Institute (NCI) Comorbidity Index and the Centers for Medicare and Medicaid Services (CMS) Chronic Condition Warehouse coding algorithms were used to define each mental health disorder and age-related comorbidity of interest (Supplemental Table 1).[18-20] Combat exposure was defined as having met the combat Veteran VA eligibility requirements.[21]

Descriptive analyses

Descriptive analyses were performed to characterize and compare patients who were and were not ever diagnosed with PTSD by socio-demographics (age at HIV diagnosis, sex, race/ethnicity, marital status, educational attainment, and household income), military history (branch, component, rank/grade, length of service, occupation, number of deployments, combat exposure, in-theater injuries, and discharge character), HIV clinical history (first [≤6 months after HIV diagnosis], nadir, and last [≤6 months before censorship] CD4 counts; and first [≤6 months after HIV diagnosis] and last [≤6 months before censorship] HIV viral loads), mental health history, and age-related comorbidities and all-cause mortality. Fisher's exact tests or chi-square tests for categorical data and Mann-Whitney-Wilcoxon tests for continuous data were performed as appropriate. Time from military separation to HIV and PTSD diagnoses, as well as time between HIV and PTSD diagnoses, were also calculated and their distributions were examined.

Inferential analyses

Marginal structural Cox models (MSCM) were fitted for each outcome of interest (age-related comorbidities and all-cause mortality) with a time-dependent exposure (PTSD), adjusted

for time-independent confounders (age at HIV diagnosis, sex, race/ethnicity, marital status, educational attainment, household income, MST, and TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, and SUD).[22] To adjust for both time-dependent confounding and informative censoring, inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCW) were estimated by weighted pooled logistic regression models and used to calculate the final stabilized weights.[22] Final stabilized weights for each outcome of interest were aggregated by one-year increments and their distributions were examined. Crude and adjusted hazard ratios (aHR) were calculated to estimate the overall associations between PTSD and each outcome of interest; whereas adjusted risk differences (aRD) were calculated to estimate the association between PTSD and each outcome of interest over time, under the hypothetical of always versus never exposed.[22] Bootstrapping procedures were applied to calculate 95% confidence intervals (CI). All analyses were performed under three scenarios: (1) no effect modification, (2) effect modification by number of deployments, and (3) effect modification by combat exposure. Multiple imputation was performed for each outcome of interest to address missingness among all time-independent confounders (except MST and TBI) using the Markov Chain Monte Carlo (MCMC) approach.

Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC), and the %MSM SAS macro (CAUSALab, Harvard University, Boston, MA) was employed for all inferential analyses.[22] Probability values <0.05 were considered statistically significant. All work was conducted in accordance with the Declaration of Helsinki. The study was approved by the Emory University Institutional Review Board and the Atlanta VA Medical Center Research and Development Committee.

Results

Of the 1,570,654 OEF/OIF/OND Veterans enrolled in the VA, 3,949 (0·3%) were diagnosed with HIV prior to 31 December 2020; of whom, 3,206 (81·2%) had initiated ART, contributing a total of 20,121 person-years (PY, mean [standard deviation, SD] = 6·3 [4·0] PY). Patients not diagnosed with PTSD (n=1,855, 57·9%) contributed 10,772 PY (mean [SD] = 5·8 [3·9] PY); whereas those diagnosed with PTSD (n=1,351, 42·1%) contributed 9,349 PY (mean [SD] = 6·9 [3·9] PY). Of the 3,206 patients in the analytic sample, 138 died (4·3%), 892 (27·8%) were LTFU, and 2,176 (67·9%) survived past the study period.

Characteristics

Most patients were male (97·4%), Black (50·4%), never married (51·1%), high school educated (70·0%), and had an annual household income of USD $40,000-74,999; the median (interquartile range [IQR]) age at HIV diagnosis was 31·7 (9·5) years (Table 1). Regarding their military history, most patients were Army Veterans (50·0%), served as active-duty (78·3%), ranked as enlisted E5-E9 (53·8%), worked in service/supply (56·3%), deployed only once (78·6%), unexposed to combat (76·8%), never sustained combat (97·3%) or noncombat (75·9%) injuries, and were honorably discharged (97·0%); the median (IQR) length of service was 6·6 (7·8) years. Patients diagnosed with PTSD were significantly different only by age at HIV diagnosis and marital status in their sociodemographics, and only by nadir CD4 count and first HIV viral load in their HIV clinical history compared to those not diagnosed with PTSD. However, patients diagnosed with PTSD were significantly different across all factors of military history assessed,

all mental health disorders examined, and across all morbidity and mortality outcomes assessed (except cancer, DM, and mortality) compared to those not diagnosed with PTSD.

Nearly all patients were diagnosed with HIV after military separation (95·6%), with 900 (28·1%) and 1,925 (60·0%) diagnosed within the first year and five years, respectively In parallel, among patients diagnosed with PTSD, almost all were diagnosed after military separation (95·0%), with 324 (24·0%) and 829 (61·4%) diagnosed within the first year and five years, respectively. Among those diagnosed with HIV before military separation (4·4%), 28 (66·7%) and 14 (33·3%) were diagnosed with PTSD before and after HIV diagnosis, respectively; among those diagnosed with HIV after military separation (95·6%), 702 (53·6%) and 607 (46·4%) were diagnosed with PTSD before and after HIV diagnosis, respectively (Supplemental Figure 1).

Overall associations

PTSD significantly increased the overall risks (aHR [95% CI]) for AIDS by 11% (1·11 [1·00, 1·23]), CKD by 21% (1·21 [1·02, 1·43]), COPD by 46% (1·46 [1·10, 1·92]), multimorbidity by 49% (1·49 [1·24, 1·81]), CVD by 57% (1·57 [1·25, 1·97]), and arthritis two-fold (1·95 [1·76, 2·15]). PTSD also increased the overall risks for cancer by 12% (1·12 [0·36, 3·50]), liver disease by 21% (1·21 [0·87, 1·68]), CeVD by 49% (1·49 [0·59, 3·75]), and asthma two-fold (1·84 [0·94, 3·62]), but these were statistically insignificant. PTSD did not affect the overall risk for DM (1·01 [0·62, 1·65]); however, it reduced the overall risk for mortality by 10% (0·90 [0·77, 1·05]), but this too was statistically insignificant. Associations with PTSD appeared most pronounced at 1·5 years for multimorbidity, 2·3 years for arthritis, 2·6 years for asthma, 3·0 years for AIDS, 3·6 years for liver disease, 3·8 years for CKD, 4·4 years for cancer, 4·7 years for COPD, 7·7 years for DM, 8·3 years for CVD, and 8·7 years for CeVD, followed by gradual waning yet still elevated risks; the association plateaued at 11·1 years for mortality (Table 2, Figure 1).

Effect modification

Combat exposure decreased the association (aIRR [95% CI]) between PTSD and AIDS (1·23 [1·10, 1·38] vs· 0·63 [0·48, 0·82], p<0·001) compared to no combat exposure. No other associations were modified by combat exposure, and multiple deployments did not modify any association examined. Distributions of final stabilized weights over time from MSCM models for each outcome of interest are depicted in Supplemental Figure 2.

Discussion

The work presented represents one of the more comprehensive and robust analyses to estimate the associations between PTSD and morbidity and mortality among PWH. Results suggest PTSD increased the risks (in order of increasing magnitude) for AIDS, CKD, COPD, multimorbidity, CVD, and arthritis. And combat exposure decreased the association between PTSD and AIDS, while multiple deployments did not modify any association. Finally, these associations seemed most pronounced within the first decade post-PTSD-diagnosis, followed by gradual waning yet still elevated risks.

Many of the associations observed in this study may be wholly or partly explained by the biological, attentional, and psychological alterations induced by or otherwise associated with PTSD – namely, sympathetic overactivity, endocrinological irregularities, and modified

immunologic mechanisms; impaired risk perception and disengagement in care; and negative coping strategies including suboptimal diet, physical inactivity, poor sleep, and treatment nonadherence[23,24]. Notably, PTSD has been shown to be associated with immunosuppression, viral replication, and clinical decline in PWH.[25] Taken together, these changes contribute to immunologic dysfunction, disinhibition of the inflammatory process, accelerated biologic aging, and manifestation of early-onset age-related comorbidities.[2,7] In other words, imbalances in various systems produce secondary abnormalities through a cascade of downstream mechanisms that all play crucial roles in the maintenance of homeostasis and health – the organizing concepts of allostatic states and allostatic load.

Only seven other studies have examined the associations between PTSD and morbidity and mortality among PWH; however, due to their study designs and analytical methods, are limited in their causal inference and can variably contradict.[2-8] One cross-sectional study of 118 adults with HIV from an urban medical center found PTSD to be associated with coronary artery disease but not pulmonary disease or CKD.[2] While another prospective cohort study of 700 women with HIV from large metropolitan cities found no such association between PTSD and subclinical carotid atherosclerosis.[5] Surprisingly, no known studies have examined the association between PTSD and AIDS among PWH. Still, some studies among PWH have examined other coinfections. One cross-sectional study of 171 adult men who have sex with men (MSM) with HIV from an urban medical center found PTSD to be associated with hepatitis C virus (HCV) coinfection.[3] A second cross-sectional study of 710 ART-naïve Rwandan women with HIV found PTSD to be associated with shingles.[4] PTSD has also been shown to be associated with neurocognitive impairment in a cross-sectional study of 189 active-duty and retired U.S. military personnel with HIV,[8] and several studies have reported its association with arthritis in the general population; while no known studies in any population have examined its association with multimorbidity.

Of particular interest was the attenuating effect of combat exposure on the association between PTSD and AIDS but no other association, and that multiple deployments did not modify any association examined. It was hypothesized that both would amplify the associations with PTSD, and with good reason. One prospective cohort study of 1,000 Australian Army Veterans found each additional year of military service, deployment, and decrease in rank was associated with an increased risk for all-cause mortality.[26] Similarly, another prospective cohort study of 1,448 Dutch World War II Veterans reported that those who had been wounded, been permanently disabled, or seen someone else die during deployment had an increased risk for all-cause mortality.[27] Other environmental exposures during combat deployment may also play a role, including toxins, burn pit emissions, fuels, and other chemicals.[28] For example, in a cross-sectional study of 363 World War II Veterans who had been exposed to mustard gas, PTSD was associated with three-, four-, and five-fold increased risks for urologic disease, ophthalmologic disorder, and pulmonary disease, respectively.[29] And yet, the potentially unexpected results from this study may be due to the healthy warrior effect, as service members who either self-select or are chosen for multiple deployments or combat roles are likely healthier, more resilient, and may be less prone to age-related comorbidities later in life. Another factor that may have introduced bias is that service members who deploy and experience combat often receive additional financial incentives, may be more likely to be promoted, and therefore would be at a higher paygrade; all of which may alter their life course and health status later in life.

A major strength of this current work is its robust analysis to attempt to estimate the causal effects of PTSD on morbidity and mortality. MSCM relate the exposure and censoring history, up to time *t*, to the corresponding counterfactual outcome at time *t*. IPTW and IPCW are employed

to control for both time-dependent confounding and selection bias due to informative censoring, respectively. The reweighted pseudo-population is then a representative sample of the overall study population, in which all measured covariates are balanced across exposure groups and LTFU is a random phenomenon with respect to covariates. Resultant estimates are consistent with causal effects under the assumption of no residual confounding or other biases. Other strengths of this study include its complete enumeration and enrollment of a nationally representative population; use of large repositories of patient-level EHR and military service records; objective measures for all variables assessed, including the use of standardized coding algorithms to define the outcomes of interest[18-20]; and possible generalizability to other older Veteran and non-Veteran populations. Limitations of this study include possible misclassification of the exposure and effect modifiers; possible selection bias due to the healthy warrior effect; that the assumptions of MSCM – exchangeability, consistency, positivity, and accuracy of the weight-generating model – were presumed true; expected but still considerable LTFU; that the true index traumatic stressor could not be ascertained; and non-generalizability to VWH not on ART. Bias analyses may be able to examine the extent to which misclassification and selection bias affected results, if at all; for MSCM, only positivity was assessed, the other three cannot be verified given the observational data; IPCW addressed concerns related to LTFU; not knowing the true index traumatic stressor does not invalidate these findings; and future work will examine the effects of PTSD on ART non-adherence and treatment failure in this population.

As HIV disease shifts to one that is more manageable and chronic, it is important that all providers recognize the roles traumatic stress and PTSD may play in morbidity and mortality. As shown here, PTSD has the potential to cause detrimental health consequences; particular attention should be directed towards the first decade post-diagnosis. Due to the syndemic nature of HIV and PTSD, it is recommended that providers who work with PWH adopt a trauma-informed model of HIV care, and that providers screen Veterans for PTSD so that their unique trauma history can help guide medical decisions and treatment.[30] Future research is needed to study how PTSD may accelerate biological aging, and investigate how pre-deployment resilience training and evidenced-based treatments for PTSD may mitigate these risks in this distinct, understudied population.

Author contributions

All authors contributed to the content of the manuscript and concurred with the decision to submit it for publication. KJV contributed to the conception and design of the study, acquisition of the data, statistical analysis, interpretation, and drafting the manuscript. VCM, BKA, PSS, and JLG contributed to the conception and design of the study, interpretation, drafting and critical revision of the manuscript, and supervision. KJV and VCM had full access to all data in the study, and KJV takes full responsibility for the integrity of the data and the accuracy of the analysis.

Declaration of interests

No funding was received to assist with the preparation of this manuscript. KJV, BKA, and JLG have no relevant financial or non-financial interests to disclose. VCM received support from the Emory CFAR and NIH/NIAID. VCM has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Eli Lilly, Bayer, Gilead Sciences, Merck, and ViiV. PSS received funding from the NIH and CDC. PSS has received

investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Gilead, Merck, and ViiV.

The views expressed are those of the authors and do not reflect the official views of the Uniformed Services University of the Health Sciences, the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc, the National Institutes of Health or the Department of Health and Human Services, the Department of Defense, the Defense Health Agency, the Departments of the Army, Navy or Air Force, the Department of Veterans Affairs, and U.S. Government. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

Data sharing

The datasets in the current study were stored and analyzed on secure VA servers. Although the data are not publicly available, they may be shared with investigators with appropriate VA credentials. All work was conducted in accordance with the Declaration of Helsinki. The study was approved by the Emory University Institutional Review Board and the Atlanta VA Medical Center Research and Development Committee.

Acknowledgements

We thank all those who currently serve or have ever served in the U.S. military. We also thank Dr. Robert H. Lyles (Department of Biostatistics, Rollins School of Public Health, Emory University) for his review and critical revision of the manuscript. This is an unfunded study and therefore at no point were sponsors involved.

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Table 1. Characteristics of OEF/OIF/OND Veterans with HIV by PTSD diagnosis (2001-2022).

	N=3,206[1] n (%)[2]	PTSD n=1,351 n (%)[2]	No PTSD n=1,855 n (%)[2]	P-value[3]
Sociodemographics				
Age at HIV diagnosis (years), median (IQR)	31·7 (9·5)	31·5 (9·3)	32·3 (9·6)	0·024
Sex, male	3,123 (97·4)	1,310 (97·0)	1,813 (97·7)	0·18
Race/ethnicity[5]				0·29
Black	1,493 (50·4)	609 (48·9)	884 (51·5)	
White	1,328 (44·8)	572 (45·9)	756 (44·1)	
Other	141 (4·8)	65 (5·2)	76 (4·4)	
Marital status[4,5]				<0·001
Married	651 (21·2)	312 (24·3)	339 (19·0)	
Never married	1,570 (51·1)	577 (44·9)	993 (55·6)	
Divorced/separated/widowed	851 (27·7)	397 (30·9)	454 (25·4)	
Educational attainment[4-6]				0·43
High school	1,629 (70·0)	690 (71·4)	939 (69·0)	
Vocational/technical	558 (24·0)	219 (22·7)	339 (24·9)	
College/university	140 (6·0)	57 (5·9)	83 (6·1)	
Household income (USD, annual)[4,5]				0·18
<20,000	537 (17·2)	214 (16·2)	323 (17·9)	
20,000-39,999	763 (24·4)	341 (25·9)	422 (23·4)	
40,000-74,999	1,146 (36·7)	492 (37·3)	654 (36·2)	
≥75,000	679 (21·7)	271 (20·6)	408 (22·6)	
Military history[7]				
Branch[4,8]				<0·001
Air Force	452 (14·1)	153 (11·3)	299 (16·1)	
Army	1,606 (50·0)	811 (60·0)	795 (42·7)	
Coast Guard	6 (0·2)	2 (0·1)	4 (0·2)	
Marines	377 (11·7)	179 (13·2)	198 (10·6)	
Navy	771 (24·0)	207 (15·3)	564 (30·3)	
Component[4,8]				0·0072
Active-duty	2,710 (78·3)	1,107 (76·3)	1,603 (79·7)	
Guard	398 (11·5)	196 (13·5)	202 (10·0)	
Reserve	354 (10·2)	148 (10·2)	206 (10·2)	
Rank/grade[4]				0·0071
Enlisted, E1-E4	910 (39·7)	366 (37·9)	544 (40·9)	
Enlisted, E5-E9	1,234 (53·8)	495 (51·3)	739 (55·6)	
Officer, O1-O9	151 (6·6)	104 (10·8)	47 (3·5)	
Length of service (years), median (IQR)[4]	6·6 (7·8)	6·3 (7·3)	6·9 (8·0)	0·019
Occupation[4,8]				<0·001
Infantry	400 (10·8)	212 (13·5)	188 (8·7)	
Service/supply	2,094 (56·3)	912 (58·2)	1,182 (54·9)	
All others	862 (23·2)	278 (17·7)	584 (27·1)	
Non-qualified/undesignated	363 (9·8)	165 (10·5)	198 (9·2)	
Number of deployments[4]				0·0033
1	2,442 (78·6)	984 (75·8)	1,458 (80·7)	
2	490 (15·8)	227 (17·5)	263 (14·6)	
≥3	174 (5·6)	88 (6·8)	86 (4·8)	
Combat exposure[9]	743 (23·2)	337 (24·9)	406 (21·9)	0·043
In-theater injuries (ever)[4]				
Combat	87 (2·7)	53 (3·9)	34 (1·8)	<0·001
Noncombat	772 (24·1)	390 (28·9)	382 (20·6)	<0·001
Discharge character[4]				0·003
Dishonorable	89 (3·0)	51 (4·0)	38 (2·2)	
Honorable	2,921 (97·0)	1,215 (96·0)	1,706 (97·8)	
HIV clinical history				
First CD4 count (cells/mL), median (IQR)[4]	569 (351)	555 (309)	585 (366)	0·17
Nadir CD4 count (cells/mL), median (IQR)[4]	407 (308)	379 (296)	425 (313)	<0·001
Last CD4 count (cells/mL), median (IQR)[4]	676 (386)	670 (369)	681 (397)	0·26
First HIV viral load (copies/mL), median (IQR)[4]	6,440 (56,950)	8,363 (64,950)	4,671 (50,563)	0·0034
Last HIV viral load (copies/mL), median (IQR)[4]	50 (30)	50 (30)	50 (30)	0·69
Mental health history				
Anxiety	1,382 (43·1)	772 (57·1)	610 (32·9)	<0·001
Depression	1,063 (33·2)	632 (46·8)	431 (23·2)	<0·001
High-risk sexual behavior	246 (7·8)	121 (9·0)	125 (6·7)	0·020
Military sexual trauma	351 (11·0)	223 (16·5)	128 (7·0)	<0·001
Substance use disorder	1,584 (49·4)	863 (63·9)	721 (38·9)	<0·001
Traumatic brain injury	28 (0·9)	21 (1·6)	7 (0·4)	<0·001
Morbidity and mortality				
Age-related comorbidities[10]				
AIDS	2,472 (77·1)	1,109 (82·1)	1,363 (73·5)	<0·001
Arthritis	486 (15·2)	281 (20·8)	205 (11·1)	<0·001
Asthma	236 (7·4)	137 (10·1)	99 (5·3)	<0·001
Cancer	42 (1·3)	19 (1·4)	23 (1·2)	0·68
Cardiovascular disease	157 (4·9)	91 (6·7)	66 (3·6)	<0·001
Cerebrovascular disease	50 (1·6)	32 (2·4)	18 (1·0)	0·0021
Chronic kidney disease	429 (13·4)	212 (15·7)	217 (11·7)	0·001
Chronic obstructive pulmonary disease	230 (7·2)	129 (9·6)	101 (5·4)	<0·001
Diabetes mellitus	235 (7·3)	109 (8·1)	126 (6·8)	0·17
Liver disease	300 (9·4)	157 (11·6)	143 (7·7)	<0·001
Multimorbidity[11]	1,204 (37·6)	623 (46·1)	581 (31·3)	<0·001
All-cause mortality	138 (4·3)	61 (4·5)	77 (4·2)	0·62

AIDS, acquired immunodeficiency syndrome; CMS, Centers for Medicare and Medicaid Services; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IQR, interquartile range; NCI, National Cancer Institute; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; USD, United States dollar; VA, United States Department of Veterans Affairs. [1]Includes all OEF/OIF/OND Veterans who became eligible for VA healthcare benefits between 7 October 2001 and 31 December 2020, who were diagnosed with HIV before 31 December 2020, and followed until 31 December 2022. [2]Percentages may not add to 100% due to rounding up to the nearest tenth. [3]Fisher's exact and χ^2 tests for categorical data; Mann-Whitney-Wilcoxon tests for continuous data. [4]Missing [PTSD, no PTSD]: race (n=105, n=139); marital status (n=65, n=48); education (n=385, n=494); household income (n=33, n=48), branch (n=53, n=50), component (n=53, n=69), rank (n=386, n=50), length of service (n=54, n=53), number of deployments (n=52, n=48), in-theater injuries (n=52, n=48), discharge character (n=85, n=111), military sexual trauma (n=3, n=13), first CD4 count(n=165, n=295), nadir CD4 count (n=174, n=311), last CD4 count (n=164, n=300), first HIV viral load (n=58, n=127), last HIV viral load (n=58, n=127). [5]Last updated on 31 December 2019. [6]College/university includes graduate school. [7]Last updated at military separation. [8]Not mutually exclusive categories. [9]Meets combat Veteran eligibility requirements. [10]ICD-9 and ICD-10 codes from NCI Comorbidity Index and CMS Chronic Condition Warehouse. [11]Co-occurrence of ≥2 age-related co-morbidities.

Table 2. Hazard ratios for age-related comorbidities and all-cause mortality due to PTSD, modified by number of deployments and combat exposure, among OEF/OIF/OND Veterans with HIV estimated by marginal structural Cox models (2001-2022, n=3,206).

	Crude HR[1,2] (95% CI)	P-value	Adjusted HR[1,2] (95% CI)	P-value
AIDS[3]	1·36 (1·17, 1·57)	<0·001	1·11 (1·00, 1·23)	0·042
Number of deployments		0·81		0·90
1	1·14 (0·93, 1·41)	0·062	1·27 (1·03, 1·57)	0·025
≥2	1·23 (1·02, 1·50)	0·034	1·37 (1·13, 1·67)	<0·001
Combat exposure[4]		<0·001		<0·001
No	1·53 (1·41, 1·66)	<0·001	1·23 (1·10, 1·38)	<0·001
Yes	0·57 (0·43, 0·74)	<0·001	0·63 (0·48, 0·82)	<0·001
Arthritis[3]	1·78 (1·58, 2·00)	<0·001	1·95 (1·76, 2·15)	<0·001
Number of deployments		0·84		0·97
1	1·62 (1·28, 2·06)	<0·001	1·80 (1·42, 2·29)	<0·001
≥2	2·00 (1·54, 2·60)	<0·001	2·22 (1·71, 2·89)	<0·001
Combat exposure[4]		0·16		0·14
No	1·86 (1·48, 2·33)	<0·001	2·03 (1·55, 2·67)	<0·001
Yes	2·21 (1·47, 3·32)	<0·001	2·45 (1·63, 3·69)	<0·001
Asthma[3]	1·77 (1·30, 2·40)	<0·001	1·84 (0·94, 3·62)	0·076
Number of deployments		0·99		0·99
1	1·73 (1·37, 2·68)	<0·001	1·92 (1·37, 2·68)	<0·001
≥2	1·41 (0·59, 3·38)	0·34	1·57 (0·66, 3·75)	0·31
Combat exposure[4]		0·19		0·18
No	1·57 (0·88, 2·78)	0·13	1·73 (0·76, 3·96)	0·19
Yes	1·59 (0·94, 2·73)	0·055	1·77 (1·04, 3·03)	0·036
Cancer[3]	1·07 (0·42, 2·74)	0·89	1·12 (0·36, 3·50)	0·84
Number of deployments		0·22		0·26
1	1·20 (0·49, 2·93)	0·59	1·33 (0·54, 3·26)	0·54
≥2	0·89 (0·44, 1·82)	0·89	0·99 (0·49, 2·02)	0·98
Combat exposure[4]		0·89		0·83
No	0·69 (0·25, 1·90)	0·48	1·07 (0·50, 2·30)	0·86
Yes	1·28 (0·53, 3·08)	0·48	1·42 (0·59, 3·42)	0·44
Cardiovascular disease[3]	1·68 (1·33, 2·14)	<0·001	1·57 (1·25, 1·97)	<0·001
Number of deployments		0·22		0·13
1	1·68 (1·41, 2·48)	<0·001	1·87 (1·41, 2·48)	<0·001
≥2	1·21 (0·82, 1·76)	0·15	1·34 (0·91, 1·96)	0·14
Combat exposure[4]		0·39		0·73
No	1·37 (0·92, 2·05)	0·12	2·01 (1·24, 3·25)	0·0052
Yes	1·79 (1·40, 2·30)	<0·001	1·99 (1·55, 2·55)	<0·001
Cerebrovascular disease[3]	1·88 (0·82, 4·29)	0·13	1·49 (0·59, 3·75)	0·40
Number of deployments		0·54		0·65
1	1·05 (0·49, 2·29)	0·75	1·17 (0·54, 2·54)	0·68
≥2	2·08 (1·12, 3·88)	0·010	2·31 (1·24, 4·31)	0·0094
Combat exposure[4]		0·50		0·57
No	1·87 (0·93, 3·76)	0·081	1·19 (0·55, 2·58)	0·67
Yes	1·80 (0·59, 5·55)	0·25	2·00 (0·65, 5·32)	0·23
Chronic kidney disease[3]	1·18 (1·00, 1·39)	0·054	1·21 (1·02, 1·43)	0·028
Number of deployments		0·66		0·61
1	1·04 (0·80, 1·34)	0·30	1·15 (0·89, 1·49)	0·27
≥2	0·98 (0·74, 1·30)	0·63	1·09 (0·82, 1·44)	0·57
Combat exposure[4]		0·93		0·67
No	1·11 (0·87, 1·42)	0·41	1·20 (0·88, 1·63)	0·26
Yes	1·05 (0·59, 1·86)	0·64	1·17 (0·66, 2·07)	0·59
Chronic obstructive pulmonary disease[3]	1·39 (1·06, 1·83)	0·018	1·46 (1·10, 1·92)	0·0082
Number of deployments		0·87		0·89
1	1·30 (0·96, 1·75)	0·062	1·44 (1·07, 1·94)	0·017
≥2	0·95 (0·77, 1·18)	0·65	1·06 (0·86, 1·31)	0·59
Combat exposure[4]		0·85		0·68
No	1·20 (0·86, 1·68)	0·28	1·11 (0·90, 1·37)	0·34
Yes	1·31 (0·75, 2·32)	0·21	1·46 (0·83, 2·58)	0·19
Diabetes mellitus[3]	0·99 (0·72, 1·38)	0·97	1·01 (0·62, 1·65)	0·96
Number of deployments		0·76		0·80
1	0·85 (0·63, 1·13)	0·62	0·94 (0·70, 1·26)	0·69
≥2	1·03 (0·84, 1·25)	0·22	1·14 (0·93, 1·39)	0·20
Combat exposure[4]		0·73		0·85
No	1·00 (0·85, 1·17)	0·98	1·06 (0·59, 1·90)	0·84
Yes	0·82 (0·44, 1·53)	0·84	0·91 (0·49, 1·70)	0·77
Liver disease[3]	1·22 (1·05, 1·42)	0·011	1·21 (0·87, 1·68)	0·26
Number of deployments		0·13		0·14
1	1·19 (1·02, 1·39)	0·012	1·32 (1·13, 1·54)	<0·001
≥2	1·00 (0·67, 1·50)	0·91	1·11 (0·74, 1·67)	0·60
Combat exposure[4]		0·41		0·52
No	1·33 (1·15, 1·55)	<0·001	1·32 (1·18, 1·48)	<0·001
Yes	0·91 (0·53, 1·56)	0·87	1·01 (0·59, 1·73)	0·96
Multimorbidity[5]	1·49 (1·33, 1·67)	<0·001	1·49 (1·24, 1·81)	<0·001
Number of deployments		0·41		0·25
1	1·38 (1·15, 1·67)	0·0042	1·53 (1·28, 1·84)	<0·001
≥2	1·26 (0·99, 1·60)	0·056	1·40 (1·10, 1·78)	0·0052
Combat exposure[4]		0·50		0·81
No	1·49 (1·24, 1·80)	<0·001	1·50 (1·25, 1·81)	<0·001
Yes	1·23 (1·13, 1·34)	<0·001	1·37 (1·25, 1·49)	<0·001
All-cause mortality	0·95 (0·73, 1·23)	0·68	0·90 (0·77, 1·05)	0·17
Number of deployments		0·23		0·21
1	0·86 (0·50, 1·50)	0·97	0·96 (0·55, 1·67)	0·89
≥2	1·10 (0·74, 1·62)	0·37	1·22 (0·82, 1·80)	0·33
Combat exposure[4]		0·92		0·73
No	0·89 (0·62, 1·29)	0·55	0·75 (0·44, 1·30)	0·31
Yes	0·80 (0·52, 1·22)	0·54	0·89 (0·58, 1·36)	0·60

AIDS, acquired immunodeficiency syndrome; CI, confidence interval; CMS, Centers for Medicare and Medicaid Services; HIV, human immunodeficiency virus; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; MST, military sexual trauma; NCI, National Cancer Institute; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; Ref, reference; SUD, substance use disorder; TBI, traumatic brain injury; VA, United States Department of Veterans Affairs. [1]Includes all OEF/OIF/OND Veterans who became eligible for VA healthcare benefits between 7 October 2001 and 31 December 2020, diagnosed with HIV before 31 December 2020, and censored on 31 December 2022. [2]Marginal structural Cox models with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, sex, education, income, marital status, MST, race, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. [3]ICD-9 and ICD-10 codes from NCI Comorbidity Index and CMS Chronic Condition Warehouse. [4]Meets VA combat Veteran eligibility requirements. [5]Co-occurrence of ≥2 age-related co-morbidities.

Supplemental Table 1. Diagnostic codes used to define variables of interest.

Variables	ICD-9 codes[1]	ICD-10 codes[1]
Acquired immunodeficiency syndrome	112.4, 112.84, 114.1, 114.2, 114.3, 114.9, 115.01, 115.02, 115.03, 115.04, 115.11, 115.12, 115.13, 115.14, 115.91, 115.92, 115.93, 115.94, 176, 200, 202.0, 202.1, 202.8, 200.5, 031.2, 010, 011, 012, 013, 014, 015, 016, 017, 018, 136.3, 046.3, 130	B20, B21, B22, B24
Anxiety disorder	300.00, 300.02, 300.09	F41.1, F41.3, F41.8, F41.9
Arthritis	714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91	M05.00, M05.011, M05.012, M05.019, M05.021, M05.022, M05.029, M05.031, M05.032, M05.039, M05.041, M05.042, M05.049, M05.051, M05.052, M05.059, M05.061, M05.062, M05.069, M05.071, M05.072, M05.079, M05.09, M05.20, M05.211, M05.212, M05.219, M05.221, M05.222, M05.229, M05.231, M05.232, M05.239, M05.241, M05.242, M05.249, M05.251, M05.252, M05.259, M05.261, M05.262, M05.269, M05.271, M05.272, M05.279, M05.29, M05.30, M05.311, M05.312, M05.319, M05.321, M05.322, M05.329, M05.331, M05.332, M05.339, M05.341, M05.342, M05.349, M05.351, M05.352, M05.359, M05.361, M05.362, M05.369, M05.371, M05.372, M05.379, M05.39, M05.40, M05.411, M05.412, M05.419, M05.421, M05.422, M05.429, M05.431, M05.432, M05.439, M05.441, M05.442, M05.449, M05.451, M05.452, M05.459, M05.461, M05.462, M05.469, M05.471, M05.472, M05.479, M05.49, M05.50, M05.511, M05.512, M05.519, M05.521, M05.522, M05.529, M05.531, M05.532, M05.539, M05.541, M05.542, M05.549, M05.551, M05.552, M05.559, M05.561, M05.562, M05.569, M05.571, M05.572, M05.579, M05.59, M05.60, M05.611, M05.612, M05.619, M05.621, M05.622, M05.629, M05.631, M05.632, M05.639, M05.641, M05.642, M05.649, M05.651, M05.652, M05.659, M05.661, M05.662, M05.669, M05.671, M05.672, M05.679, M05.69, M05.70, M05.711, M05.712, M05.719, M05.721, M05.722, M05.729, M05.731, M05.732, M05.739, M05.741, M05.742, M05.749, M05.751, M05.752, M05.759, M05.761, M05.762, M05.769, M05.771, M05.772, M05.779, M05.79, M05.7A, M05.80, M05.811, M05.812, M05.819, M05.821, M05.822, M05.829, M05.831, M05.832, M05.839, M05.841, M05.842, M05.849, M05.851, M05.852, M05.859, M05.861, M05.862, M05.869, M05.871, M05.872, M05.879, M05.89, M05.8A, M05.9, M06.00, M06.011, M06.012, M06.019, M06.021, M06.022, M06.029, M06.031, M06.032, M06.039, M06.041, M06.042, M06.049, M06.051, M06.052, M06.059, M06.061, M06.062, M06.069, M06.071, M06.072, M06.079, M06.08, M06.09, M06.0A, M06.1, M06.20, M06.211, M06.212, M06.219, M06.221, M06.222, M06.229, M06.231, M06.232, M06.239, M06.241, M06.242, M06.249, M06.251, M06.252, M06.259, M06.261, M06.262, M06.269, M06.271, M06.272, M06.279, M06.28, M06.29, M06.30, M06.311, M06.312, M06.319, M06.321, M06.322, M06.329, M06.331, M06.332, M06.339, M06.341, M06.342, M06.349, M06.351, M06.352, M06.359, M06.361, M06.362, M06.369, M06.371, M06.372, M06.379, M06.38, M06.39, M06.80, M06.811, M06.812, M06.819, M06.821, M06.822, M06.829, M06.831, M06.832, M06.839, M06.841, M06.842, M06.849, M06.851, M06.852, M06.859, M06.861, M06.862, M06.869, M06.871, M06.872, M06.879, M06.88, M06.89, M06.8A, M06.9, M08.00, M08.011, M08.012, M08.019, M08.021, M08.022, M08.029, M08.031, M08.032, M08.039, M08.041, M08.042, M08.049, M08.051, M08.052, M08.059, M08.061, M08.062, M08.069, M08.071, M08.072, M08.079, M08.08, M08.09, M08.0A, M08.1, M08.20, M08.211, M08.212, M08.219, M08.221, M08.222, M08.229, M08.231, M08.232, M08.239, M08.241, M08.242, M08.249, M08.251, M08.252, M08.259, M08.261, M08.262, M08.269, M08.271, M08.272, M08.279, M08.28, M08.29, M08.2A, M08.3, M08.40, M08.411, M08.412, M08.419, M08.421, M08.422, M08.429, M08.431, M08.432, M08.439, M08.441, M08.442, M08.449, M08.451, M08.452, M08.459, M08.461, M08.462, M08.469, M08.471, M08.472, M08.479, M08.48, M08.4A, M08.80, M08.811, M08.812, M08.819, M08.821, M08.822, M08.829, M08.831, M08.832, M08.839, M08.841, M08.842, M08.849, M08.851, M08.852, M08.859, M08.861, M08.862, M08.869, M08.871, M08.872, M08.879, M08.88, M08.89, M08.90, M08.911, M08.912, M08.919, M08.921, M08.922, M08.929, M08.931, M08.932, M08.939, M08.941, M08.942, M08.949, M08.951, M08.952, M08.959, M08.961, M08.962, M08.969, M08.971, M08.972, M08.979, M08.98, M08.99, M08.9A, M15.0, M15.1, M15.2, M15.3, M15.4, M15.8, M15.9, M16.0, M16.10, M16.11, M16.12, M16.2, M16.30, M16.31, M16.32, M16.4, M16.50, M16.51, M16.52, M16.6, M16.7, M16.9, M17.0, M17.10, M17.11, M17.12, M17.2, M17.30, M17.31, M17.32, M17.4, M17.5, M17.9, M18.0, M18.10, M18.11, M18.12, M18.2, M18.30, M18.31, M18.32, M18.4, M18.50, M18.51, M18.52, M18.9, M19.011, M19.012, M19.019, M19.021, M19.022, M19.029, M19.031, M19.032, M19.039, M19.041, M19.042, M19.049, M19.071, M19.072, M19.079, M19.09, M19.111, M19.112, M19.119, M19.121, M19.122, M19.129, M19.131, M19.132, M19.139, M19.141, M19.142, M19.149, M19.171, M19.172, M19.179, M19.19, M19.211, M19.212, M19.219, M19.221, M19.222, M19.229, M19.231, M19.232, M19.239, M19.241, M19.242, M19.249, M19.271, M19.272, M19.279, M19.29, M19.90, M19.91, M19.92, M19.93, M45.0, M45.1, M45.2, M45.3, M45.4, M45.5, M45.6, M45.7, M45.8, M45.9, M47.011, M47.012, M47.013, M47.014, M47.015, M47.016, M47.019, M47.021, M47.022, M47.029, M47.10, M47.11, M47.12, M47.13, M47.20, M47.21, M47.22, M47.23, M47.24, M47.25, M47.26, M47.27, M47.28, M47.811, M47.812, M47.813, M47.814, M47.815, M47.816, M47.817, M47.818, M47.819, M47.891, M47.892, M47.893, M47.894, M47.895, M47.896, M47.897, M47.898, M47.899, M47.9, M48.8X1, M48.8X2, M48.8X3, M48.8X4, M48.8X5, M48.8X6, M48.8X7, M48.8X8, M48.8X9
Asthma	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92	J45.20, J45.21, J45.22, J45.30, J45.31, J45.32, J45.40, J45.41, J45.42, J45.50, J45.51, J45.52, J45.901, J45.902, J45.909, J45.990, J45.991, J45.998, J82.83

Cancer	174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 154.0, 154.1, 230.3, 230.4, V10.05, V10.06, 182.0, 233.2, V10.42, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11, 185, 233.4, V10.46	C50.011, C50.012, C50.019, C50.021, C50.022, C50.029, C50.111, C50.112, C50.119, C50.121, C50.122, C50.129, C50.211, C50.212, C50.219, C50.221, C50.222, C50.229, C50.311, C50.312, C50.319, C50.321, C50.322, C50.329, C50.411, C50.412, C50.419, C50.421, C50.422, C50.429, C50.511, C50.512, C50.519, C50.521, C50.522, C50.529, C50.611, C50.612, C50.619, C50.621, C50.622, C50.629, C50.811, C50.812, C50.819, C50.821, C50.822, C50.829, C50.911, C50.912, C50.919, C50.921, C50.922, C50.929, D05.00, D05.01, D05.02, D05.10, D05.11, D05.12, D05.80, D05.81, D05.82, D05.90, D05.91, D05.92, Z85.3, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, D01.0, D01.1, D01.2, Z85.038, Z85.040, Z85.048, C54.1, C54.2, C54.3, C54.8, C54.9, D07.0, Z85.42, C34.00, C34.01, C34.02, C34.10, C34.11, C34.12, C34.2, C34.30, C34.31, C34.32, C34.80, C34.81, C34.82, C34.90, C34.91, C34.92, D02.20, D02.21, D02.22, Z85.110, Z85.118, C61, D07.5, Z85.46
Cardiovascular disease	427.31, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9, 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.4, 414.8, 414.9, 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91, 093.0, 440.0, 440.1, 440.2, 440.3, 440.4, 440.5, 440.6, 440.7, 440.8, 440.9, 441.0, 441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, 441.8, 441.9, 443.1, 443.2, 443.3, 443.4, 443.5, 443.6, 443.7, 443.8, 443.9, 447.1, 557.1, 557.9, V43.4	I48.0, I48.1, I48.11, I48.19, I48.2, I48.20, I48.21, I48.91, I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9, I20.0, I20.1, I20.8, I20.9, I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I24.0, I24.1, I24.8, I24.9, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.3, I25.41, I25.42, I25.5, I25.6, I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9, I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9, 170.0, 170.1, 170.2, 170.3, 170.4, 170.5, 170.6, 170.7, 170.8, 170.9, 171.0, 171.1, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9, 173.1, 173.8, 173.9, 177.1, 179.0, 179.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	363.34, 430.0, 430.1, 430.2, 430.3, 430.4, 430.5, 430.6, 430.7, 430.8, 430.9, 431.0, 431.1, 431.2, 431.3, 431.4, 431.5, 431.6, 431.7, 431.8, 431.9, 432.0, 432.1, 432.2, 432.3, 432.4, 432.5, 432.6, 432.7, 432.8, 432.9, 433.0, 433.1, 433.2, 433.3, 433.4, 433.5, 433.6, 433.7, 433.8, 433.9, 434.0, 434.1, 434.2, 434.3, 434.4, 434.5, 434.6, 434.7, 434.8, 434.9, 435.0, 435.1, 435.2, 435.3, 435.4, 435.5, 435.6, 435.7, 435.8, 435.9, 436.0, 436.1, 436.2, 436.3, 436.4, 436.5, 436.6, 436.7, 436.8, 436.9, 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.7, 437.8, 437.9, 438.0, 438.1, 438.2, 438.3, 438.4, 438.5, 438.6, 438.7, 438.8, 438.9, 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02	G45.0, G45.1, G45.2, G45.3, G45.4, G45.5, G45.6, G45.7, G45.8, G45.9, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, G46.9, H34.0, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62.0, I62.1, I62.2, I62.3, I62.4, I62.5, I62.6, I62.7, I62.8, I62.9, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.7, I63.8, I63.9, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.7, I64.8, I64.9, I65.0, I65.1, I65.2, I65.3, I65.4, I65.5, I65.6, I65.7, I65.8, I65.9, I66.0, I66.1, I66.2, I66.3, I66.4, I66.5, I66.6, I66.7, I66.8, I66.9, I67.0, I67.1, I67.2, I67.3, I67.4, I67.5, I67.6, I67.7, I67.8, I67.9, I68.0, I68.1, I68.2, I68.3, I68.4, I68.5, I68.6, I68.7, I68.8, I68.9, I69.0, I69.1, I69.2, I69.3, I69.4, I69.5, I69.6, I69.7, I69.8, I69.9, G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, G97.31, G97.32, I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.20, I60.21, I60.22, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.00, I63.011, I63.012, I63.013, I63.019, I63.02, I63.031, I63.032, I63.039, I63.09, I63.10, I63.111, I63.112, I63.113, I63.119, I63.12, I63.131, I63.132, I63.133, I63.139, I63.19, I63.20, I63.211, I63.212, I63.213, I63.219, I63.22, I63.231, I63.232, I63.233, I63.239, I63.29, I63.30, I63.311, I63.312, I63.313, I63.319, I63.321, I63.322, I63.323, I63.329, I63.331, I63.332, I63.333, I63.339, I63.341, I63.342, I63.343, I63.349, I63.39, I63.40, I63.411, I63.412, I63.413, I63.419, I63.421, I63.422, I63.423, I63.429, I63.431, I63.432, I63.433, I63.439, I63.441, I63.442, I63.443, I63.449, I63.49, I63.50, I63.511, I63.512, I63.513, I63.519, I63.521, I63.522, I63.523, I63.529, I63.531, I63.532, I63.533, I63.539, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.8, I63.81, I63.89, I63.9, I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22, I66.23, I66.29, I66.3, I66.8, I66.9, I67.841, I67.848, I67.89, I97.810, I97.811, I97.820, I97.821
Chronic kidney disease	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4	A18.11, A52.75, B52.0, C64.1, C64.2, C64.9, C68.9, D30.00, D30.01, D30.02, D41.00, D41.01, D41.02, D41.10, D41.11, D41.12, D41.20, D41.21, D41.22, D59.3, E08.21, E08.22, E08.29, E08.65, E09.21, E09.22, E09.29, E10.21, E10.22, E10.29, E10.65, E11.21, E11.22, E11.29, E11.65, E13.21, E13.22, E13.29, E74.8, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I70.1, I72.2, K76.7, M10.30, M10.311, M10.312, M10.319, M10.321, M10.322, M10.329, M10.331, M10.332, M10.339, M10.341, M10.342, M10.349, M10.351, M10.352, M10.359, M10.361, M10.362, M10.369, M10.371, M10.372, M10.379, M10.38, M10.39, M32.14, M32.15, M35.04, N00.0, N00.1, N00.2, N00.3, N00.4, N00.5, N00.6, N00.7, N00.8, N00.9, N00.A, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N01.A, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N02.A, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N03.A, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N04.A, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N05.A, N06.0, N06.1, N06.2, N06.3, N06.4, N06.5, N06.6, N06.7, N06.8, N06.9, N06.A, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N07.A, N08, N13.1, N13.2, N13.30, N13.39, N14.0, N14.1, N14.2, N14.3, N14.4, N15.0, N15.8, N15.9, N16, N17.0, N17.1, N17.2, N17.8, N17.9, N18.1, N18.2, N18.3, N18.30, N18.31, N18.32, N18.4, N18.5, N18.6, N18.9, N19, N25.0, N25.1, N25.81, N25.89, N25.9, N26.1, N26.9, Q61.02, Q61.11, Q61.19, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8, Q62.0, Q62.2, Q62.10, Q62.11, Q62.12, Q62.31, Q62.32, Q62.39, R94.4
Chronic obstructive pulmonary disease	490, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496	J40, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9, J47.0, J47.1, J47.9
Depressive disorder	296.3	F33.1, F33.2, F33.3, F33.4, F33.5, F33.6, F33.7, F33.8, F33.9
Diabetes mellitus	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01,	E08.00, E08.01, E08.10, E08.11, E08.21, E08.22, E08.29, E08.311, E08.319, E08.321, E08.3211, E08.3212, E08.3213, E08.3219, E08.329, E08.3291, E08.3292, E08.3293, E08.3299, E08.331,

	250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41	E08.3311, E08.3312, E08.3313, E08.3319, E08.339, E08.3391, E08.3392, E08.3393, E08.3399, E08.341, E08.3411, E08.3412, E08.3413, E08.3419, E08.349, E08.3491, E08.3492, E08.3493, E08.3499, E08.351, E08.3511, E08.3512, E08.3513, E08.3519, E08.3521, E08.3522, E08.3523, E08.3529, E08.3531, E08.3532, E08.3533, E08.3539, E08.3541, E08.3542, E08.3543, E08.3549, E08.3551, E08.3552, E08.3553, E08.3559, E08.359, E08.3591, E08.3592, E08.3593, E08.3599, E08.36, E08.37X1, E08.37X2, E08.37X3, E08.37X9, E08.39, E08.40, E08.41, E08.42, E08.43, E08.44, E08.49, E08.51, E08.52, E08.59, E08.610, E08.618, E08.620, E08.621, E08.622, E08.628, E08.630, E08.638, E08.641, E08.649, E08.65, E08.69, E08.8, E08.9, E09.00, E09.01, E09.10, E09.11, E09.21, E09.22, E09.29, E09.311, E09.319, E09.321, E09.3211, E09.3212, E09.3213, E09.3219, E09.329, E09.3291, E09.3292, E09.3293, E09.3299, E09.331, E09.3311, E09.3312, E09.3313, E09.3319, E09.339, E09.3391, E09.3392, E09.3393, E09.3399, E09.341, E09.3411, E09.3412, E09.3413, E09.3419, E09.349, E09.3491, E09.3492, E09.3493, E09.3499, E09.351, E09.3511, E09.3512, E09.3513, E09.3519, E09.3521, E09.3522, E09.3523, E09.3529, E09.3531, E09.3532, E09.3533, E09.3539, E09.3541, E09.3542, E09.3543, E09.3549, E09.3551, E09.3552, E09.3553, E09.3559, E09.359, E09.3591, E09.3592, E09.3593, E09.3599, E09.36, E09.37X1, E09.37X2, E09.37X3, E09.37X9, E09.39, E09.40, E09.41, E09.42, E09.43, E09.44, E09.49, E09.51, E09.52, E09.59, E09.610, E09.618, E09.620, E09.621, E09.622, E09.628, E09.630, E09.638, E09.641, E09.649, E09.65, E09.69, E09.8, E09.9, E10.10, E10.11, E10.21, E10.22, E10.29, E10.311, E10.319, E10.321, E10.3211, E10.3212, E10.3213, E10.3219, E10.329, E10.3291, E10.3292, E10.3293, E10.3299, E10.331, E10.3311, E10.3312, E10.3313, E10.3319, E10.339, E10.3391, E10.3392, E10.3393, E10.3399, E10.341, E10.3411, E10.3412, E10.3413, E10.3419, E10.349, E10.3491, E10.3492, E10.3493, E10.3499, E10.351, E10.3511, E10.3512, E10.3513, E10.3519, E10.3521, E10.3522, E10.3523, E10.3529, E10.3531, E10.3532, E10.3533, E10.3539, E10.3541, E10.3542, E10.3543, E10.3549, E10.3551, E10.3552, E10.3553, E10.3559, E10.359, E10.3591, E10.3592, E10.3593, E10.3599, E10.36, E10.37X1, E10.37X2, E10.37X3, E10.37X9, E10.39, E10.40, E10.41, E10.42, E10.43, E10.44, E10.49, E10.51, E10.52, E10.59, E10.610, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.10, E11.11, E11.21, E11.22, E11.29, E11.311, E11.319, E11.321, E11.3211, E11.3212, E11.3213, E11.3219, E11.329, E11.3291, E11.3292, E11.3293, E11.3299, E11.331, E11.3311, E11.3312, E11.3313, E11.3319, E11.339, E11.3391, E11.3392, E11.3393, E11.3399, E11.341, E11.3411, E11.3412, E11.3413, E11.3419, E11.349, E11.3491, E11.3492, E11.3493, E11.3499, E11.351, E11.3511, E11.3512, E11.3513, E11.3519, E11.3521, E11.3522, E11.3523, E11.3529, E11.3531, E11.3532, E11.3533, E11.3539, E11.3541, E11.3542, E11.3543, E11.3549, E11.3551, E11.3552, E11.3553, E11.3559, E11.359, E11.3591, E11.3592, E11.3593, E11.3599, E11.36, E11.37X1, E11.37X2, E11.37X3, E11.37X9, E11.39, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.51, E11.52, E11.59, E11.610, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.00, E13.01, E13.10, E13.11, E13.21, E13.22, E13.29, E13.311, E13.319, E13.321, E13.3211, E13.3212, E13.3213, E13.3219, E13.329, E13.3291, E13.3292, E13.3293, E13.3299, E13.331, E13.3311, E13.3312, E13.3313, E13.3319, E13.339, E13.3391, E13.3392, E13.3393, E13.3399, E13.341, E13.3411, E13.3412, E13.3413, E13.3419, E13.349, E13.3491, E13.3492, E13.3493, E13.3499, E13.351, E13.3511, E13.3512, E13.3513, E13.3519, E13.3521, E13.3522, E13.3523, E13.3529, E13.3531, E13.3532, E13.3533, E13.3539, E13.3541, E13.3542, E13.3543, E13.3549, E13.3551, E13.3552, E13.3553, E13.3559, E13.359, E13.3591, E13.3592, E13.3593, E13.3599, E13.36, E13.39, E13.40, E13.41, E13.42, E13.43, E13.44, E13.49, E13.51, E13.52, E13.59, E13.610, E13.618, E13.620, E13.621, E13.622, E13.628, E13.630, E13.638, E13.641, E13.649, E13.65, E13.69, E13.8, E13.9
High-risk sexual behavior	V69.2	Z72.51, Z72.52, Z72.53
Human immunodeficiency virus	042, V08	B20, Z21
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.0, 570.1, 570.2, 570.3, 570.4, 570.5, 570.6, 570.7, 570.8, 570.9, 571.0, 571.1, 571.2, 571.3, 571.4, 571.5, 571.6, 571.7, 571.8, 571.9, 573.3, 573.4, 573.8, 573.9, V42.7, 456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.5, 572.6, 572.7, 572.8	B18.0, B18.1, B18.2, B18.3, B18.4, B18.5, B18.6, B18.7, B18.8, B18.9, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73.0, K73.1, K73.2, K73.3, K73.4, K73.5, K73.6, K73.7, K73.8, K73.9, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6, K74.7, K74.8, K74.9, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Posttraumatic stress disorder	309.81	F43.12`
Substance use disorder	291, 292, 303, 304, 305	F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F55
Traumatic brain injury	800.0, 800.1, 800.2, 800.3, 800.4, 800.5, 800.6, 800.7, 800.8, 800.9, 801.0, 801.1, 801.2, 801.3, 801.4, 801.5, 801.6, 801.7, 801.8, 801.9, 803.0, 803.1, 803.2, 803.3, 803.4, 803.5, 803.6, 803.7, 803.8, 803.9, 804.0, 804.1, 804.2, 804.3, 804.4, 804.5, 804.6, 804.7, 804.8, 804.9, 805.1, 805.2, 805.3, 805.4, 805.5, 805.9, 851.0, 851.1, 851.2, 851.3, 851.4, 851.5, 851.6, 851.7, 851.8, 851.9, 852.0, 852.1, 852.2, 852.3, 852.4, 852.5, 852.6, 852.7, 852.8, 852.9, 853.0, 853.1, 853.2, 853.3, 853.4, 853.5, 853.6, 853.7, 853.8, 853.9, 854.0, 854.1, 959.01	S02.0, S02.1, S02.8, S02.91, S04.02, S04.03, S04.04, S06.0, S06.1, S06.2, S06.3, S06.4, S06.5, S06.6, S06.7, S06.8, S06.9, S07.1, T74.4

CMS, Centers for Medicare and Medicaid Services; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; NCI, National Cancer Institute. [1]ICD-9 and ICD-10 codes from NCI Comorbidity Index and CMS Chronic Condition Warehouse.

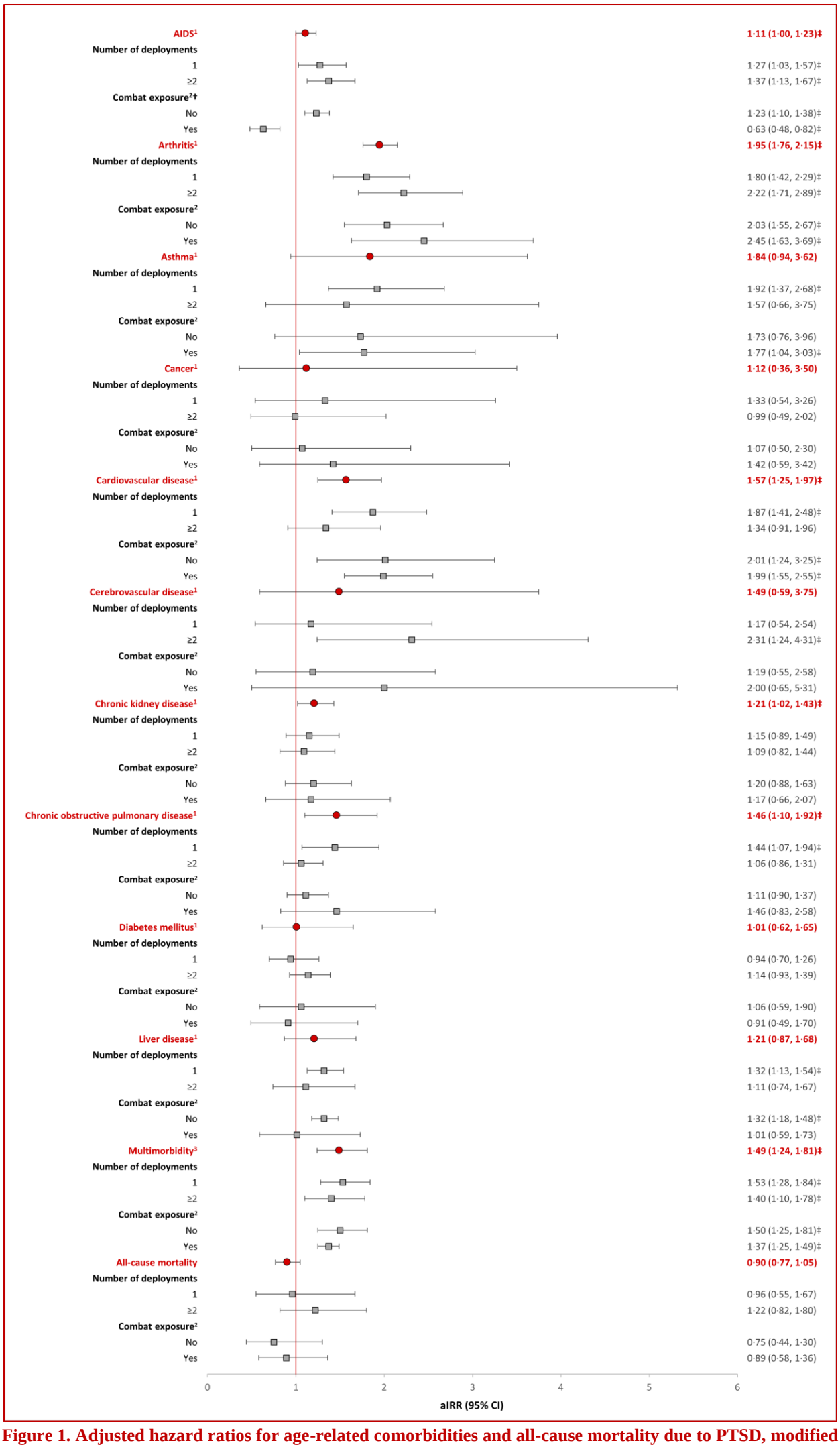


Figure 1. Adjusted hazard ratios for age-related comorbidities and all-cause mortality due to PTSD, modified by number of deployments and combat exposure, among OEF/OIF/OND Veterans with HIV estimated by marginal structural Cox models (2001-2022, n=3,206). Includes all OEF/OIF/OND Veterans who became eligible for VA healthcare benefits between 7 October 2001 and 31 December 2020, diagnosed with HIV before 31 December 2020, and censored on 31 December 2022. Reference group defined as those without PTSD. Marginal structural Cox models with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, sex, education, income, marital status, MST, race, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. "Positive" marker denotes effect estimates are statistically significant at α=0.05. [1]Age-related comorbidities defined using ICD-9 and ICD-10 codes from NCI Comorbidity Index and CMS Chronic Condition Warehouse. [2]Meets VA combat Veteran eligibility requirements. [3]Multimorbidity defined as co-occurrence of ≥2 age-related co-morbidities. AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CI, confidence interval; CMS, Centers for Medicare and Medicaid Services; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; NCI, National Cancer Institute; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; VA, United States Department of Veterans Affairs. †Wald test for interaction statistically significant at α=0.05. ‡Adjusted IRR statistically significant at α=0.05.

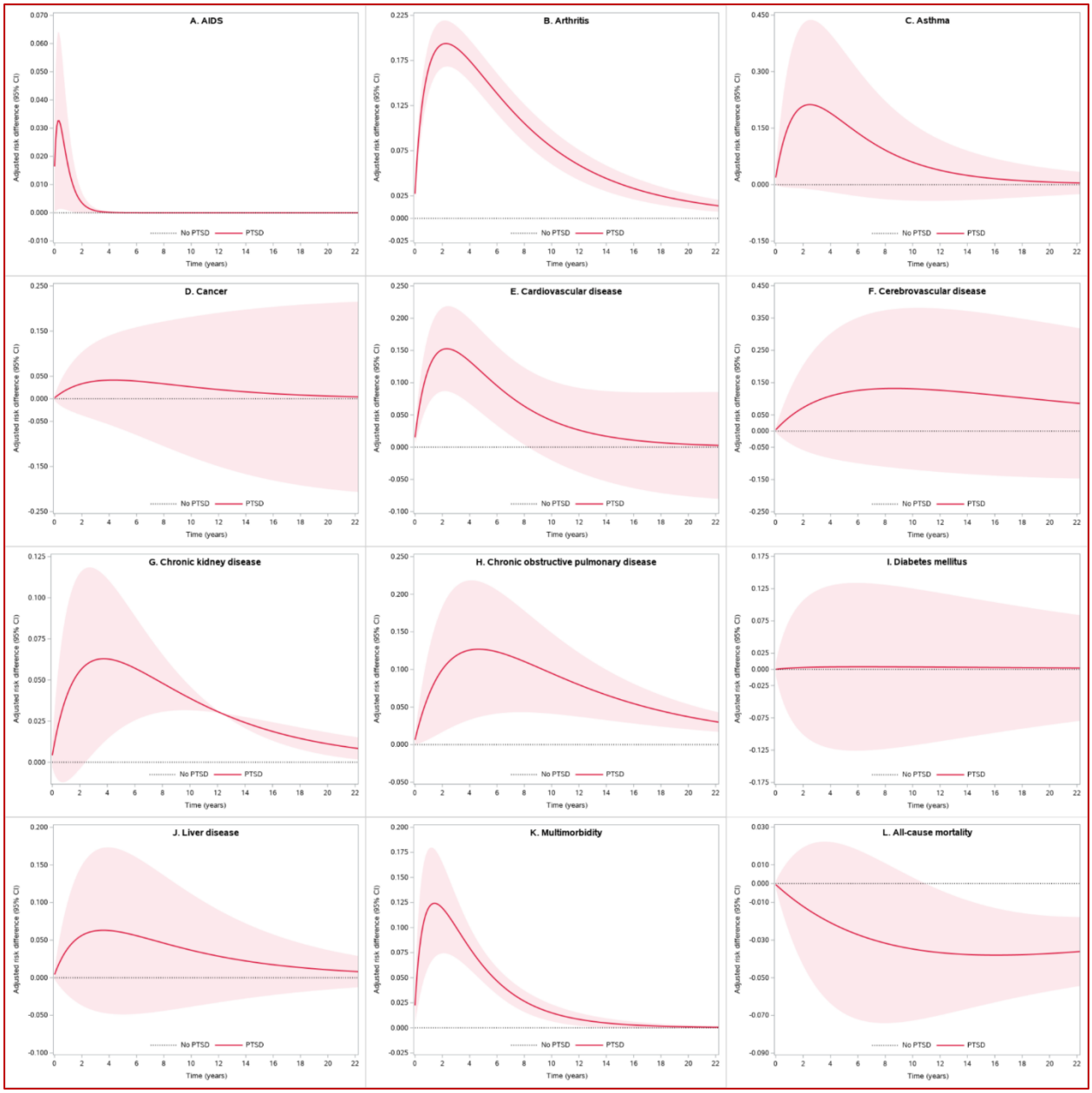
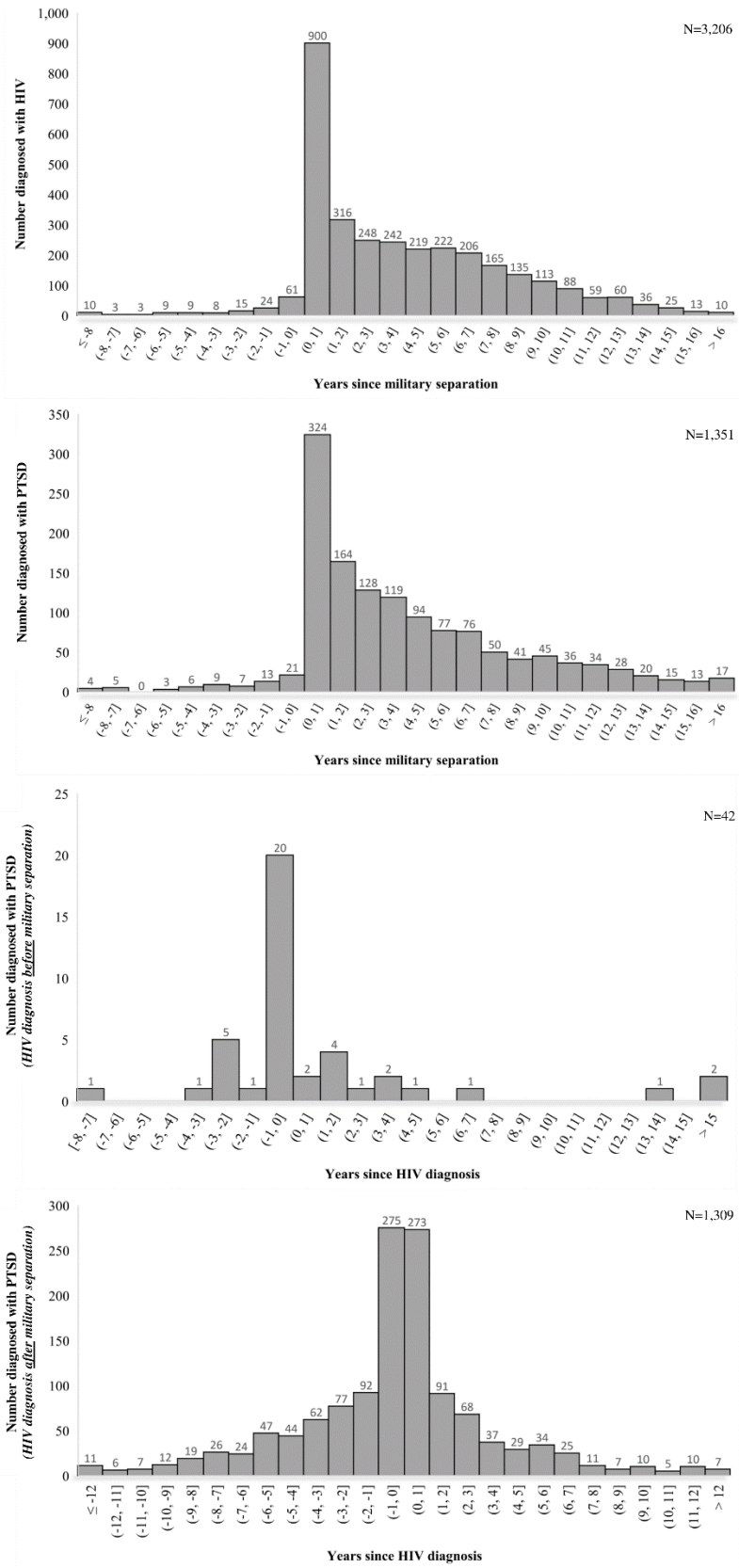
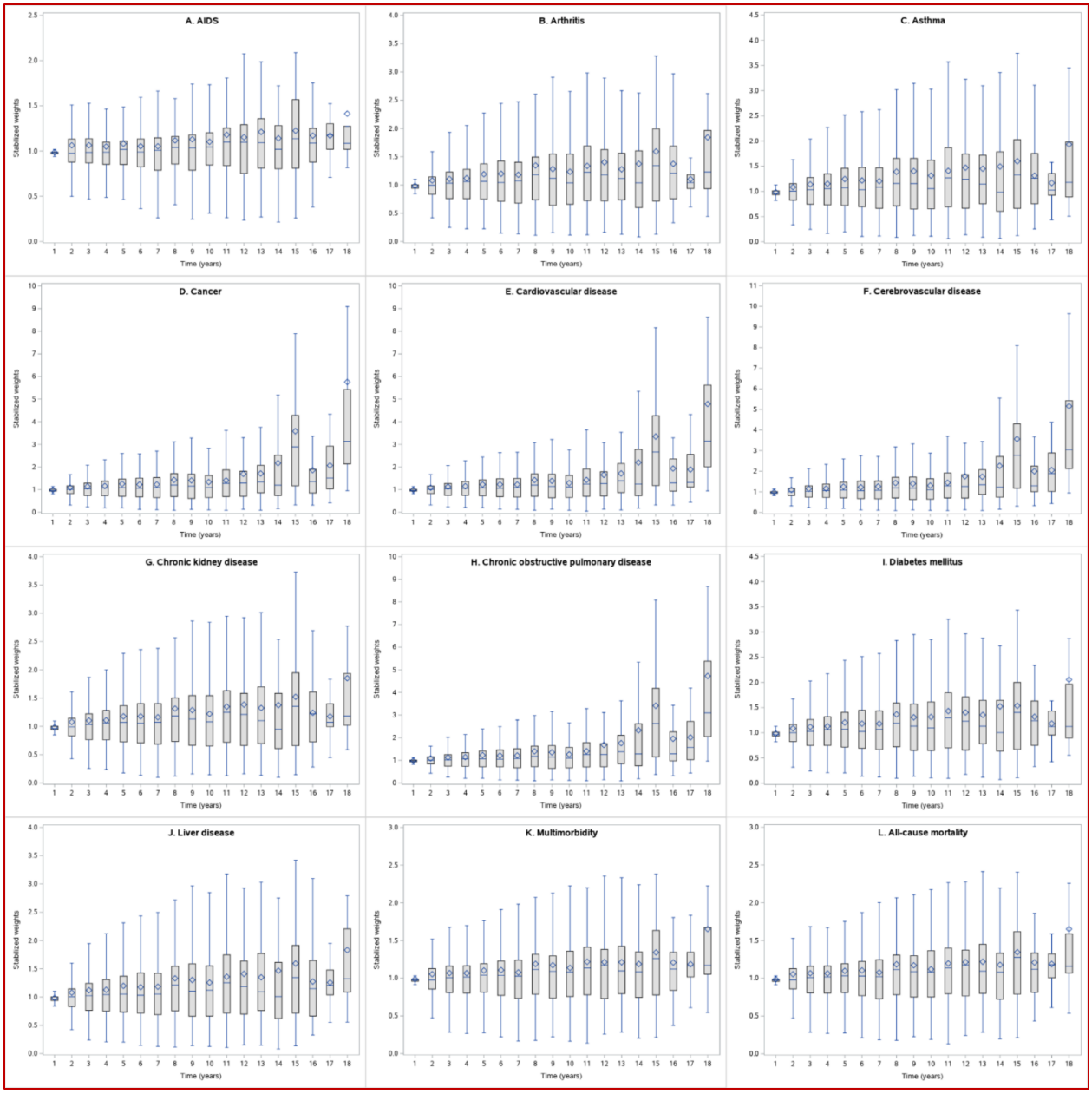


Figure 2. Adjusted risk differences of age-related comorbidities and all-cause mortality between those diagnosed with and without PTSD among OEF/OIF/OND Veterans with HIV on ART estimated by marginal structural Cox models (2001-2022, n=3,206). Includes all OEF/OIF/OND Veterans who became eligible for VA healthcare benefits between 7 October 2001 and 31 December 2020, diagnosed with HIV before 31 December 2020, and censored on 31 December 2022. Reference group defined as those without PTSD. Marginal structural Cox models with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, sex, education, income, marital status, MST, race, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. Age-related comorbidities defined using ICD-9 and ICD-10 codes from NCI Comorbidity Index and CMS Chronic Condition Warehouse. Multimorbidity defined as co-occurrence of ≥2 age-related co-morbidities. AIDS, acquired immunodeficiency syndrome; aIRR, adjusted incidence rate ratio; ART, antiretroviral therapy; CI, confidence interval; CMS, Centers for Medicare and Medicaid Services; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; NCI, National Cancer Institute; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; VA, United States Department of Veterans Affairs.



Supplemental Figure 1. Time of HIV and PTSD diagnoses since military separation, and time between HIV and PTSD diagnoses, among OEF/OIF/OND Veterans with HIV on ART (2001-2022). Includes all OEF/OIF/OND Veterans who became eligible for VA healthcare benefits between 7 October 2001 and 31 December 2020, who were diagnosed with HIV before 31 December 2020, and followed until 31 December 2022. ART, antiretroviral therapy; HIV, human immunodeficiency virus; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; VA, United States Department of Veterans Affairs.



Supplemental Figure 2. Distribution of final stabilized weights over time from marginal structural Cox models to estimate the effect of PTSD on age-related comorbidities and all-cause mortality among OEF/OIF/OND Veterans with HIV on ART (2001-2022, n=3,206). Includes all OEF/OIF/OND Veterans who became eligible for VA healthcare benefits between 7 October 2001 and 31 December 2020, who were diagnosed with HIV before 31 December 2020, and followed until 31 December 2022. Marginal structural Cox models with a time-dependent exposure (PTSD), adjusted for time-independent confounders (age at HIV diagnosis, sex, education, income, marital status, MST, race, TBI) and time-dependent confounders (anxiety disorder, depressive disorder, high-risk sexual behavior, SUD) by IPTW and IPCW. Age-related comorbidities defined using ICD-9 and ICD-10 codes from NCI Comorbidity Index and CMS Chronic Condition Warehouse. Multimorbidity defined as co-occurrence of ≥2 age-related co-morbidities. AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CMS, Centers for Medicare and Medicaid Services; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IPCW, inverse probability of censoring weighting; IPTW, inverse probability of treatment weighting; NCI, National Cancer Institute; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom, and New Dawn; PTSD, posttraumatic stress disorder; VA, United States Department of Veterans Affairs.

Chapter 6: Discussion

Major findings

Our data show that those with a PTSD diagnosis have increased STI incidence. Results also show that the incidence of PTSD diagnoses has declined over time in this population. However, renewed concern should be directed at recent increases in the incidences of gonorrhea, HIV, HPV, and syphilis. Results also suggest PTSD increases the rates (in order of increasing magnitude) of HPV, HIV, HBV, genital HSV, any STI, syphilis, chlamydia, gonorrhea, and HCV. Moreover, multiple deployments and combat exposure act antagonistically or synergistically with PTSD, if at all, depending on the STI examined. And that these associations between PTSD and STI incidence have increased and remain statistically significant.

Our data also suggest PTSD significantly increases the risk of ART non-adherence and the rate of ART modifications but may have more of an attenuated effect on treatment failure. Moreover, increased number of deployments amplifies the association between PTSD and ART non-adherence but not on ART modifications or treatment failure; combat exposure does not modify any of the associations examined. Moreover, this association between PTSD and ART modifications gradually increases during the first decade post-PTSD-diagnosis but subsequently stabilizes and remains statistically significant; while the associations with treatment failure also increases but are not statistically significant.

Finally, our data also suggests that PTSD increases the risks (in order of increasing magnitude) for AIDS, CKD, COPD, multimorbidity, CVD, and arthritis. Additionally, combat exposure decreases the association between PTSD and AIDS, while multiple deployments did not modify any association examined. And that these associations seem most pronounced within the first decade post-PTSD-diagnosis, followed by gradual waning yet still elevated risks.

Strengths and limitations

Strengths of this current work greatly outweigh the limitations. One strength includes its use of multiple large, nationally representative datasets: (1) CDW, a repository of over 20 million unique patient-level EHR data aggregated from across the VA's national health delivery system; (2) DaVINCI, a consolidated view of EHR for over 4 million unique Veterans during and after their military service; and (3) USVETS, which combines data from the VA, DoD, and commercial sources and contains data such as utilization of VA services and benefits, military history, geography, demographics, and socioeconomic factors for nearly 40 million Veterans. Our study also includes very large sample sizes of 1,570,654 Veterans and 3,206 VWH . Moreover, all three data sources allow a longitudinal analysis that spans 22 years of follow-up, much longer than any other study that has examined these same associations of interest. Further, because all three datasets are a complete record of the source population, analyses are expected to be generalizable to all Veterans. Results may also be transportable to external target populations, including older patients who receive government-sponsored healthcare, such as through Medicare and Medicaid. A second strength includes its use of a vast number of behavioral, clinical, laboratory, and pharmaceutical datapoints from EHRs, resulting in objective assessments of the exposure and most outcomes, and reducing the possibility of recall or social desirability biases. Nearly all other studies that have examined these associations of interest have used self-reported screening measures for PTSD; some have even used self-reported laboratory values and medical diagnoses. Here, all outcomes of interest were objectively measured. In addition, most outcomes were

operationalized using multiple definitions, such as in treatment failure, or used internationally recognized standards, such as NCI and CMS guidelines to map ICD-9 and -10 codes to co-morbidities. A third and final strength of this work is that it recognizes that there are biases, yes, but attempts to control for these to produce valid estimates of the truth. For example, time-dependent confounding and selection biases due to loss-to-followup were addressed using marginal structural models.

Although the datasets used in this current work are sources of strength, they are also a limitation in that they are secondary data sources designed for an entirely different purpose than to examine the associations of interest. The estimates may therefore be susceptible to unmeasured and residual confounding as covariates may have been either simply missing from the datasets or may have been recorded imperfectly or have some error. A second limitation is that there is likely misclassification of the effect modifier, combat exposure, as not all those who were exposed to combat may be eligible for or even apply to be a combat Veteran, as defined by the VA. A third and final limitation is that the data from Veterans who seek healthcare services from private providers, such as through the Veterans Choice Program, may be incomplete as these records are not readily available.

Potential impact

This current work is novel in many ways, including its breadth, depth, duration, and size. It is the first to examine the association between PTSD and the full gamut of STI experience, from infection and treatment to morbidity and mortality. Military service members and Veterans who have been exposed to combat should receive close and sustained attention in the form of screening, intervention, and other support services to identify and mitigate negative coping mechanisms associated with PTSD that may contribute to STI infection, treatment non-adherence, and morbidity and mortality.[1] Early after deployment or military discharge, wartime Veterans have reported feeling misunderstood or feared that they may be understood, in many social relationships and by strangers.[2] Clinicians should explore and validate these feelings of difficulty readjusting to civilian life.[2] However, the motivations underlying high-risk behaviors differ for each individual. For Veterans who experience PTSD symptoms of avoidance and who engage in high-risk behaviors to reduce loneliness, less riskier means of building human connection may be healthier.[2] Whereas for Veterans who experience PTSD symptoms of hyperarousal and who engage in HRSBs for a distraction or to achieve a "high," less risky activities that induce a similar "high" may be more beneficial.[2]

As OEF/OIF/OND Veterans age, it is important that policy-makers understand the long-term effects of combat, which may not directly relate to injuries sustained during deployment; and that healthcare workers be similarly informed of the associations between combat exposure, PTSD, and health in later life.[3] Clinicians should consider a trauma-informed model of care for VWH, which would include a routine integration of PTSD measurement over the course of HIV care, and psychotherapies and pharmacotherapies that can manage or alleviate PTSD symptoms.[4] Clinicians should also consider monitoring posttraumatic growth, whereby Veterans exhibit positive mental health growth in the face of traumatic life events.[4]

References

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