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Comorbidities among persons living with HIV (PLWH) in Florida: A Network Analysis.

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Abstract

People living with HIV (PLWH) experience a higher rate of age-related comorbidities at younger ages. Understanding common comorbidities among PLWH and their relationship to one another could be significant in improving aging for PLWH. The goal of the present study is to identify the most common comorbidities among PLWH and the relationship between them using a network analysis. We used abstracted electronic medical record (EMR) data of PLWH from the Florida Cohort study, a prospective cohort study conducted in eight cities in Florida, USA. We used International Classification of Diseases (10^{th} revision, ICD-10) code to classify comorbidities and organ systems. Network analysis was conducted to determine the degree and betweenness centrality among comorbidities. We included 756 PLWH with an average age of 46.4 years (SD 11.3) in the analysis. Infectious diseases (A00-B99, 50.8%), mental and behavioral (F01-F99, 47.0%), endocrine, nutritional and metabolic (E00-E88, 45.2%), and circulatory (I00-I99, 39%) disorders were the most prevalent system comorbidities among PLWH. Hypertensive disorder (I10-I1635.8%), dyslipidemia (E78, 25.7%), and major depressive disorder (F32-F33, 23.9%) were the most common non-infectious conditions affecting PLWH. Viral hepatitis (B15-B19, 17.1%) and syphilis (A15-A53, 12%) were the most common coinfections among

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PLWH. Hypertension, dyslipidemia, and major depressive disorder were the most central of the comorbidities among PLWH. Comorbidities among PLWH were most prevalent for chronic disease and mental illness. Targeting shared disease risk factors in addition to monitoring known pathological pathways may prevent comorbidities among PLWH.

INTRODUCTION

The likelihood of developing simultaneous chronic illness comorbidities increases with age (Barnett et al., 2012; Marengoni et al., 2011; Poduri & Vanushkina, 2018; Yancik et al., 2007). According to the latest HIV surveillance report in 2018, half of people living with HIV (PLWH) in the United States (US) are 50 years and older (Centers for Disease Control and Prevention, 2020). Florida has the second-highest rate of new HIV diagnoses in the US (Centers for Disease Control and Prevention, 2020), and half of PLWH in Florida (53.4%) are over 50 years of age (Florida Department of Health [FDOH], 2020). With the improvement in antiretroviral therapy (ART) and resulting increased longevity of PLWH, research interest has increasingly shifted toward optimizing successful aging with HIV.

Both infectious and non-infectious comorbidities are prevalent among PLWHs (Althoff et al., 2015; Guaraldi et al., 2015; Ruzicka, Imai, Takahashi, & Naito, 2019) as a result of HIV-associated immune disruption (Effros et al., 2008), the effect of long term ART use (Cahill & Valadéz, 2013; Gebo, 2006). PLWHs are at increased risk of behavioral and lifestyle factors such as smoking, substance use, and obesity (Yang, Beymer, & Suen, 2019). which may make them more susceptible to developing comorbidities in comparison to HIV-negative individuals (Gallant, Hsue, Shreay, & Meyer, 2017; Goulet et al., 2007; Schouten et al., 2014). In fact, PLWH are disproportionately affected by age associated chronic comorbidities, at earlier ages than the general population (Guaraldi et al., 2011; Pathai, Bajillan, Landay, & High, 2014; Sabin & Reiss, 2017). Even after controlling the healthcare encounter, PLWH were diagnosed at a significantly younger age (between 1 to 10 years earlier) then HIV-negative controls (Nanditha et al., 2021).

Morbidities such as cardiovascular diseases (CVD), hypertension, diabetes, malignancy, renal, hepatic, bone diseases, psychiatric disorders, are more common in PLWH than those living without HIV (Guaraldi et al., 2015; Maciel, Klück, Durand, & Sprinz, 2018; Ruzicka et al., 2019). With the earlier onset of osteopenia, even middle-aged PLWH have a higher risk of falls (Erlandson et al., 2012; Erlandson, Schrack, Jankowski, Brown, & Campbell, 2014), and a threefold increased risk of fracture (Pramukti et al., 2020; Sharma et al., 2015; Van Epps & Kalayjian, 2017). The risk of sudden death due to myocardial infarction or heart failure is two times higher in PLWH (Freiberg et al., 2013; Freiberg et al., 2017) some of whom are known to have lipid abnormalities due to some side effects of ART. Therefore, understanding the common comorbidities and how they relate to each other among PLWH is key to risk modification for successful aging (Marcus et al., 2020).

The clustering of diseases indicates a complex interaction which can share a common pathophysiological mechanism and deserved more research attention (Moni & Liò, 2014). A network analysis approach can facilitate the understanding of how different comorbidities relate and co-exist among PLWH. Previous research on disease transmission of infectious

diseases including HIV/AIDS and other sexually transmitted diseases (STDs), health behaviors and health services has demonstrated the utility of comorbidity network analysis; this data-driven approach focuses on patterns and linkages that are highly graphical (Luke & Harris, 2007). Networks are constructed as a set of nodes (symptoms/disorders/diseases/infections) and edges (connection between nodes, coexistence of disease (comorbidity) (Price, Legrand, Brier, & Hébert-Dufresne, 2019). The centrality of a node is established corresponding to its importance or prominence in the connecting structure, therefore the more prevalent a disorder is in comorbidity combinations, the more integral it becomes in the linking networks.

Using this network analysis approach, the present study will focus on the centrality of each disorder reported by PLWHs from the Florida Cohort study. The specific research questions are: (1) *What are the most prevalent comorbidities among PLWHs in the Florida Cohort?*; and (2) *What is the relationship between common comorbidities in PLWH?* A better understanding of common comorbidities and relationships could potentially forecast disease development leading to early intervention and better clinical outcomes.

METHODS

Study population

We used data from the Florida Cohort study, a prospective cohort of PLWH in eight cities in Florida between 2014 and 2018 that recruited 932 PLWH aged 18 years of age or older. Detailed methodology of the Florida cohort is described elsewhere (Ibanez et al., 2020). Data were collected on health status, HIV-related health risk behavior, alcohol and substance use, mental health symptoms, and interpersonal factors. A list of current medical diagnoses [using International Statistical Classification of Diseases (ICD)], current medications, and recent laboratory results were abstracted from the electronic medical record (EMR).

Sociodemographic variables

The Florida Cohort used a structured questionnaire to collect demographic information that included age, gender identity, sexual orientation, race, and ethnicity at baseline. Socioeconomic information collected included educational attainment, housing, employment, income, and type of health insurance. History of HIV, HIV-related health behavior, alcohol and drug use, and mental health symptoms were also collected. The questionnaire was self-administered on paper or on a computer; although the majority chose the paper form. In cases of low literacy, the participant also had the choice of having the research assistant administer the questionnaire.

Comorbidity classification

The EMRs contained codes to classify diseases using ICD 9th version (ICD-9) and 10th version (ICD-10), SNOMED (Systematized Nomenclature of Medicine) clinical terms, or descriptions of the disease condition. All codes were converted to ICD-10 code to classify comorbidities and the organ systems. ICD-9 codes were converted using the 2018 general equivalence mapping guideline of the Center for Medicare and Medicaid Services (U.S. Centers for Medicare & Medicaid, 2017). SNOMED terminologies were converted

to ICD-10 using the Interactive Map-Assisted Generation of ICD Codes (I-MAGIC) algorithm (National Library of Medicine, 2018). Study team physicians reviewed all SNOMED terminologies and descriptions, before assigning a final ICD-10 code. The study utilized both specific disease diagnosis and classification by organ systems. The ICD-10 corresponding to the diagnosis are listed in table 2 and table 3. Unspecific descriptions (total of 16) were excluded from the analysis. A total of 17 organ systems and the top 30 co-occurring conditions were included in the network analysis.

Analysis

Descriptive characteristics of the sample were presented using SPSS for Windows version 20 (SPSS, Chicago, IL, USA). Comorbidity matrices were then constructed by system category and specific disease diagnosis, and input into UCINET (Borgatti, Everett, & Freeman, 2002), a software package for analysis of social network data, to determine the degree and betweenness centrality of both networks. We used the weighted edge-to-edge list of organ system or disease to analyze the centrality measures. Degree centrality measures the number of direct connections with each node (in our case comorbidity) to other nodes in the network. Higher values of degree centrality indicate a higher number of direct connections to a node, where a degree centrality of zero would indicate that no other comorbidity was named with the condition. Comorbid organ systems or conditions with high degree centrality are most connected within a network. For the 17 organ systems and the top 30 co-occurring conditions the degree centrality range between 0–12,096 and 0–21,924, respectively. Betweenness centrality measures the number of times a node lies on the shortest path between other nodes and shows which nodes are ‘bridges’ between nodes in a network. Higher values of betweeness centrality indicate that the node serves as a ‘bridge’ for many other nodes, where a betweeness centrality of zero would indicate that the comorbidity only shares a connection with one other comorbidity, and therefore does not serve as a ‘bridge’. Matrices were then imported into NETDRAW (Borgatti et al., 2002) a program for visualizing social network data, to construct networks and displayed by ‘scaling/ordination’ where systems/conditions most central are placed closer to the center of the network.

RESULTS

Sample characteristics

Of the 932 participants recruited, 756 were included in the analysis as had complete comorbidity information. The sample had an average age of 46.4 years [Standard Deviation (SD): 11.3 years; median (25^{th} −75^{th} percentile): 48 years (39–54 years)], with the majority of the participants between 30 to 50 years of age (46.3%), male (63.2%), and African American (59.4%). The median time since first positive HIV test to interview was 13 years (25^{th} −75^{th} percentile: 5–21). Notably, 92% of PLWH had insurance coverage or access to some financial support for healthcare (Table 1).

Common comorbidities

Half of the PLWH had diseases of infectious or communicable origin (A00-B99), excluding HIV (Table 2). About 47% of the PLWH had mental and behavioral disorders (F01-F99).

Endocrine, nutritional and metabolic disorders (E00-E88) were prevalent among 45% of the PLWH. The disorder of circulatory (I00-I99) and respiratory (J00-J99) systems were prevalent among 39 % and 29.5% of the PLWH, respectively. About 70% of the PLWH had factors influencing health status and contact with health service (Z00-Z99; e.g. routine encounter for HIV care, general examination, immunization), and 47% had signs, symptoms, and abnormal clinical and laboratory findings without any specific diagnosed disease.

In terms of the specific diagnosis of the comorbidities, hypertensive disorders (I10-I16: 35.8%) was the predominant cause of comorbidities followed by dyslipidemia (E78: 25.7%) (Table 3). Viral hepatitis was the major infectious disease (B15-B19: 17.1%) followed by all stages of syphilis (A51-A53:12.0%) and other sexually transmitted infections (STIs) (A54-A59, A63–64) at 8.7% that include gonococcal, chlamydial, and/or trichomononas infection. Any site herpes simplex virus (A60, B00) was prevalent among 7.8% of the PLWH. About 23.9% of the PLWH had major depressive disorder (F32-F33), 8.1% had anxiety disorder (A41), and 7.9% had bipolar disorder (F31). Nicotine dependence (F17: 12.8%), alcohol (F10: 5.4%), and cocaine-related disorders (F14: 5.8%) were the major psychoactive substance use disorders among our sample. About 3.0% of the PLWH had cannabis related (F12) and 3.4% had inhalant related (F18) disorders. Diabetes mellitus (E08-E13), chronic respiratory disease including chronic obstructive pulmonary disease (J45), and asthma (J44) were prevalent at 11.8%, 5.4%, and 7.9% of PLWH respectively.

Network analysis

Among the system-based diseases, infectious diseases had the highest degree of centrality and betweenness, followed by endocrine, nutritional, and metabolic, and mental and behavioral disorders (supplemental table 1). Figure 1 shows the network of conditions by system, where those most central are closest to the center of the network, and the ties (line connecting two organ systems) are weighted by the number of times two organ systems was listed. For example, the width of the line connecting circulatory system disorders and mental health conditions are thicker than width of the line connecting mental health conditions and musculoskeletal disorders. This indicated that metal health and circulatory conditions are more connected than mental health and musculoskeletal disorders.

Among the 30 most common conditions, hypertension had the highest degree of centrality and betweenness, followed by depression, and dyslipidemia (supplemental table 1). Figure 2 shows a condition network, where those most central are closest to the center of the network, and the ties were weighted by the number of times two disease was listed together. For example, hypertension has stronger connection with dyslipidemia than then neuropathies (Figure 2). To improve clarity, comorbidities with <20 connection were removed from the network.

DISCUSSION

This study reported the most common comorbidities among PLWH and identified the most central comorbid conditions using a network analysis approach. Similar to previous studies among PLWH, we found that the most substantial comorbidities were cardio-metabolic diseases and mental illness (Gallant et al., 2017; Guaraldi et al., 2011; Ruzicka et al.,

2019). Similarly, prevalence rates of hypertension, dyslipidemia, diabetes, and obesity in our sample was similar to a previous research study using US administrative claims data of PLWH (Gallant et al., 2017). The results on major depressive disorders (23.9%) in our study was lower than the results reported previously (27%) (Gokhale et al., 2019). Future interventions that focus on prevention and management of chronic conditions alongside clinical HIV outcomes should be considered among PLWH to promote successful ageing among this population.

The network analysis revealed patterns of clustering of comorbidities by organ systems and disease conditions. Likewise, in previous studies, CVD, metabolic disorders, infections, and mental health disorders are the central of the comorbidities by organ systems (De Francesco et al., 2018). Specifically, hypertension, dyslipidemia, and depression were the most central comorbidities among PLWH. Common pathological mechanism such as chronic immune activation, ART side effects, and infectious disease confection play role in the development of certain common comorbidities in PLWH (Lerner, Eisinger, & Fauci, 2019). HIV associated chronic inflammation may lead to an increase in cardio-metabolic morbidities among PLWH (Hsue, Deeks, & Hunt, 2012). It is also found that depressive disorder can cause autonomic nervous system dysfunction, which can lead to development of CVDs (Carney, Freedland, & Veith, 2005). Major depression increases peripheral inflammatory biomarkers, and patients with inflammatory disease also had a higher rate of depression (Amodeo, Trusso, & Fagiolini, 2017). All these findings reemphasized the central role of inflammation for the most important driving factor of comorbidities among PLWH.

Clustering of CVD and mental health condition especially depression reemphasize the interrelationship between these two conditions. Studies reported that depression among PLWH doubled the risk of CVD (Park et al., 2021). Depression can cause deregulation in the sympathetic nervous systems which can lead to hypertension and other CVDs (Dhar & Barton, 2016). Beyond the biological mechanism depression can result in noncompliance to healthy lifestyle and treatment regimen. It was reported that depressed PLWH are 42% less adherent to ART (Uthman, Magidson, Safren, & Nachega, 2014). It has been reported that nonadherence to ART is related both CVD and non-CVD related mortality (Castillo-Mancilla et al., 2021). We also found certain established cardio-metabolic risk factors including overweight or obesity and nicotine dependence (Kim et al., 2012) linked with all central comorbidities indicating common preventable risk factors for central comorbidities among PLWH. Cocaine and other drug use was also connected with hypertension and depression. Nicotine, cocaine and other substance use was also interlinked in the network. Beside routine monitoring of viral suppression and adherence ART, screening for mental health conditions such as depression, as well as cardiometabolic risk factors might prevent comorbidities among PLWH.

Coinfections also cause inflammation and immune activation among PLWH (Slim & Saling, 2016) despite having a suppressed HIV viral load. We found that viral hepatitis specifically hepatitis C was the most common coinfection among PLWH followed by syphilis and other STDs. Coinfection can occur due to the shared route of transmission (Koziel & Peters, 2007), high risk sexual behaviors (Du et al., 2015), which are common among PLWH. Our network analysis found that infections were linked with central comorbidities. Prevention of

coinfections might also prevent development of chronic comorbidities which need further explorations.

We found that a significant portion of our sample had substance use disorders, including nicotine, alcohol, and cocaine related disorders, which had more considerable implications for development of comorbidities as well as disruptions for ART adherence and viral load suppression. Nicotine and alcohol use are common risk factors for acute and chronic diseases and affect various organ systems (Rehm et al., 2010; US Department of Health Human Services, 2014). Nicotine or tobacco consumption is also associated with unsuppressed viral load and low CD4 count (Aralis et al., 2018; Hile, Feldman, Alexy, & Irvine, 2016). Our previous study found that heavy alcohol consumption was significantly associated with poor viral suppression and non-adherence to ART (Cook et al., 2017). We also found that different types of substance use were interconnected, as polysubstance use is common among PLWH (Mimiaga et al., 2013). Further development of research on substance use disorders and their role in the development of comorbidities and viral suppression is warranted.

Low-grade or intermittent viremia, even at undetectable viral load, can cause persistent inflammation (Slim & Saling, 2016) and associate with comorbidities among PLWH. The role of inflammation on clustering of comorbidities needs further exploration. Prospective studies with PLWH at different undetectable viral load under ART might elucidate the relationship between inflammation and the clustering of multimorbidities in PLWH. Considering the clustering of comorbidities and central role of inflammation, clinical practice should include screening for comorbidities and check-up for inflammatory markers beside the regular HIV care continuum. Clinical practice should also promote non-pharmacological intervention such as nutritional and lifestyle intervention (Aparecida Silveira, Falco, Santos, Noll, & de Oliveira, 2020) along with the ART as long term a ART increase the risk of cardiometabolic disease such ad dyslipidemia, diabetes, obesity, and hypertension. Furthermore, network analysis stratified by demographic factors such as age, gender, and race could help identify specific patter of comorbidities and risk factors across different groups which might be useful for specific targeted intervention.

One of the strengths of the study was the use of EMRs from the participant's care providers. The robust classification of diagnoses and procedure used in the EMRs provided unified coding system across sites or medical facilities. Moreover, multisite recruitment yielded a diverse population that spanned an entire state, including counties with high HIV incidence. The networks analysis visualized the clustering of comorbidities and used a statistical approach to identify most important condition among all the comorbidities, which can help to understand high-risk comorbidities that need prioritization for clinical management.

Limitations

This study has a few limitations despite its strengths. Our network analysis was not directional and the analysis was cross-sectional in nature. So, we cannot ascertain trajectories of comorbidities to ascertain which condition occurred first. In addition, we do not know the strength of each connection in our network. This study lacked generalizability as participants were recruited from specific clinics which might not represent PLWH

community. However, the recruitment of participants was from multiple locations in Florida. Furthermore, The majority of our study participants, for example, are African-american and low SES. Research shows that African Americans are insufficiently engage in HIV care continuum, and mat underutilize or lack access to healthcare in general, which might make them more susceptible to multi-morbidities (Freeman et al., 2017). Finally, we are unable to compare the distribution of comorbidities with individuals without HIV.

CONCLUSION

Life expectancy of PLWH increased due to the advancement of ART. However, due to immune dysregulation and, exposure to various behavioral risk factors such as obesity and substance use, PLWH are more prone to develop comorbidities, which increase cost of care. Cardiometabolic disease and mental health issues remains the center of the comorbidities among PLWH. Multi-component intervention combining enhanced ART adherence and linkage to care, mental health interventions, and behavioral and risk factor modifications should be expanded to reduce development of comorbidities and to promote healthy aging among PLWH. Continuation of current guidelines for preventative therapy such as lipid control and diabetes control might prevent comorbidities, especially chronic disease among PLWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Ethics approval and consent to participate

The study was approved by IRBs at the University of Florida, Florida Department of Health, and Florida International University.

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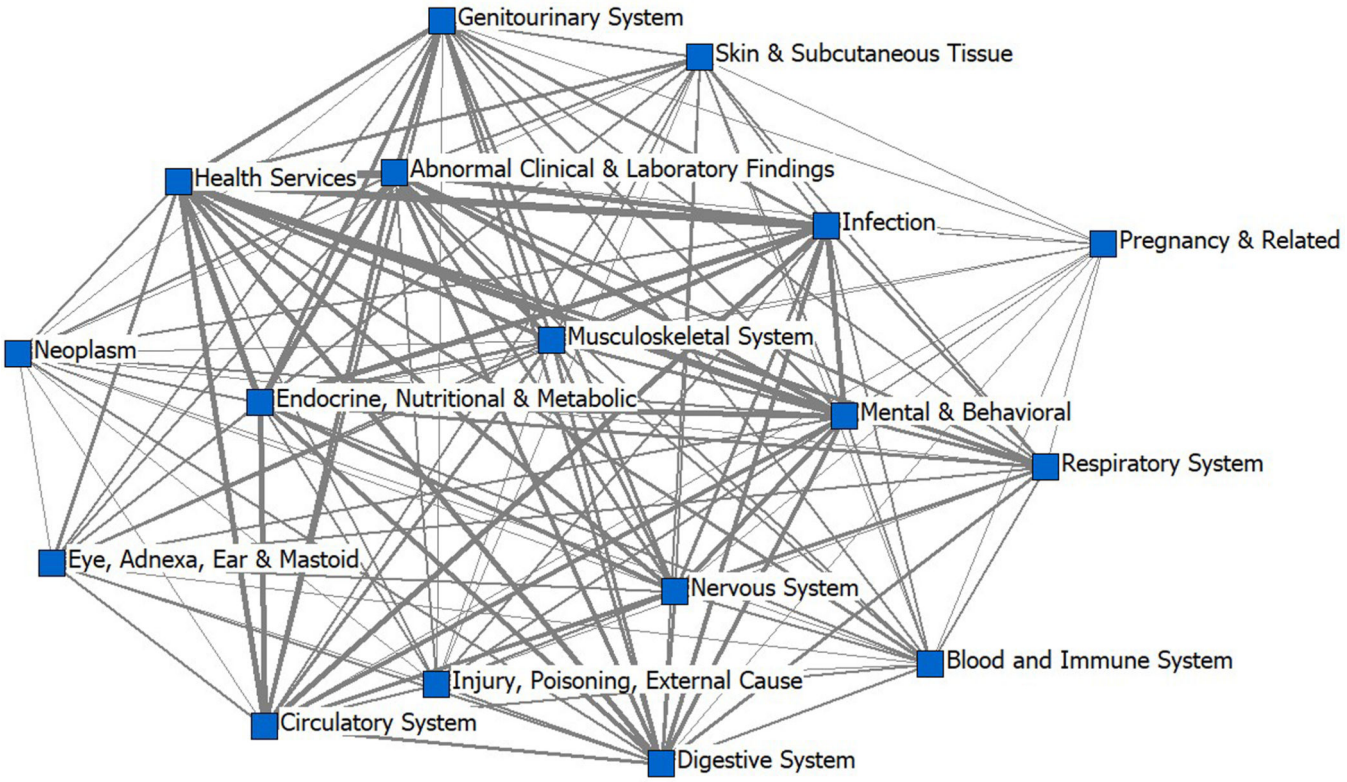

Figure 1:
Comorbidity networks of system based conditions among people living with HIV in Florida

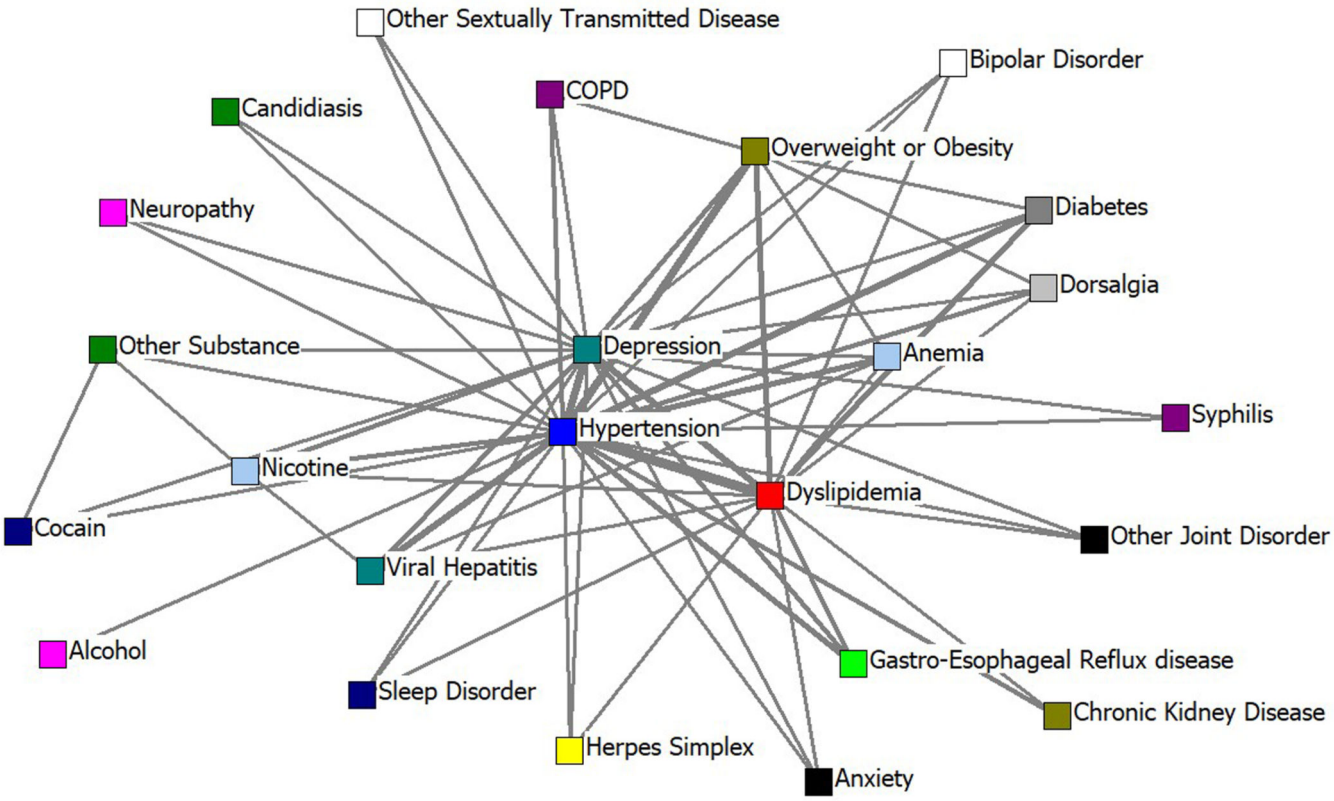

Figure 2:
Comorbidity network of conditions among people living with HIV in Florida

Table 1:

Characteristics of the participants

Characteristics	N (%)
Age (years)	46.4 (11.3)[†]
Age distribution	
≤ 30 Years	75 (9.9)
30–39 Years	125 (16.5)
40–49 Years	225 (29.8)
50–59 Years	256 (33.9)
≥60 Years	75 (9.9)
Gender Identity	
Male	473 (62.6)
Female	259 (34.3)
Transgender	24 (3.2)
Race	
White / Caucasian	230 (30.5)
Black / African American	448 (59.4)
Multi-racial	35 (4.6)
Other	41 (5.5)
Hispanic or Latino Origin	146 (19.3)
US born	637 (84.9)
Level of Education	
Elementary or below	25 (3.3)
Some high school	237 (31.5)
High school graduate	227 (30.1)
Some college	160 (21.2)
College graduate	104 (13.8)
Employment Status	
Currently employed	181 (24.6)
Not working	201 (27.3)
Unable to work or retired	354 (48.1)
Health insurance	
Uninsured	46 (6.3)
Insured	685 (93.7)
Years since contracted HIV	15 (7–22)[‡]
Year since first positive HIV test [‡]	13 (5–21)[‡]

[†]Mean (SD)

[‡]Median (25^{th}–75^{th} %tile)

Table 2:

Major Classification of Co-morbidities among of People Living with HIV across 8 Florida Clinics; Florida Cohort, 2014– 2018, N= 756.

Type of Disorders	ICD10 code	Count	%
Infection	A00-B99	384	50.8
Neoplasm	C00-D49	60	7.9
Blood and immune system disorders	D50-D89	106	14.0
Endocrine, nutritional & metabolic disorders	E00-E88	342	45.2
Mental & behavioral disorders	F01-F99	355	47.0
Nervous system disorders	G00-G99	186	24.6
Disorders of eye, adnexa, ear & mastoid	H00-H59, H60-H95	102	13.5
Circulatory system disorders	I00-I99	295	39.0
Respiratory system disorders	J00-J99	186	24.6
Digestive system disorders	K00-K95	223	29.5
Disorders of skin & subcutaneous tissue	L00-L99	105	13.9
Musculoskeletal system disorders	M00-M99	195	25.8
Genitourinary system disorders	N00-N99	201	26.6
Perinatal, congenital & pregnancy related disorders	O00-O9A, P00-P96, Q00-Q99	9	1.2
Abnormal clinical &laboratory findings	R00-R99	355	47.0
Injury, poisoning external cause	S00-T88, V00-Y99	94	12.4
Factors influencing health status and contact with health services*	Z00-Z99	518	68.5

*factors influencing health status and contact with heath service include routine encounter for HIV care, general examination, immunization etc

Table 3:

Top 30 causes of morbidity among of People Living with HIV across 8 Florida Clinics; Florida Cohort, 2014–2018, N= 756.

Organ System/ Group	Comorbidities	ICD-10 Code	n	%
Infection	Tuberculosis	A15-A19	35	4.6
	Syphilis	A51-A53	91	12.0
	Other STD	A54-A59, A63-A64	66	8.7
	Herpesviral [herpes simplex] infections	A60, B00	59	7.8
	Viral hepatitis	B15-B19	129	17.1
	Hepatitis B	B16, B17.0 B18.0, B18.1, B19.1	33	4.4
	Hepatitis C	B17.1, B18.2, B19.2	84	11.1
	Dermatophytosis	B35	46	6.1
	Candidiasis	B37	63	8.3
Anemia	Anemias and related disorders	D50-D64	89	11.8
Endocrine/Metabolic	Diabetes mellitus	E08-E13	89	11.8
	Overweight/Obesity	E66	133	17.6
	Dyslipidemia	E78	194	25.7
Substance use	Alcohol related disorders	F10	41	5.4
	Cocaine related disorders	F14	44	5.8
	Nicotine dependence	F17	97	12.8
	Other Substance	F18	72	9.5
Mental Health	Bipolar disorder	F31	60	7.9
	Major depressive disorder	F32-F33	181	23.9
	Anxiety disorders	F41	61	8.1
Nervous system	Sleep disorders	G47	52	6.9
	Hereditary and idiopathic neuropathy	G60	52	6.9
Cardiovascular	Hypertensive Disease	I10-I16	271	35.8
Respiratory	Allergic/Chronic rhinitis, nasopharyngitis and pharyngitis	J30-J31	44	5.8
	Chronic Obstructive Pulmonary Disease	J45	60	7.9
	Asthma	J44	41	5.4
Gastro-intestinal	Gastro-esophageal reflux disease	K21	68	9.0
Musculoskeletal	Other Joint Disorders	M20-M25	62	8.2
	Dorsalgia/ Back Pain	M54	71	9.4
Urogenital	Chronic Kidney Disease	N18	56	7.4
	Male erectile dysfunction	N52	32	4.2
	Inflammation of vagina and vulva	N76	26	3.4