The risk of mental illness in people living with HIV in the UK

Gooden, Tiffany; Gardner, Michael; Wang, Jingya; Chandan, Joht; Beane, Abi ; Haniffa, Rashan ; Taylor, Stephen; Greenfield, Sheila; Manaseki-Holland, Semira; Thomas, G Neil; Nirantharakumar, Krishnarajah

DOI:
10.1016/S2352-3018(21)00319-2

Document Version
Peer reviewed version

Citation for published version (Harvard):
Gooden, T, Gardner, M, Wang, J, Chandan, J, Beane, A, Haniffa, R, Taylor, S, Greenfield, S, Manaseki-Holland, S, Thomas, GN & Nirantharakumar, K 2022, 'The risk of mental illness in people living with HIV in the UK: a propensity-score matched cohort study', *The Lancet HIV*, vol. 9, no. 3, pp. e172-e181. https://doi.org/10.1016/S2352-3018(21)00319-2

The risk of mental illness in people living with HIV in the UK: a propensity-score matched cohort study

Author names:

Tiffany E Gooden, Mike Gardner, Jingya Wang, Joht S Chandan, Abi Beane, Rashan Haniffa, Stephen Taylor, Sheila Greenfield, Semira Manaseki-Holland, G Neil Thomas, Krishnarajah Nirantharakumar

Author affiliations and addresses:

Institute for Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom (Ms Tiffany E Gooden MPH, Dr Mike Gardner PhD, Dr Jingya Wang PhD, Dr Joht S Chandan MBBS, Dr Stephen Taylor PhD, Professor Sheila Greenfield PhD, Dr Semira Manaseki-Holland PhD, Professor G Neil Thomas PhD, Professor Krishnarajah Nirantharakumar MD)

Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand (Dr Abi Beane PhD, Professor Rashan Haniffa PhD)

Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (Dr Abi Beane PhD, Professor Rashan Haniffa PhD)

Department of Infection and Immunology, University Hospitals Birmingham, Birmingham, United Kingdom (Dr Stephen Taylor PhD)

Corresponding authors:

G Neil Thomas, Institute for Applied Health Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom. E-mail: G.N.Thomas@bham.ac.uk

Semira Manaseki-Holland, Institute for Applied Health Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom. E-mail: S.ManasekiHolland@bham.ac.uk

Keywords: comorbidity, HIV, depression, anxiety, severe mental illness

Abstract

Background

Prevalence of mental illness is higher in people living with HIV (PLWH) compared to the general population, but the incidence of composite mental illness and its components is unclear. We aimed to identify the risk of incident mental illness along with individual conditions of depression, anxiety and severe mental illness (SMI) in PLWH in the UK.

Methods

Data for this population-based cohort was extracted from the IQVIA Medical Research Database, a nationally representative UK-based database of primary care electronic health records. We included adult (≥18y) PLWH, matched with people without HIV using propensity-score matching (1:1 ratio). The primary outcome was composite mental illness comprising a diagnosis of depression, anxiety or SMI. Secondary outcomes were individual mental health conditions. Cox proportional hazard regression models were used to compare the risk of each outcome between people with and without HIV. Each model excluded those with the outcome at baseline. Study period was from January 2000 to January 2020.

Findings

Of 7167 PLWH without mental illness at baseline, 586 developed a mental illness (Incidence Rate (IR) 19·6 per 1000 person-years) compared with 418 of the 7167 people without HIV (IR 12·1 per 1000 person-years), resulting in an adjusted hazard ratio [aHR] of 1·63 (95% CI 1·44, 1·85). PLWH had higher IRs for depression (15·4 per 1000 person-years), anxiety (7·2 per 1000 person-years) and SMI (1·6 per 1000 person-years) compared to people without HIV (7·9, 5·0 and 0·6 per 1000 person-years, respectively), translating to aHRs of 1·94 (95% CI 1·68, 2·24) for depression, 1·38 (95% CI 1·15, 1·66) for anxiety and 2·18 (95% CI 1·41, 3·39) for SMI.

Interpretation

PLWH have an increased risk for developing composite mental illness, depression, anxiety and SMI when compared to people without HIV. PLWH should be regularly screened for mental illness; however, there is a strong need to improve prevention of mental illness in PLWH and for more outreach programmes to ensure no PLWH are being underdiagnosed.

Funding

This study has no funding to report.

Research in context

Evidence before this study

Pubmed was systematically searched from database inception to 26th August 2021. Key terms were used such as ("HIV" AND "inciden*") AND ("depression" OR "anxiety" OR "schizophrenia" OR "bipolar" OR "psychosis"). No restrictions to the search were applied. All citations were assessed for studies that report the incidence of the aforementioned mental health conditions in people living with HIV (PLWH). Most studies that investigated the risk of mental illness in adult PLWH reported incidence rates with no comparison group. Only four studies were found to use comparison groups, two were conducted in the USA, one in South Korea and one in Denmark with follow-up times ranging from 1 to 17 years. The latter two were population-based. The South Korean study investigated the risk of depression only and was the only study to use a matched comparison group (by age and sex); however, they excluded those with a noncommunicable disease, did not control for alcohol use and neglected to report the exact incident rate ratio (IRR). One of the USA studies used a cohort of men who have sex with men from four major cities (thus excluded females and PLWH in rural areas) and reported a higher risk of depression in PLWH with or without sleep disturbances compared to people without HIV with or without sleep disturbances. The other USA study used a cohort of military members which were predominantly male (97%) and reported a significant increased risk of depression (IRR 2·9), bipolar disorder (IRR 3·3), anxiety (IRR 2·0) and psychosis/schizophrenia (IRR 6·2). The Danish study also reported an increased risk for schizophrenia (IRR 4·1) and psychosis (IRR 7·6).

Added value of this study

To our knowledge, this is the first study to report the risk of incident composite mental illness (comprised of depression, anxiety and severe mental illness including bipolar disorder, schizophrenia and psychosis) in PLWH compared to a matched comparison group of people without HIV. Additionally, this will be the first population-based study to report the risk of incident anxiety and severe mental illness using a matched comparison group. Between 2000 and 2020, we used a large UK primary care dataset representative of the UK population to report a 63% increased risk for incident composite mental illness, 94% increased risk for depression, 38% increased risk for anxiety and a 2-fold risk for severe mental illness in PLWH compared to people without HIV. Mental illness impacts wellbeing and quality of life in the general population, but in PLWH, it also impacts adherence to antiretroviral therapy and retention in care. The consequences of this is a weakened immune system and increased viral load which increases the risk of onward transmission of HIV and PLWH's risk for coinfections, AIDS and death. Our study highlights a large burden of mental illness among PLWH compared to those without HIV in the UK. Given the personal and public health ramifications of this, these findings are vital for policy and practice in the UK and other high-income countries.

Implications of all the available evidence

In combination with existing evidence, our findings improve the global understanding of the increased burden of mental illness in PLWH compared to people without HIV. Given the strengths of our study, our results are not only important for the UK, but also other high-income countries. Our findings support regular screening for mental illness in PLWH, but also highlights the need to improve prevention and ensure all PLWH are being reached by the existing screening programmes.

Introduction

People living with HIV (PLWH) often experience multiple coexisting conditions.[1] Mental illness is among the most common comorbidity in PLWH, including depression, anxiety and severe mental illness (SMI) (such as psychoses, schizophrenia and bipolar disorder).[1] In the UK, the prevalence of depression and anxiety in PLWH has been reported to range from 27-47% and 22-49%, respectively.[2] For PLWH, comorbid mental illness is associated with non-adherence to antiretroviral therapy (ART) and retention in HIV care[3] which can result in a loss of virologic control and worsening immune suppression. In turn, this increases the risk of onward transmission of HIV, the development of opportunistic infections, AIDS and death. Additional impacts of mental illness in PLWH include unemployment, increased hospitalisation, lowered quality of life and further comorbidities.[1,4,5] Thus, mental illness in PLWH is an important personal and public health issue.

Due to complex biological and psychosocial factors, a bidirectional relationship between mental illness and HIV is presumed.[6,7] High-risk behaviours such as injecting drug use, sex work, unprotected sex and multiple sexual partners are variable among people with mental illness; however, some evidence suggests that people with mental illness are more likely to engage in such behaviours and therefore more likely to be exposed to and become infected with HIV.[8,9] Conversely, potential drivers for developing mental illness in PLWH include persistent stress, stigma, discrimination, social isolation, drug-related side effects and neurological effects from the HIV infection.[7] Such negative experiences may support the development of mental illness in PLWH or exacerbate the effects of pre-existing psychosocial factors associated with HIV exposure.[7]

Many studies that have investigated the risk of incident mental illness in PLWH suffer from major limitations. One USA study reported more than a 2-fold risk for depression, anxiety and SMI; though, the sample comprised 97% male PLWH in the military and a non-matched comparison group.[10] Another USA study reported a higher risk for depression in PLWH compared to a non-matched comparison group which comprised only men who have sex with men (MSM) from urban settings.[11] A population-based Danish study reported a 7-fold risk for psychosis and 4-fold risk for schizophrenia;[6] however, a non-matched comparison group was used. The only population-based study to use a matched comparison group was conducted in South Korea; they reported an increased risk for depression (exact risk not reported); however, individuals with any noncommunicable disease (i.e. not only mental illness) at baseline were excluded and alcohol use was not controlled for.[12] No study has reported the risk of composite mental illness. Additionally, no study has investigated the risk of incident mental illness in PLWH within the UK where healthcare is free and access to HIV and mental healthcare is largely available. In the UK, HIV-specific services (for example, ART prescriptions and viral load testing) are available at HIV clinics. If mental health symptoms are identified and are not ART-related, these individuals are referred to their general practitioner or signposted to self-refer to mental health services as part of the National Health Service (NHS). Some larger HIV clinics have specialised psychological support; though this is limited. When a

general practitioner suspects or diagnosis mental illness, they too may signpost PLWH to self-refer to NHS mental health services for specialised psychology or psychiatry care. General practitioners can prescribe medication for depression and anxiety if necessary. PLWH can also access mental health support from non-governmental organisations available across the UK that offer free services such as helplines, peer support and tips for improving mental wellbeing.

To enable the development of effective interventions for reducing mental illness in PLWH, it is important to improve global understanding of whether PLWH experience an increased burden of mental illness compared to people without HIV and whether the risk differs across key groups of PLWH. We conducted the first population-based matched cohort study aimed at investigating the risk of incident composite mental illness in PLWH compared to people without HIV in the UK. Additionally, we aimed to report the risk of depression, anxiety and SMI in PLWH.

Methods

Study design and data source

Data for this population-based matched cohort study was derived from the IQVIA Medical Research Database (IMRD)-UK (formally known as The Health Improvement Network (THIN)). IMRD-UK is a nationally representative UK-based database of primary care electronic records.[13] Compared to external statistics and individual studies, diagnoses, lifestyle and anthropometric data within IMRD-UK is considered well-recorded and accurate.[14,15] Such data is recorded as Read codes, a hierarchical clinical coding system utilised in the UK since 1985 and checked for accuracy every 12 months.[16] To reduce the risk of under-recording of conditions and improve data quality, primary care practices were included 12 months after they installed electronic medical records and from the practice's acceptable mortality recording date. The study period was from 1st January 2000 to 1st January 2020.

Anonymised data were used throughout the study. Studies using IMRD-UK received initial ethical approval from the NHS South-East Multicentre Research Ethics Committee and the IQVIA Scientific Review Committee approved the study protocol (reference: 20SRC067).

Procedures

Individuals were eligible for the study if they were aged 18 years or older and had been registered with a primary care practice for at least 12 months (for data quality purposes). A Read code indicative of HIV infection such as HIV positive (e.g. code 43C.11), AIDS (e.g. code A788.00) or any cancers (e.g. code A789500) or coinfections (e.g. code A789300) resulting from HIV infection were required for PLWH whereas the absence of such Read codes were required for possible controls (supplemental table 1 page 2). For each outcome, PLWH and controls with the outcome of interest at baseline were excluded prior to propensity-score matching (PSM) and analysis.

Matching was done in two stages. Controls were extracted from IMRD-UK through exact matching to PLWH (20:1 ratio) based on region, age within 1 year, sex, ethnicity and deprivation. To match on further characteristics, PLWH were then matched to one of the extracted controls (1:1 ratio) using propensity scores calculated from logistic regression models with a caliper width of 0·2. The balance of matching was tested by comparing the propensity score density before and after matching and the standard mean difference (SMD) of propensity scores between the two groups.

The index date for PLWH was the date of the first Read code related to an HIV diagnosis for incident infections (diagnosed during the study period) and the date they became eligible for the study for those with a previous recorded Read code related to HIV (prevalent infections); controls were given the same index date as their matched counterpart. The exit date for each individual was the earliest date of the: outcome event, transfer date, last medical record available, death date or study end date. Individuals were followed-up prospectively from their index date to their exit date.

Covariates for PSM and for adjusted analyses were decided a priori based on biological and clinical importance and data availability.[6,17] These included the following covariates measured at the index date for each participant: age and index year as continuous variables and sex, ethnicity, smoking status, body mass index (BMI), substance abuse status, social deprivation, geographical region and status of existing cardiometabolic diseases (cardiovascular disease, hypertension and diabetes) as categorical variables. Substance abuse was a binary variable comprising those with or without a Read code indicative of alcohol, cocaine or other substance misuse (including injecting drug use). Townsend quintiles were used for social deprivation, which are based on employment status, household overcrowding and house/car ownership.[18] When investigating the risk for depression, existing anxiety and SMI were also entered as covariates for PSM and adjusted analyses; for investigating the risk of anxiety, existing depression and SMI were entered; and for investigating the risk of SMI, existing depression and anxiety were entered.

Outcomes

The primary outcome was composite mental illness, defined through Read codes (composite measure of depression, anxiety and SMI; each defined in supplemental table 1 page 2). Diagnoses are shared with the person's general practice in the majority of cases unless the person dissents to the sharing of their data. Secondary outcomes were the individual mental health conditions of depression, anxiety and SMI. We expected the coding of depression and SMI to be well coded as they form part of the Quality Outcome Framework which are performance indicators linked to general practice payments in the UK.[19] Additionally, we expected anxiety to be well coded as previous studies have demonstrated similar prevalence in IMRD-UK compared with national survey data.[20] For each outcome, only the first diagnosis was used; subsequent diagnoses were not considered.

Statistical methods

We used descriptive statistics to report baseline characteristics, presenting means for continuous variables and proportions for categorical variables. Crude and adjusted hazard ratios (aHRs) with their corresponding 95% CIs were calculated using Cox proportional hazard regression models. Using multinomial logistic regression, twenty multiple imputations by chained equations were undertaken to impute missing data for smoking, BMI, deprivation and ethnicity after matching; all variables used within the adjusted Cox regressions were entered in the regression. Due to the high proportion of missing ethnicity data, a missing indicator was added to adjusted regressions to control for any non-observable confounders that may contribute to the non-randomness of missing ethnicity data.[21] All statistical tests were two-tailed and P <0·05 was considered statistically significant. All analyses were conducted in Stata 14·0 (College Station, Texas, USA).

Sub-group analysis was undertaken to identify the risk of mental illness across various groups of PLWH compared to their HIV-negative counterparts. Sub-groups were determined a priori based on existing literature[17] and included the following: age (<40 and ≥40 years old), sex (male and female), index year (2000-2009 and 2010-2019), deprivation level (least deprived/lower two quintiles and most deprived/upper two quintiles), ethnicity (White and non-White), BMI (<30 and ≥30 kg/m^2), smoking status (current/ex-smoker and never smoked) and substance abuse status (substance abuser and non-substance abuser). Cox proportional hazard regression models were used to present aHRs with 95% CIs for each sub-group between people with and without HIV.

To test the robustness of PSM, we applied bounding and simulation sensitivity analyses as suggested by Becker[22] and Nannicini[23], respectively. To control for potential bias of including prevalent HIV infections, a sensitivity analysis was conducted among incident HIV infections only for each outcome. For the primary outcome, a sensitivity analysis was conducted that excluded those with missing ethnicity data to check whether the high proportion of missingness introduced bias. For each secondary outcome, a sensitivity analysis was undertaken that excluded individuals with a baseline diagnosis of any mental illness to check for potential bias.

Role of the funding source

There was no funding source for this study.

Results

Data was available for 15,837,846 people across all available general practices (figure 1). After applying the appropriate study period, age and data quality requirements, 9233 PLWH were identified and matched with 172,860 possible controls. Exclusion of those with mental illness at baseline left 7167 eligible PLWH for investigating the primary outcome; they were then matched with 7167 eligible controls. We included 7612 depression-free PLWH matched with 7612 depression-free controls for investigating the risk of depression, 8562 anxiety-free PLWH

matched with 8562 anxiety-free controls for the anxiety outcome and 9040 SMI-free PLWH matched with 9040 SMI-free controls for the SMI outcome.

No difference was found between density curves or SMDs after PSM; therefore, people with and without HIV were similar in age, sex, ethnicity, deprivation, BMI, smoking status and substance abuse for each outcome (table 1). For the primary outcome, the mean follow-up years were only slightly higher for people without HIV (4·8 years) than PLWH (4·2 years) (table 2). During follow-up, there were 586 and 418 diagnoses of mental illness in people with and without HIV, respectively. This resulted in an IR of 19·6 per 1000 person-years for PLWH and 12·1 for people without HIV. IRs for individual mental health conditions were also higher for PLWH compared to people without HIV (table 2).

After fully adjusting the models, PLWH had a 63% elevated risk for incident composite mental illness (95% CI 1·44, 1·85) (table 2). PLWH had a 94% increased risk for depression (95% CI 1·68, 2·24), 38% increased risk for anxiety (95% CI 1·15, 1·66) and a 2-fold risk for SMI (aHR 2·18, 95% CI 1·41, 3·39). When prevalent cases were removed from the model, PLWH remained at an increased risk for composite mental illness and depression whereas the effect size for anxiety and SMI were reduced (supplemental table 2 page 14). The risk of depression, anxiety and SMI were broadly similar when those with any mental illness at baseline were excluded (supplemental table 3 page 15). Removing those with missing ethnicity data did not impact the effect size for composite mental illness (data not shown).

Table 3 provides aHRs and 95% CIs for each outcome across sub-groups. Here we summarise the findings. Compared to males without HIV, male PLWH had an increased risk for composite mental illness, depression, anxiety and SMI. Aside from SMI, effect sizes for males were significantly larger compared to females. Female PLWH were not at a higher risk for any condition. Irrespective of age, PLWH had a heightened risk for all outcomes. Compared to White people without HIV, White PLWH had an increased risk for composite mental health, depression and anxiety. Non-White PLWH were only at a heightened risk for depression. The least and most deprived PLWH were at an increased risk for composite mental illness, depression and anxiety. Only the most deprived PLWH had a higher risk for SMI; though, the effect size for the least deprived was 4-fold. Obese PLWH only had an increased risk for depression. Non-obese PLWH had an increased risk for all outcomes. Regardless of smoking status, PLWH had a higher risk for composite mental illness, depression and SMI. Only PLWH that were current/ex-smokers had a higher risk for anxiety. PLWH substance abusers did not have an increased risk for any outcome. Non-substance abusers had an increased risk for all outcomes. PLWH had an elevated risk for composite mental illness and depression in the earlier (2000-2009) and later (2010-2019) index years. PLWH only had an increased risk for anxiety in the later index years and for SMI in the earlier index years.

Discussion

As access to ART continues to improve globally, ensuring optimal mental health will be imperative for healthy aging in PLWH. Understanding the relationship between HIV infection and mental illness will allow for improved interventions for prevention and treatment. To our knowledge, this is the first study to investigate the development of composite mental illness in PLWH compared to people without HIV. Using a population-based matched cohort derived from medical records, our findings demonstrates that PLWH are at a heightened risk for developing composite mental illness and individual conditions of depression, anxiety and SMI. The risk differed across sub-groups, most notably with sex. However, the risk for composite mental illness was elevated for PLWH irrespective of age, deprivation and smoking status, and the risk did not change over the 20-year study period.

Our results for the risk of depression, anxiety and SMI are in line with existing evidence.[6,10-12] However, our study may not be directly comparable due to differences in setting, sample characteristics, comparison group used and methods for classifying the exposure (i.e. HIV) and outcomes. Mental illness is detrimental to the wellbeing and quality of life of PLWH[4] and also poses a public health concern. PLWH with depression are 14% less likely to use ART than PLWH without depression which increases the risk of AIDS-defining infections and secondary transmission of HIV.[3] Thus, our findings of an 94% increased risk of depression in PLWH highlights a major implication for incident HIV and the healthy ageing and clinical care of PLWH in the UK. Current guidelines from the British HIV Association recommend annual screening for new or changes in mental health symptoms in PLWH,[24] of which our findings support. This could mean that PLWH may be more likely to be screened and diagnosed with mental illness compared with people without HIV. However, Public Health England reports that 75% of PLWH in the UK have unmet need for receiving help regarding isolation and loneliness and 10% of PLWH avoid accessing healthcare due to stigma and other reasons.[25] Therefore, it is also possible that PLWH are less likely to be screened and diagnosed with mental illness. Annual screening may not be sufficient for identifying all PLWH suffering from mental illness, particularly given the impact of mental illness on retention in care.

Considering the similarities of demographic and lifestyle characteristics between people with and without HIV in our study, PLWH's increased risk of mental illness appears to be from biological or psychosocial factors or a combination of the two. Persistent immune activation caused by HIV infection leads to the release of pro-inflammatory cytokines and central nervous system disturbances, potentially contributing to the pathophysiology of depression and schizophrenia.[26-28] Further to this, PLWH face significant social isolation due to stigma perpetuated by negative attitudes, behaviours and discrimination from society, community members and healthcare professionals.[29] HIV-related stigma can induce the development of mental illness, particularly when other risk factors are present.[7,29] HIV is often inextricably intertwined with social and psychological adversities. For instance, PLWH are more likely to be socially disadvantaged and suffer from financial, employment, housing and food insecurities, inadequate social networks and trauma caused by sexual or physical abuse.[7,8] Indeed, nearly a quarter of our sample were considered most deprived. Such circumstances are associated with mental illness in the general

population;[20] though, this syndemic with HIV creates barriers to accessing and utilising resources for mitigating the further psychological effects of living with HIV.[8] The biological mechanisms behind the increased risk of mental illness in PLWH should be further investigated to inform the development of pharmacological interventions. However, to address the complex relationship between mental illness and HIV-related psychosocial factors, stigma must be addressed and eliminated within the community and in healthcare settings. Furthermore, social and economic policy must be evaluated, improved and applied to conduce large-scale prevention of mental illness in this vulnerable population.

We found that male PLWH have a 2-fold risk for composite mental illness when compared to males without HIV, and this was significantly higher than the risk for female PLWH. Sexual orientation is not well recorded in primary care[30] though it is plausible that the proportion of MSM is higher within PLWH,[8] a group more targeted from various organisations and therefore more likely to be referred for mental health screening compared to MSM without HIV. The proportion of MSM may also be lower in people without HIV than in PLWH. However, MSM are often more socially disadvantaged and experience more discrimination, stigma and inequalities, thus more likely to develop mental illness.[8] Interestingly, White, non-obese and non-substance abusers had an increased risk for composite mental illness whilst non-White, obese and substance abusers did not. The latter three groups are more susceptible to social and economic inequalities and subsequently to mental illness; however, these groups have lower diagnoses and treatment rates in the UK.[20] Thus, our sub-group results may provide an indication that these groups of PLWH are vulnerable to being underdiagnosed rather than an indication of no risk of developing mental illness. This should be verified in future research.

Despite the strengths of using a population-based matched cohort and 20-year follow-up period, there are some limitations to mention. The main limitation is the lack of ART, CD4 and viral load data which is managed in HIV clinics rather than general practice. Between 2003 and 2015, Efavirenz was one of the most commonly prescribed antiretroviral agents, a drug associated with central nervous system and mood disturbances.[31] Such mood disturbances may have been recorded as a mental health condition and not as a drug-related phenomenon. Without ART data, it is unclear how the use of Efavirenz may have impacted our results. Transmission mode nor sexual orientation was available in our dataset which can be used to identify key populations of PLWH.[8] Nonetheless, our sub-group analysis on sex and substance abuse provides a valuable insight. Poorly recorded ethnicity data poses another limitation; however, we took a number of steps to limit and understand the potential bias caused. Our results are likely only generalisable to other high-income countries due to differences in cultural, environmental, societal and healthcare challenges with lower-income countries. Some of our sensitivity and sub-group analyses suffered from limited power and results should be interpreted with caution. The sensitivity analysis suffers from a reduced follow-up time which may impact results for conditions with long duration between symptom onset and diagnosis. It is possible that residual confounders between the groups could still exist after PSM; however, our sensitivity analyses indicated that it is unlikely that an unobserved

confounder would have largely impacted our results. Lastly, although the prevalence of HIV in IMRD-UK is close to national estimates (0.11% vs 0.15%, respectively),[32] it is possible that some PLWH may dissent to the sharing of their HIV diagnosis with their general practice.

We provide first-time evidence that PLWH are at an increased risk of developing composite mental illness compared to people without HIV. PLWH had a 63% increased risk for incident composite mental illness, a 94% increased risk for depression, a 38% increased risk for anxiety and a 2-fold risk for SMI. Our findings support current UK guidelines to annually screen for mental illness in PLWH; however, future research should investigate whether screening is sufficient for identifying all PLWH at risk for mental illness and how to reach groups of PLWH at risk for underdiagnosis. Our findings highlight the need to determine effective interventions for reducing mental illness in PLWH, including pharmacological interventions, reducing stigma and improving social and economic policies for addressing the complex psychosocial factors associated with mental illness among PLWH.

Contributors

This study contributed to the PhD thesis for the main author TEG. The following authors contributed to the conceptualisation of the study: TEG, MG, JW, AB, RH, GNT and KN. TEG, MG, JW, KN and GNT developed the protocol for the study. TEG, MG and JW completed the ethics application. TEG completed the literature search, drafted the manuscript and conducted all analyses with guidance from JSC and ST. JW validated the data. Supervisors of the study were SG, SMH, GNT and KN. All authors reviewed and critically appraised the manuscript revision, approved the final version for submission, had full access to all the data in this study, and had responsibility for the decision to submit for publication.

Funding

There is no funding to declare in this study.

Declaration of Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

IMRD-UK data governance does not allow us to share individual patient data, and therefore, only metadata are presented. Researchers may apply for individual patient data access at https://www.iqvia.com/solutions/real-world-value-and-outcomes (contact tab).

References

1. De Francesco D, Sabin CA, Reiss P. Multimorbidity patterns in people with HIV. *Curr Opin HIV AIDS*. 2020;**15**:110-7.
2. Chaponda M, Aldhouse N, Kroes M, Wild L, Robinson C, Smith A. Systematic review of the prevalence of psychiatric illness and sleep disturbance as co-morbidities of HIV infection in the UK. *Int J STD AIDS*. 2018;**29**:704-13.
3. Tao J, Vermund SH, Qian H-Z. Association between depression and antiretroviral therapy use among people living with HIV: a meta-analysis. *AIDS Behav*. 2018;**22**:1542-50.
4. Bagheri Z, Taheri M, Motazedian N. The impacts of depression and anxiety on quality of life among patients with HIV/AIDS and their spouses: testing dyadic dynamics using the actor-partner interdependence model. *AIDS Care*. 2019;**31**:1500-8.
5. Miners A, Phillips A, Kreif N, Rodger A, Speakman A, Fisher M, et al. Health-related quality-of-life of people with HIV in the era of combination antiretroviral treatment: a cross-sectional comparison with the general population. *Lancet HIV*. 2014;**1**:e32-e40.
6. Helleberg M, Pedersen MG, Pedersen CB, Mortensen PB, Obel N. Associations between HIV and schizophrenia and their effect on HIV treatment outcomes: a nationwide population-based cohort study in Denmark. *Lancet HIV*. 2015;**2**:e344-e50.
7. Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. *Curr Psychiatry Rep*. 2015;**17**:530.
8. UNAIDS. 2020 Global AIDS Update. Seizing the moment, tackling entrenched inequalities to end epidemics. UNAIDS; 2020.
9. Meade CS, Sikkema KJ. HIV risk behavior among adults with severe mental illness: a systematic review. *Clin Psychol Rev*. 2005;**25**:433-57.
10. Mirza RA, Eick-Cost A, Otto JL. The risk of mental health disorders among US military personnel infected with human immunodeficiency virus, active component, US Armed Forces, 2000-2011. Armed forces health surveillance center silver spring md; 2012.
11. Irwin MR, Archer G, Olmstead R, Brown TT, Teplin LA, Patel SR, et al. Increased risk of depression in non-depressed HIV infected men with sleep disturbance: prospective findings from the Multicenter AIDS Cohort Study. *EBioMedicine*. 2018;**36**:454-60.
12. Kim JH, Noh J, Kim W, Seong H, Kim JH, Lee WJ, et al. Trends of age-related non-communicable diseases in people living with HIV and comparison with uninfected controls: A nationwide population-based study in South Korea. *HIV Med*. 2021.
13. IQVIA. U EMR - IQVIA Medical Reserach Data. Improving patient outcomes with evidence-based research: IQVIA; 2020. https://www.iqvia.com/library/fact-sheets/uk-emr-iqvia-medical-research-data (accessed 08 Sept 2021).
14. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2007;**16**:393-401.
15. Blak B, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *J Innov Health Inform*. 2011;**19**:251-5.

16. Booth N. What are the read codes? *Health libraries review*. 1994;**11**:177-82.
17. Remien RH, Stirratt MJ, Nguyen N, Robbins RN, Pala AN, Mellins CA. Mental health and HIV/AIDS: the need for an integrated response. *AIDS (London, England)*. 2019;**33**:1411.
18. Yousaf S, Bonsall A. UK Townsend Deprivation Scores from 2011 census data. Economic and Social Research Council; 2017.
19. NHS Digital. Quality and Outcomes Framework (QOF) business rules v42 2019-2020 baseline release: NHS Digital. https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/quality-and-outcomes-framework-qof/quality-and-outcome-framework-qof-business-rules/quality-and-outcomes-framework-qof-business-rules-v42-2019-2020-baseline-release (accessed 08 Sept 2021).
20. McManus S, Bebbington P, Jenkins R, Brugha T. Mental health and wellbeing in England: Adult psychiatric morbidity survey 2014. 2016. NHS Digital: Leeds; 2016.
21. Sholle ET, Pinheiro LC, Adekkanattu P, Davila III MA, Johnson SB, Pathak J, et al. Underserved populations with missing race ethnicity data differ significantly from those with structured race/ethnicity documentation. *J Am Med Inform Assoc*. 2019;**26**:722-9.
22. Becker SO, Caliendo M. Sensitivity analysis for average treatment effects. *Stata J*. 2007;**7**:71-83.
23. Nannicini T. Simulation-based sensitivity analysis for matching estimators. *Stata J*. 2007;**7**:334-50.
24. Angus B, Brook G, Awosusi F, Barker G, Boffito M, Das S, et al. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals. British HIV Association; 2019.
25. Nash S, Desai S, Croxford S, Guerra L, Lowndes C, Connor N, et al. Progress towards ending the HIV epidemic in the United Kingdom: 2018 report. London: Public Health England; 2018.
26. Köhler C, Freitas T, Maes Md, De Andrade N, Liu C, Fernandes B, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand*. 2017;**135**:373-87.
27. Müller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. *Schizophr Bull.* 2018;**44**:973-82.
28. Poudel-Tandukar K, Bertone-Johnson ER, Palmer PH, Poudel KC. C-reactive protein and depression in persons with human immunodeficiency virus infection: the Positive Living with HIV (POLH) Study. *Brain Behav Immun*. 2014;**42**:89-95.
29. Rueda S, Mitra S, Chen S, Gogolishvili D, Globerman J, Chambers L, et al. Examining the associations between HIV-related stigma and health outcomes in people living with HIV/AIDS: a series of meta-analyses. *BMJ Open*. 2016;**6**:e011453.
30. Lau F, Antonio M, Davison K, Queen R, Devor A. A rapid review of gender, sex, and sexual orientation documentation in electronic health records. *J Am Med Inform Assoc*. 2020;**27**:1774-83.
31. Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). *HIV Med*. 2014;**15**:1-85.
32. Public Health England. Prevalence of HIV infection in the UK in 2018. England: Public Health England; 2019.