Satyanarayana S et al. *Journal of the International AIDS Society* 2021, **24**:e25679
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25679/full | https://doi.org/10.1002/jia2.25679

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Estimating HIV transmissions in a large U.S. clinic-based sample: effects of time and syndemic conditions

Satyanand Satyanarayana[1,§], Steven A Safren[1,2], Brooke G Rogers[1,3], Sierra A Bainter[1], Katerina A Christopoulos[4], Rob J Fredericksen[5], William C Mathews[6], Richard D Moore[7], Michael J Mugavero[8], Sonia Napravnik[9], Adam W Carrico[10], Matthew J Mimiaga[2,11,12,13], Kenneth H Mayer[2,14,15] and Heidi M Crane[5]

[§]**Corresponding author:** Satyanand Satyanarayana, Department of Psychology, University of Miami, P.O. Box 248185, Coral Gables, FL 33124, USA. Tel: +1 305 2433508. (ssatyanarayana@miami.edu)

Abstract

Introduction: Little is known about onward HIV transmissions from people living with HIV (PLWH) in care. Antiretroviral therapy (ART) has increased in potency, and treatment as prevention (TasP) is an important component of ending the epidemic. Syndemic theory has informed modelling of HIV risk but has yet to inform modelling of HIV transmissions.

Methods: Data were from 61,198 primary HIV care visits for 14,261 PLWH receiving care through the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) at seven United States (U.S.) sites from 2007 to 2017. Patient-reported outcomes and measures (PROs) of syndemic conditions – depressive symptoms, anxiety symptoms, drug use (opiates, amphetamines, crack/cocaine) and alcohol use – were collected approximately four to six months apart along with sexual behaviours (mean = 4.3 observations). Counts of syndemic conditions, HIV sexual risk group and time in care were modelled to predict estimated HIV transmissions resulting from sexual behaviour and viral suppression status (HIV RNA < 400/mL) using hierarchical linear modelling.

Results: Patients averaged 0.38 estimated HIV transmissions/100 patients/year for all visits with syndemic conditions measured (down from 0.83, first visit). The final multivariate model showed that per 100 patients, each care visit predicted 0.05 fewer estimated transmissions annually (95% confidence interval (CI): 0.03 to 0.06; $p < 0.0005$). Cisgender women, cisgender heterosexual men and cisgender men of undisclosed sexual orientation had, respectively, 0.47 (95% CI: 0.35 to 0.59; $p < 0.0005$), 0.34 (95% CI: 0.20 to 0.49; $p < 0.0005$) and 0.22 (95% CI: 0.09 to 0.35; $p < 0.005$) fewer estimated HIV transmissions/100 patients/year than cisgender men who have sex with men (MSM). Each within-patient syndemic condition predicted 0.18 estimated transmissions/100 patients/year (95% CI: 0.12 to 0.24; $p < 0.0005$). Each between-syndemic condition predicted 0.23 estimated HIV transmissions/100 patients/year (95% CI: 0.17 to 0.28; $p < 0.0005$).

Conclusions: Estimated HIV transmissions among PLWH receiving care in well-resourced U.S. clinical settings varied by HIV sexual risk group and decreased with time in care, highlighting the importance of TasP efforts. Syndemic conditions remained a significant predictor of estimated HIV transmissions notwithstanding the effects of HIV sexual risk group and time in care.

Keywords: Cohort studies; HIV prevention; HIV care continuum; viral suppression; treatment; North America

Additional information may be found under the Supporting Information tab for this article.

Received 13 June 2020; **Accepted** 27 January 2021

1 | INTRODUCTION

Recent studies establishing antiretroviral therapy (ART)'s efficacy in preventing transmission of HIV from people living with HIV (PLWH) to their sexual partners have yielded updated per-act estimates for HIV sexual transmission in the treatment-as-prevention (TasP) era [1,2]. Together with per-act estimates of HIV transmission when virally unsuppressed [3], these figures illustrate the impact of TasP and undetectable = untransmittable (U = U), wherein consistent adherence to ART by PLWH effectively suppresses their HIV RNA and eliminates their transmission to seronegative partners [4-6]. As outlined in the UNAIDS 90–90–90 target to end the AIDS epidemic and the United States (U.S.) government's Ending the HIV Epidemic strategy [7,8], connecting PLWH to ART and achieving sustained viral suppression are critical goals for improving patient health and preventing the onward transmission of HIV. Recent per-act estimates of HIV transmission risk highlight the impact of these goals.

Modelling HIV transmissions using per-act estimates of HIV transmissibility and individually collected behavioural data are rare. Using a three-country sample (Brazil, Thailand and Zambia) of sexually active PLWH in care, Safren and colleagues in the HIV Prevention Trials Network 063 study estimated the number of transmissions over 15 months using then-current-for-2016 per-act estimates [9]. That study estimated 3.81 HIV transmissions per 100 patients over 15 months, with between-country and risk group variations [9]. In the U.S., other studies have based modelling of HIV transmissions on data from U.S. behavioural health surveys and have estimated HIV infections ranging from 0 to 0.2 (for PLWH in care virally suppressed) and 3.8 to 6.1 (for PLWH in care not virally suppressed) transmissions per 100 patients annually [10,11]. Analyses quantifying the impact of biobehavioural transmission risk behaviour (condomless anal or vaginal sex while virally unsuppressed) among patients in care on estimated HIV transmissions could better inform decision-making regarding the allocation of treatment and prevention resources to achieve the 90–90–90 goals, particularly given that virologically unsuppressed PLWH in care are estimated to account for 8.5–19.8% of HIV transmissions in the U.S. [11,12].

Key to this resource allocation will be an understanding of the predictors of estimated HIV transmissions among PLWH in care. Syndemic theory has concerned itself with co-occurring psychosocial, health and biomedical comorbidities that amplify risk of HIV acquisition [13], and much of syndemic research has focused on analysing the co-occurrence of psychosocial variables – notably, depressive and/or anxiety symptoms, single- or poly-drug use, alcohol use, childhood sexual abuse (CSA) and intimate partner violence (IPV) – to predict HIV acquisition risk by seronegative individuals [14-34]. More recent syndemic research has focused on co-occurring syndemic conditions among PLWH as predictors of HIV transmission risk (e.g. ART nonadherence, uncontrolled viral load or biobehavioural transmission risk behaviour) [35-43]. Other studies have linked psychosocial variables (notably, depression) and substance use (notably, stimulants), though not their additive effects, to elevated viral load and worse HIV clinical outcomes [9,44-52]. To our knowledge, no prior analysis has quantified the impact of co-occurring syndemic conditions among PLWH on HIV transmission, estimated or otherwise.

Using a large, longitudinal sample of U.S. PLWH in care, we sought to estimate HIV transmissions using recent per-act estimates and to model the effects of syndemic conditions over and above HIV sexual risk group and time in care on estimated HIV transmissions.

2 | METHODS

2.1 | Participants

Participants were 14,261 PLWH receiving care between June 2007 and April 2017 at seven U.S. Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) sites, all of which are well-resourced, university-affiliated research medical centres providing the latest treatments in HIV care (see Table 1). Patients 18 years or older were approached at care appointments to participate in CNICS; no reimbursement was offered for participation [53,54]. Patient-informed consent was obtained during initial enrolment in CNICS. Procedures involving human participants were in accordance with institutional review boards at the CNICS-affiliated universities and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Table 1. CNICS sites included in analyses

CNICS site	U.S. City, State
University of Alabama at Birmingham	Birmingham, Alabama
University of California San Francisco	San Francisco, California
University of Washington	Seattle, Washington
University of California San Diego	San Diego, California
Fenway Health/Harvard University	Boston, Massachusetts
University of North Carolina at Chapel Hill	Chapel Hill, North Carolina
Johns Hopkins University	Baltimore, Maryland

CNICS, Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems.

2.2 | Data sources

The CNICS data repository integrates data from electronic health records and institutional data sources with data collected upon study enrolment [53,54]. Self-administered patient-reported outcomes and measures (PROs) are collected at least four to six months apart as part of clinical care via touch-screen tablets or computers [53,54].

2.3 | Procedures and measures

2.3.1 | Measures

PROs include: past-two-week depressive symptoms measured by the Patient Health Questionnaire–9 (PHQ–9) [55]; past-month panic symptoms measured by five items from the Brief Patient Health Questionnaire (PHQ–5) [56]; past-three-month use of amphetamines, illicit opioids and crack/cocaine measured using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [57]; past-year alcohol consumption measured using versions of the Alcohol Use Disorders Identification Test (AUDIT) or the first three questions of the AUDIT (AUDIT-C) [58]; and past-six-month number of sexual partners and frequency of sex and condom use measured by a modified version of the HIV Risk Assessment for Positives (HRAP) [59].

2.3.2 | HIV risk group classification

Patients were initially classified into HIV sexual risk groups based on sex, gender identity and self-identified sexual orientation where available. After reviewing self-reported lifetime sexual behaviours of self-identified cisgender men who have sex with men (MSM) in the sample, a lifetime history of anal sex and no lifetime history of vaginal sex were used as criteria to classify additional cisgender men with undisclosed sexual orientation as MSM. (Most remaining cisgender men of undisclosed sexual orientation reported histories of vaginal and anal sex (1741), whereas smaller numbers reported vaginal sex

only (630) or no sex (578)). This overall process yielded 2,239 cisgender women (15.7%), 163 transgender women (1.1%), 1,183 cisgender heterosexual men (8.3%), 7,727 cisgender MSM (54.2%) and 2,949 cisgender men of undisclosed sexual orientation (20.7%).

2.3.3 | Imputation of missing PROs

Rates of missingness for complete responses on the PHQ–9, the PHQ–5, the ASSIST, the AUDIT/AUDIT-C and the HRAP during clinic visits when PROs were administered are included in Table 2. Multilevel multiple imputation using the fully conditional specification algorithm in Blimp (versions 2.1.3 or greater) was used to generate 100 complete data sets [60-62]. Demographic variables, HIV-related treatment variables and PRO responses were included in imputation models at each imputation stage to minimize potential for bias [63]. All PROs, with the exception of sexual behaviours, were imputed in the first imputation stage; due to skip patterns in the HRAP questionnaire, imputation of missing sexual behaviour data took place in successive stages [64]. All subsequent data analyses were completed across all 100 imputed data sets.

Table 2. Missingness of non-imputed patient-reported outcomes and measures (PROs)

PROs	Number of complete responses	Number of incomplete/ missing responses	Percentage of missingness
PHQ–9	53,574	7,624	12.5%
PHQ–5	55,850	5,348	8.7%
ASSIST			
Cocaine/crack	53,924	7,274	11.9%
Illicit opioids	50,530	10,668	17.4%
Methamphetamine	53,927	7,271	11.9%
AUDIT/AUDIT–C	54,450	6,748	11.0%
Sexual behaviours[a]			
Anal sex, seronegative partner	46,301	14,897	24.3%
Condom use	47,719	13,479	22.0%
Anal sex: serostatus unknown	49,507	11,691	19.1%
Condom use	48,061	13,137	21.5%
Vaginal sex: seronegative partner	48,055	13,143	21.5%
Condom use	48,387	12,811	20.9%
Vaginal sex: serostatus unknown	49,328	11,870	19.4%
Condom use	49,110	12,088	19.8%

PRO, patient-reported outcomes and measures.
[a]High missing data rates for sexual behaviours recorded using the HIV Risk Assessment for Positives (HRAP) were due in part to transitions to a new sexual risk measure in late 2016/early 2017 (date varied by site, median date 9/2016).

2.3.4 | Quantification of sexual behaviours

In four separate questions, the HRAP queried past-six-month frequency of sexual behaviour by type of sex (anal and vaginal) and by serostatus of partner (seronegative and serostatus-unknown). Responses were converted to count values: *a few times each week* as 78 (three per week over 6 months); *a few times each month* as 18 (three per month for six months); *a few times or less* as 1.5; and *never* as zero. The HRAP also queried frequency of condom use for each type of sexual behaviour; responses were converted to proportions as follows: *all of the time* as 100%; *most of the time* as 75 %; *some of the time* as 25% and *never* as 0%.

2.3.5 | Estimation of HIV transmissions from sexual behaviours

Procedures to derive estimates of HIV transmissions were similar to those used in the HPTN063 study but with updated per-act estimates [9]. Condom-use proportions were multiplied by appropriate sex-act counts to calculate totals for eight separate sexual behaviours based on sex act, condom use and partner serostatus. Each total was multiplied by the appropriate per-act estimate of HIV transmission risk based on viral suppression, sex act and condom use as indicated in Table 3 [1-3]. Where unavailable in the literature, per-act estimates for sex with condoms were calculated by reducing per-act estimates of the corresponding condomless sex acts by 80% [3,65]. Because the HRAP did not query whether anal sex was insertive or receptive, per-act estimates for insertive and receptive anal sex were averaged for all groups except cisgender heterosexual men and cisgender women (Table 3).

To account for different viral load thresholds across time and sites, viral suppression was set at HIV RNA < 400/mL, with viral suppression status extracted from patients' electronic health records. Estimated transmissions to serostatus-unknown partners were reduced by 25% based upon an assumption that one in four such partners were seropositive. The resulting eight estimates were summed to calculate totals of estimated HIV transmissions per patient per six-month observation period, which were then doubled to represent annualized estimates. For ease of interpretation, annualized estimates were multiplied by 100 to reflect the number of estimated HIV transmissions per 100 patients annually. Sensitivity analyses were conducted to account for 10% preexposure prophylaxis (PrEP) adherence among seronegative partners (PrEP), 50% seropositivity among serostatus-unknown partners and 0% transmission risk for virally suppressed patients using condoms.

2.3.6 | Syndemic conditions

Four syndemic conditions were assessed from PROs: (1) clinically elevated depressive symptoms (≥5 on the PHQ–9) [55]; (2) any anxiety symptoms rated on the PHQ–5 (experiencing an anxiety attack in the previous four weeks); (3) screening positive for a substance use disorder (≥4 on the ASSIST for

Table 3. Per-sex-act percentage estimates of HIV transmission risk

		Cisgender heterosexual men (% per act)		Cisgender MSM (% per act)		Cisgender men of undisclosed sexual orientation (% per act)		Cisgender women (% per act)		Transgender women (% per act)	
		Condom use		Condom use		Condom use		Condom use		Condom use	
Sex act	Virally suppressed	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Vaginal	Yes	0.00078[a]	0.0039[b]	0.00078[a]	0.0039[b]	0.00078[a]	0.0039[b]	0.00078[a]	0.0039[b]	0.00078[a]	0.0039[b]
Vaginal	No	0.016[c]	0.081[c]	0.016[c]	0.081[c]	0.016[c]	0.081[c]	0.008[c]	0.042[c]	0.016[c]	0.081[c]
Anal	Yes	0.00088[a]	0.0044[b]	0.00088[a]	0.0044[b]	0.00088[a]	0.0044[b]	0.00088[a]	0.0044[b]	0.00088[a]	0.0044[b]
Anal	No	0.334[d]	1.67[e]	0.181[f]	0.905[g]	0.181[f]	0.905[g]	0.028[d]	0.14[e]	0.181[f]	0.905[g]

[a]Per-act estimates drawn from Supervie and Breban and downwardly adjusted by 80%, consistent with Patel and colleagues and the findings of Weller and Davis-Beaty[1,3,65]; [b]per-act estimates drawn from Supervie and Breban[1]; [c]per-act estimates drawn from Patel and colleagues[3]; [d]per-act estimates drawn from Baggaley and colleagues and downwardly adjusted by 80% consistent with Patel and colleagues and the findings of Weller and Davis-Beaty[2,3,66]; [e]per-act estimates drawn from Baggaley and colleagues[2]; [f]average of insertive and receptive anal sex per-act estimates drawn from Baggaley and colleagues and downwardly adjusted by 80% consistent with Patel and colleagues and the findings of Weller and Davis-Beaty[2,3,48]; [g]average of insertive and receptive anal sex per-act estimates drawn from Baggaley and colleagues [2].

cocaine/crack, illicit opioids or amphetamines) [67] and 4) screening positive for heavy drinking/active alcohol use disorders (≥ 4 for cisgender men and transgender women or ≥3 for cisgender women) on the AUDIT-C or the first three questions of the AUDIT [58].

Between-person syndemic scores (mean number of syndemic conditions) were calculated for each patient for between-patient comparisons. Within-person syndemic scores (observed number of syndemic conditions minus between-person syndemic score) were calculated for each observation to model individual variations in patients' syndemic conditions over time.

2.3.7 | *Time in care*

Because patients were seen on different dates at different stages of treatment and for differing periods of time, time in care was measured by number of visits since PRO collection began in their respective clinic.

2.4 | Data analysis

Hierarchical linear modelling using restricted maximum likelihood estimation was employed for analyses across 100 imputed data sets using R version 4.0.0 and the lme4, lmerTest and mitml packages [68-71]. Standard errors were computed using Satterthwaite's approximation.

A series of models was fitted to determine the effect of syndemic conditions on estimated HIV transmissions; control variables – time in care and HIV sexual risk group – were limited to those most closely hypothesized to be related to estimated HIV transmissions over and above syndemic conditions. Model 1, an intercept-only model, was run with estimated HIV transmissions as the outcome to determine the proportion of variance attributable to between-person differences in estimated HIV transmissions. Model 2 added the fixed effects of time in care. Model 3 added the fixed effects of HIV sexual risk group. Model 4 added the fixed effects of within-person syndemic scores, whereas Model 5 added the fixed effects of between-person syndemic scores.

3 | RESULTS

Tables 4 and 5 contain descriptive statistics of relevant data for patients at first PRO visit (Table 4) and for all PRO visits (Table 5). Across all visits, depressive symptoms were most prevalent (46.4%) followed by anxiety symptoms (26.9% all visits), then alcohol consumption (23.9% all visits) and then illicit drug use (14.9% all visits) (Table 5). At first PRO visit, rates of viral suppression were lower, and estimated HIV transmissions and syndemic condition prevalence higher, than for subsequent visits (Tables 4, 5). Across all visits, patients had 0.38 estimated HIV transmissions per 100 patients annually (SD = 4.23) (down from 0.83 (SD = 6.66) at first PRO visit), with transgender women having the greatest number and cisgender women the least (Tables 4, 5). Table 6 provides descriptive statistics of estimated HIV transmissions per 100 patients annually by syndemic condition count and HIV sexual risk group for all visits.

Estimates from the five iterative models are displayed in Table 7. Model 1, the intercept-only model, yielded an intraclass correlation (ICC) of .086, indicating 8.6% of variability in estimated HIV transmissions was attributable to individual-level differences. Model 2 showed that each subsequent visit predicted 0.05 fewer estimated HIV transmissions per 100 patients annually, an effect that remained the same in all subsequent models. Model 3 showed that, controlling for the effects of time, cisgender women, cisgender heterosexual men and cisgender men of undisclosed sexual orientation had, respectively, 0.47, 0.39 and 0.20 fewer estimated HIV transmissions per 100 patients annually relative to cisgender MSM. Model 4 revealed that each within-person syndemic condition predicted 0.18 estimated HIV transmissions per 100 patients annually, controlling for time in care and risk group, whereas the effects of the risk group remained largely unchanged from Model 3.

Table 4. 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 Sex. Orient. (n = 2949)	Cisgender women (n = 2,239)	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	8,234 (57.7)	437 (36.9)	5,268 (68.2)	1,723 (58.4)	743 (33.2)	63 (38.6)
Black	4,696 (32.9)	682 (57.7)	1,621 (21.0)	970 (32.9)	1,355 (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/PacificIslander	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: (%)	2,018 (14.2)	135 (11.4)	1,221 (15.8)	399 (13.5)	212 (9.5)	51 (31.3)
Syndemic condition: (%)[a]						
Depressive Sxs	7,228 (50.7)	503 (42.5)	3,882 (50.2)	1,538 (52.2)	1,202 (53.7)	102 (62.6)
Anxiety Sxs	4,097 (28.7)	206 (17.4)	2,297 (29.7)	875 (29.7)	644 (28.8)	75 (46.0)
Illicit Drug Use	2,607 (18.3)	188 (15.9)	1,328 (17.2)	725 (24.6)	330 (14.7)	35 (21.5)
Alcohol consumption	3,957 (27.7)	267 (22.6)	2,330 (30.2)	839 (28.5)	487 (21.8)	34 (20.8)
No. of syndemic conditions: M (SD)[a]	1.25 (1.08)	0.98 (1.02)	1.27 (1.06)	1.35 (1.12)	1.19 (1.07)	1.51 (1.09)
Virally suppressed: (%)[b]	10,760 (75.5)	944 (79.8)	5,868 (75.9)	2148 (72.8)	1,675 (74.8)	125 (76.7)
Est. No. of HIV Trans. per 100 pts. per year: M (SD)[a]	0.83 (6.66)	0.34 (6.23)	1.20 (8.11)	0.59 (4.81)	0.10 (0.79)	1.30 (5.94)

M, mean; PRO, patient-reported outcomes and measures; pts, patients; SD, standard deviation; Sex. Orient., sexual orientation; Sxs, symptoms; Trans., transmissions; MSM, men who have sex with men.
[a]Values from imputed data sets; [b]viral suppression defined as <400 RNA/mL.

Model 5 included the effects of between-person syndemic conditions with the prior set of predictors. Controlling for time in care and risk group, each between-person syndemic condition predicted an additional 0.23 estimated HIV transmissions per 100 patients annually, whereas as in Model 4, each within-person syndemic condition predicted 0.18 estimated HIV transmissions per 100 patients annually. Cisgender women, cisgender heterosexual men and cisgender men of undisclosed sexual orientation had, respectively, 0.47, 0.34 and 0.22 fewer estimated HIV transmissions per 100 patients annually compared to cisgender MSM. Sensitivity analyses assuming scenarios that 10% of seronegative partners were PrEP-adherent, 50% seropositivity among serostatus-unknown partners and 0% transmission risk when virally suppressed and using condoms did not alter the general pattern of estimates (see Table S1).

4 | DISCUSSION

To our knowledge, our modelling study is the first to demonstrate the significant effects of syndemic conditions, HIV sexual risk group and time in care on estimated HIV transmissions using a large sample of PLWH in clinical care. We found syndemic conditions – both within-patient and between-patient – predicted increased estimated HIV transmissions, whereas each additional patient visit predicted smaller but significant decreases in estimated HIV transmissions. Our modelling also predicted fewer estimated HIV transmissions for cisgender women, cisgender heterosexual men and cisgender men of undisclosed sexual orientation compared to cisgender MSM; transgender women's point estimate was higher than cisgender MSM's, but the difference between groups was not significant, likely due to the small number of transgender women in the sample.

While the effects of syndemic conditions on estimated HIV transmissions were modest, they should be contextualized within the treatment settings where they arose and alongside the significant effects of time in care. CNICS clinics are resource-rich, research medical centres where viral suppression rates approached 90% in recent years [72], and where patients have access to a variety of case management services and HIV prevention messaging. They also boast retention-in-care (RIC) outcomes nearly a third greater than the U.S. clinic average [73]. Within this context and the availability of more potent and administrable ART regimens in recent years, syndemic conditions still predicted estimated HIV transmissions, even after accounting for time in care and attendant increases in viral suppression; the effect of syndemic conditions on estimated HIV transmissions might potentially be greater in more

Table 5. Sample characteristics, All PRO visits

	Risk group					
Variable	All (N = 61,198)	Cisgender heterosexual men (n = 5,983)	Cisgender MSM (n = 37,019)	Cisgender men, undisclosed Sex. Orient. (n = 7,782)	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)	2,541 (42.5)	25,697 (69.4)	4,593 (59.0)	3,326 (33.9)	287 (47.8)
Black	20,504 (33.5)	3,153 (52.7)	8,442 (22.8)	2,658 (34.2)	6,017 (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	1,287 (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)	1,413 (3.8)	336 (4.3)	223 (2.3)	44 (7.3)
Hispanic/Latinx: (%)	8,699 (14.2)	850 (14.2)	5,753 (15.5)	1,008 (13.0)	907 (9.2)	181 (30.2)
No. 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)
No. of days between visits: M (SD)	359.2 (293.3)	353.1 (315.9)	356.7 (271.5)	360.4 (304.1)	363.2 (337.8)	465.5 (408.8)
Syndemic condition: (%)[a]						
Depressive Sxs	28,382 (46.4)	2,380 (39.8)	16,915 (45.7)	3,911 (50.3)	4,815 (49.1)	361 (60.2)
Anxiety Sxs	16,484 (26.9)	1,145 (19.1)	9,985 (27.0)	2,301 (29.6)	2,799 (28.5)	255 (42.5)
Illicit drug use	9,129 (14.9)	833 (13.9)	5,258 (14.2)	1,714 (23.1)	1,218 (12.4)	106 (17.7)
Alcohol consumption	14,626 (23.9)	1,188 (19.9)	9,366 (25.3)	2,024 (26.1)	1,918 (19.5)	130 (21.7)
No. of syndemic conditions: M (SD)[a]	1.12 (1.05)	0.93 (1.02)	1.12 (1.03)	1.28 (1.11)	1.10 (1.05)	1.42 (1.08)
Virally suppressed: (%)[b]	52,077 (85.1)	5,275 (88.2)	31,983 (86.4)	6,219 (79.9)	8,084 (82.4)	516 (86.0)
Est. No. of HIV Trans. per 100 pts per year: M (SD)[a]	0.38 (4.23)	0.14 (2.96)	0.50 (4.90)	0.39 (4.23)	0.07 (0.52)	0.68 (4.21)
No. of patient years of sexual behaviour	27,462.2	2656.3	16,584.7	3572.2	4,378.2	270.8

M, mean; MSM, men who have sex with men; pts, patients; PRO, patient-reported outcomes and measures; SD, standard deviation; Sex. Orient., sexual orientation; Sxs, symptoms; Trans., transmissions.
[a]Values from imputed data sets; [b]viral suppression defined as <400 RNA/mL.

Table 6. Estimated HIV Transmissions by syndemic condition count and sexual risk group

	Estimated HIV transmissions per 100 patients per year: M (SD)[a]					
No. of Syndemic conditions[a]	All	Cisgender heterosexual men	Cisgender MSM	Cisgender men, undisclosed Sex. Orient.	Cisgender women	Transgender Women
0	0.19 (2.70)	0.05 (0.49)	0.25 (3.31)	0.25 (2.62)	0.05 (0.31)	0.15 (1.34)
1	0.30 (3.39)	0.12 (1.09)	0.37 (3.82)	0.31 (4.04)	0.06 (0.40)	0.91 (5.06)
2	0.53 (5.22)	0.14 (2.42)	0.69 (5.99)	0.57 (5.84)	0.07 (0.38)	0.35 (2.81)
3	0.87 (6.66)	0.42 (6.40)	1.18 (7.93)	0.52 (4.07)	0.15 (1.02)	1.51 (6.54)
4	1.32 (8.72)	1.62 (15.98)	1.83 (9.61)	0.80 (4.08)	0.25 (1.87)	2.21 (6.68)

M, mean; MSM, men who have sex with men; SD, standard deviation; Sex. Orient., sexual orientation.
[a]Values from imputed data sets.

resource-constrained settings. Moreover, the longitudinal assessment of within-patient changes in syndemic conditions was predictive of transmission risk beyond between-patient differences, suggesting the value of monitoring individual-level syndemic trajectories over time with tools like PROs embedded in routine care. Such monitoring could result in additional

Table 7. Models of predicting estimated HIV transmissions over time

	Model 1[a] (Intercept-only)	Model 2[b] (Time in care)	Model 3[c] (Risk Group)	Model 4[d] (Within-Person Syndemic Conditions)	Model 5[e] (Between-Person Syndemic Conditions)
Fixed effects					
Intercept: β_{00} (SE)	0.42 (0.023)***	0.61 (0.032)***	0.75 (0.039)***	0.74 (0.039)***	0.47 (0.048)***
95% CI	0.38 to 0.47	0.55 to 0.67	0.67 to 0.82	0.67 to 0.82	0.37 to 0.56
Time in care: β_{10} (SE)		−0.05 (0.006)***	−0.05 (0.006)***	−0.05 (0.006)***	−0.05 (0.006)***
95% CI		−0.06 to −0.04	−0.06 to −0.04	−0.06 to −0.04	−0.06 to −0.03
Risk group[#]:					
Cisgender heterosexual men: β_{21} (SE)			−0.39 (0.076)***	−0.39 (0.076)***	−0.34 (0.075)***
95% CI			−0.54 to −0.24	−0.54 to −0.24	−0.49 to −0.20
Cisgender men, Und. Sex. Orient.: β_{22} (SE)			−0.20 (0.066)**	−0.20 (0.066)**	−0.22 (0.066)**
95% CI			−0.33 to −0.07	−0.32 to −0.07	−0.35 to −0.09
Cisgender women: β_{23} (SE)			−0.47 (0.061)***	−0.47 (0.061)***	−0.47 (0.061)***
95% CI			−0.59 to −0.35	−0.59 to −0.35	−0.59 to −0.35
Transgender women: β_{24} (SE)			0.12 (0.233)	0.12 (0.233)	0.06 (0.232)
95% CI			−0.34 to 0.57	−0.34 to 0.57	−0.39 to 0.52
Within-person Syndemic Conditions: β_{30} (SE)				0.18 (0.031)***	0.18 (0.031)***
95% CI				0.12 to 0.24	0.12 to 0.24
Between-person syndemic conditions: β_{40} (SE)					0.23 (0.027)***
95% CI					0.17 to 0.28
Random effects					
Intercept:σ^2_{u0}	1.59	1.56	1.52	1.53	1.49
Residual:σ^2_e	16.50	16.50	16.50	16.48	16.48

95% CI, 95% confidence interval; SE, standard error; Und. Sex. Orient., undisclosed sexual orientation.
*$p < .05$; **$p < .005$; ***$p < .0005$; [#]Cisgender men who have sex with men as referent group.
[a]Model 1: $\text{transmission}_{ti} = \beta_{00} + u_{0i} + e_{ti}$; [b]Model 2: $\text{transmission}_{ti} = \beta_{00} + \beta_{10}\ \text{time} + u_{0i} + e_{ti}$; [c]Model 3: $\text{transmission}_{ti} = \beta_{00} + \beta_{10}\ \text{time} + \beta_{20}\ \text{riskgroup} + u_{0i} + e_{ti}$; [d]Model 4: $\text{transmission}_{ti} = \beta_{00} + \beta_{10}\ \text{time} + \beta_{20}\ \text{riskgroup} + \beta_{30}\ \text{withinperson}_{ti} + u_{0i} + \text{eti}$; [e]Model 5: $\text{transmission}_{ti} = \beta_{00} + \beta_{10}\ \text{time} + \beta_{20}\ \text{riskgroup} + \beta_{30}\ \text{withinperson}_{ti} + \beta_{40}\ \text{betweenperson}_{ti} + u_{0i} + e_{ti}$.

RIC efforts towards vulnerable patients as well as referrals to alleviate distress associated with syndemic conditions as they arise, with the critical benefit of also diminishing potential onward HIV transmission. Increased efforts accordingly must be made in HIV care settings to consistently screen for syndemic conditions [74,75].

Our study adds to growing literature on syndemic conditions and transmission risk behaviour among PLWH. Prior studies of syndemic conditions among PLWH showed additive associations with increased odds of ART non-adherence [36-40,43], virological non-suppression [38,40,43] and condomless sex with serodiscordant partners while virally unsuppressed [42,43]. However, these studies have generally treated the outcomes of interest as dichotomous outcomes: ART adherent versus non-adherent [36,39,40,43]; virally suppressed versus unsuppressed [40,43]; and the presence or absence of condomless sex while virally unsuppressed [42,43]. Our study builds upon these past findings by quantifying estimated HIV transmissions longitudinally associated with co-occurring syndemic conditions among a diversity of risk groups of PLWH in care.

Our study also adds to the literature regarding the prevalence of syndemic conditions among PLWH in care. Prevalence in our sample for clinically significant depressive symptoms (46.4% all visits), anxiety symptoms (26.9% all visits), current (3-month) illicit drug use (not including marijuana) (14.9% all

visits) and risky drinking (23.9% all visits) are generally consistent with estimates of prevalence for these conditions among PLWH, acknowledging that different studies have used different measures and cut-points with particular subsets of patients [76,77]. Patients in all HIV risk groups averaged a greater number of syndemic conditions at first PRO visit compared to all PRO visits. Transgender women in our sample averaged the greatest number of syndemic conditions among HIV sexual risk groups, consistent with other literature highlighting their elevated syndemic burden and the need for affirming and supportive interventions for this population [66].

The effects of time in care on estimated HIV transmissions, whereas smaller, were nevertheless significant. At a cohort level, the increase in viral suppression over time has been attributed, in part, to the advent of integrase strand transfer inhibitors (ISTIs). At the individual level, our finding raises questions for future study as to whether the effects of time in care are a function of retention in care and resultant viral suppression, of decreased sexual activity over time (or once in care), and/or of increased prevention behaviours resulting from clinic prevention messaging.

This study comes with several limitations. First, our study focused on PLWH in care and therefore excluded PLWH who never received, or were not retained in, care. Second, no actual HIV transmissions were measured as part of this modelling study. Third, because this was an observational study, causality cannot be inferred despite the longitudinal design. Fourth, certain syndemic conditions in the HIV syndemic literature – IPV, CSA and violence exposure – were not measured via PRO during the study period and therefore not modelled. Fifth, our measure of sexual transmission risk behaviour did not account for PrEP use by seronegative partners nor serostatus of serostatus-unknown partners, though sensitivity analyses accounting for 10% PrEP adherence among seronegative partners and the unlikely scenario of 50% of serostatus-unknown partners being seropositive did not alter our pattern of estimates. Sixth, assumptions were made regarding the quantification of qualitative responses on the HRAP. Seventh, our modelling assumed small but non-zero per-act estimates of HIV transmission risk and an 80% reduction in transmission risk when condoms were used, based on estimates in the literature; however, a sensitivity analysis assuming 0% risk of transmission when virally suppressed and using condoms did not alter the pattern of results. Eighth, our study averaged per-act estimates for insertive and receptive anal sex for anal sex behaviours by cisgender MSM, cisgender men of undisclosed sexual orientation and transgender women due to the limitations of the HRAP questionnaire, which may have failed to account for other HIV risk mitigation strategies (e.g. increased condom use during insertive anal sex or increased rates of receptive anal sex generally) [78]. Ninth, the use of a viral suppression threshold of HIV RNA < 400/mL is higher than the typical threshold of HIV RNA < 200/mL and suggests our estimates of HIV transmissions from this sample are conservative.

A future direction of study is the measurement of structural syndemic conditions (e.g. housing instability, criminal justice involvement, poverty [43,79]) to understand how structural barriers influence individual transmission risk. Measurement of structural syndemic conditions would bolster a case for testing interaction effects among the syndemic conditions to enable an understanding of how variables at multiple levels exacerbate HIV health outcomes [80,81]. Our study's focus on individual-level syndemic conditions measured at clinic visits made the case for testing interaction effects less persuasive. Particularly in the context of clinical settings where psychosocial interventions for depression, anxiety and drug and alcohol abuse are provided to patients individually, judgements of both clinician and patient are critical in guiding decisions of which patient-level problems to address and how and when to address them. As such, testing for interactions between individual-level syndemic conditions, with an eye to potentially deploying single-component interventions, is of arguably less importance, particularly as effective transdiagnostic treatments of mood, anxiety and substance use disorders emerge to treat multiple syndemic conditions [82].

5 | CONCLUSIONS

This study quantifies estimated HIV transmissions among PLWH in care at well-resourced U.S. clinics and predicts the effects of syndemic conditions on HIV transmissions over and above time in care and HIV sexual risk group. Compared to the effects of the HIV sexual risk group or cumulative time in care, the impact of syndemic conditions on estimated HIV transmissions was modest but persistent over time. The effect of syndemic conditions on HIV transmissions might be more dramatic in resource-constrained settings or among PLWH not in care. However, clinics like the CNICS sites, which provide potent ART regimens, strong case management services and psychosocial referrals, are providing patient care leading to fewer estimated HIV transmissions over time. Our findings strongly suggest the need for increased allocation of resources towards linkage-to-care and retention-in-care initiatives to stem the tide of the HIV epidemic.

AUTHORS' AFFILIATIONS

[1]Department of Psychology, University of Miami, Coral Gables, FL, USA; [2]The Fenway Institute at Fenway Health, Boston, MA, USA; [3]Warren Alpert Medical School of Brown University, Providence, RI, USA; [4]Department of Medicine, UCSF School of Medicine, San Francisco, CA, USA; [5]Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA; [6]UCSD School of Medicine, San Diego, CA, USA; [7]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [8]UAB School of Medicine, Birmingham, AL, USA; [9]UNC School of Medicine, Chapel Hill, NC, USA; [10]Department of Public Health Sciences, University of Miami School of Medicine, Miami, FL, USA; [11]UCLA Center for LGBTQ Advocacy, Research, and Health (C-LARAH), Los Angeles, CA, USA; [12]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA; [13]Department of Psychiatry and Biobehavioral Sciences, UCLA David Geffen School of Medicine, Los Angeles, CA, USA; [14]Massachusetts General Hospital Center for Global Health, Boston, MA, USA; [15]Harvard Medical School, Boston, MA, USA

COMPETING INTERESTS

Dr. Safren receives royalties from Oxford University Press, Springer/Humana Press and Guilford Publications for books on cognitive behavioural therapy.

AUTHORS' CONTRIBUTIONS

SS and SAS devised the study design in consultation with MJM2, HMC and AWC. SS performed statistical analyses for the study with assistance and advising from SAB and BGR. SS wrote the first draft of the manuscript with assistance from SAS. KAC, RJF, WCM, RDM, MJM1, SN, KHM and HMC were site investigators overseeing the collection of CNICS data. All authors reviewed, approved and contributed to editing the final manuscript.

ACKNOWLEDGEMENTS

We thank the University of Miami Department of Public Health Sciences, and Daniel J. Feaster and Raymond R. Balise specifically, for furnishing computing resources to aid with missing data imputation; Craig K. Enders and Brian T. Keller for consultation regarding the imputation process; and the participants in the CNICS cohort for their time and effort to complete study assessments and procedures.

FUNDING

The Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) is a funded program made possible by the National Institute of Allergy and Infectious Diseases and the National Heart, Lung and Blood Institute, grant R24 AI067039. Additional support was provided from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) [U24AA020801, U01AA020793 and U01AA020802] and the National Institute on Drug Abuse (NIDA) [R01DA047045]. The CFAR sites involved in CNICS include the University of Alabama at Birmingham (grant P30 AI027767), the University of Washington (grant P30 AI027757), the University of California San Diego (grant P30 AI036214), the University of California San Francisco (grant P30 AI027763), the Case Western Reserve University (grant P30 AI036219), the Johns Hopkins University (grant P30 AI094189, U01 DA036935), Fenway Health/Harvard Medical School (grant P30 AI060354) and the University of North Carolina Chapel Hill (grant P30 AI50410). Author time was supported in part by the National Institute on Drug Abuse grant K24DA040489 and some support was from the National Institutes of Mental Health (1P30MH116867), and the National Institute for Allergy and Infectious Diseases grant 5P30A1073961-09 awarded to the Miami Center for AIDS Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases, the National Heart, Lung and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse or the National Institute of Mental Health.

REFERENCES

1. Supervie V, Breban R. Per sex-act risk of HIV transmission under antiretroviral treatment: A data-driven approach. J Acquir Immune Defic Syndr. 2018;79(4):440–4.
2. Baggaley RF, Owen BN, Silhol R, Elmes J, Anton P, McGowan I, et al. Does per-act HIV-1 transmission risk through anal sex vary by gender? An updated systematic review and meta-analysis. Am J Reprod Immunol. 2018;80:e13039.
3. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS. 2014;28(10):1509–19.
4. Bavinton BR, Pinto AN, Phanuphak N, Grinsztejn B, Prestage GP, Zablotska-Manos IB, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. Lancet HIV. 2018;5(8):e438–47.
5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375(9):830–9.
6. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Jv Lunzen, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 2016;316(2):171–81.
7. Joint United Nations Programme on HIV/AIDS. 90–90–90: An ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS; 2014.
8. Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. Ending the HIV epidemic: a plan for the United States. JAMA. 2019;321(9):844–5.
9. Safren SA, Hughes JP, Mimiaga MJ, Moore AT, Friedman RK, Srithanaviboonchai K, et al. Frequency and predictors of estimated HIV transmissions and bacterial STI acquisition among HIV-positive patients in HIV care across three continents. J Int AIDS Soc. 2016;19:21096.
10. Gopalappa C, Farnham PG, Chen YH, Sansom SL. Progression and transmission of HIV/AIDS (PATH 2.0). Med Decis Making. 2017;37(2):224–33.
11. Li Z, Purcell DW, Sansom SL, Hayes D, Hall HI. Vital signs: HIV transmission along the continuum of care - United States, 2016. MMWR Morb Mortal Wkly Rep. 2019;68(11):267–72.
12. Skarbinski J, Rosenberg E, Paz-Bailey G, Hall HI, Rose CE, Viall AH, et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA Int Med. 2015;175(4):588.
13. Singer M. AIDS and the health crisis of the U.S. urban poor; the perspective of critical medical anthropology. Soc Sci Med. 1994;39(7):931–48.
14. Dyer TP, Shoptaw S, Guadamuz TE, Plankey M, Kao U, Ostrow D, et al. Application of syndemic theory to Black men who have sex with men in the Multicenter AIDS Cohort Study. J Urban Health. 2012;89:697–708.
15. Hart TA, Noor SW, Adam BD, Vernon JRG, Brennan DJ, Gardner S, et al. Number of psychosocial strengths predicts reduced HIV sexual risk behaviors above and beyond syndemic problems among gay and bisexual men. AIDS Behav. 2017;21(10):3035–46.
16. Jain JP, Strathdee SA, Patterson TL, Semple SJ, Harvey-Vera A, Magis-Rodriguez C, et al. Perceived barriers to pre-exposure prophylaxis use and the role of syndemic factors among female sex workers in the Mexico-United States border region: a latent class analysis. AIDS Care. 2019;32(5):557–66.
17. Martinez O, Arreola S, Wu E, Muñoz-Laboy M, Levine EC, Rutledge SE, et al. Syndemic factors associated with adult sexual HIV risk behaviors in a sample of Latino men who have sex with men in New York City. Drug Alcohol Depend. 2016;166:258–62.
18. Muñoz-Laboy M, Martinez O, Levine EC, Mattera BT, Fernandez MI. Syndemic conditions reinforcing disparities in HIV and other STIs in an urban sample of behaviorally bisexual Latino men. J Immigr Minor Health. 2018;20(2):497–501.
19. Starks TJ, Tuck AN, Millar BM, Parsons JT. Linking syndemic stress and behavioral indicators of main partner HIV transmission risk in gay male couples. AIDS Behav. 2016;20(2):439–48.
20. Tulloch TG, Rotondi NK, Ing S, Myers T, Calzavara LM, Loutfy MR, et al. Retrospective reports of developmental stressors, syndemics, and their association with sexual risk outcomes among gay men. Arch Sex Behav. 2015;44(7):1879–89.
21. Williams JK, Wilton L, Magnus M, Wang L, Wang J, Dyer TP, et al. Relation of childhood sexual abuse, intimate partner violence, and depression to risk factors for HIV among Black men who have sex with men in 6 US cities. Am J Public Health. 2015;105(12):2473–81.
22. Mimiaga MJ, O'Cleirigh C, Biello KB, Robertson AM, Safren SA, Coates TJ, et al. The effect of psychosocial syndemic production on 4-year HIV incidence and risk behavior in a large cohort of sexually active men who have sex with men. J Acquir Immune Defic Syndr. 2015;68(3):329–36.
23. Mustanski B, Garofalo R, Herrick A, Donenberg G. Psychosocial health problems increase risk for HIV among urban young men who have sex with men: preliminary evidence of a syndemic in need of attention. Ann Behav Med. 2007;34(1):37–45.
24. Parsons JT, Grov C, Golub SA. Sexual compulsivity, co-occurring psychosocial health problems, and HIV risk among gay and bisexual men: Further evidence of a syndemic. Am J Public Health. 2011;102(1):156–62.
25. Guadamuz TE, McCarthy K, Wimonsate W, Thienkrua W, Varangrat A, Chaikummao S, et al. Psychosocial health conditions and HIV prevalence and incidence in a cohort of men who have sex with men in Bangkok, Thailand: Evidence of a syndemic effect. AIDS Behav. 2014;18(11):2089–96.
26. Jiang H, Li J, Chen X, Cheng W, Yang Y. Syndemic factors associated with sexual HIV risk behaviors among men who have sex with men in Guangzhou. China. Int J Infect Dis. 2018;73:246–7.
27. Jie W, Ciyong L, Xueqing D, Hui W, Lingyao H. A syndemic of psychosocial problems places the MSM (men who have sex with men) population at greater risk of HIV infection. PLoS One. 2012;7:e32312.
28. Mimiaga MJ, Biello KB, Robertson AM, Oldenburg CE, Rosenberger JG, O'Cleirigh C, et al. High prevalence of multiple syndemic conditions associated with sexual risk behavior and HIV infection among a large sample of Spanish- and Portuguese-speaking men who have sex with men in Latin America. Arch Sex Behav. 2015;44(7):1869–78.
29. Santos GM, Do T, Beck J, Makofane K, Arreola S, Pyun T, et al. Syndemic conditions associated with increased HIV risk in a global sample of men who have sex with men. Sex Transm Infect. 2014;90(3):250–3.
30. Wim VB, Christiana N, Marie L. Syndemic and other risk factors for unprotected anal intercourse among an online sample of Belgian HIV negative men who have sex with men. AIDS Behav. 2014;18(1):50–8.
31. Brennan J, Kuhns LM, Johnson AK, Belzer M, Wilson EC, Garofalo R, et al. Syndemic theory and HIV-related risk among young transgender women: The role of multiple, co-occurring health problems and social marginalization. Am J Public Health. 2012;102(9):1751–7.
32. Parsons JT, Antebi-Gruszka N, Millar BM, Cain D, Gurung S. Syndemic conditions, HIV transmission risk behavior, and transactional sex among transgender women. AIDS Behav. 2018;22(7):2056–67.
33. Oldenburg CE, Perez-Brumer AG, Reisner SL. Poverty matters: Contextualizing the syndemic condition of psychological factors and newly diagnosed HIV infection in the United States. AIDS. 2014;28(18):2763–9.

34. Stall R, Mills TC, Williamson J, Hart T, Greenwood G, Paul J, et al. Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. Am J Public Health. 2003;93(6):939–42.
35. Kuhns LM, Hotton AL, Garofalo R, Muldoon AL, Jaffe K, Bouris A, et al. An index of multiple psychosocial, syndemic conditions is associated with antiretroviral medication adherence among HIV-positive youth. AIDS Patient Care STDS. 2016;30(4):185–92.
36. Blashill AJ, Bedoya CA, Mayer KH, O'Cleirigh C, Pinkston MM, Remmert JE, et al. Psychosocial syndemics are additively associated with worse ART adherence in HIV-infected individuals. AIDS Behav. 2015;19(6):981–6.
37. Harkness A, Bainter SA, O'Cleirigh C, Mendez NA, Mayer KH, Safren SA. Longitudinal effects of syndemics on ART non-adherence among sexual minority men. AIDS Behav. 2018;22(8):2564–74.
38. Friedman MR, Stall R, Silvestre AJ, Wei C, Shoptaw S, Herrick A, et al. Effects of syndemics on HIV viral load and medication adherence in the multicentre AIDS cohort study. AIDS. 2015;29(9):1087–96.
39. Biello KB, Oldenburg CE, Safren SA, Rosenberger JG, Novak DS, Mayer KH, et al. Multiple syndemic psychosocial factors are associated with reduced engagement in HIV care among a multinational, online sample of HIV-infected MSM in Latin America. AIDS Care. 2016;28 Suppl 1:84–91.
40. Mizuno Y, Purcell DW, Knowlton AR, Wilkinson JD, Gourevitch MN, Knight KR. Syndemic vulnerability, sexual and injection risk behaviors, and HIV continuum of care outcomes in HIV-positive injection drug users. AIDS Behav. 2015;19(4):684–93.
41. Halkitis PN, Kupprat SA, Hampton MB, Perez-Figueroa R, Kingdon M, Eddy JA, et al. Evidence for a syndemic in aging HIV-positive gay, bisexual, and other MSM: implications for a holistic approach to prevention and healthcare. Ann Anthropol Pract. 2012;36(2):365–86.
42. Harkness A, Bainter SA, O'Cleirigh C, Albright C, Mayer KH, Safren SA. Longitudinal effects of syndemics on HIV-positive sexual minority men's sexual health behaviors. Arch Sex Behav. 2019;48(4):1159–70.
43. Glynn TR, Safren SA, Carrico AW, Mendez NA, Duthely LM, Dale SK, et al. High levels of syndemics and their association with adherence, viral non-suppression, and biobehavioral transmission risk in Miami, a U.S. city with an HIV/AIDS epidemic. AIDS Behav. 2019;23:2956–65.
44. Carrico AW, Johnson MO, Colfax GN, Moskowitz JT. Affective correlates of stimulant use and adherence to anti-retroviral therapy among HIV-positive methamphetamine users. AIDS Behav. 2010;14(4):769–77.
45. Carrico AW, Johnson MO, Moskowitz JT, Neilands TB, Morin SF, Charlebois ED, et al. Affect regulation, stimulant use, and viral load among HIV-positive persons on anti-retroviral therapy. Psychosom Med. 2007;69:785–92.
46. Carrico AW, Riley ED, Johnson MO, Charlebois ED, Neilands TB, Remien RH, et al. Psychiatric risk factors for HIV disease progression: the role of inconsistent patterns of antiretroviral therapy utilization. J Acquir Immune Defic Syndr. 2011;56(2):146–50.
47. Horvath KJ, Carrico AW, Simoni J, Boyer EW, Amico KR, Petroll AE. Engagement in HIV medical care and technology use among stimulant-using and nonstimulant-using men who have sex with men. AIDS Res Treat. 2013;2013:121352.
48. Mayer KH, Skeer MR, O'Cleirigh C, Goshe BM, Safren SA. Factors associated with amplified HIV transmission behavior among American men who have sex with men engaged in care: implications for clinical providers. Ann Behav Med. 2014;47(2):165–71.
49. Morin SF, Steward WT, Charlebois ED, Remien RH, Pinkerton SD, Johnson MO, et al. Predicting HIV transmission risk among HIV-infected men who have sex with men: Findings from the Healthy Living Project. J Acquir Immune Defic Syndr. 2005;40(2):226–35.
50. Okafor CN, Cook RL, Chen X, Surkan PJ, Becker JT, Shoptaw S, et al. Trajectories of marijuana use among HIV-seropositive and HIV-seronegative MSM in the Multicenter AIDS Cohort Study (MACS), 1984–2013. AIDS Behav. 2017;21(4):1091–104.
51. Tsuyuki K, Shoptaw SJ, Ransome Y, Chau G, Rodriguez-Diaz CE, Friedman RK, et al. The longitudinal effects of non-injection substance use on sustained HIV viral load undetectability among MSM and heterosexual men in Brazil and Thailand: the role of ART adherence and depressive symptoms (HPTN 063). AIDS Behav. 2019;23:649–60.
52. White JM, Gordon JR, Mimiaga MJ. The role of substance use and mental health problems in medication adherence among HIV-infected MSM. LGBT Health. 2014;1(4):319–22.
53. Mimiaga MJ, Biello K, Reisner SL, Crane HM, Wilson J, Grasso C, et al. Latent class profiles of internalizing and externalizing psychosocial health indicators are differentially associated with sexual transmission risk: findings from the CFAR Network of Integrated Clinical Systems (CNICS) cohort study of HIV-infected men engaged in primary care in the United States. Health Psychol. 2015;34(9):951–9.
54. Kitahata MM, Rodriguez B, Haubrich R, Boswell S, Mathews WC, Lederman MM, et al. Cohort profile: the centers for AIDS research network of integrated clinical systems. Int J Epidemiol. 2008;37(5):948–55.
55. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. J Gen Intern Med. 2001;16(9):606–13.
56. Spitzer RL, Kroenke K, Williams JBW; Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. JAMA. 1999;282(18):1737–44.
57. WHO Assist Working Group. The alcohol, smoking and substance involvement screening test (ASSIST): development, reliability and feasibility. Addiction. 2002;97(9):1183–94.
58. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Arch Intern Med. 1998;158 (16):1789–95.
59. Crane HM, Crane PK, Tufano JT, Ralston JD, Wilson IB, Brown TD, et al. HIV provider documentation and actions following patient reports of at-risk behaviors and conditions when identified by a web-based point-of-care assessment. AIDS Behav. 2017;21(11):3111–21.
60. Enders CK, Keller BT, Levy R. A fully conditional specification approach to multilevel imputation of categorical and continuous variables. Psychol Methods. 2018;23(2):298–317.
61. Enders CK, Du H, Keller BT. A model-based imputation procedure for multilevel regression models with random coefficients, interaction effects, and nonlinear terms. Psychol Methods. 2020;25(1):88–112.
62. Keller BT, Enders CK. Blimp user's manual (version 2.2). Los Angeles, CA: 2020.
63. Enders CK. Multiple imputation as a flexible tool for missing data handling in clinical research. Behav Res Ther. 2017;98:4–18.
64. Carpenter JR, Kenward MG. Survival data, skips and large datasets. In: Carpenter JR, Kenward MG, editors. Multiple imputation and its application. Statistics in practice;10.1002/9781119942283.ch8. London: John Wiley & Sons, Ltd; 2013. p. 165-202.
65. Weller SC, Davis-Beaty K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev. 2002. http://doi.org/10.1002/14651858.cd003255
66. Mimiaga MJ, Hughto JMW, Biello KB, Santostefano CM, Kuhns LM, Reisner SL, et al. Longitudinal analysis of syndemic psychosocial problems predicting HIV risk behavior among a multicity prospective cohort of sexually active young transgender women in the United States. J Acquir Immune Defic Syndr. 2019;81(2):184–92.
67. Humeniuk R, Ali R, Babor TF, Farrell M, Formigoni ML, Jittiwutikarn J, et al. Validation of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). Addiction. 2008;103(6):1039–47.
68. R Core Team. R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
69. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Soft. 2015;67(1):1–48.
70. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. J Stat Soft. 2017;82(13):1–26.
71. Grund S, Robitzsch A, Luedtke O, mitml: tools for multiple imputation in multilevel modeling. R package version 0.3-7 ed. 2019.
72. Nance RM, Delaney JAC, Simoni JM, Wilson IB, Mayer KH, Whitney BM, et al. HIV viral suppression trends over time among HIV-infected patients receiving care in the United States, 1997 to 2015: a cohort study. Ann Intern Med. 2018;169(6):376–84.
73. Oliver CD, Rebeiro PF, Shepherd BE, Keruly J, Mayer KH, Mathews WC, et al. Clinic-level factors associated with retention in care among people living with HIV in a multi-site United States cohort, 2010–2016. Clin Infect Dis. 2019;71(10):2592–8.
74. Substance Abuse and Mental Health Services Administration and Health Resources and Service Administration. The case for behavioral health screening in HIV care settings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2016.
75. Shacham E, Nurutdinova D, Satyanarayana V, Stamm K, Overton ET. Routine screening for depression: Identifying a challenge for successful HIV care. AIDS Patient Care STDS. 2009;23(11):949–55.
76. Chander G, Himelhoch S, Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. Drugs. 2006;66(6):769–89.
77. Brandt C, Zvolensky MJ, Woods SP, Gonzalez A, Safren SA, O'Cleirigh CM. Anxiety symptoms and disorders among adults living with HIV and AIDS: a

critical review and integrative synthesis of the empirical literature. Clin Psychol Rev. 2017;51:164–84.
78. Vallabhaneni S, Li X, Vittinghoff E, Donnell D, Pilcher CD, Buchbinder SP. Seroadaptive practices: association with HIV acquisition among HIV-negative men who have sex with men. PLoS One. 2012;7:e45718.
79. Blashill AJ, Brady JP, Rooney BM, Rodriguez-Diaz CE, Horvath KJ, Blumenthal J, et al. Syndemics and the PrEP cascade: results from a sample of young latino men who have sex with men. Arch Sex Behav. 2020;49(1):125–35.
80. Tsai AC, Burns BFO. Syndemics of psychosocial problems and HIV risk: a systematic review of empirical tests of the disease interaction concept. Soc Sci Med. 2015;139:26–35.
81. Tsai AC, Mendenhall E, Trostle JA, Kawachi I. Co-occurring epidemics, syndemics, and population health. Lancet. 2017;389:978–82.
82. Mimiaga MJ, Closson EF, Pantalone DW, Safren SA, Mitty JA. Applying behavioral activation to sustain and enhance the effects of contingency management for reducing stimulant use among individuals with HIV infection. Psychol Health Med. 2019;24(3):374–81.

SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article.

Table S1. Sensitivity analyses of final model predicting estimated HIV transmissions over time