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Longitudinal Associations of Syndemic Conditions with Antiretroviral Therapy Adherence and HIV Viral Suppression Among HIV-Infected Patients in Primary Care

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Abstract

Psychosocial syndemic conditions have received more attention regarding their deleterious effects on HIV acquisition risk than for their potential impact on HIV treatment and viral suppression. To examine syndemic conditions' impact on the HIV care continuum, we analyzed data collected from people living with HIV ($N = 14{,}261$) receiving care through The Centers for AIDS Research Network of Integrated Clinical Systems at seven sites from 2007 to 2017 who provided patient-reported outcomes ~4–6 months apart. Syndemic condition count (depression, anxiety, substance use, and hazardous drinking), sexual risk group, and time in care were modeled to predict antiretroviral therapy (ART) adherence and viral suppression (HIV RNA <400 copies/mL) using multilevel logistic regression. Comparing patients with each other, odds of ART adherence were 61.6% lower per between-patient syndemic condition [adjusted odds ratio (AOR) = 0.384; 95% confidence interval (CI), 0.362–0.408]; comparing patients with themselves, odds of ART adherence were 36.4% lower per within-patient syndemic condition (AOR = 0.636 95% CI, 0.606–0.667). Odds of viral suppression were 29.3% lower per between-patient syndemic condition (AOR = 0.707; 95% CI, 0.644–0.778) and 27.7% lower per within-patient syndemic condition (AOR = 0.723; 95% CI, 0.671–0.780). Controlling for the effects of adherence (AOR = 5.522; 95% CI, 4.67–6.53), each additional clinic visit was associated with 1.296 times higher odds of viral suppression (AOR = 1.296; 95% CI, 1.22–1.38), but syndemic conditions were not significant.

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Deploying effective interventions within clinics to identify and treat syndemic conditions and bolster ART adherence and continued engagement in care can help control the HIV epidemic, even within academic medical settings in the era of increasingly potent ART.

Keywords: HIV, syndemic conditions, treatment as prevention, patient-reported outcomes, adherence

Introduction

Syndemic theory has often concerned itself with co-occurring psychosocial and structural variables' influence on physical health, and physical health's influence on psychosocial outcomes, among people living with HIV (PLWH) and those at risk of contracting HIV.[1] Much of the syndemic literature focused on the measurement of psychosocial variables and their co-occurrence has enabled better understanding of how additive syndemic conditions predict increased risk of HIV acquisition or seropositivity in predominantly seronegative samples.[2–22] By comparison, fewer studies have examined additive syndemic conditions' association with HIV care continuum outcomes. This growing literature has focused on antiretroviral therapy (ART) nonadherence, uncontrolled viral load, and biobehavioral transmission risk behavior (i.e., condomless sex while virally unsuppressed) as primary outcomes of interest, mostly in samples of men who have sex with men (MSM).[23–31] Other studies have linked psychological predictors and substance use, although not their additive effects, to viral nonsupression and worse HIV clinical outcomes.[32–41]

In the treatment as prevention (TasP) era, consistent adherence to ART effectively suppresses HIV RNA, minimizing transmission to seronegative partners.[42–44] Connecting PLWH to care and achieving ART adherence are key to the UNAIDS 95-95-95 treatment target and the US government's Ending the HIV Epidemic strategy.[45,46] If co-occurring syndemic conditions significantly predict ART adherence and viral suppression among PLWH in care, measuring and addressing syndemic conditions in clinics could aid greatly in identifying patients most in need of intervention to improve their physical and mental health and potentially avert new HIV transmissions. Moreover, whether syndemic conditions are differentially associated with ART adherence and viral suppression across HIV sexual risk groups bears examination given most studies' focus on MSM.

The current study explored whether additive syndemic conditions among PLWH in care predicted ART adherence and viral suppression across diverse HIV sexual risk groups using the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, a large, longitudinal sample of PLWH in care in urban centers across the United States. While previous CNICS studies have examined the effects of depression and substance use on ART adherence and viral suppression,[47–49] none to date has examined the additive effects of syndemic conditions on the HIV care continuum.

Methods

Participants

Participants were 14,261 PLWH receiving care at seven CNICS sites between June 2007 and April 2017. Patients 18 years or older were approached at routine HIV care appointments to participate in CNICS.[50,51] No reimbursement was offered for patients' participation.[50,51] Informed consent was obtained from all individuals during the initial enrollment. All procedures were in accordance with Institutional Review Boards at the CNICS-affiliate universities, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data sources

The CNICS data repository integrates data from electronic health records, institutional data sources, and data collected upon study enrollment with self-administered patient-reported outcomes and measures (PROs) collected at least 4–6 months apart as part of clinical care.[50,51]

Procedures and measures

Measures. PROs include the following: (i) depressive symptoms over the last 2 weeks measured by the Patient Health Questionnaire-9 (PHQ-9);[52] (ii) anxiety symptoms over the past month measured by five items from the Brief Patient Health Questionnaire (PHQ-5);[53] (iii) use of methamphetamines, illicit opioids, marijuana, and crack/cocaine over the past 3 months measured by the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST);[54] (iv) alcohol consumption over the past year measured using versions of the Alcohol Use Disorders Identification Test (AUDIT) or the first three questions of the AUDIT (AUDIT-C);[55] (v) a yes/no question asking whether the patient was taking ART; (vi) past-month ART adherence measured by the visual analog scale (VAS) with scores ranging from 0 to 100;[56] and (vii) past-month ART adherence measured by the self-rating scale item (SRSI).[57]

HIV risk group classification

Patients were classified into HIV sexual risk groups—cisgender MSM, cisgender women, cisgender heterosexual men, and transgender women—based on sex, self-identified gender identity, and self-identified sexual orientation where available. In addition, cisgender men with a lifetime history of anal sex, no lifetime history of vaginal sex, and no self-reported sexual orientation were classified as cisgender MSM. This yielded 2239 cisgender women (15.7%), 163 transgender women (1.1%), 1183 cisgender heterosexual men (8.3%), 7727 cisgender MSM (54.2%), and 2949 cisgender men of undisclosed sexual orientation (20.7%).

Imputation of missing PROs

Multilevel multiple imputation using the fully conditional specification algorithm in Blimp version 2.2 generated 20 imputed data sets with complete scores for the PHQ-9, the PHQ-5, the ASSIST, and the AUDIT/AUDIT-C, and complete responses on whether ART was being received.[58–60] All subsequent preparation and data analyses were completed across all 20 imputed data sets.

Creation of adherence and viral suppression variables

Patients were classified as ART-adherent based either on scores of ≥95 on the VAS[61] or ''Excellent'' on the SRSI.[62] To account for changing viral load thresholds over time and across sites, viral suppression was set at HIV RNA <400 copies/mL.

Syndemic conditions

PROs were used to identify four syndemic conditions: (i) clinically significant depressive symptoms (≥5 on the PHQ-9)[52]; (ii) clinically significant anxiety (an anxiety attack in the previous 4 weeks as rated on the PHQ-5); (iii) screening positive for a substance use disorder (≥4 on the ASSIST for the use of cocaine/crack, illicit opioids, methamphetamines, or marijuana)[54]; and (iv) screening positive for hazardous drinking (≥4 for cisgender men and transgender women or ≥3 for cisgender women on the AUDIT-C or the first three questions of the AUDIT).[55]

Between-patient comparisons were facilitated through the calculation of between-person syndemic scores for each participant (i.e., patient's average number of syndemic conditions over the period of observation), which were centered for analyses. Within-person syndemic scores were calculated for each observation by subtracting patients' between-person syndemic scores from their observed number of syndemic conditions to model the effect of variations in patients' syndemic conditions over time.

Time in care

Time in care was measured by the number of visits a patient completed since PRO collection began in the respective clinics, which were centered for analyses.

Data analysis

Hierarchical generalized linear modeling was used for longitudinal analyses across 20 imputed data sets using R version 4.0.2 and the lme4, lmerTest, and mitml packages.[63–66] Standard errors were computed using Satterthwaite's approximation.

The same series of five models were run for two outcome variables—ART adherence and viral suppression—to determine the effects of syndemic conditions, time in care, and HIV sexual risk group. First, an intercept-only model was run. Next, an unconditional longitudinal model added fixed and random effects of time in care. The third model added fixed effects for within-person syndemic scores. The fourth model added fixed effects for between-person syndemic scores. The fifth model added fixed effects of HIV sexual risk group. (Only patients taking ART were included in the ART adherence analyses.)

Because of the potential association of syndemic conditions with adherence, and because adherence is needed to effectively suppress viral load, a final model was fitted to determine syndemic conditions' effects on viral suppression, controlling for ART adherence, time in care, and HIV sexual risk group. (Only patients taking ART were included in this final model.)

To account for increasingly potent ART medications and the advent of universal TasP during the observation period, sensitivity analyses were conducted using data from 2012 to 2017 to assess the effects of syndemic conditions on ART adherence and viral suppression (both before and after controlling for ART adherence).

Table 1. Sample Characteristics at First PRO Visit

		Risk group				
Variable	*All (N = 14,261)*	*Cisgender heterosexual men (n = 1183)*	*Cisgender MSM (n = 7727)*	*Cisgender men, undisclosed sexual orientation (n = 2949)*	*Cisgender women (n = 2239)*	*Transgender women (n = 163)*
Age: *M* (SD)	43.7 (11.0)	48.5 (10.5)	42.1 (10.8)	45.0 (10.9)	45.4 (10.8)	41.2 (10.6)
Race (%)						
White	8234 (57.7)	437 (36.9)	5268 (68.2)	1723 (58.4)	743 (33.2)	63 (38.6)
Black	4696 (32.9)	682 (57.7)	1621 (21.0)	970 (32.9)	1355 (60.5)	68 (41.7)
Native American	125(0.9)	8 (0.7)	60 (0.8)	28 (0.9)	26 (1.2)	3 (1.8)
Asian/Pacific Islander	359 (2.5)	14 (1.2)	260 (3.3)	49 (1.7)	29 (1.3)	7 (4.3)
Multiracial	87 (0.6)	0 (0.0)	66 (0.9)	16 (0.5)	3 (0.1)	2 (1.2)
Other/unknown	760 (5.3)	42 (3.6)	452 (5.8)	163 (5.5)	83 (3.7)	20 (12.3)
Hispanic/Latinx (%)	2018 (14.2)	135 (11.4)	1221 (15.8)	399 (13.5)	212 (9.5)	51 (31.3)
Syndemic condition (%)[a]						
Depressive symptoms	7236 (50.7)	506 (42.8)	3886 (50.3)	1540 (52.2)	1200 (53.6)	103 (63.2)
Anxiety symptoms	4104 (28.8)	206 (17.4)	2301 (29.8)	878 (29.8)	645 (28.8)	75 (46.0)
Illicit drug use	5183 (36.3)	381 (32.2)	2853 (36.9)	1285 (43.6)	599 (26.8)	66 (40.5)
Hazardous drinking	3964 (27.8)	267 (22.6)	2331 (30.2)	843 (28.6)	489 (21.8)	34 (20.8)
Number of syndemic conditions						
M (SD)[a]	1.44 (1.15)	1.15 (1.10)	1.47 (1.14)	1.54 (1.18)	1.31 (1.14)	1.71 (1.15)
Mdn (IQR)[a]	1 (0–2)	1 (0–2)	1 (1–2)	1 (1–2)	1 (0–2)	2 (1–3)
Prescribed ART (%)[a]	11,524 (80.8)	1023 (86.5)	6254 (80.9)	2338 (79.3)	1770 (79.1)	139 (85.7)
ART adherence (%)[b]	8238 (78.3)	771 (81.1)	4697 (79.7)	1454 (73.9)	1230 (77.0)	86(71.7)
Virally suppressed (%)[c]	10,760 (75.5)	944 (79.8)	5868 (75.9)	2148 (72.8)	1675 (74.8)	125 (76.7)

[a]Values from imputed data sets.
[b]Percentage of ART adherence calculated based on available responses for ART adherence.
[c]Viral suppression defined as <400 RNA/mL.
ART, antiretroviral therapy; IQR, interquartile range; *M*, mean; Mdn, median; MSM, men who have sex with men; PRO, patient-reported outcomes and measures; SD, standard deviation.

Results

Mean age at first PRO visit was 43.7 years [standard deviation (SD) = 11.0] (Table 1), compared with 46.1 years (SD = 10.8) across all visits (Table 2). A majority of patients were White (60.0%), followed by patients who were Black (33.5%), although this order was reversed among cisgender heterosexual men (52.7% Black, 42.5% White) and cisgender women (61.3% Black, 33.9% White); 14.2% of visits were with Latinx patients (Table 2). Among syndemic conditions, clinically significant depressive symptoms were most prevalent (50.7% first PRO visit, 46.4% all visits) followed by substance use (36.4% first PRO visit, 31.5% all visits), clinically significant anxiety symptoms (28.8% first PRO visit, 27.0% all visits), and hazardous drinking (27.8% first PRO visit, 23.9% all visits) (Tables 1 and 2). The mean number of syndemic conditions was lower for all PRO visits (1.29, SD = 1.13) than for first visit (1.44, SD = 1.15), a trend that was true for all risk groups except for cisgender MSM (Tables 1 and 2). Overall rates of ART adherence were similar when comparing first PRO visit (78.3%) with all PRO visits (78.6%) (Tables 1 and 2). Overall rates of viral suppression were lower at first PRO visit (75.5%) than for all visits (85.1%) (Tables 1 and 2).

ART adherence

Results of ART adherence models are displayed in Table 3, with odds ratios for the final adherence model displayed in Fig. 1. The final adherence model showed significant effects for within- and between-person syndemic conditions. Specifically, each within-person syndemic condition had 36.4% lower odds of adherence [adjusted odds ratio (AOR) = 0.636; 95% confidence interval (CI), 0.606–0.667], while each additional between-person syndemic condition had 61.6% lower odds of adherence (AOR = 0.384; 95% CI, 0.362–0.408) (Fig. 1). The sensitivity analysis revealed comparable effects of syndemic conditions during 2012–2017 (Supplementary Tables S1 and S2).

Significant differences emerged in the final ART adherence model between cisgender MSM (referent group), and, respectively, cisgender heterosexual men and cisgender men of undisclosed sexual orientation. Relative to cisgender MSM, cisgender heterosexual men had 32.2% lower odds of being ART adherent (AOR = 0.678; 95% CI, 0.541–0.849), while cisgender men of undisclosed sexual orientation had 35.4% lower odds of being ART adherent (AOR = 0.646; 95% CI, 0.515–0.810), with no other significant group differences from cisgender MSM (Fig. 1). Data from 2012 to 2017 similarly revealed significant differences in ART

Table 2. Sample Characteristics for All PRO Visits

	Risk group					
Variable	*All (N = 61,198)*	*Cisgender heterosexual men (n = 5983)*	*Cisgender MSM (n = 37,019)*	*Cisgender men, undisclosed sexual orientation (n = 7782)*	*Cisgender women (n = 9814)*	*Transgender women (n = 600)*
Age: *M* (SD)	46.1 (10.8)	49.6 (10.1)	45.1 (10.8)	46.4 (10.7)	47.3 (10.5)	43.4 (9.8)
Race (%)						
White	36,444 (60.0)	2541 (42.5)	25,697 (69.4)	4593 (59.0)	3326 (33.9)	287 (47.8)
Black	20,504 (33.5)	3153 (52.7)	8442 (22.8)	2658 (34.2)	6017 (61.3)	234 (39.0)
Native American	463 (0.8)	36 (0.6)	257 (0.7)	52 (0.7)	105 (1.1)	13 (2.2)
Asian/Pacific Islander	1287 (2.1)	69 (1.2)	979 (2.6)	103 (1.3)	117 (1.2)	19 (3.2)
Multiracial	300 (0.5)	0 (0.0)	231 (0.6)	40 (0.5)	26 (0.3)	3 (0.5)
Other/unknown	2200 (3.6)	184 (3.1)	1413 (3.8)	336 (4.3)	223 (2.3)	44 (7.3)
Hispanic/Latinx (%)	8699 (14.2)	850 (14.2)	5753 (15.5)	1008 (13.0)	907 (9.2)	181 (30.2)
Number of clinic visits						
M (SD)	4.29 (3.82)	5.06 (4.29)	4.79 (3.93)	2.64 (2.35)	4.38 (4.15)	3.68 (3.32)
Mdn (IQR)	3 (2–6)	4 (2–7)	3 (2–6)	2 (1–4)	3 (2–7)	3 (1–5)
Syndemic condition (%)[a]						
Depressive symptoms	28,389 (46.4)	2382 (39.8)	16,916 (45.7)	3917 (50.3)	4813 (49.0)	361 (60.2)
Anxiety symptoms	16,496 (27.0)	1144 (19.1)	9993 (27.0)	2306 (29.6)	2799 (28.5)	254 (42.3)
Illicit drug use	19,283 (31.5)	1742 (29.1)	11,884 (32.1)	3212 (41.3)	2210 (22.5)	235 (39.2)
Hazardous drinking	14,652 (23.9)	1191 (19.9)	9376 (25.3)	2033 (26.1)	1922 (19.6)	131 (21.8)
Number of syndemic conditions						
M (SD)[a]	1.29 (1.13)	1.08 (1.11)	1.30 (1.11)	1.47 (1.17)	1.20 (1.12)	1.63 (1.14)
Mdn (IQR)[a]	1 (0–2)	1 (0–2)	1 (0–2)	1 (1–2)	1 (0–2)	2 (1–2)
Prescribed ART (%)[a]	54,830 (89.6)	5488 (91.7)	33,563 (90.1)	6707 (86.2)	8529 (86.9)	544 (90.7)
ART adherence (%)[b]	38,549 (78.6)	3995 (81.7)	24,338 (79.5)	4123 (73.5)	5752 (76.8)	341 (75.3)
Virally suppressed (%)[c]	52,077 (85.1)	5275 (88.2)	31,983 (86.4)	6219 (79.9)	8084 (82.4)	516 (86.0)

[a]Values from imputed data sets.
[b]Percentage of ART adherence calculated based on available responses for ART adherence.
[c]Viral suppression defined as <400 RNA/mL.
ART, antiretroviral therapy; IQR, interquartile range; *M*, mean; Mdn, median; MSM, men who have sex with men; PRO, patient-reported outcomes and measures; SD, standard deviation.

adherence between cisgender MSM and, respectively, cisgender heterosexual men (AOR = 0.608; 95% CI, 0.465–0.795) and cisgender men of undisclosed sexual orientation (AOR = 0.662; 95% CI, 0.512–0.857), and no other significant group differences relative to cisgender MSM (Supplementary Tables S1 and S2).

Viral suppression

Results of the first five viral suppression models are displayed in Table 4, with odds ratios for the fifth viral suppression model displayed in Fig. 2. Significant effects emerged for time in care and for both within- and between-person syndemic conditions. Each additional within-person syndemic condition had 27.7% lower odds of viral suppression (AOR = 0.723; 95% CI, 0.671–0.780), while each additional between-person syndemic condition had 29.3% lower odds of viral suppression (AOR = 0.707; 95% CI, 0.644–0.778); each additional care visit had 1.57 times the odds of viral suppression (AOR = 1.570; 95% CI, 1.48–1.67) (Fig. 2). Data from 2012 to 2017 revealed significant effects for time in care and within- and between-person syndemic conditions: each additional within-person syndemic condition had 33.0% lower odds of viral suppression (AOR = 0.670; 95% CI, 0.593–0.756), while each additional between-person syndemic condition had 28.1% lower odds of viral suppression (AOR = 0.719; 95%CI, 0.633–0.816); each additional care visit associated with 1.577 times the odds of viral suppression (AOR = 1.577; 95% CI, 1.47–1.70) (Supplementary Tables S3 and S4).

Significant differences in viral suppression emerged in the fifth model between cisgender MSM (referent group) and, respectively, cisgender heterosexual men and cisgender men of undisclosed sexual orientation. Relative to cisgender MSM, cisgender heterosexual men had 34.8% lower odds of being virally suppressed (AOR = 0.652; 95% CI, 0.440–0.966), while cisgender men of undisclosed sexual orientation had 42.0% lower odds of being virally suppressed (AOR = 0.580; 95% CI, 0.388–0.866); no other significant group differences emerged relative to cisgender MSM (Fig. 2). Notably, results of the sensitivity analysis revealed no significant differences between cisgender MSM and other HIV sexual risk group with respect to viral suppression (Supplementary Tables S3 and S4).

Viral suppression after accounting for adherence

Results of adding ART adherence to the viral suppression model are displayed in Table 5 and Fig. 3. Controlling for ART adherence and time in care, no significant differences in viral suppression emerged with respect to within- or between-person syndemic conditions or between risk groups relative to cisgender MSM; significant effects emerged for ART adherence and time in care (Fig. 3). Specifically, ART-adherent patients had 5.522 times the odds of being virally suppressed (AOR = 5.522; 95% CI, 4.67–6.53), while each additional clinic visit had 1.296 times the odds of viral suppression (AOR = 1.296; 95% CI, 1.22–1.38) (Fig. 3). The sensitivity analysis using data from 2012 to 2017 revealed even stronger

Table 3. Models of ART Adherence Over Time

	Model 1a	*Model 2a*	*Model 3a*	*Model 4a*	*Model 5a*
Fixed effects					
Intercept: β_{00} (SE)	2.247 (0.039)***	2.315 (0.043)***	2.338 (0.043)***	2.323 (0.040)***	2.451 (0.097)***
95% CI	2.170–2.323	2.232–2.399	2.253–2.423	2.244 – 2.402	*2.260–2.642*
Time in care: β_{10} (SE)		0.027 (0.010)*	0.021 (0.010)*	0.005 (0.009)	0.003 (0.009)
95% CI		0.007–0.047	0.0004–0.041	–0.014 to 0.023	–0.016 to 0.021
Within-person syndemic conditions: β_{20} (SE)			–0.462 (0.025)***	–0.453 (0.024)***	–0.453 (0.024)***
95% CI			–0.510 to –0.414	–0.500 to –0.405	–0.501 to –0.406
Between-person syndemic conditions: β_{30} (SE)				–0.959 (0.031)***	–0.956 (0.031)***
95% CI				–1.020 to –0.899	–1.017 to –0.895
Risk group[a]					
Cisgender heterosexual men: β_{41} (SE)					–0.389 (0.115)**
95% CI					–0.614 to –0.164
Cisgender men, undisclosed sexual orientation: β_{42} (SE)					–0.437 (0.116)***
95% CI					–0.664 to –0.211
Cisgender women: β_{43} (SE)					–0.008 (0.099)
95% CI					–0.202 to 0.187
Transgender women: β_{44} (SE)					–0.317 (0.272)
95% CI					–0.850 to 0.215
Random effects					
Intercept: σ^2_{u0}	5.141	5.438	5.681	4.745	4.697
Time: σ^2_{u1}		0.035	0.033	0.031	0.031

[a]Cisgender MSM as referent group.
*$p < 0.05$; **$p < 0.005$; ***$p < 0.0005$.
ART, antiretroviral therapy; CI, confidence interval; SE, standard error.

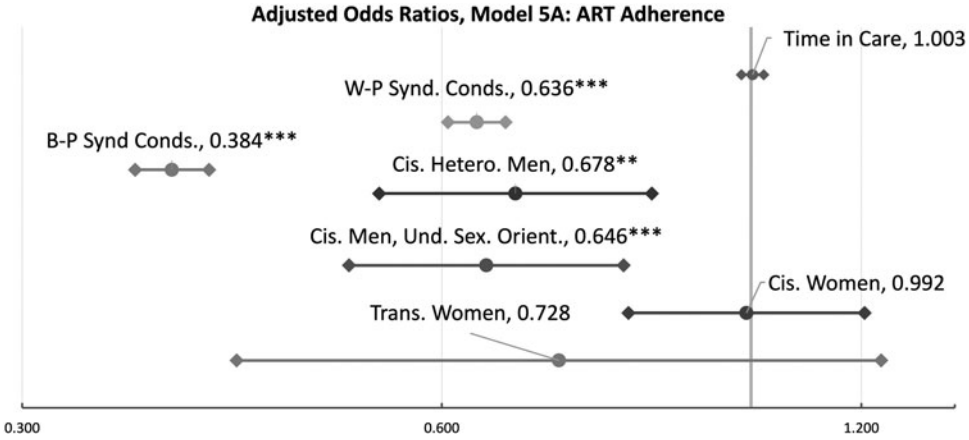

FIG. 1. Adjusted odds ratios, Model 5A: ART adherence. $^{**}p < 0.005$; $^{***}p < 0.0005$. Cisgender MSM were the referent group for HIV sexual risk group comparisons. ART, antiretroviral therapy; B-P, between-person; cis., cisgender; hetero., heterosexual; MSM, men who have sex with men; synd. conds., syndemic conditions; trans., transgender; und. sex. orient., undisclosed sexual orientation; W-P, within-person.

effects of ART adherence on viral suppression, with ART-adherent patients having 7.68 times the odds of being virally suppressed (AOR = 7.68; 95% CI, 5.98–9.85) and each additional clinic visit having 1.28 times the odds of viral suppression (AOR = 1.28; 95% CI, 1.19–1.37) (Supplementary Table S5 and S6).

Discussion

This study showed the negative additive effects of syndemic conditions on the HIV care continuum in a large, longitudinal sample of PLWH in care and strongly suggests the negative effects of syndemic conditions on viral suppression via deleterious effects on ART adherence. Comparing patients with one another based on the average number of syndemic conditions revealed that each between-patient syndemic condition was associated with 61.6% lower odds of ART adherence, while each additional within-patient syndemic condition a patient experienced from visit to visit was associated with 36.4% lower odds of ART adherence. Moreover, we found that each between-patient syndemic condition was associated with 29.3% lower odds of viral suppression, while each within-patient syndemic condition was associated with 27.7% lower odds of viral suppression.

Table 4. Models of Viral Suppression Over Time

	Model 1b	*Model 2b*	*Model 3b*	*Model 4b*	*Model 5b*
Fixed effects					
Intercept: β_{00} (SE)	3.096 (0.055)***	8.431 (0.130)***	8.440 (0.129)***	8.355 (0.130)***	8.516 (0.206)***
95% CI	2.987–3.204	8.177–8.685	8.188–8.692	8.100–8.609	8.112–8.919
Time in care: β_{10} (SE)		0.477 (0.032)***	0.475 (0.032)***	0.462 (0.032)***	0.451 (0.031)***
95% CI		0.415–0.539	0.413–0.537	0.400–0.524	0.390–0.513
Within-person syndemic conditions: β_{20} (SE)			–0.326 (0.039)***	–0.322 (0.038)***	–0.324 (0.038)***
95% CI			–0.402 to –0.249	–0.398 to –0.247	–0.399 to –0.248
Between-person syndemic conditions: β_{30} (SE)				–0.347 (0.048)***	–0.346 (0.048)***
95% CI				–0.441 to –0.253	–0.441 to –0.251
Risk group[a]					
Cisgender heterosexual men: β_{41} (SE)					–0.428 (0.201)*
95% CI					–0.821 to –0.035
Cisgender men, undisclosed sexual orientation: β_{42} (SE) (SE)					–0.545 (0.205) *
95% CI					–0.946 to –0.144
Cisgender women: β_{43} (SE)					–0.077 (0.181)
95% CI					–0.431 to 0.277
Transgender women: β_{44} (SE)					0.175 (0.494)
95% CI					–0.794 to 1.143
Random effects					
Intercept: σ^2_{u0}	6.568	50.316	50.251	47.952	47.102
Time: σ^2_{u1}		7.407	7.305	6.900	6.764

[a]Cisgender MSM as referent group.
$^{*}p < 0.05$; $^{***}p < 0.0005$.
CI, confidence interval; MSM, men who have sex with men; SE, standard error.

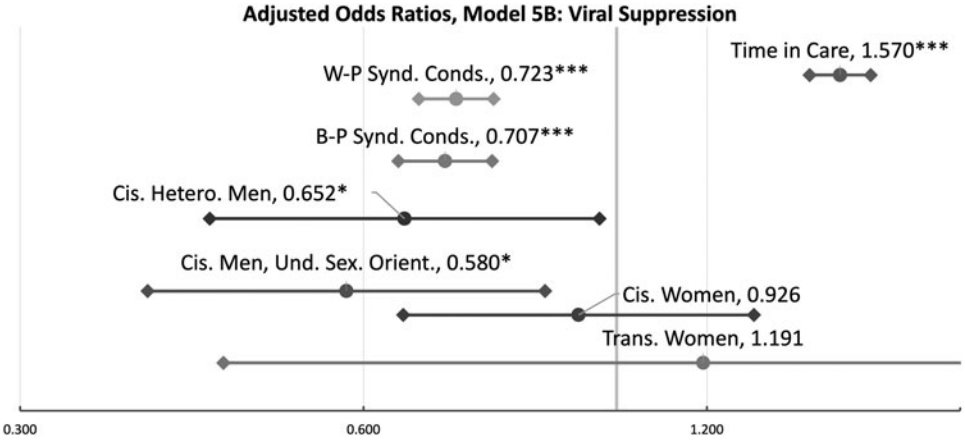

FIG. 2. Adjusted odds ratios, Model 5B: Viral suppression. *$p < 0.05$; ***$p < 0.0005$. Viral suppression status was set at HIV RNA <400 copies/mL. Cisgender MSM were the referent group for HIV sexual risk group comparisons. ART, antiretroviral therapy; B-P, between-person; cis., cisgender; hetero., heterosexual; MSM, men who have sex with men; synd. conds., syndemic conditions; trans., transgender; und. sex. orient., undisclosed sexual orientation; W-P, within-person.

Controlling for ART adherence, the effects of syndemic conditions on viral suppression were no longer significant, while ART adherence was associated with 5.52 times the odds of viral suppression. Moreover, our sensitivity analyses, which focused on data from 2012 to 2017, confirmed the significant effects of syndemic conditions on ART adherence and viral suppression during the universal TasP era.

Table 5. Model of Viral Suppression Controlling for ART Adherence Over Time

	Model 6
Fixed effects	
Intercept: β_{00} (SE)	7.575 (0.242)***
95% CI	7.100–8.049
Time in care: β_{10} (SE)	0.259 (0.032)***
95% CI	0.196–0.322
Within-person syndemic conditions: β_{20} (SE)	–0.085 (0.056)
95% CI	–0.194 to 0.024
Between-person syndemic conditions: β_{30} (SE)	–0.047 (0.064)
95% CI	–0.172 to 0.078
Risk group[a]	
Cisgender heterosexual men: β_{41} (SE)	–0.296 (0.256)
95% CI	–0.797 to 0.206
Cisgender men, undisclosed sexual orientation: β_{42} (SE)	–0.368 (0.256)
95% CI	–0.869 to 0.134
Cisgender women: β_{43} (SE)	0.085 (0.225)
95% CI	–0.357 to 0.527
Transgender women: β_{44} (SE)	–0.080 (0.615)
95% CI	–1.285 to 1.124
ART adherence: β_{50} (SE)	1.709 (0.086)***
95% CI	1.541–1.877
Random effects	
Intercept: σ^2_{u0}	51.163
Time: σ^2_{u1}	4.890

[a]Cisgender MSM as referent group.
***$p < 0.0005$.
ART, antiretroviral therapy; CI, confidence interval; SE, standard error.

Results regarding the effects of syndemic conditions on ART adherence and viral suppression are consistent with previous findings.[24–28,31] With a longitudinal sample of over 14,000 patients and over 60,000 care visits spread across seven CNICS sites, this study's findings elucidate the associations of syndemic conditions with ART adherence and viral suppression in one of the largest and most geographically diverse national samples of patients and patient visits to date. They further suggest how measuring PROs at routine patient visits to identify syndemic conditions could facilitate referrals to psychosocial intervention for patients to alleviate their distress and avert worse HIV clinical outcomes. This is particularly true given our significant findings regarding the effects of within-person syndemic conditions: when a patient's number of syndemic conditions increased over time, their odds of both ART adherence and viral suppression decreased, and the negative effects of within-person syndemic conditions on viral suppression were even more pronounced in later years (2012–2017). The within-patient findings suggest that monitoring an individual patient's trajectory of syndemic conditions from visit to visit, with appropriate psychosocial intervention as syndemic conditions increase, could potentially avert nonadherence to ART and uncontrolled viral load.

Time in care was associated with increased odds of viral suppression, even after controlling for ART adherence. Our model showed that each additional clinic visit was associated with 1.57 times the odds of being virally suppressed. Controlling for ART adherence, each additional clinic was still significantly associated with 1.30 times the odds of viral suppression. The effects of time in care on viral suppression are most likely explained by increasingly potent ART regimens available to CNICS patients and the resultant positive health benefits. Prior analyses of the CNICS cohort demonstrated how increases in viral suppression over time are likely attributable to the emergence of more potent, flexible regimens with respect to adherence, specifically the advent of integrase strand transfer inhibitor use in treating patients.[67] Those findings are consistent with increased effects of ART adherence on viral suppression observed within this study's sensitivity analysis examining data from 2012 to 2017. Overall, this study suggests that, given the benefits of time in care and ART adherence on viral suppression, redoubled efforts at ART adherence counseling and retention-in-care efforts are needed, even for patients with multiple syndemic conditions.

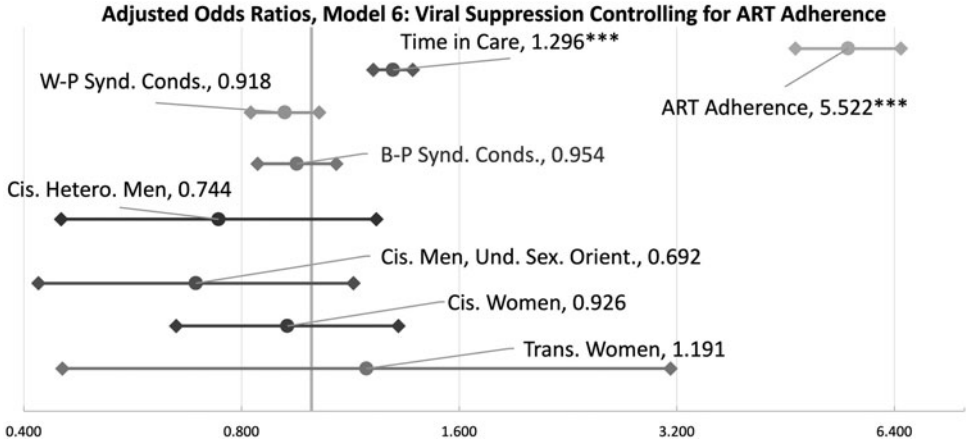

FIG. 3. Adjusted odds ratios, Model 6: Viral suppression controlling for ART adherence. ***$p < 0.0005$. Viral suppression status was set at HIV RNA <400 copies/mL. Cisgender MSM were the referent group for HIV sexual risk group comparisons. ART, antiretroviral therapy; B-P, between-person; cis., cisgender; hetero., heterosexual; MSM, men who have sex with men; synd. conds., syndemic conditions; trans., transgender; und. sex. orient., undisclosed sexual orientation; W-P, within-person.

Lastly, although the study found significant differences between cisgender MSM and, respectively, cisgender heterosexual men and cisgender men of undisclosed sexual orientation regarding ART adherence and viral suppression after controlling for syndemic conditions, a sensitivity analysis revealed that, in later years, there were no significant effects of HIV sexual risk group on viral suppression after controlling for syndemic conditions, whether or not controlling for ART adherence.

This study comes with several limitations. First, although our study is based upon a longitudinal sample, causality cannot be inferred due to its observational nature. Second, certain syndemic conditions discussed in the HIV syndemic literature—including intimate partner violence, childhood sexual abuse, and violence exposure generally—were not measured via PRO during the study period and therefore not modeled (they have since been added to PRO assessments in CNICS clinics). Measurement of structural syndemic conditions would also have permitted an understanding of how variables at multiple levels potentially exacerbate HIV health outcomes. Third, and relatedly, syndemic conditions were analyzed as count variables, and interactions between the syndemic conditions were not analyzed due to the complexity of doing so; measurement of structural variables would have made a stronger case for testing interaction effects among the syndemic conditions and creates opportunities for future study.[68,69] Fourth, a viral suppression threshold of HIV RNA <400 copies/mL is higher than the typical threshold of HIV RNA <200 copies/mL, suggesting that our estimates for the effects of syndemic conditions on viral suppression may be conservative.

This study establishes the significant, enduring effects of syndemic conditions on ART adherence and viral suppression over and above the HIV sexual risk group among PLWH in a large, longitudinal, and geographically diverse sample receiving care at well-resourced US HIV clinics. This strongly suggests that using PROs in clinic settings to identify syndemic conditions could help target psychosocial interventions for patients at potentially greater risk of ART nonadherence and uncontrolled viral load. It further highlights the critical need for counseling on adherence and ''Undetectable = Untransmittable,''[70] and retention-in-care and stigma reduction[71,72] efforts, directed toward these same patients. Our study also demonstrated that increased time in care was associated with significant increases in viral suppression, even after controlling for ART adherence, a testament to the increasing effectiveness and potency of newer ART regimens.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5
Supplementary Table S6

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