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Original article

Do metropolitan HIV epidemic histories and programs for people who inject drugs and men who have sex with men predict AIDS incidence and mortality among heterosexuals?

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ABSTRACT

Purpose: We focus on a little-researched issue—how human immunodeficiency virus (HIV) epidemics and programs in key populations in metropolitan areas affect epidemics in other key populations. We consider (1) How are earlier epidemics among people who inject drugs (PWID) and men who have sex with men (MSM) related to later AIDS incidence and mortality among heterosexuals?; (2) Were prevention programs targeting PWID or MSM associated with lower AIDS incidence and mortality among heterosexuals?; and (3) Was the size of the potential bridge population of noninjecting drug users (NIDUs) in a metropolitan area associated with later AIDS incidence and mortality among heterosexuals?
Methods: Using data for 96 large U.S. metropolitan areas, Poisson regression assessed associations of population prevalences of HIV-infected PWID and MSM (1992); NIDU population prevalence (1992–1994); drug use treatment coverage for PWID (1993); HIV counseling and testing coverage for MSM and for PWID (1992); and syringe exchange presence (2000) with CDC data on AIDS incidence and mortality among heterosexuals in 2006–2008, with appropriate socioeconomic controls.
Results: Population density of HIV+ PWID and of NIDUs were positively related, and prevention programs for PWID negatively related to later AIDS incidence among heterosexuals and later mortality among heterosexuals living with AIDS. HIV+ MSM population density and prevention programs for MSM were not associated with these outcomes.
Conclusions: Efforts to reduce HIV transmission among PWID and NIDUs may reduce AIDS and AIDS-related mortality among heterosexuals. More research is needed at metropolitan area, network, and individual levels into HIV bridging across key populations and how interventions in one key population affect HIV epidemics in other key populations.

Introduction

Community network studies, research on group sex events [1,2], and other data show that sexual relationships among people who inject drugs (PWID), among men who have sex with men (MSM), among noninjecting drug users (NIDUs), and among other heterosexuals are common [3–11]. NIDUs may be a group through which human immunodeficiency virus (HIV) is transmitted from PWID and MSM to heterosexuals [12–19].

Insofar as we know, little research has been conducted on how epidemics and programs in one key population affect those in other key populations, although one phylogenetic study [20], one historical study, and some attempts to use mathematical modeling [21,22] have explored this issue. Previously, we investigated the association between HIV prevalence among MSM and that among PWID in 96 large metropolitan statistical areas in 1992 [23,24]. Here, in the absence of adequate metropolitan-level data on HIV incidence or prevalence among heterosexuals after 1992, we focus on an important subset of research questions on this topic: (1)

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Table 1
Descriptive statistics on independent variables for 96 large U.S. metropolitan statistical areas

Variable	*N*	Median (range)	Mean (SD)	1st Quartile	3rd Quartile	Data source
Epidemiologic factors						
HIV-positive high-risk heterosexuals per 10,000 adult population 1992*	96	1.35 (0.20–19.14)	2.63 (3.48)	0.83	2.60	Holmberg [38]
HIV-positive PWID per 10,000 adult population 1992*	96	4.06 (0.74–80.63)	9.20 (13.88)	2.28	9.97	Holmberg [38]
HIV-positive MSM per 10,000 adult population 1992*	96	11.25 (2.64–134.07)	15.63 (15.29)	7.97	17.62	Holmberg [38]
NIDUs per 10,000 adult population 1992–1994	92	456.88 (90.30–3371.61)	598.52 (484.34)	319.50	651.48	TEDS [86] and Tempalski et al. [29]
Economic conditions						
Household Gini coefficient 1989	95	0.43 (0.38–0.51)	0.43 (0.02)	0.41	0.44	Harper [87]
Percent living below poverty level 1989	96	11.15 (4.23–52.87)	11.92 (5.61)	9.47	13.15	US Census [88,89]
Racial/ethnic residential segregation						
Black/White Dissimilarity Index 1990†	90	64.31 (37.52–89.95)	64.49 (11.86)	56.26	73.21	Mumford Center [90]
Social cohesion						
Religious membership per 10,000 adult population 1990	95	1314.22 (294.65–4945.15)	1669.51 (1036.00)	859.28	2148.30	ARDA [91]
Congregations per 10,000 adult population 1990	95	6.16 (3.19–15.91)	7.01 (2.88)	5.08	8.07	ARDA [91]
Interventions						
SEP 2000	96	0.00 (0–1)	0.44 (0.50)	-	-	Beth Israel Medical Center [92]
Hard drug arrests per 10,000 adult population 1993‡	94	11.42 (0.53–71.87)	15.06 (14.18)	4.47	20.41	FBI [93]
Drug use treatment coverage for PWID (% among total PWID pop in 1993)	90	5.60 (0.80–16.40)	6.76 (3.71)	4.20	9.40	Tempalski et al. [35]
HIV Counseling and Testing coverage for PWID (% among PWID at risk in 1992)	79	7.70 (0.14–31.51)	9.16 (6.42)	4.78	12.52	CTS [94] and Holmberg [38]
HIV Counseling and Testing coverage for MSM (% among MSM at risk in 1992)	81	7.09 (0.03-31.38)	7.78 (5.00)	5.00	8.74	CTS [94] and Holmberg [38]

SD = standard deviation.
Reminder: Some variables have substantial measurement error.
* Holmberg [38] has already reported on these variables.
† Values on the Index of Dissimilarity are independent of the number of Black and White residents in each MSA.
‡ These arrests are an intervention to remove drug users from the street, deter drug use, and perhaps provide medical and social services to those arrested. See reference Friedman et al. [26,27,34] for data on their relationship to key parameters for people who inject drugs.

How are earlier metropolitan HIV epidemics among PWID and MSM related to later AIDS incidence and mortality among heterosexuals?; (2) Were prevention programs that targeted PWID or MSM associated with lower AIDS incidence and mortality among heterosexuals?; and (3) Was the size of the potential bridge population of NIDUs in a metropolitan area associated with later AIDS incidence and mortality among heterosexuals [25–29]? We use the term "heterosexuals" here to mean heterosexuals who do not inject drugs, although we note that an undetermined proportion of those so classified may have injected drugs but not reported it.

Methods

We studied these questions using longitudinal data from 1992 to 2008 on a cohort of metropolitan statistical areas (MSAs). The U.S. Census Bureau defines MSAs as contiguous counties containing a central city of 50,000 people or more that form a socioeconomic unity [30]; we used MSA boundaries as they were defined in 1992. Our studies of HIV epidemics among PWID at the MSA level [23–25,31–37] have shown that each MSA has its own epidemic history, HIV prevalence rate, history of prevention programming, and socioeconomic contexts.

This article is part of a study on HIV epidemics among PWID in the 96 MSAs that had populations of 500,000 or more in 1992. The study design is a longitudinal study at the MSA level of analysis. As such, it can be considered an "ecological cohort" study of MSAs as social and epidemiologic units. Given the complex pathways likely to connect HIV epidemics among different key populations, this design has important strengths and limitations that are described in the Discussion section. Due to missing data on dependent and key independent variables, the number of MSAs in the models presented in Tables 3 and 4 is less than 96 and varies depending on which variables are included in a given model.

Data

Data on both outcomes (AIDS incidence; and mortality among heterosexuals aged 15–64 years living with AIDS) for 2006–2008 in each MSA were obtained by special request from the U.S. Centers for Disease Control and Prevention. We divided these by the number of adults (aged 15–64 years) living in each MSA to calculate population-based rates.

Other data sources are described in Table 1. Estimates of numbers of HIV-positive MSM and PWID and on population numbers of MSM and PWID in 1992 were taken from Holmberg [38]. Although reported in Table 1, data on HIV-positive high-risk heterosexuals per 10,000 adult population were not included in the statistical analyses because they were highly correlated with HIV prevalence estimates for PWID ($r = 0.88$) and because they were for the hard-to-define "high-risk" heterosexual population rather than for the entire heterosexual population, which is the population this article is studying. These were calculated using methods such as back-calculation that have become more complicated after the development and spread of highly active antiretroviral therapy [39]. Although these techniques have been used to create national-level incidence estimates [39], they would be very time-consuming and less accurate at the metropolitan area level. Although estimates for numbers of PWID for these metropolitan areas are available (Table 1), estimates of numbers of MSM are available only for 1992

and estimates of HIV incidence among heterosexuals for metropolitan areas are not available after 1992.

NIDUs were defined as people who use heroin, cocaine, nonprescription methadone or amphetamines, but do not inject drugs. The population prevalence of NIDUs in 1992–1994 was estimated by multiplying PWID population prevalence by an adjustment factor: the ratio of events (reported by TEDS, as cited in Table 1) in which NIDUs entered drug use treatment divided by the sum of the numbers of events in which PWID or NIDUs entered treatment.

CDC data on numbers of HIV counseling and testing sessions (CTS) in 1992 for MSM and PWID were used to estimate "coverage rates" for CDC-funded CTS for these populations. These coverage rates are defined as the number of testing events performed per member of the population in question (and expressed as a percent). Data on syringe exchange program (SEP) presence come from the Beth Israel Syringe Exchange Survey for 2000; many of them were established previous to that [36,37]. Other intervention data are described in Table 1.

The time ordering of variables is important. Our focus here is on associations between the size of the HIV epidemics among MSM and among PWID in 1992 and AIDS-related outcomes in 2006–2008. We also want to determine how prevention programs affected these outcomes. As discussed above, HIV counseling and testing coverage for MSM could only be calculated for 1992, so we used PWID coverage data for this year as well. Because the number of U.S. syringe exchanges increased rapidly in the 1990s (and because SEPs are important not only as way to prevent HIV transmission but also as major referral sources for both NIDUs and PWID to drug use treatment programs and to HIV care that would slow disease progression [40–42]), we used 2000 as our year for measuring this variable even though there would be few if any instances in which infections prevented among PWID in 2000 would transmit HIV to a heterosexual who would develop AIDS by 2006.

Our previous research on HIV and AIDS among PWID in these MSAs [23,24,26,27,31,34] has indicated that a number of social and economic variables (Table 1) should be controlled for. Some of these were available only for Census years 1990 and 2000. In these cases, their values for the two years were correlated with $r > 0.90$, so we entered the earlier value into the statistical model building process. Similarly, for treatment coverage for PWID, the values for 1993 and 2000 had $r = 0.76$; we used the 1993 value which had a higher correlation with the dependent variables.

Statistical approach

Because this is a study of all U.S. MSAs with populations of 500,000 or more in 1992 that had data available on our key variables, our sample is a fully enumerated universe. This means there is no sampling error. Nonetheless, we report statistical significance and confidence intervals (CIs) as heuristic guides to the importance of a variable in an equation [27,43]. We compute them as if we had a random sample of MSAs, but interpret results as "pseudo-*P*-values" and "pseudo-CIs" to guide our interpretation (as in previous articles: [23,31,44]). In addition, a number of our variables have substantial measurement error (as is true in much of epidemiology and related fields)—which standard statistics do not take account of—and this may affect the accuracy of our results.

Poisson regression with a log link function, used to model count data [45], was used for bivariate and multivariate analyses of AIDS incidence and mortality rates (per 10,000 adult population) in 2006–2008. As suggested by Stokes et al. [46] as well as Cameron and Trivedi [47], a modified Poisson approach, using the Repeated statement in SAS PROC GENMOD, was used to estimate models with robust standard errors. Because we did find evidence of underdispersion, our use of robust standard errors was an appropriate correction that resulted in smaller standard errors and narrower CIs [46,47].

Continuous independent variables were rescaled before inclusion in bivariate or multivariate analysis. The standard deviation of the predictor was chosen as the scaling distance, which standardized continuous predictors such that a 1-unit change represented a change of 1 standard deviation [48]. Rescaling predictors allowed for more meaningful interpretation of regression coefficients [48]. Regression coefficients were exponentiated to obtain incidence rate ratios (IRR) for independent variables to ease interpretation of results.

Bivariate relationships between each independent variable and outcome measure were assessed using Poisson regression [45]. For each dependent variable, predictors with an IRR $\leq$0.83 or an IRR $\geq$1.20 were entered into multivariate models unless colinearity issues were present [44]. These IRR values were chosen to select variables with moderate associations for further exploratory analysis. For variables with data at more than one time point, earlier years were generally selected for use in multivariate models. In one case, SEPs, we used a later year (2000) to reflect the large growth in SEPs during the 1990s [37,49,50]. These results constitute model 1 in each of Tables 3 and 4.

Because existing theory and research has relatively little to say about the cross-population processes being studied, we used exploratory analytic techniques to study these relationships by conducting backward model selection based on IRRs. Using the same IRR cutoffs as in the bivariate analysis, predictors were eliminated one at a time until all variables in the model had an IRR $\leq$0.83 or an IRR $\geq$1.20. The minimal equation based on these specifications is presented as model 2. Because data on HIV counseling and testing coverage were not available for over 15 of our MSAs (Table 1), these variables were added to model 2 to form a separate model (model 3) based on this smaller data set.

As a further exploratory step, we estimated an additional model 4 using Akaike information criteria (AIC) for model selection [51]. AIC combines estimation and model selection and is particularly useful when comparing multiple models [52,53]. Assessing AIC involves comparing AIC values to a minimum AIC or "best" model using the formula: $\Delta_i = \mathrm{AIC}_i - \mathrm{AIC}_{\min}$; models with $\Delta_i \leq 2$ demonstrate substantial support, models with $4 \leq \Delta_i \leq 7$ have less support, and models where $\Delta_i > 10$ have essentially no support [53]. AIC was used because of the following reasons: (1) it let us compare multiple models in an exploratory way; (2) it let us compare models that were not nested; (3) it helped us identify and avoid over-fitted models; while (4) avoiding choice of models that overly restrict the number of variables included because they use model fit statistics like the Bayes Information Criterion [54] that more heavily penalize extra variables. Starting with model 1, one variable at a time was removed and AIC values were compared. The model with the lowest AIC value was selected before moving to the next round of variable removal. Model 4 in Tables 3 and 4 represents the minimal equation with the lowest AIC value. HIV counseling and testing coverage was added to the final model produced through AIC selection to produce model 5.

Results

There are wide variations across MSAs in HIV population prevalence rates among MSM, PWID, and heterosexuals in 1992 (Table 1). In bivariate analyses (Table 2), a wide range of epidemiologic, economic, racial disparity, social cohesion, and intervention indicators were associated with subsequent AIDS incidence rates among heterosexuals and mortality rates among heterosexuals living with AIDS. Many of these variables were intercorrelated, so

Table 2
Bivariate results for AIDS incidence and mortality rates among heterosexuals (per 10,000 adult population) in large U.S. metropolitan statistical areas, 2006–2008

Variable	AIDS incidence rates	AIDS mortality rates
	IRR (95% CI)	IRR (95% CI)
Epidemiologic factors		
HIV-positive PWID per 10,000 adult population 1992	1.37**** (1.25–1.50)	1.44**** (1.27–1.63)
HIV-positive MSM per 10,000 adult population 1992	1.21* (0.99–1.46)	1.24** (1.00–1.55)
NIDUs per 10,000 adult population 1992–1994	1.36**** (1.26–1.47)	1.51**** (1.40–1.64)
Economic conditions		
Gini 1989	1.47**** (1.27–1.71)	1.77**** (1.44–2.18)
Percent living below poverty 1989	1.14 (0.84–1.55)	1.26 (0.82–1.91)
Racial disparity		
Black/White Dissimilarity Index 1990	1.32**** (1.12–1.56)	1.41*** (1.13–1.77)
Social cohesion		
Religious membership per 10,000 adult population 1990	0.96 (0.81–1.14)	0.90 (0.71–1.14)
Congregations per 10,000 adult population 1990	0.78** (0.62–0.98)	0.64** (0.43–0.95)
Interventions		
SEP 2000	0.73* (0.49–1.07)	0.50*** (0.31–0.83)
Hard drug arrests per 10,000 adult population 1993	1.18* (1.00–1.41)	1.26** (1.01–1.58)
IDU drug use treatment coverage 1993	0.61**** (0.49–0.77)	0.46**** (0.33–0.65)
CTS coverage PWID 1992	0.62**** (0.50–0.77)	0.52**** (0.37–0.73)
CTS coverage MSM 1992	0.86 (0.66–1.13)	0.77* (0.59–1.02)

IRRs and 95% CIs for IRRs presented. All *P* and CIs are pseudo-*P*s and pseudo CIs, as is discussed in the Methods section of the text; and some variables have substantial measurement error.
*$P < .10$, **$P < .05$, ***$P < .01$, ****$P < .001$.
*Estimates of HIV prevalence per 10,000 heterosexual population were omitted from the statistical analysis because they were highly correlated with HIV prevalence estimates for PWID ($r = 0.88$) and because they were for the hard-to-define "high-risk" heterosexual population rather than the entire heterosexual population, which is the denominator for the outcomes.

additional exploratory analyses were conducted. (Refer Table 3 for AIDS incidence results and Table 4 for mortality results).

Using the IRR criteria (IRR $\geq$ 1.20 or IRR $\leq$ 0.83), model 2 shows that AIDS incidence rates among heterosexuals were higher where there was a higher population prevalence of HIV-positive PWID in 1992, where there was a higher population prevalence of NIDUs in 1992–1994, and where there were no syringe exchange programs in 2000 (Table 3).

In model 3, we added data on CDC-funded HIV counseling and testing program coverage for PWID (and for MSM, data not shown). HIV counseling and testing coverage for PWID was associated with lower AIDS incidence among heterosexuals, although coverage for MSM was not. The reduced sample size in model 3 ($N = 75$ in models that include HIV counseling and testing coverage) increased the IRR for SEPs to slightly over the criterion value of 0.83.

The alternative approach to model reduction, using AIC rather than IRR as the criterion for backward selection, yielded a somewhat different model (model 4). As in model 2, AIDS incidence rates among heterosexuals were higher where there was a higher population prevalence of HIV-positive PWID in 1992 and where there was a higher population prevalence of NIDUs in 1992–1994 (although the IRR on this variable [1.18] was <1.20). Drug use treatment coverage rates for PWID in 1993 were associated with less AIDS incidence; and Black/White Residential Dissimilarity in 1990 was slightly (1.11) associated with higher AIDS incidence. When HIV counseling and testing coverage for PWID and for MSM

Table 3
Multivariate results for AIDS incidence rates among heterosexuals (per 10,000 adult population) in large U.S. metropolitan statistical areas, 2006–2008

Variable	Model 1: Selected variables from bivariate using IRR ($n = 85$)	Model 2: Backward selection of model 1 using IRR ($n = 91$)	Model 3: Model 2* with HIV counseling and testing coverage ($n = 75$)	Model 4: Backward selection of model 1 using AIC ($n = 85$)	Model 5: Model 4* with HIV counseling and testing coverage ($n = 71$)
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
HIV-positive PWID per 10,000 adult population 1992	1.23*** (1.09–1.39)	1.32**** (1.20–1.45)	1.22**** (1.12–1.33)	1.31**** (1.17–1.46)	1.27**** (1.13–1.43)
HIV-positive MSM per 10,000 adult population 1992	1.09 (0.94–1.26)	—	—	—	—
NIDUs per 10,000 adult population 1992–1994	1.11** (1.01–1.22)	1.30**** (1.22–1.39)	1.47**** (1.26–1.72)	1.18**** (1.12–1.26)	1.24*** (1.05–1.46)
Gini 1989	1.04 (0.89–1.23)	—	—	—	—
Black/White Dissimilarity Index 1990	1.11 (0.97–1.26)	—	—	1.11* (0.98–1.27)	1.15 (0.96–1.37)
Congregations per 10,000 adult population 1990	0.89 (0.77–1.04)	—	—	—	—
SEP 2000	0.92 (0.69–1.23	0.82 (0.60–1.11)	0.86 (0.62–1.19)	—	—
IDU drug use treatment coverage 1993	0.64**** (0.52–0.78)	—	—	0.66**** (0.54–0.80)	0.65**** (0.53–0.79)
CTS coverage PWID 1992	—	—	0.73**** (0.62–0.87)	—	0.78** (0.62–0.98)
CTS coverage MSM 1992	—	—	—	—	1.22 (0.91–1.64)
AIC value	147.77	151.07	125.11	140.78	119.77

IRRs and 95% CIs for IRRs presented. All *P* and CIs are pseudo-*P*s and pseudo CIs, as is discussed in the Methods section of the text; and some variables have substantial measurement error.
*$P < .10$, **$P < .05$, ***$P < .01$, ****$P < .001$.
* Estimates of HIV prevalence per 10,000 heterosexual population were omitted from the statistical analysis because they were highly correlated with HIV prevalence estimates for PWID ($r = 0.88$) and because they were for the hard-to-define "high-risk" heterosexual population rather than the entire heterosexual population, which is the denominator for the outcomes.

Table 4
Multivariate results for mortality rates among heterosexuals living with AIDS (per 10,000 adult population) in large U.S. metropolitan statistical areas, 2006–2008

Variable	Model 1: Selected variables from bivariate using IRR ($n = 84$)	Model 2: Backward selection of model 1 using IRR ($n = 91$)	Model 3: Model 2* with HIV counseling and testing coverage ($n = 75$)	Model 4: Backward selection of model 1 using AIC ($n = 85$)	Model 5: Model 4* with HIV counseling and testing coverage ($n = 72$)
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
HIV-positive PWID per 10,000 adult population 1992	1.23*** (1.06–1.42)	1.24**** (1.10–1.40)	1.23**** (1.09–1.40)	1.43**** (1.24–1.64)	1.35**** (1.16–1.57)
HIV-positive MSM per 10,000 adult population 1992	1.07 (0.89–1.28)	—	—	—	
NIDUs per 10,000 adult population 1992–1994	1.10* (0.99–1.23)	—	—	1.30**** (1.21–1.39)	1.50**** (1.19–1.88)
Gini 1989	1.20** (1.01–1.42)	1.31**** (1.15–1.50)	1.26**** (1.10–1.43)	—	—
Black/White Dissimilarity Index 1990	1.09 (0.89–1.34)	—	—	—	—
Congregations per 10,000 adult population 1990	0.80** (0.65–0.97)	0.72**** (0.60, 0.86)	0.71*** (0.57–0.89)	—	—
SEP 2000	0.69** (0.51–0.96)	0.71** (0.54–0.93)	0.77* (0.56–1.05)	—	—
Hard drug arrests per 10,000 adult population 1993	1.04 (0.84–1,28)	—	—	—	—
IDU drug use treatment coverage 1993	0.53**** (0.42–0.67)	0.51**** (0.42–0.61)	0.51**** (0.40–0.67)	0.55**** (0.42–0.71)	0.58**** (0.42–0.80)
CTS coverage PWID 1992	—	—	0.81** (0.67–1.00)	—	0.79* (0.61–1.01)
AIC value	90.03	86.78	72.99	82.23	68.68

IRRs and 95% CIs for IRRs presented. All *P* and CIs are pseudo-*P*s and pseudo CIs, as is discussed in the Methods section of the text; and some variables have substantial measurement error.
*$P < .10$, **$P < .05$, ***$P < .01$, ****$P < .001$.
* Estimates of HIV prevalence per 10,000 heterosexual population were omitted from the statistical analysis because they were highly correlated with HIV prevalence estimates for PWID ($r = 0.88$) and because they were for the hard-to-define "high-risk" heterosexual population rather than the entire heterosexual population, which is the denominator for the outcomes.

were added to the model, counseling and testing for PWID was protective (IRR = 0.78); but CTS for MSM was not protective. (Its apparent association with *higher* rates of heterosexual AIDS incidence is probably an artifact of high correlations with CTS for PWID [$r = 0.50$], PWID drug use treatment coverage [$r = 0.39$], and Black/White dissimilarity index [$r = -0.36$]).

In model 2, AIDS mortality rates among heterosexuals in 2006–2008 were higher where there was a higher population prevalence of HIV-positive PWID in 1992 or a higher Gini coefficient of income inequality; and lower where there was one or more SEPs in 2000, higher drug use treatment coverage for PWID in 1993, and more religious congregations per capita in 1990 (Table 4). In model 3, with reduced *N*, HIV counseling and testing coverage for PWID in 1992 was associated with lower mortality rates in 2006–2008.

In the alternative model 4, using the AIC criterion for model selection, a higher population prevalence of HIV-positive PWID in 1992 and lower drug use treatment rates among PWID remained associated with higher mortality. The only other predictor in this equation, however, was a higher population prevalence of NIDUs in 1992–1994. In model 5, these variables remained in the equation and higher coverage rates of HIV counseling and testing among PWID in 1992 was associated with lower mortality rates.

Discussion

These analyses suggest the possibility that AIDS burden among heterosexuals in 2006–2008 may have been shaped by bridging from HIV-infected PWID to heterosexuals and possibly, although to a lesser degree, from HIV-positive MSM to heterosexuals. Such bridging may have taken the form of sexual transmission from PWID (or MSM) to NIDUs and then, perhaps, from NIDUs to (other) heterosexuals. Network studies have shown that many PWID and many MSM have sex with NIDUs and that NIDUs have sex with people who do not use injectable drugs [8,11].

Programs to reduce HIV transmission to and from PWID are statistically associated in this study with smaller later AIDS epidemics among heterosexuals. In our exploratory analyses using different methods of model selection, there were some differences in which programs entered into which models. Overall, however, the data suggest that syringe exchange, drug use treatment coverage for PWID, and HIV counseling and testing coverage for PWID all were associated with lower rates of AIDS incidence among heterosexuals and with lower mortality rates among heterosexuals living with AIDS in 2006–2008, which may be an example of combination prevention [55–59] across population groups. Although our ecological cohort design cannot establish causality, these findings are consistent with the possibility that these relationships were causal of MSA-specific rates (but clearly not of individual infection or disease progression); we suggest that further research be conducted to clarify possible causal patterns. Possible pathways might include these programs leading to lower HIV incidence among PWID or to their facilitating access to successful antiretroviral therapy and thus to lower viral load among HIV-positive PWID, making the population of PWID less likely to transmit HIV to heterosexuals. SEPs also reduce sexual risk behaviors among PWID [60,61], as does knowing that one is HIV-positive, thus making HIV-positive PWID less likely to transmit HIV to heterosexual NIDUs or other heterosexuals. These programs may possibly have also helped produce a programmatic and social context where infected heterosexual NIDUs or other heterosexuals were more able to get and to adhere to antiretroviral and other treatment, which could rapidly reduce probabilities of developing AIDS or of dying from it thereafter [62,63].

Counseling and testing for MSM, however, did not seem to be associated with reduced rates of either AIDS incidence or mortality among heterosexuals. Given the continued high rates of HIV transmission among MSM (as opposed to among PWID, where transmission has fallen, in part due to the high effectiveness of SEPs where they have been implemented [42,64–66]), this could imply that counseling and testing among MSM has had limited effect on transmission behaviors by infected MSM—perhaps because it has not been reaching the highest-risk MSM [11,67,68]. It also is possible that there is a correlation between high rates of counseling and testing services among MSM and better prevention or medical services for those heterosexuals more likely to have sex with MSM. Further research is clearly needed to understand these results.

To our knowledge, this is one of the first empirical analyses to discover a relationship between racial/ethnic residential

segregation, a form of institutional racism [69] at the *supra*-individual level, and rates of HIV or other sexually transmitted infections. Biello et al. [70] have recently found that MSAs with higher levels of two dimensions of segregation (isolation and unevenness) had higher rates of gonorrhea among black residents. Segregation may generate vulnerability to HIV and other sexually transmitted infections among black adults through several mechanisms, including by affecting the structure of sexual networks [3,71–76]. Also, segregation may limit access to health care [73] and, thus, reduce access to HIV testing and counseling and to therapies that slow the progression of HIV infection.

There is some evidence in these data that income inequality may be associated with greater mortality among heterosexuals living with AIDS and that social cohesion (as indicated by religious congregation population density) may be protective. Such findings are parallel to other studies of social causation of mortality [77–82].

Our findings are subject to several limitations. Causal mechanisms are hard to study at a single level of analysis: Both higher-level variables (such as economic changes or changes in health systems at the global, national, or regional level) and lower-level variables (such as locally generated behavioral fads) may affect observed relationships. It is important both to avoid interpretations that make the ecological fallacy and consider interpretations that are valid at a single level of analysis. We have only limited ability to study how our independent variables come to be associated with outcomes. As with many studies, including some on social determinants of health [83–85], we cannot specify mechanisms through which differences in MSA characteristics like NIDU prevalence or racial residential segregation might affect AIDS incidence or mortality among heterosexuals. Similarly, we cannot specify the time lags between cause and effect for any pathways that might be causal, which could mean that the effects of slower-acting causal variables would be missed in these analyses. Also, all our variables are subject to measurement error, which may limit the accuracy of our analyses, and our estimates of numbers of NIDUs have not been subjected to rigorous validation. In constructing the dependent variables, for example, we divided by the total adult population to create rate estimates because no data on MSM populations in 2006–2008 were available. This may have overestimated the dependent variables for MSAs with particularly large MSM populations. Because data on deaths from AIDS were not available, we used mortality among people living with AIDS as our denominator—which will erroneously include some deaths unrelated to the disease. If missing data were correlated with variables we studied, this might have affected observed relationships. Further research using data for all years during this period for all variables might also strengthen our analytic ability to study these issues—but this would require having estimates for MSM HIV prevalence and population prevalence that would be difficult to estimate for the MSAs.

This is a study of the *universe* of large U.S. MSAs with available data rather than of a *sample*. Samples let researchers make statistical inferences to indicate the uncertainty about whether their findings accurately describe relationships within the universe from which the sample was taken. Our findings are descriptive of the relationships of the measured variables in this universe. They do not, however, imply that these findings can necessarily be extended to smaller MSAs, nonmetropolitan localities, and other periods or other countries.

Associations between the independent variables and the outcome variables might come about through any of the following processes: (1) They might be spurious—that is, both the values of the independent variables and those of the dependent variables might result from some prior unobserved causal variable; (2) The independent variables might have affected rates of HIV incidence among heterosexuals; or (3) The independent variables might have affected rates of access to and adherence to antiretroviral therapy or in other ways affected rates of disease progression to AIDS or death among heterosexuals infected with HIV.

Our ability to study sexual bridging from MSM and PWID through heterosexual (and bisexual) NIDUs and then to other heterosexuals is greatly limited by the lack of data about whether people diagnosed with AIDS are NIDUs. (This leads to inability to determine whether heterosexuals with AIDS who die were NIDUs.) This is because the U.S. HIV surveillance system does not collect data on whether people with HIV are NIDUs.

This exploratory study at the MSA level of analysis showed that efforts to reduce HIV transmission between PWID and NIDUs were associated with reduced AIDS and AIDS-related mortality among heterosexuals. Research on bridging mechanisms and pathways at the community, network, and individual levels, including investigation of possible alternative MSA-level predictors that might produce these associations, is clearly needed. Research into whether interventions in one key population affect HIV epidemics in other key populations will be of high policy relevance and should be a priority.

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