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Risk factors and impact of patterns of co-occurring comorbidities in people living with HIV

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Short title: Determinants and impact of patterns of comorbidity in PLWH

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Abstract

Aims: To assess associations of comorbidity patterns observed in people living with HIV (PLWH) with risk factors and health outcomes.

Methods: Common patters of comorbidities in PLWH participating in the POPPY study were determined using principal component analysis and a severity score for each pattern was derived. Associations between each pattern's severity score and risk factors were assessed using median regression. The independent associations of patterns' severity scores with self-reported physical and mental health (SF-36 summary scores) were assessed using linear regression, with functional impairment (Lawton IADL<8) and hospitalization in last year using logistic regression and with number of general practitioner (GP) visits using Poisson regression.

Results: 1073 PLWH were analysed: 85.2% male, median (IQR) age 52 (47-59) years, 98% on therapy. Duration of HIV was associated with higher severity in 4/6 of patterns: cardiovascular diseases (CVD), mental health problems, metabolic disorders and chest/other infections (all p's≤0.001). Prior AIDS was associated with higher severity scores for the same patterns and for the pattern of cancers (p<0.001). CVD was associated with poorer physical health (p=0.02), higher risk of functional impairment (p=0.02) and hospitalization (p<0.001) and with higher number of GP visits (p<0.001). Severity of mental health (all p's<0.001) and of chest/other infections patterns negatively affected all the five health outcomes.

Conclusion: Common patterns of comorbidities seen in PLWH appear to have different risk factors and to differently affect health outcomes. These findings may assist the development of targeted intervention to prevent, treat and manage the increasingly prevalent multimorbidity in PLWH.

Key words: HIV; comorbidities; patterns of comorbidities; multimorbidity

Introduction

The widespread use of combination antiretroviral treatment (cART) has led to an increase in life expectancy of people living with HIV (PLWH) in many regions of the world [1], resulting in major demographic changes that are expected to continue. For example, studies have estimated that up to 73% of PLWH in the Netherlands will be aged 50 years or older in 2030 [2], with similar proportions in Italy and the USA [3]. As a result, PLWH are experiencing an increasing burden of comorbidities [4] that is also expected to further increase; the same studies have estimated that the proportions of PLWH with at least one comorbidity would reach 84% in the Netherlands by 2030 and 89% in Italy and the USA by 2035.

We have reported a tendency for comorbidities to co-occur in the same HIV-positive individual at prevelances that are higher than those expected by chance alone and to occur in specific patterns [5]. Whilst knowledge of frequent patterns of comorbidities could inform decisions for prevention strategies, a better understanding of the mechanistic basis underlying these patterns and the burden they pose on PLWH and on the healthcare system is required.

Both in the general population and in populations of PLWH, most of the research published to date has focused on determinants of multimorbidity rather than of specific patterns. Among PLWH, studies have reported associations of multimorbidity with age and obesity [6], smoking [7] and duration of HIV infection [8, 9]. However, considering the diverse nature of conditions and comorbidities that could be encompassed into a definition of multimorbidity, these findings are unlikely to provide generalizable evidence of the causes underlying specific patterns. The two previous studies that focused on data-driven patterns of comorbidities in PLWH only investigated associations with one selected factor: Goulet et al. [10] found hepatits C virus co-infection to be associated with patterns of mental health problems and alcohol-related complications, while Kim et al. [11] reported an association of obesity with metabolic and behavioral problems. Little is known about the impact of HIV-related factors and other non-HIV-related modifiable and non-modifiable factors on specific patterns of comorbidities commonly seen in PLWH.

Similarly, whilst there is some evidence of the impact of multimorbidity on health outcomes such as quality of life of PLWH [12] and healthcare costs [13], there are no data on the impact of specific patterns of comorbidities to reveal those with the greatest burden for both patients and the healthcare system. Different patterns of comorbidities can be expected to differentially affect quality of life and use of healthcare resources. Moreover, the effect of a certain pattern can be greater (or lower) than the sum of the independent effects of all comorbidities within the pattern.

The aims of this study were (i) to investigate HIV-related and non-HIV-related risk factors for common patterns of comorbidities observed in PLWH seen for care in the UK and Ireland, and (ii) to evaluate associations of each pattern with self-reported health outcomes such as quality of life, functional impairment and healthcare resource use.

Methods

Study participants

The Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) study is an observational study that aims to examine the effects of ageing on the clinical outcomes of PLWH in the UK and Ireland. Full details have been described previously [14]. Briefly, two cohorts of PLWH were recruited from eight HIV outpatient clinics in London, Brighton (UK) and Dublin (Ireland) between April 2013 and January 2016: an 'older' group of PLWH aged ≥50 years and a younger group of PLWH aged between 18 and 50 years. Inclusion criteria were: documented presence of HIV infection, white or black-African ethnicity, likely route of HIV acquisition via sexual exposure and ability to comprehend the study information leaflet. The younger group of PLWH was frequency matched on gender, ethnicity, sexual orientation and location (in or out of London) to the older PLWH. In addition, the study recruited a group of HIV-negative individuals aged ≥50 years which was not included in the present analysis. These inclusion criteria were selected to ensure that study participants were representative of the wider population of PLWH over the age of 50 in the UK and Ireland, as has previously been shown [14]. The study was approved by the UK National Research Ethics Service (NRES; Fulham London, UK number 12/LO/1409). All participants provided written informed consent.

Patterns of comorbidities

We considered a list of 65 individual comorbidities (see Supplementary Table 1) obtained as follows. Full clinical history, medications and healthcare resources used over the year preceding the study visit were obtained via a structured interview with trained staff who, where possible, also reviewed hospital notes to validate the presence of comorbidities. Participants were asked whether they ever experienced any of the comorbidities or medical conditions from a detailed list and to report any other relevant comorbidity not included in the initial list. Answers to these free-text questions, reasons for any healthcare utilization over the previous year, and use of (non-antiretroviral) medication in the previous year were also examined to update the existing list of comorbidities or to include additional ones. Congenital diseases and conditions with a prevalence <1.5% () in the study population were subsequently excluded.

As previously described [5], principal component analysis (PCA) with *oblimin* rotation was applied to the matrix containing the pairwise associations (as measured by the Somers' *D*) between the 65 comorbidities. Six components (i.e. patterns) were extracted as suggested by very simple structure criterion [15] and comorbidities associated with each pattern (i.e. with a correlation >0.40) were reported. For each participant and each pattern, a severity score for that pattern was obtained using data on the presence/absence of comorbidities and coefficients returned by the PCA (rescaled so that the lowest score is 0). Severity scores were proportional to the number of comorbidities included in the pattern that were present in an individual, with higher scores indicating a greater number of comorbidities characterising the pattern.

Risk factors

We considered a range of potential risk factors for each comorbidity pattern, including socio-demographic, lifestyle and HIV-specific characteristics. Age, gender, ethnicity, sexual orientation (MSM or heterosexual), previous/current smoking and alcohol consumption, current recreational drug use (within the six months preceding study visit) and history of injection drug use were self-reported by study participants via a structured interview. Body mass index (BMI) was also measured at study visit and historical data on HIV-specific parameters were obtained via linkage with the UK CHIC study [16] and the Mater Misericordiae University Hospital Infectious Diseases cohort for participants recruited in Ireland [17]. Years since HIV diagnosis, nadir $CD4^+$ T cell count and prior AIDS (defined as a previous report of a category C event [18]) were considered as potential risk factors.

Health outcomes

Five health-related outcomes were considered: patient-reported physical and mental health, number of GP visits, hospitalisation and functional impairment. Physical and mental health summary scores were obtained from the Short Form Health Survey (SF-36) questionnaire [19]. Briefly, scores for eight subscales (physical functioning, physical limitation, emotional limitation, energy/fatigue, emotional well-being, social functioning, pain and general health) were derived as recommended by the developers of the SF-36 [284] and then standardized into z-scores (with a mean of 0 and a standard deviation of 1) using gender- and age-specific means and standard deviations obtained from the 1996 Health Survey for England (HSE) dataset [285]. Standardized scores were then combined to obtain the two summary scores of physical and mental health and re-scaled to have a mean of 50 and a standard deviation of 10.

Functional impairment was assessed using the Lawton IADL tool [20] and defined as impairment in ≥1 activity of daily living. The number of GP visits and hospitalization (yes or no) in the year preceding study visit were derived from information collected on healthcare resource use.

Statistical analysis

For each pattern's severity score, a multivariable median regression model was fitted to assess the independent associations with risk factors previously described. Associations of socio-demographic, lifestyle and HIV-specific factors with each pattern's severity score are reported as associated average change (with 95% confidence interval) in the median severity score.

The independent associations of each pattern severity score and each health-related outcome considered were assessed using a different multivariable model, depending on the type and distribution of the outcome. In each model, all pattern severity scores were added simultaneously to account for the correlations between the scores. For physical and mental health summary scores, linear regression models were used and regression coefficients (β: average increase/decrease in the physical/mental score associated with a one-unit increase in the severity score of a pattern, while holding all other severity scores constant) are reported.

Logistic regression was used for hospitalization and functional impairment and odds ratios (ORs) are reported. The number of GP visits was analyzed using Poisson regression and incident risk ratios (IRRs) associated with a one-unit increase in severity scores are reported.

All analyses were performed using the statistical software R v3.3.3; p-values <0.05 were considered statistically significant.

Results

Characteristics of study participants

A total of 1073 PLWH were recruited into the POPPY study: 699 older and 374 younger PLWH. Socio-demographic and HIV-related characteristics are summarised in Table 1. Participants were predominantly male (85.2%), of white ethnicity (84.1%), men who have sex with men (MSM: 76.0%) with a median (interquartile range: IQR) age of 52 (47, 59). The median (IQR) $CD4^+$ T-cell count was 624 (475, 811) cells/□L and 89.9% had a suppressed viral load (<50 copies/mL). Current smoking was reported by 24.9% of study participants, current recreational drug use and history of injection drug use were reported by 28.6% and 10.5%, respectively.

The numbers of participants with completed information on the five health outcomes were 886 for SF-36 physical and mental health scores, 1020 for functional impairment and 1073 for number of GP visits and hospitalization in the last year. The median (IQR) physical and mental health score were 52.4 (42.3, 56.3) and 51.0 (41.6, 57.2), respectively. Functional impairment was observed in 14.5% of PLWH, 65.0% had been hospitalized in the year preceding the study visit and the median (IQR) number of GP visits was 1 (1, 2).

Patterns of comorbidities

The prevalence of individual comorbidities is reported in Supplementary Table 1. The six patterns obtained using the PCA are described in Figure 1, with full details reported elsewhere [5]. The patterns were termed as follow: cardiovascular disease (CVD), sexually transmitted diseases (STDs), mental health problems, cancers, metabolic disorders and chest problems and other infection.

The distribution, with median and (IQR), of the severity scores of the six patterns in study participants are reported in Figure 1. Highest severity scores were observed for the STDs pattern with a median (IQR) of 1.34 (0.01, 2.83). There was high variability on the metabolic and mental health pattern scores, with PLWH reporting either very low or relatively high scores. The distribution of CVD and cancer severity scores were similar, with only a small proportion of individuals reporting extremely high scores compared to the majority of PLWH. There was less variability in the severity scores for the chest/other infections pattern for which the median (IQR) score was 0.17 (0.03, 0.34).

Risk factors of patterns of comorbidities

Older age [0.06 (0.04, 0.07) per each 10-year older, p<0.001], greater BMI [0.03 (0.01, 0.05) per 5-kg/m^2 increment, p=0.009], longer time since HIV diagnosis [0.04 (0.02, 0.06) per 10-year increment, p<0.001] and prior AIDS [0.08 (0.04, 0.12), p<0.001] were independently associated with higher CVD severity scores (Table 2). MSM [1.45 (1.33, 1.57), p<0.001] and those with a history of injection drug use [1.24 (0.64, 1.84), p<0.001] had significantly higher severity scores for the STD pattern compared to heterosexuals and those who never reported using injection drugs, respectively. Mental health severity scores were significantly associated with injection drug use [1.27 (0.87, 1.66), p<0.001], longer time since HIV diagnosis [0.14 (0.07, 0.21) per 10-year increment, p<0.001] and prior AIDS [0.15 (0.04, 0.26), p=0.007]. Women also appeared to have higher mental health scores [0.12 (0.01, 0.23), p=0.03] than men.

The cancer and metabolic pattern scores were each significantly associated with older age (both p's<0.001) and greater BMI (p=0.03 and p=0.006, respectively). In addition, cancer scores were significantly higher in MSM [0.06 (0.02, 0.09), p=0.005] than in heterosexuals and those with prior AIDS [0.15 (0.12, 0.19), p<0.001], whilst the associations with nadir $CD4^+$ T cell count and time since HIV diagnosis did not reach statistical significance (p=0.08 and p=0.09, respectively). On the other hand, metabolic scores appeared to be significantly associated with longer time since HIV diagnosis [0.11 (0.05, 0.16) per 10-year increment, p<0.001], prior AIDS (p=0.05) and nadir $CD4^+$ T cell count p=0.07). Finally, older age (p<0.001), prior AIDS (p<0.001) and a longer time since HIV diagnosis (p=0.001) were all independent predictors of chest/other infections severity scores. Neither smoking status nor alcohol consumption appeared to be significant risk factors for any of the six patterns.

Associations with patient reported health outcomes

The CVD pattern was associated with poorer physical health scores (p=0.02), higher odds of functional impairment (p=0.02) and hospitalisation (p<0.001) and higher number of GP visits (p<0.001; Table 3). Higher STDs severity scores were associated with better physical health (p<0.001) and a lower number of GP visits (p<0.001). In addition, weaker evidence was found regarding their association with a lower risk of functional impairment (p=0.08) and a higher risk of hospitalization (p=0.12).

The mental health pattern was negatively associated with all the outcomes considered (all p's<0.001), in particular with poorer physical [β (95% conf. int.): -2.62 (-3.40, -1.84)] and mental [β (95% conf. int.): -5.46 (-6.19, -4.72)] health scores and increased odds of functional impairment [OR (95% conf. int.): 1.88 (1.53, 2.32)]. Significantly poorer physical health scores (p=0.03) and a higher risk of functional impairment (p=0.01) were observed for the cancers pattern. Higher metabolic severity scores were associated with better physical (p=0.04) and mental (p=0.04) health and lower risk of functional impairment (p=0.007).

Finally, the chest/other infections pattern was negatively associated with all the outcomes. Higher severity scores were particularly associated with poorer physical health [β (95% conf. int.): 9.15 (-11.74, -6.56), p<0.001], an almost 5-time higher risk of functional impairment

[OR (95% conf. int.): 4.83 (2.54, 9.17), p<0.001] and a higher number of GP visits [IRR (95% conf. int.): 1.45 (1.24, 1.69), p<0.001]. Also significant were the associations with mental health (p=0.03) and hospitalization (p=0.02).

Discussion

Common patterns of comorbidities seen in PLWH appear to have different HIV-related and non-HIV-related risk factors and demonstrate different associations with quality of life, functional status and healthcare resource use.

As we previously reported [5], disease patterns identified are consistent with those reported by other studies in PLWH [10] and in the general population [21-23] with the addition of the pattern of STDs, reflecting the high exposure to risk-taking sexual behaviours that is prevalent in PLWH [25]. Associations with risk factors varied from pattern to pattern with several associations reflecting previously known risk factors, for example BMI and age for both CVDs and metabolic disorders. STDs were more prevalent in MSM and PLWH with a history of injection drug use, consistent with reports of high-risk sexual behaviours in both groups [24, 25]. Injection drug use was also associated with mental health pattern severity. Whilst it is not possible to determine the direction of associations seen, evidence suggests that mental health problems can both lead to, and be a consequence of, injection drug use [26]]. Age and BMI were associated with both the cancers and the chest/other infections pattern severity scores, however strong links with these patterns were also observed for HIV-specific factors such as the time since HIV diagnosis and prior clinical AIDS. AIDS-defining malignancies were considered separately from the three cancers that form the pattern (i.e. skin cancer, hematological and solid organ cancers). Therefore, this could reflect a genuine association where prolonged immune activation and inflammation and/or severe immunosuppression may have contributed to an increased burden of non-AIDS-defining cancers, as also suggested by a previous study [27]. Moreover, the time since HIV diagnosis and a prior AIDS diagnosis were associated with other patterns (CVDs, mental health and metabolic), independently of age, suggesting a link between persistent immune activation and inflammation with CVDs and metabolic disorders as well as with mental health problems.

In contrast to what would be expected, neither tobacco smoking nor alcohol consumption were identified as potential risk factors for any pattern. This could reflect the generally moderate frequency of smoking and alcohol consumption in POPPY PLWH [the median (IQR) self-reported number of cigarettes smoked per day and units of alcohol consumed per week were 10 (5, 20) and 7 (2, 18), respectively]. Alternatively the lack of association could reflect reverse causation due to most comorbidities preceding the time when smoking and alcohol consumption were assessed (i.e. at baseline study visit). Current alcohol abstinence and/or non-smoking status may reflect previous hazardous over consumption which may have led to disorders which, in turn, may have caused people to stop smoking and/or consuming alcohol.

Patterns were also significantly associated with health outcomes with differential effects from pattern to pattern. Of the six patterns identified, chest/other infections demonstrated the

strongest associations with patient-reported physical health, functional impairment and hospitalization. Several of the infections included in this pattern, cytomegalovirus in particular, have been reported to act as pro-inflammatory agents, also involved in the process of chronic inflammation [28, 29]. Given its association with age, time since HIV diagnosis and prior AIDS, this pattern is likely to be accompanied by prolonged immune activation and inflammation which, in turn, may have led to poorer physical health and functional limitations as also shown in different settings [30, 31]. The mental health pattern showed strong associations with all health outcomes considered, independently from the associations between mental health and other patterns. Beside the expected link with patient-reported mental health, these results seem to support a strong link with physical functioning and healthcare resource use. Interestingly, the STDs pattern appeared to be associated with better physical health and a lower number of GP visits, once accounting for the severity of the other patterns. Whilst results seem to suggest a positive effect, they should be read with caution as they are relative to the severity of other patterns and also to the average outcomes seen in the cohort. Nevertheless, this apparently positive effect may reflect the fact that treated STDs may no longer pose a serious health danger and/or PLWH with multiple STDs may be healthier overall than their counterparts with other patterns of comorbidities, such as CVDs or mental health disorders.

There are some limitations to our study that need to be considered. First, since there is not a uniform list of comorbidities and medical conditions to define multimorbidity, the list of comorbidities considered here can be debated. Some comorbidities may have been missed; some of those considered require a medical diagnosis, while others consist more of symptoms and were therefore less objectively defined. Second, although the self-reported nature of data collection may have led to under or over reporting of some comorbidities, our approach consisted in a structured interview conducted by trained staff to ensure consistency across study participants and that allowed to capture all the comorbidities with same standardized procedure. Thirdly, the cross-sectional nature of the analysis does not permit an assessment of causality or the direction of the associations seen (and whether they are bidirectional); longitudinal studies are on plan and would allow to shed light on the direction of associations. Finally, our cohort was designed to be representative of the population of PLWH seen in care in UK and Ireland, predominantly characterized by white MSM; therefore, results could be less generalizable to populations of PLWH within different HIV epidemic settings.

With an increasingly ageing population of PLWH [33] and the consequent increase in the prevalence of multimorbidity [34], these findings highlight the need for targeted interventions and guidelines for the prevention, diagnosis, treatment and prognosis of multimorbidity in PLWH. The identification of risk factors for specific patterns of comorbidities could help the development of targeted interventions towards modifiable risk factors in PLWH presenting with one or more of the comorbidities in the pattern to prevent the onset of new comorbidities that are likely to co-occur with the existing ones. Similarly, treatment of comorbidities in patterns with the highest impact on quality of life and healthcare resource use could lead to potential benefits for both the patient and the healthcare system. Further longitudinal studies

are justified to assess the change over time in patterns' severity and to elucidate the causal link with health outcomes.

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Authors' contributions

D.D.F. contributed to study concept and design, literature search, data analysis and interpretation, figures, writing of the manuscript. P.W.G.M., A.W., C.A.S. contributed to study concept and design, data collection and interpretation, critical revision of manuscript. E.B. contributed to data analysis and interpretation, critical revision of the manuscript. J.U., J.A. and F.A.P. contributed to data collection and critical revision of manuscript. I.W.,

J.H.V., M.B., M.J. contributed to data collection. All authors read and approved the final manuscript.

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Conflicts of Interest

J.A. has accepted fees for consultancy and educational activities from Gilead Sciences, Merk Sharp and Dohm, ViiV healthcare, Bristol Myers Squibb, Janssen and KPMG. C.A.S. has received funding from Gilead Sciences, ViiV Healthcare, and Janssen-Cilag for membership of data safety and monitoring boards, advisory boards, and speaker panels and for preparation of educational materials. F.A.P has received research grants from Gilead Sciences and ViiV Healthcare, and fees from Gilead Sciences, ViiV Healthcare, MSD and Janssen for membership of Advisory Boards, Speaker Panels and/or for the preparation of educational materials. P.W.G.M. has received funding for Advisory Boards, speaker panels, preparation of educational materials and/or research grants to his institution from Gilead Sciences, ViiV Healthcare, BMS, MSD, Abbvie and Janssen-Cilag.

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Tables

Table 1: Characteristics of study participants

n (%) or median (IQR)	All PLWH (n=1073)	PLWH ≥50 (n=699)	PLWH <50 (n=374)
Gender			
Male	914 (85.2%)	612 (87.5%)	302 (80.8%)
Female	159 (14.8%)	87 (12.5%)	72 (19.2%)
Age [years]	52 (47, 59)	57 (53, 62)	43 (37, 47)
Ethnicity			
Black-African	171 (15.9%)	96 (13.7%)	75 (19.8%)
White	902 (84.1%)	603 (86.3%)	299 (80.2%)
Sexual orientation			
MSM/homosexual	816 (76.0%)	548 (78.4%)	268 (71.7%)
Heterosexual	257 (24.0%)	151 (21.6%)	106 (28.3%)
BMI [kg/m^2]	25.5 (23.2, 28.2)	25.7 (23.4, 28.5)	25.2 (23.0, 27.8)
Smoking			
Smoker	267 (24.9%)	158 (22.6%)	109 (29.1%)
Ex-smoker	365 (34.0%)	263 (37.6%)	102 (27.3%)
Never smoked	436 (40.6%)	275 (39.4%)	161 (43.1%)
Alcohol consumption			
Current consumption	858 (80.0%)	555 (79.4%)	303 (81.0%)
Previous consumption only	125 (11.6%)	87 (12.4%)	38 (10.2%)
Never consumed	90 (8.4%)	57 (8.2%)	33 (8.8%)
Recreational drug use	307 (28.6%)	177 (25.3%)	130 (34.8%)
History of ID use	112 (10.5%)	62 (8.9%)	50 (13.5%)
Duration of HIV [years]	13.2 (7.8, 20.5)	15.8 (9.8, 22.4)	9.7 (5.5, 15.2)
$CD4^+$ T cell count [$cells/mm^3$]	624 (476, 811)	610 (468, 792)	661 (500, 847)
Nadir $CD4^+$ count [$cells/mm^3$]	202 (101, 304)	180 (85, 273)	253 (152, 376)
Prior AIDS	311 (29.0%)	241 (34.5%)	70 (18.7%)
On ART	1046 (97.5%)	690 (98.7%)	356 (95.2%)
HIV RNA <50 copies/ml	965 (89.9%)	644 (91.8%)	323 (86.4%)
SF-36 physical health score	52.4 (42.3, 56.3)	51.7 (41.9, 56.3)	53.2 (45.7, 56.1)
SF-36 mental health score	51.0 (41.6, 57.2)	51.0 (41.3, 57.2)	50.9 (42.3, 57.0)
Functional impairment	148 (14.5%)	108 (16.2%)	40 (11.3%)
Number of GP visit in the last year	1 (1, 2)	1 (1, 3)	1 (0, 2)
Hospitalized in the last year	697 (65.0%)	479 (68.5%)	218 (58.3%)

IQR: interquartile range; MSM: men having sex with men; BMI: body-mass index; ART: antiretroviral therapy; ID: injection drug

Table 2: Regression coefficients (with 95% confidence interval) and associated p-value from separate multivariable median regression models predicting patterns' severity scores

Risk factor	Severity score					
	CVDs	**STDs**	**Mental health**	**Cancers**	**Metabolic**	**Chest/ other infections**
Age (per 10-year)	0.06 (0.04, 0.07) p<0.001	-0.02 (-0.06, 0.01) p=0.23	0.01 (-0.02, 0.04) p=0.52	0.04 (0.03, 0.05) p<0.001	0.09 (0.05, 0.12) p<0.001	0.03 (0.02, 0.05) p<0.001
Male vs. Female	0.02 (-0.04, 0.07) p=0.53	0.05 (-0.04, 0.16) p=0.31	-0.12 (-0.23, -0.01) p=0.03	-0.04 (-0.09, 0.01) p=0.15	0.08 (-0.01, 0.18) p=0.09	-0.01 (-0.07, 0.05) p=0.73
White vs. Black-African	-0.03 (-0.08, 0.02) p=0.26	-0.03 (-0.13, 0.08) p=0.61	0.10 (-0.03, 0.22) p=0.12	0.01 (-0.04, 0.06) p=0.68	0.00 (-0.09, 0.10) p=0.93	-0.03 (-0.09, 0.04) p=0.47
Heterosexual vs. MSM	0.01 (-0.04, 0.06) p=0.77	-1.45 (-1.57, -1.33) p<0.001	-0.03 (-0.16, 0.09) p=0.60	-0.06 (-0.09, -0.02) p=0.005	-0.06 (-0.15, 0.03) p=0.22	-0.03 (-0.10, 0.04) p=0.34
BMI (per 5-Kg/m^2)	0.03 (0.01, 0.05) p=0.009	-0.04 (-0.07, 0.01) p=0.06	0.04 (0.00, 0.09) p=0.06	0.02 (0.00, 0.03) p=0.03	0.05 (0.02, 0.09) p=0.006	0.02 (-0.01, 0.04) p=0.07
Smoking						
Smoker vs. never smoked	-0.02 (-0.06, 0.01) p=0.26	-0.10 (-0.27, 0.07) p=0.23	0.12 (-0.04, 0.28) p=0.15	-0.02 (-0.05, 0.01) p=0.12	0.05 (-0.02, 0.11) p=0.17	0.02 (-0.03, 0.07) p=0.45
Ex-smoker vs. never smoked	0.00 (-0.04, 0.04) p=0.94	0.06 (-0.06, 0.17) p=0.34	0.04 (-0.05, 0.12) p=0.39	0.00 (-0.03, 0.03) p=0.82	0.04 (-0.04, 0.11) p=0.33	0.03 (-0.01, 0.07) p=0.18
Alcohol						
Current consumption vs. never consumed	-0.01 (-0.07, 0.04) p=0.60	0.01 (-0.06, 0.09) p=0.72	-0.02 (-0.15, 0.11) p=0.75	0.02 (-0.03, 0.07) p=0.53	-0.08 (-0.17, 0.01) p=0.06	0.01 (-0.05, 0.07) p=0.68
Previous consumption vs. never consumed	-0.01 (-0.08, 0.05) p=0.71	-0.03 (-0.15, 0.09) p=0.61	0.04 (-0.16, 0.23) p=0.71	0.03 (-0.03, 0.08) p=0.31	-0.04 (-0.16, 0.09) p=0.56	0.04 (-0.03, 0.11) p=0.27
Recreational	-0.01 (-	0.23 (-	0.04 (-	0.03	-0.05 (-	0.03 (-

drugs (yes vs. no)	0.04, 0.02) p=0.43	0.13, 0.59) p=0.21	0.06, 0.14) p=0.47	(0.00, 0.06) p=0.06	0.11, 0.02) p=0.15	0.01, 0.07) p=0.16
History of ID use (yes vs. no)	-0.01 (-0.06, 0.04) p=0.73	1.24 (0.64, 1.84) p<0.001	1.27 (0.87, 1.66) p<0.001	0.02 (-0.02, 0.06) p=0.34	-0.06 (-0.14, 0.02) p=0.12	0.03 (-0.04, 0.09) p=0.45
Prior AIDS (yes vs. no)	0.08 (0.04, 0.12) p<0.001	-0.07 (-0.15, 0.01) p=0.11	0.15 (0.04, 0.26) p=0.007	0.15 (0.12, 0.19) p<0.001	-0.08 (-0.16, 0.00) p=0.05	0.19 (0.15, 0.24) p<0.001
Nadir $CD4^+$ T cell count (per 100 cells/µl)	0.01 (-0.01, 0.02) p=0.16	0.01 (-0.02, 0.03) p=0.64	0.02 (-0.01, 0.05) p=0.23	-0.01 (-0.01, 0.00) p=0.08	0.02 (-0.01, 0.04) p=0.07	0.00 (-0.01, 0.01) p=0.74
Years since HIV diagnosis (per 10-year)	0.04 (0.02, 0.06) p<0.001	0.03 (-0.03, 0.09) p=0.31	0.14 (0.07, 0.21) p<0.001	0.02 (0.00, 0.04) p=0.09	0.11 (0.05, 0.16) p<0.001	0.04 (0.02, 0.07) p=0.001

Table 3: Associations of pattern severity scores with patient-reported health outcomes

Pattern	Physical health score	Mental health score	Functional impairment	Number of GP visits in last year	Hospitalized in the last year
	β (95% conf. int.)	β (95% conf. int.)	OR (95% conf. int.)	RR (95% conf. int.)	OR (95% conf. int.)
CVDs	-1.40 (-2.55, -0.25) p=0.02	0.52 (-0.56, 1.61) p=0.34	1.38 (1.05, 1.81) p=0.02	1.15 (1.08, 1.23) p<0.001	1.75 (1.28, 2.40) p<0.001
STDs	0.90 (0.48, 1.31) p<0.001	-0.07 (-0.47, 0.32) p=0.71	0.90 (0.79, 1.01) p=0.08	0.93 (0.91, 0.96) p<0.001	1.07 (0.98, 1.16) p=0.12
Mental health	-2.62 (-3.40, -1.84) p<0.001	-5.46 (-6.19, -4.72) p<0.001	1.88 (1.53, 2.32) p<0.001	1.32 (1.25, 1.38) p<0.001	1.42 (1.21, 1.67) p<0.001
Cancers	-1.48 (-2.78, -0.17) p=0.03	0.87 (-0.36, 2.10) p=0.17	1.45 (1.08, 1.96) p=0.01	0.96 (0.88, 1.04) p=0.32	1.27 (0.96, 1.69) p=0.10
Metabolic	1.01 (0.07, 1.95) p=0.04	0.95 (0.07, 1.84) p=0.04	0.69 (0.52, 0.90) p=0.007	1.00 (0.94, 1.06) p=0.92	0.84 (0.69, 1.02) p=0.08
Chest/other infections	-9.15 (-11.74, -6.56) p<0.001	-2.66 (-5.10, -0.22) p=0.03	4.83 (2.54, 9.17) p<0.001	1.45 (1.24, 1.69) p<0.001	1.98 (1.13, 3.49) p=0.02

Note: physical and mental health scores were analyzed using linear regression; functional impairment (yes vs. no) and hospitalization in the last year (yes vs. no) were analyzed using binary logistic regression; number of GP visits over the past year was analyzed using Poisson regression.

Figure legends

Figure 1: Patterns of comorbidities and distribution of their severity scores in all study participants (n=1073)