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Reconciling the evaluation of co-morbidities among HIV care patients in two large data systems: the Medical Monitoring Project and CFAR Network of Integrated Clinical Systems

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ABSTRACT

The estimated burden of chronic disease among people living with HIV (PLWH) varies considerably by data source, due to differences in case definitions, analytic approaches, and underlying patient populations. We evaluated the burden of diabetes (DM) and chronic kidney disease (CKD) in two large data systems that are commonly queried to evaluate health issues affecting HIV care patients: the Medical Monitoring Project (MMP), a nationally representative sample, and the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a clinical cohort. In order to reconcile these two data sources, we addressed issues common to observational data, including selection bias, missing data, and development of case definitions. The overall adjusted estimated prevalence of DM and CKD in MMP was 12.7% and 7.6%, respectively, and the overall prevalence of DM and CKD in CNICS was 9.9% and 8.3%, respectively; prevalence estimates increased with age in both data sources. After reconciling the approach to analyzing MMP and CNICS data, sub-group specific prevalence estimates of DM and CKD was generally similar in both data sources. Both data sources suggest a considerable burden of disease among older adults in HIV care. MMP and CNICS can provide reliable data to monitor HIV co-morbidities in the US.

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Introduction

Although the majority of adults receiving HIV care in high income countries are virally suppressed (Althoff et al., 2012; Bradley, Mattson, Beer, Huang, & Shouse, 2016; Raymond, Hill, & Pozniak, 2014), people living with HIV (PLWH) are nonetheless disproportionately affected by cancer (Grulich, van Leeuwen, Falster, & Vajdic, 2007; Rasmussen et al., 2015), cardiovascular disease (Freiberg et al., 2013; Lang et al., 2010; Rasmussen et al., 2015; Triant, Lee, Hadigan, & Grinspoon, 2007; Womack et al., 2014), kidney disease (Abraham et al., 2015; Goulet et al., 2007; Guaraldi et al., 2011; Rasmussen et al., 2015), liver disease (Goulet et al., 2007; Rasmussen et al., 2015), metabolic disorders (Monroe, Glesby, & Brown, 2015; Samaras, 2009), and other chronic diseases (Rasmussen et al., 2015). The excess burden of chronic disease among people living with HIV (PLWH) is attributable to HIV infection, its treatment, and greater exposure to traditional chronic disease risk factors, including smoking, drug and alcohol use, and chronic viral infections (Warriner, Burkholder, & Overton, 2014). The high prevalence of chronic disease among PLWH has implications for how HIV medical care is organized, the training of HIV medical providers, and the costs of medical care.

Large-scale surveillance systems and clinical cohorts have been established in the United States to monitor the health of PLWH, though their design, representativeness of the PLWH population, and approach to analyses vary widely. Not surprisingly, the estimated burden of co-morbidities varies substantially by data source. For example, the estimated prevalence of kidney disease was 3% among Veterans Administration patients (measured by ICD-9 codes) (Goulet et al., 2007), 8% among Medicare beneficiaries (measured by ICD-9

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codes) (Gilden, Kubisiak, & Gilden, 2007), and 15% in a CDC cohort study (measured by medical record data on diagnoses, medications, and lab results) (Buchacz et al., 2012). The extent to which these differences in estimated prevalence are attributable to differences in patient population, case definition, study design, or analytical approach is difficult to discern. Evaluations of chronic disease in the general population commonly face these challenges (Goodman, Posner, Huang, Parekh, & Koh, 2013).

The Medical Monitoring Project (MMP) and the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) are two of ten data systems considered by the Institute of Medicine as the "most useful for tracking the impact of the NHAS [National HIV/AIDS Strategy] and the ACA [Affordable Care Act] on HIV care" (IOM, 2012). MMP was designed to monitor health indicators in a sample representative of the HIV care patient population and provides annual point prevalence estimates for many behavioral and clinical outcomes (Frankel et al., 2012). CNICS collects longitudinal data in a large cohort of patients receiving care in eight university-affiliated clinics, thus enabling patient health trajectories and causal relationships to be assessed (CNICS, 2014). Even though MMP and CNICS have different purposes and designs, they are often queried to assess the same health issues, including HIV co-morbidities. These two data systems have never been directly compared, though they provide the opportunity for data triangulation.

Our primary objective is to demonstrate methodological tactics that can enhance the comparability of independent data sources. Our secondary objective is to estimate and compare the prevalence of diabetes (DM) and chronic kidney disease (CKD) in MMP and CNICS.

Methods

Data sources

Medical monitoring project (MMP)

MMP is a Centers for Disease Control and Prevention-funded HIV surveillance project that collects annual cross-sectional clinical, socio-demographic, and behavioral data. Prior to the 2015 data collection cycle, MMP used a three-stage sampling design to generate samples representative of adults receiving HIV care in the US. The three hierarchical levels of sampling were states/territories, HIV care facilities (in selected jurisdictions), and patients who received care at participating facilities in January–April in a given year. Detailed interviews and medical record abstractions (MRAs) are conducted by health departments in 16 states and Puerto Rico. Data are weighted for unequal selection probabilities and non-response. A more detailed description of the MMP methodology is available elsewhere (Frankel et al., 2012).

For this analysis, we analyzed MRA records from the 2013 MMP cycle (data collected June 2013–May 2014). All sampled jurisdictions participated in MMP. Of the 598 sampled facilities, 480 (85%) facilities participated. Of the 9,371 sampled patients, MRAs were completed for 6,412 patients (70% of eligible, sampled patients). Clinical records dated within two years before the MMP interview were abstracted for MRA data collection. For MRAs conducted under surveillance authority without corresponding interview data, records dated within two years before the date of first contact attempt were abstracted.

In accordance with guidelines for defining public health research (CDC, 2010), CDC determined MMP was public health surveillance used for disease control, program, or policy purposes. Local institutional review board approval was obtained when required. Informed consent was obtained from all interviewed participants.

Centers for AIDS research network of integrated clinical systems (CNICS)

CNICS is a research network involving eight large Centers for AIDS Research (CFAR) clinics that prospectively collect comprehensive patient data at point-of-care through electronic medical record data and other sources. The eight CFAR clinics are located in the following locations: Baltimore MD, Birmingham AL, Boston MA, Chapel Hill NC, Cleveland OH, San Diego CA, San Francisco CA, Seattle WA. Patients who receive HIV care at the eight clinics are included in the CNICS cohort; the median follow-up for each patient is about 4 years. Approximately 1400 patients are newly enrolled each year; <10% of patients leave the CFAR clinical sites (and thus CNICS) annually (Kitahata et al., 2008). For this analysis, we included CNICS patients who had a visit in 2013 ($n = 13{,}842$) and analyzed records dated within the two years preceding each patient's last visit in 2013. Sites received institutional review board approval for CNICS and written informed consent was obtained from participants.

National HIV surveillance system (NHSS)

To illustrate how MMP and CNICS participants compare to the US PLWH population, we compared the demographic characteristics of MMP and CNICS participants to the US PLWH population using aggregate NHSS data summaries. The NHSS data presented

corresponds to PLWH diagnosed, reported, and presumed living in 2013, and were adjusted for reporting delays (CDC, 2015).

Analysis

Case definitions

For this analysis, we applied case definitions developed and validated by CNICS investigators to MMP and CNICS datasets. The case definitions are described in Table 1.

Management of missing data

In addition to diagnostic and prescription information, case definitions rely upon laboratory measurements: the DM definition relies upon HbA1c and glucose measurements, and the CKD definition relies upon creatinine measurements. If a patient did not have the measures specified by the case definition in the two year observation period, and did not otherwise meet the case definition, their disease status was set to missing. The percent missing for each condition is listed in Table 3.

We considered three approaches to managing missing data: (1) assume that patients with missing values for a given condition did *not* have the condition, (2) exclude patients with a missing value for a given condition from analyses of that condition ("complete case" analysis), and (3) impute disease status for patients with missing values. Table 3 contrasts how the approach impacted prevalence estimates.

Ultimately, we imputed disease status for patients with missing values by implementing multiple imputation by chained equations (MICE) using IVEware Version 0.2, a SAS-callable macro. (Vizcarra&Sukasih, 2013) This process involved: (1) generating ten datasets in which missing values were imputed (described below); (2) running the analysis of interest (e.g., generating sub-group specific disease prevalence estimates) on each of the imputed datasets; and (3) pooling the estimates of prevalence and standard error[1] across the imputed datasets. For each imputed dataset, regression models were executed to estimate the relationships between each variable with missing data and a set of covariates, which were assumed to fully account for the occurrence of missingness. The set of covariates used to impute missing MMP data included five additional covariates that were unavailable in CNICS; otherwise, the covariates included in the MI models were identical in MMP and CNICS.[2] The fitted regression models were used to predict values for individual missing values.

Table 1. Case definitions applied to medical monitoring project (MMP) and CFAR network of integrated clinical systems (CNICS) data.

Condition	Case Criteria
Chronic Kidney Disease	Two eGFR[a] values <60 ml/min 90 or more days apart without an intervening normal value.
Diabetes	1. HbA1c ≥6.5%; OR 2. "Diabetes-specific" medication[b]; OR 3. Diabetes diagnosis AND "diabetes-related" medication[c]; OR 4. ≥ 2 random glucose tests ≥200 mg/dL

Note: All criteria assessed in a 2 year observation period.
[a]eGFR = Estimated Glomerular Filtration Rate. eGFR is routinely used to assess kidney function. We applied the CKD-EPI creatinine equation (Levey et al., 2009) to MMP and CNICS data to estimate participants' GFR.
[b]DM-specific medications: Alogliptin, Canagliflozin, Chlorpropamide, Exenatide, Glimepiride, Glipizide, Glipizide, Glyburide, Insulin, Linagliptin, Liraglutide, Nateglinide, Pramlintide, Repaglinide, Saxagliptin, Sitagliptin, Tolazamide, Tolbutamide.
[c]DM-related medications: Acarbose, Metformin, Miglitol, Pioglitazone, Rosiglitazone, Troglitazone.

Estimation of diabetes and chronic kidney disease prevalence

Stratum, cluster, and weighting design variables were included in all analyses of MMP data, thereby generating results representative of the population of adults receiving HIV care in the United States. All analyses were stratified by sex at birth, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other), and age group (18–34, 35–54, ≥55 years). For each demographic sub-group, we calculated a Z statistic to test whether the proportion classified as having DM or CKD significantly differed between MMP and CNICS.

Sensitivity analysis: addressing potential selection bias in MMP

To be included in the MMP sampling frame, patients must have had an HIV care visit during January –April of the sampling year (the "Population Definition Period (PDP)"). Using CNICS data, we evaluated whether the relative risk of meeting the CKD and DM case criteria differed between CNICS patients who did and did not have a visit during January – April. We estimated the adjusted relative risk (aRR) of each condition given the presence (versus absence) of visit during January – April, controlling for potential confounders (age, sex, race, and body mass index), by implementing a Poisson regression model with robust error variance. If a significant association was observed, then we calculated a modified prevalence estimate based upon following input parameters: mean and standard error (SE) of disease by sub-group among MMP participants, aRR and SE of disease given presence (versus absence) of January – April visit among CNICS patients, and percent of CNICS patients with a January – April visit. We assumed

Table 2. Characteristics of medical monitoring project (MMP) and CFAR network of integrated clinical systems patients (CNICS) participants, relative to people with an HIV diagnosis reported to the national HIV surveillance system (NHSS), United States, 2013.

	MMP (n = 6,412) %	CNICS (n = 13,842) %	NHSS (n = 933, 941) %
Age group			
18–34	15	14	18
35–54	57	58	57
≥55	28	27	25
Race/ethnicity			
Non-Hispanic White	31	44	32
Non-Hispanic Black	43	39	43
Hispanic	21	14	20
Other	5	3	5
Sex at birth			
Male	73	82	76
Female	27	18	24
Region[a]			
Midwest	14	7	12
Northeast	19	8	25
South	39	40	43
West	23	45	19
US Territories	5	0	2

Source for NHSS data: Centers for Disease Control and Prevention. HIV Surveillance Report, 2014; vol. 26. http://www.cdc.gov/hiv/library/reports/surveillance/. Published November 2015. Accessed August 2016.

[a]"Region" = the unweighted percent of the MMP and CNICS sample receiving HIV care in the five listed regions. Regions are defined by the US Census Bureau and used in CDC's National HIV Surveillance System:
Northeast: CT, ME, MA, NH, **NJ**, **NY**, **PA**, RI, VT.
Midwest: **IL**, **IN**, IA, KS, **MI**, MN, MO, NE, ND, OH, SD, WI.
South: AL, AR, **DE**, DC, **FL**, **GA**, KY, LA, MD, **MS**, **NC**, OK, SC, TN, **TX**, **VA**, WV.
West: AK, AZ, **CA**, CO, HI, ID, MT, NV, NM, **OR**, UT, **WA**, WY.
US Territories: **PR**, AS, GU, MP.
In the above list, jurisdictions that participate in MMP are bolded and jurisdictions with clinics that participate in CNICS are underlined.

disease prevalence and aRR estimates were normally distributed and ran 1,000 simulated observations in Stata drawing from these distributions. To estimate disease prevalence corrected for PDP sampling and account for uncertainty in the adjusted point estimates, we applied the following equation to the simulated observations:

$$P_c = P \times (V_1 + (V_0 \times aRR))$$

In this equation, P connotes prevalence, c connotes correction factor, V_1 connotes the proportion with a PDP visit, V_2 connotes the proportion without a PDP visit, and RR connotes the adjusted relative risk of disease. To obtain the overall adjusted point prevalence, we estimated the mean adjusted prevalence across the 1,000 simulations. The corresponding standard error was the standard deviation of the simulated mean adjusted prevalence estimates.

Results

Patient demographic characteristics

This analysis included clinical records from 6,412 MMP participants and 13,842 CNICS patients. Age was similarly distributed in MMP and CNICS, with more than half of patients between the ages of 35 and 54. The age distribution is older in MMP and CNICS than that of all prevalent HIV cases reported to the National HIV Surveillance System (NHSS) (see Table 2). The distribution of sex, race/ethnicity, and region in MMP was more similar to NHSS than CNICS. Compared to MMP and NHSS, a larger proportion of CNICS patients were male, non-Hispanic (NH) White, and residing in the western U.S.

Comparison of overall prevalence estimates yielded by three approaches to managing missing data

The percent missing values for CKD and DM was similar between MMP and CNICS (Table 3). Missingness was

Table 3. Overall prevalence of diabetes and chronic kidney disease among MMP and CNICS participants, estimated by three different approaches to addressing missingness.

		Disease prevalence when participants with missing values were …		
	% Missing	Assumed to NOT have condition % (95% CI)	Excluded from Analysis ("Complete Case") % (95% CI)	Assigned Disease Status Given Demographic and Health Characteristics[a] ("Multiple Imputation") % (95% CI)
Diabetes				
MMP	9.1	10.6 (10.1, 11.1)	13.2 (12.7, 13.7)	12.7 (12.0, 13.3)
CNICS	11.7	8.3 (7.8, 8.7)	9.4 (8.9, 9.9)	9.9 (9.2, 10.5)
Chronic kidney disease				
MMP	10.3	7.3 (6.9, 7.6)	7.6 (7.2, 7.9)	7.6 (7.2, 8.0)
CNICS	13.2	7.5 (7.1, 8.0)	8.7 (8.2, 9.2)	8.3 (7.8, 8.8)

Abbreviations: MMP = Medical Monitoring Project; CNICS = Centers for AIDS Research Network of Integrated Clinical Systems; CKD = Chronic Kidney Disease; DM = Diabetes Mellitus.

Notes: Patients with less than 2 creatinine measures (separated by 90 days) in the 2 year observation period were considered missing CKD status. Patients without a single HbA1c or two glucose measures in the two year observation period who did not otherwise meet the case criteria, were assigned missing values for diabetes status.

[a]The following variables were included in the MMP imputation models that assessed CKD and DM : age, sex, race, ethnicity, nativity, risk transmission category, years since HIV diagnosis, history of male-to-male sex, history of injection drug use, region, project area, body mass index, average eGFR, average systolic blood pressure, average diastolic blood pressure, dialysis, CKD status, DM status, HTN status, and dyslipidemia status. The following variables were included in the CNICS imputation models that assessed CKD and DM: age, sex race, ethnicity, risk transmission category, region, body mass index, site, average eGFR, average systolic blood pressure, average diastolic blood pressure, CKD status, DM status, HTN status, and dyslipidemia status.

slightly greater for CKD (10% in MMP and 13% in CNICS) than DM (9% in MMP and 12% in CNICS); missingness decreased with age (data not shown).

In both MMP and CNICS, prevalence was lowest when patients with missing values were assumed to be free of disease and highest when patients with missing values were excluded from analyses. The estimates yielded by the MI models tended to be closer in value to estimates yielded by the complete case analysis. The overall prevalence of DM and CKD (estimated through MI) in MMP was 12.7% (95% CI: 12.0, 13.3) and 7.6% (95% CI: 7.2, 8.0), respectively. The overall prevalence of DM and CKD (estimated through MI) in CNICS was 9.9% (95% CI: 9.2, 10.5), 8.3% (95% CI: 7.8, 8.8), respectively.

Chronic kidney disease (CKD)

The estimated CKD prevalence increased with age (Table 4, Supplementary Figure 1). Across MMP and CNICS, the CKD prevalence ranged from 0–2.4% in the youngest age group (<35 years); 1.2–10.8% in the middle age group (35–54 years); and 7.5–31.9% in the oldest age group (≥55 years). Among NH-White and NH-Black patients, the estimated prevalence was greater for women than men. Significant differences in age- and sex-specific prevalence estimates were observed between MMP and CNICS among NH-Blacks ≥35 years old, with greater prevalence observed in CNICS than in MMP. The CKD burden found in CNICS was greater among NH-Black patients than NH-White and Hispanic patients; however, in MMP, age- and sex-specific prevalence estimates were similar across racial groups.

Table 4. Prevalence of chronic kidney disease among adults in HIV care in 2013, estimated with MMP and CNICS data.

	MMP Prevalence % (95% CI)	CNICS Prevalence % (95% CI)
Overall	7.6 (7.2, 8.0)	8.3 (7.8, 8.8)
NH-White Men		
18–34	0.1 (0, 3.5)	0.5 (0.0, 2.3)
35–54	4.1 (2.6, 5.6)	3.0 (2.4, 3.6)
≥55	16.8 (13.4, 20.3)	12.7 (11.0, 14.4)
NH-Black Men		
18–34	0.4 (0, 2.3)	2.4 (0.0, 6.0)
35–54	6.6 (4.4, 8.8)†	9.7 (8.3, 11.0)†
≥55	15.4 (12.2, 18.7)†	20.8 (18.3, 23.3)†
Hispanic Men		
18–34	1.4 (0, 3.8)	0.5 (0.0, 1.6)
35–54	2.9 (1.3, 4.4)	1.2 (0.5, 1.8)
≥55	17.8 (11.3, 24.3)	12.7 (8.5, 16.9)
NH-White Women		
18–34	2.2 (0, 7.1)	0 (0, 0)
35–54	9.1 (3.6, 14.5)	8.8 (5.7, 12.0)
≥55	23.8 (14, 33.6)	23.2 (16.5, 30.0)
NH-Black Women		
18–34	2.0 (0, 8.1)	1.4 (0.0, 3.4)
35–54	5.6 (3.8, 7.3)‡	10.8 (8.9, 12.8)‡
≥55	20.2 (16, 24.4)‡	31.9 (27.9, 35.9)‡
Hispanic Women		
18–34	0.3 (0, 3.6)	0 (0, 0)
35–54	4.6 (0, 9.1)	2.8 (0.1, 5.6)
≥55	17.0 (9.1, 24.8)	7.5 (0.0, 15.8)

Abbreviations: MMP = Medical Monitoring Project; CNICS = Centers for AIDS Research Network of Integrated Clinical Systems; NH = Non-Hispanic; CKD = Chronic Kidney Disease; eGFR = Estimated Glomerular Filtration Rate; MI = Multiple Imputation.

Notes: The CKD case criterion was two eGFR values <60, which were ≥ 90 days apart without an intervening normal value. Prevalence estimates presented reflect the results from multiple imputation model; across all strata and data sources, the difference between the point estimates estimated from complete case (not presented) and MI analyses was less than one percentage point. MMP prevalence estimates were adjusted for MMP's sampling frame (see Methods section). Significant differences in prevalence estimated by MMP and CNICS are indicated with †($p < .05$) and ‡($p < .01$).

Diabetes (DM)

Among patients classified as having diabetes in MMP and CNICS, respectively, 66% and 76% had ≥1 HbA1c measures > 6.5%, 63% and 60% had a DM-specific medication, 36% and 18% had a DM diagnosis and a DM-related medication, and 31% and 44% had ≥2 random glucose tests ≥200 mg/dL. Only 3% of CNICS cases and 5% of MMP cases met the glucose criteria and no other diabetes case criteria. The estimated DM prevalence increased with age (Table 5, Supplementary Figure 2). In the youngest age group (<35 years), the DM prevalence ranged from 1.6–8.1%; in the middle age group (35–54 years), the DM prevalence ranged from 6.9–14.9%; in the oldest age group (≥55 years) the DM prevalence ranged from 12.7–40.4%. Within demographic strata, prevalence estimates were fairly consistent between MMP and CNICS. In the youngest age group, DM prevalence tended to be higher among women than men; in the older age groups DM prevalence was more similar between men and women. There was a pattern suggesting that prevalence tended to be lowest for NH-Whites and highest for Hispanics.

Sensitivity analysis: addressing potential selection bias in MMP

Accounting for differences in patients with and without a January – April visit, the adjusted relative risk of CKD and DM was 0.82 (95% CI= 0.71, 0.95) and 0.93 (95% CI= 0.82, 1.07), respectively. Since a significant association existed between having a January – April visit and CKD, we re-estimated the CKD prevalence, adjusting for MMP's sampling design, and compared the adjusted prevalence estimates to the original estimates presented in Table 4. The adjusted estimates differed by less than 1 percentage point from the original MMP prevalence estimates (Supplemental Table 1).

Table 5. Prevalence of diabetes among adults in HIV care in 2013, estimated with MMP and CNICS data.

	MMP Prevalence % (95% CI)	CNICS Prevalence % (95% CI)
Overall	12.7 (12.0, 13.3)	9.9 (9.2, 10.5)
NH-White Men		
18–34	1.8 (0, 5.1)	1.8 (0.2, 3.4)
35–54	7.6 (5.2, 10)	6.9 (5.8, 7.9)
≥55	14.4 (10.6, 18.2)	15.0 (12.8, 17.1)
NH-Black Men		
18–34	1.6 (0, 5.1)	1.9 (0.9, 2.9)
35–54	11.2 (8.1, 14.3)	10.1 (8.7, 11.5)
≥55	22.1 (16.6, 27.5)	18.0 (15.7, 20.3)
Hispanic Men		
18–34	3.4 (0, 8.9)	1.6 (0.1, 3.0)
35–54	12.8 (9.4, 16.3)†	7.9 (6.0, 9.7)†
≥55	28.2 (19, 37.3)	20.1 (15.0, 25.2)
NH-White Women		
18–34	5.3 (0, 18.1)	3.2 (0.0, 7.5)
35–54	8.9 (2.7, 15.1)	10.3 (7.0, 13.5)
≥55	17.4 (6.6, 28.2)	12.7 (7.4, 18.0)
NH-Black Women		
18–34	3.4 (0, 8.8)	6.7 (2.4, 10.9)
35–54	11.9 (7.5, 16.3)	11.7 (9.7, 13.7)
≥55	25.2 (17.6, 32.9)	18.2 (14.9, 21.5)
Hispanic Women		
18–34	8.1 (0, 20.4)	4.4 (0.0, 12.7)
35–54	14.9 (5.9, 23.8)	7.7 (3.0, 12.3)
≥55	40.4 (25.9, 54.9)	22.5 (9.4, 35.6)

Abbreviations: MMP = Medical Monitoring Project; CNICS = Centers for AIDS Research Network of Integrated Clinical Systems; NH = Non-Hispanic; DM = Diabetes Mellitus; MI = Multiple Imputation.

Notes: The DM case criteria include (1) HbA1C ≥ 6.5% OR (2) diabetes-specific medication OR (3) diabetes diagnosis AND "diabetes-related" medication OR (4) ≥ 2 random glucose tests ≥ 200 mg/dL. Prevalence estimates presented reflect the results from multiple imputation model; across all strata and data sources, the difference between the point estimates estimated from complete case (not presented) and MI analyses was less than one percentage point. MMP prevalence estimates were adjusted for MMP's sampling frame (see Methods section). Significant differences in prevalence estimated by MMP and CNICS are indicated with †($p < .05$) and ‡($p < .01$).

Discussion

In our effort to reconcile measurement of the burden of DM and CKD in MMP and CNICS, we encountered several common challenges, including non-standard case definitions, missing data, and potential for selection bias. We detailed how we decided to manage these issues and how these decisions influenced our results. After reconciling our approach to analyzing MMP and CNICS data, we demonstrated a considerable burden of DM and CKD among older adults receiving care at facilities included in these two prominent data systems.

MMP and CNICS differ dramatically in their design. MMP is a probability sample of HIV care patients who receive care from clinics located in geographically diverse areas across the United States; clinical data is manually abstracted from medical records by trained health department staff. CNICS is a census of almost all patients receiving care at eight, large university-affiliated clinics that uses integrated electronic medical record systems to enable data entered at point-of-care to be readily deposited into a central repository. Given these differences, one might expect prevalence estimates to vary widely by data source. However, the estimated prevalence of DM and CKD was generally similar across MMP and CNICS, which may be attributable to our concerted effort to reconcile how DM and CKD are defined and statistically evaluated.

We have several recommendations for evaluating DM and CKD and other chronic conditions in the context of HIV. First, analysts should be cautious about how disease status is assigned for patients without complete documentation corresponding to the case criteria. In our analysis, patients without laboratory measures specified by the case definition who did not otherwise meet the case definition were assigned missing values for disease status; their probable disease status was subsequently assigned through multiple imputation. This was in contrast to the existing literature, which most commonly assumed that patients lacking documentation corresponding to the case definition are free of disease (Buchacz et al., 2012; Gilden et al., 2007; Goulet et al., 2007; Rasmussen et al., 2015; Schoffelen et al., 2015; Willig et al., 2015), or excluded patients without documentation from analyses. (Mocroft et al., 2015) While the absence of laboratory data (and no other diagnostic or medication data) might connote that the laboratory test was not clinically indicated, for some patients, the absence of a laboratory test, diagnostic, and prescription data could reflect other issues, such as sub-optimal engagement in care. In summary, treating the absence of documentation as being indicative of being free of disease may cause the burden of disease to be underestimated for prevalent co-morbidities. A second methodological recommendation is that standard and existing case definitions be employed, so that studies can be more easily compared. We reported the proportion of patients classified as being a DM case that met each specific component of the case definition, illustrating the sensitivity of disease status classification to decisions about case definitions. Finally, we recommend that prevalence estimates applied to a heterogeneous group be interpreted cautiously, as it might reflect the underlying demographics rather than the actual burden of disease.

With the number of PLWH over 55 years old increasing in the United States (Hood et al., 2017), HIV care programs should anticipate a growing number of their patients requiring services related to DM and CKD and likely other chronic diseases. While data sources like MMP and CNICS allow for the prevalence and risk factors of various chronic conditions to be routinely monitored, determining how best to concurrently treat and

manage HIV and common chronic conditions requires intensive investigation.

There are limitations shared by MMP and CNICS, limitations unique to each data source, and limitations of our analytic approach. Both MMP and CNICS are unlikely to capture complete information about care received outside of patients' primary facility. CNICS and MMP are vulnerable to different types of selection bias. CNICS represents patients who receive care at large, public, university-affiliated clinics in urban settings. MMP represents these patients, as well as patients who receive care at clinics that vary with regard to predominant funding base, size, and urbanicity. Perhaps consequently, the distribution of sex, race/ethnicity, and regional distribution among MMP participants is more similar to the census of all adults with diagnosed HIV (per NHSS data) than that of CNICS. However, only 70% of patients sampled for MMP in 2013 contributed data to this analysis. Although the analyses are weighted for non-response, the risk of bias is unlikely eliminated. Prior to 2015, MMP sampled from a list of patients who had a visit in January–April. We used CNICS data to explore whether this sampling approach might affect the estimated prevalence of CKD and DM. Although we observed a significant association between having a January – April visit and meeting the CKD case criteria, it did not appear to substantially affect the estimated prevalence of CKD (Supplemental Table 1).

Our analytical approach had limitations. As noted above, we used multiple imputation to assign disease status to patients without any documentation corresponding to the case definition. Although we included many demographic and clinical variables in our imputation models, it is unlikely that we fully accounted for all factors that would affect missingness, compromising the "missing at random" assumption that underlies MI procedures. A separate limitation is that a small subset of patients (about 5%) contributed data to both MMP and CNICS, as there are four clinics that participate in both MMP and CNICS. A final limitation of our analysis is that we did not rigorously evaluate racial disparities. Based on the existing literature (Abraham et al., 2015), we expected the CKD prevalence to be considerably greater among NH-Black participants than participants of other racial/ethnic backgrounds. This pattern was evident in CNICS, but not MMP. The root cause of these discordant findings is unknown.

Large data systems (like MMP and CNICS) play a pivotal role in monitoring and evaluating population health, though they face challenges common to observational studies. In this manuscript, we demonstrated how these challenges can be addressed analytically. After reconciling the analytical approach, the sub-group specific prevalence estimates were fairly consistent between MMP and CNICS and suggested a considerable burden of disease among older adults in HIV care. The consistency between the two data sources may allay concerns regarding the limitations of both data sources. MMP and CNICS can provide reliable data to monitor HIV co-morbidities in the US.

Notes

1. Standard error was calculated using Rubin's Rules (Rubin, 1987); the Taylor Series approach was used to obtain variance estimates for MMP, accounting for its survey design (Vizcarra&Sukasih, 2013).
2. The following variables were included in the multiple imputation (MI) models: age, sex, race, ethnicity, risk transmission category, region, body mass index, site, average eGFR, average systolic blood pressure, average diastolic blood pressure, CKD status, DM status, HTN status, and dyslipidemia status. The MI models implemented on MMP data also included the following variables that were unavailable in CNICS: dialysis, reported ever using injection drugs, reported ever engaging in male-to-male sex, birth country, and years since HIV diagnosis. The inclusion of these five additional variables did not meaningfully affect the prevalence estimates generated from the multiple imputation models executed on MMP data.

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