Published in final edited form as:

Soc Sci Med. 2015 August ; 139: 26–35. doi:10.1016/j.socscimed.2015.06.024.

Syndemics of psychosocial problems and HIV risk: A systematic review of empirical tests of the disease interaction concept

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Abstract

In the theory of syndemics, diseases co-occur in particular temporal or geographical contexts due to harmful social conditions (*disease concentration*) and interact at the level of populations and individuals, with mutually enhancing deleterious consequences for health (*disease interaction*). This theory has widespread adherents in the field, but the extent to which there is empirical support for the concept of disease interaction remains unclear. In January 2015 we systematically searched 7 bibliographic databases and tracked citations to highly cited publications associated with the theory of syndemics. Of the 783 records, we ultimately included 34 published journal articles, 5 dissertations, and 1 conference abstract. Most studies were based on a cross-sectional design (32 [80%]), were conducted in the U.S. (32 [80%]), and focused on men who have sex with men (21 [53%]). The most frequently studied psychosocial problems were related to mental health (33 [83%]), substance abuse (36 [90%]), and violence (27 [68%]); while the most frequently studied outcome variables were HIV transmission risk behaviors (29 [73%]) or HIV infection (9 [23%]). To test the disease interaction concept, 11 (28%) studies used some variation of a product term, with less than half of these (5/11 [45%]) providing sufficient information to interpret interaction both on an additive and on a multiplicative scale. The most frequently used specification (31 [78%]) to test the disease interaction concept was the sum score corresponding to the total count of psychosocial problems. Although the count variable approach does not test hypotheses about interactions between psychosocial problems, these studies were much more likely than others (14/31 [45%] vs. 0/9 [0%]; $\chi^2=6.25$, $P=0.01$) to incorporate language about “synergy” or “interaction” that was inconsistent with the statistical models used. Therefore, more evidence is needed to assess the extent to which diseases interact, either at the level of populations or individuals, to amplify HIV risk.

Keywords

AIDS/HIV; social determinants

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1 Introduction

The poor and underserved often face a complex constellation of health and social problems that conspire to undermine their wellbeing. The term “syndemic” was proposed by Singer (1994) to call attention to these issues, with a special focus on the frequently co-occurring problems of substance abuse, violence, and HIV (Singer, 1996, 2006). As originally described and summarized in several publications (Singer, 1994, 1996, 2006), two characteristics are central to his conceptualization of a syndemic. First, diseases co-occur in particular temporal or geographical contexts due to harmful social conditions (*disease concentration*). Second, diseases interact at the level of populations and individuals, with mutually enhancing deleterious consequences for health (*disease interaction*). As summarized by Singer and Clair (2003) in one of the more recent restatements of the theory, “a syndemic is a set of intertwined and mutually enhancing epidemics involving disease interactions at the biological level that develop and are sustained in a community/population because of harmful social conditions and injurious social connections” (p.429). In one of the first empirical studies in this literature, Stall et al. (2003) attempted to extend conceptual thinking about syndemics to understanding HIV risk among men who have sex with men in the U.S. While their analysis did not provide evidence of interacting epidemics, they did show that psychosocial problems were frequently co-occurring and that men with a greater number of psychosocial problems were more vulnerable to HIV.

The theory of syndemics is consistent with previously published theories that have been deployed to explain the existence of health disparities, including the social origins of greater health risks among the marginalized and dispossessed (Farmer, 1999, 2004; Link & Phelan, 1995; Scheper-Hughes & Bourgois, 2004) and the role of historically ingrained forces in exerting conjoint influences on HIV risk (Farmer, 1996; Farmer, Lindenbaum, & Good, 1993). The harmful effects of co-occurring psychosocial problems have also been highlighted in other literatures that have evolved largely in parallel to the literature on syndemics, including the concepts of multimorbidity (van den Akker, Buntinx, & Knottnerus, 1996; van den Akker et al., 1998) and dual diagnosis (Drake et al., 1991; Lehman, Myers, & Corty, 1989). In this regard, the concept of disease concentration is empirically well established. However, the extent to which there is empirical support for disease interaction in HIV risk remains unclear. While the theory of syndemics would remain useful for its conceptualization of disease concentration even if the concept of disease interaction were to fail empirical testing, this is an important gap in the literature because of the overall programmatic and policy importance of the syndemics orientation. A decade ago, Gerberding (2005) described U.S. Centers for Disease Control and Prevention (CDC) efforts to transform health protection research with the aim of reducing health disparities. Although complex systems theories and a syndemics orientation were explicitly incorporated into her vision for the CDC’s future, she also noted that “application of complex systems theories or syndemic science to health protection challenges is in its infancy” (p.1405). While public health researchers motivated by an interest in improving health and wellbeing in vulnerable populations have made important progress in utilizing and understanding the theory of syndemics, to date there has been no systematic summary of how the concept of disease interaction in syndemic theory has been tested in empirical work.

2 Conceptual framework

The concept of disease interaction has had a long and controversial history in the epidemiologic literature (Blot & Day, 1979; Greenland, 2009; Kaufman, 2009; Kupper & Hogan, 1978; Rothman, 1974, 1976a; Rothman, Greenland, & Walker, 1980; Saracci, 1980; Siemiatycki & Thomas, 1981; VanderWeele, 2009a; Walter & Holford, 1978). Summarized succinctly, there are two different concepts of interaction that should be distinguished: the theoretical concept of causal interaction (formerly described as “biologic interaction”), and statistical interaction. The notion of *causal interaction* is derived from a theoretical concept of causation and was originally proposed by Rothman (1974), who formally defined it as a deviation from additivity of the risk differences of the causal risk factors under investigation. A greater than additive deviation is typically described as synergy, or a positive or super-additive interaction; while a less than additive deviation is typically described as antagonism, or a negative or sub-additive interaction (Rothman, 1974, 1976b; VanderWeele & Knol, 2014). *Statistical interaction*, on the other hand, refers to a situation in which an additional parameter is required for a statistical model to adequately describe joint exposure to the risk factors under investigation. In contrast to the concept of causal interaction, which necessarily entails a concern about deviation from additivity, statistical interaction is dependent upon the underlying scale: if an additive model is employed, a statistically significant product term indicates deviation from additivity, whereas a statistically significant product term in a multiplicative model indicates deviation from multiplicativity.

In a linear (e.g., least squares) regression model fitted to a dataset in order to better understand the relationship between a dichotomous outcome variable Y and two dichotomous explanatory variables X_1 and X_2 , a simple test for causal interaction between X_1 and X_2 in the absence of confounding might proceed as follows:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$$

where, for example, Y may represent HIV infection or a risk factor for HIV infection, e.g., condomless sexual intercourse with a non-primary partner; while X_1 and X_2 may represent psychosocial problems such as substance abuse and intimate partner violence. In this model, it is apparent that the main effects of X_1 and X_2 , assuming that there is no effect of the other covariate, are given respectively as:

$$\begin{aligned} Y_{X_1=1, X_2=0} - Y_{X_1=0, X_2=0} &= \beta_0 + \beta_1 - \beta_0 = \beta_1 \\ Y_{X_1=0, X_2=1} - Y_{X_1=0, X_2=0} &= \beta_0 + \beta_2 - \beta_0 = \beta_2 \end{aligned}$$

and that the combined effect of X_1 and X_2 , compared with no effect of X_1 and X_2 , is given by adding the estimated regression coefficients on X_1 , X_2 , and their product $X_1 X_2$:

$$Y_{X_1=1, X_2=1} - Y_{X_1=0, X_2=0} = \beta_0 + \beta_1 + \beta_2 + \beta_3 - \beta_0 = \beta_1 + \beta_2 + \beta_3$$

If $\beta_3 > 0$, then the combined effect of X_1 and X_2 is greater than their sum ($\beta_1 + \beta_2$) and there is said to be a greater than additive deviation, or a positive or super-additive interaction. If $\beta_3 < 0$, then the combined effect of X_1 and X_2 is less than their sum ($\beta_1 + \beta_2$) and there is said to be a less than additive deviation, or a negative or sub-additive interaction. If $\beta_3 = 0$, then the combined effect of X_1 and X_2 is equal to the sum ($\beta_1 + \beta_2$) and there is said to be no deviation from additivity, or no interaction; by dint of their inclusion in a regression model that is linear in its parameters, X_1 and X_2 are said to have “additive” effects on the outcome.

Although use of least squares to model a *dichotomous* outcome variable is generally shunned by physicians and epidemiologists, it is standard practice among economists and is frequently referred to as the linear probability model (Angrist & Pischke, 2009; Wooldridge, 2010). Two minor disadvantages of the linear probability model are that it generates heteroskedastic standard errors and predicted values of Y that may lie outside of the interval $[0, 1]$ (Goldberger, 1964). However, as Wooldridge (2010) notes, “If the main purpose is to estimate the partial effect of [the independent variable] on the response probability, averaged across the distribution of [the independent variable], then the fact that some predicted values are outside the unit interval may not be very important” (p.455). In addition, any potential bias is lessened as the relative proportion of predicted probabilities lying inside the unit interval increases (Horrace & Oaxaca, 2006). And finally, the standard errors can easily be corrected using heteroskedasticity-consistent robust estimates of variance (Huber, 1967; White, 1980). Furthermore, a considerable advantage of the linear probability model that is germane to testing the theory of syndemics is that it is an additive model; therefore, given the usual assumptions, an estimate for the parameter β_3 is a test for causal interaction and summarizes the extent to which a departure from additivity is observed. The estimated regression coefficients can easily be interpreted as marginal effects with no additional computation required.

Although the linear probability model has many attractive features to recommend it, because of the disadvantages described above, the logit transformation is generally favored by many in the field:

$$E[Y|X_1, X_2] = \ln \left[\frac{e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2}}{1 + e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2}} \right]$$

where it is now the *logit* that is linear in its parameters and the log odds of the outcome are given by

$$\ln \left(\frac{\frac{e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2}}{1 + e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2}}}{1 - \frac{e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2}}{1 + e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2}}} \right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$$

In the logit model, it is apparent that the main effect of X_1 , assuming that there is no effect of X_2 , is given as the exponentiated estimated regression coefficient on X_1 :

$$\ln(OR_{X_1=1}) = \ln(odds_{X_1=1, X_2=0}) - \ln(odds_{X_1=0, X_2=0}) = \beta_0 + \beta_1 - \beta_0 = \beta_1$$

or,

$$OR_{X_1=1} = e^{\beta_1}$$

The main effect of X_2 , assuming that there is no effect of X_1 , is similarly given as

$$\ln(OR_{X_2=1}) = \ln(odds_{X_2=1, X_1=0}) - \ln(odds_{X_2=0, X_1=0}) = \beta_0 + \beta_2 - \beta_0 = \beta_2$$

or,

$$OR_{X_2=1} = e^{\beta_2}$$

and the combined effect of X_1 and X_2 , compared with no effect of X_1 and X_2 , is given by multiplying the odds ratios on X_1 , X_2 , and the product X_1X_2 :

$$\begin{aligned} \ln(OR_{X_1=1, X_2=1}) &= \ln(odds_{X_1=1, X_2=1}) - \ln(odds_{X_1=0, X_2=0}) = \beta_0 + \beta_1 + \beta_2 + \beta_3 - \beta_0 \\ &= \beta_1 + \beta_2 + \beta_3 \end{aligned}$$

Applying an exponential transformation,

$$OR_{X_1=1, X_2=1} = e^{\beta_1 + \beta_2 + \beta_3} = OR_{X_1} \times OR_{X_2} \times OR_{X_1X_2}$$

It is straightforwardly observed that the logit regression model is a multiplicative model, and an estimate for the parameter β_3 is a test for multiplicative interaction. If $\beta_3 > 0$, then the combined effect of X_1 and X_2 is greater than the product of the estimated odds ratios on X_1 and X_2 and there is said to be a positive deviation from multiplicativity. If $\beta_3 < 0$, then the combined effect of X_1 and X_2 is less than the product of the estimated odds ratios on X_1 and X_2 and there is said to be a negative deviation from multiplicativity. Finally, if $\beta_3 = 0$, then the combined effect of X_1 and X_2 is equal to the product of the estimated odds ratios on X_1 and X_2 and there is said to be no deviation from multiplicativity; X_1 and X_2 can still be said to be “additive,” but on the logarithmic scale. Certainly interaction can be positive on one scale but negative on another, or present on one scale but absent on another (Kupper & Hogan, 1978; Walter & Holford, 1978). For example, VanderWeele and Knol (2014) discuss a study on cigarette smoking, asbestos exposure, and lung cancer by Hilt et al. (1986) in which there is evidence of a positive interaction on the additive scale but a negative interaction on the multiplicative scale.

The preceding discussion about causal vs. statistical interaction, and additivity vs. multiplicativity, has immense relevance for the theory of syndemics. Singer (1994, 1996, 2006) did not formalize his theory's predictions about disease interaction, but his writing appears to imply that it entails causal interaction between psychosocial problems and therefore concern about the extent to which the data reveal positive deviation from additivity: "At the population level, the term syndemic refers to two or more epidemics interacting synergistically and contributing as a result to excess disease load in a population... At the individual level, the term syndemic refers to the health consequences of the biological interactions that occur when two or more diseases or health conditions are co-present in multiple individuals within a population" (Singer, 2006) (pp.39–40). Yet, although there is considerable support for the concept of disease concentration, the extent to which there is empirical support for the concept of disease interaction remains unclear. To address this gap in the literature, we conducted a systematic review of empirical research on syndemics, with a specific focus on understanding how the concept of disease interaction has been operationalized and tested.

3 Methods

3.1 Ethics statement

The study protocol was submitted for ethical review by the Partners Human Research Committee, but review was declined on the grounds that no study procedures involved human subjects research.

3.2 Systematic search protocol

The study protocol for this systematic review was not pre-registered. The systematic evidence search was conducted on January 2, 2015 with the aim of identifying empirical studies testing the disease interaction concept in the theory of syndemics. Seven bibliographic databases were used: Anthropological Index Online, Anthropological Literature, AnthroSource, the Cumulative Index to Nursing and Allied Health Literature, Embase, ProQuest Dissertations & Theses, and PubMed. The simple search "syndemic [all fields]" was applied to each database. Because some studies may be motivated by the syndemics hypothesis without specifically mentioning the term "syndemic" in any of the searchable field descriptions, we also used the Science Citation Index to identify publications citing either Singer (1994) or Singer and Clair (2003), which are his two most highly cited journal articles associated with the theory of syndemics (with 116 and 126 citations, respectively, at the time of this writing). After all citations were imported into EndNote reference management software (version X6, Thomson Reuters, New York, NY), we excluded duplicate references and reviewed the titles and abstracts to identify potentially relevant reports for inclusion in the study. The full texts of these reports were examined for a final determination of relevance for inclusion. Dissertations and theses were mapped to published journal articles where applicable. Selected reports had to have met each of the following criteria: (a) the study involved human subjects research, and (b) the study described an empirical test of the disease interaction concept in the theory of syndemics. The latter inclusion criterion was relatively broad. On this basis we included many studies that purported to test the theory of syndemics but, as will be made clearer in the below

discussion, did not actually conduct an appropriate test of interaction. We believe that qualitative research can yield robust data for understanding syndemics in vulnerable populations, but since a formal meta-synthesis (meta-ethnography) was beyond the scope of our review, we elected to exclude these articles. We also excluded commentaries and reviews that did not involve human subjects research. All disagreements were resolved by consensus. There were no language restrictions.

3.3 Data analysis

For each selected report, we extracted data on the study population, study design, sample size, and a description of the empirical test of the disease interaction concept. Specifically, we extracted the terms the authors employed to describe the test, e.g., by including the total count of psychosocial problems as a continuous variable in a logit regression model, or by specifying a product term in a linear regression model. If the test involved inclusion of a product term in a regression model, we assessed whether the presentation yielded sufficient information to interpret interaction on an additive and on a multiplicative scale (Knol et al., 2009; Knol & VanderWeele, 2012). Following the generally accepted rule of thumb that 5–10 events are required per covariate in logit or Cox regression models (Peduzzi et al., 1995; Peduzzi et al., 1996; Vittinghoff & McCulloch, 2007), we assessed whether or not each paper could have supported fully saturated regression models with product terms between all of the psychosocial problems considered. Because the article by Stall et al. (2003) is the empirical study most frequently associated with the theory of syndemics (with 256 citations identified by Science Citation Index at the time of this writing), we collected data on whether their work was cited, whether any of its limitations were mentioned, and whether its precedent was specifically invoked to motivate the analysis. Finally, we identified instances in which language related to “synergy,” “interaction,” or “additivity” were employed by the study authors.

4 Results

Of the 783 records returned from the electronic database search and the citation search, 266 duplicates were excluded, yielding 517 titles and abstracts to review (Figure 1). We excluded 379 records on the basis of the title and abstract review alone; most of these were excluded because they were based on qualitative study designs or contained empirical data not relevant to syndemics. Full text appraisal was completed for 138 records. Of these, 102 did not meet inclusion criteria, typically because they contained empirical data not relevant to syndemics. We also included 4 additional journal articles identified outside of the systematic search: one cited Singer and Clair (2003) but for unclear reasons was not captured in the Science Citation Index citation search, and the other 3 were published after the evidence search was conducted. The final sample included 40 records: 34 journal articles, 5 dissertations (one of which was mapped to a published journal article), and 1 conference abstract (see Appendix). Summary characteristics of the sample are provided in Table 1. Most studies were based on a cross-sectional design (32 [80%]), conducted in the U.S. (32 [80%]), and focused on men who have sex with men (21 [53%]). The median sample size was 596 (interquartile range, 445–1425). No studies were based on experimental or quasi-experimental designs, placing all at some risk of bias.

All studies (40/40 [100%]) reported a statistically significant association between one or more psychosocial problems (sometimes referred to as “syndemic exposures”) and one or more outcome variables. The most frequently studied psychosocial problems were related to mental health (33 [83%]), substance abuse (36 [90%]), and violence (27 [68%]). The most frequently studied outcome variables were HIV transmission risk behaviors (29 [73%]) or HIV infection (9 [23%]), but several studies specified mental health or substance use variables as the outcomes. Of the studies focused on HIV infection, only three (3/9 [33%]) studies identified incident HIV infections during the course of longitudinal follow-up, whereas the rest (6/9 [66%]) of the studies assessed prevalent HIV infection.

To test the disease interaction concept, 11 (28%) studies used some variation of a product term. All of these studies (11/11 [100%]) employed a multiplicative regression model. Statistically significant product terms were estimated in most of these studies (8/11 [73%]), suggesting departures from multiplicativity and possibly departures from additivity. However, less than half of these (5/11 [45%]) provided sufficient information to interpret interaction both on an additive and on a multiplicative scale. None of these studies characterized their findings using language about synergy or interaction that was inconsistent with the statistical models used. Of the studies included in this review, only Herrick (2011) formally calculated measures of additive interaction -- such as the relative excess risk due to interaction (RERI) (Rothman, 1974) -- and found that psychosocial problems did in fact have greater than additive associations with condomless anal intercourse. Sixteen (40%) studies would have permitted fully saturated regression models according to generally accepted rules of thumb, given their sample sizes and number of psychosocial problems considered. These studies had a median sample size of 788 (interquartile range [IQR], 493–2989), compared to a median sample size of 577 among the studies that would not have permitted fully saturated regression models (IQR, 322–926) (nonparametric test on the equality of medians, $\chi^2=0.94$; $P=0.33$).

The most frequently used specification to test the disease interaction concept was the “syndemic count variable,” i.e., sum score corresponding to the total number of psychosocial problems (31 [78%]). Compared to studies that used other specifications (e.g., product term in a multiplicative model), the studies that employed the count variable approach were much more likely to characterize their findings as demonstrating that psychosocial problems had “additive associations” with the outcomes of interest (19/31 [62%] vs. 1/9 [11%]; $\chi^2=7.03$, $P=0.008$). Although no formal tests of interaction were used in these studies, they were also much more likely to include language about “synergy” or “interaction” that was inconsistent with the statistical models used: 14/31 (45%) of these studies employed such language, compared to 0/9 (0%) of the others ($\chi^2=6.25$, $P=0.01$). The studies that used the count variable approach were more likely to have cited Stall et al. (2003) (27/31 [87%] vs. 5/9 [56%]; $\chi^2=4.34$, $P=0.04$). Nearly half of these (11/27 [41%]) specifically appealed to their precedent of testing the hypothesis in this manner, but only 4/27 (15%) mentioned limitations related to interpreting the count variable approach.

5 Discussion

In this systematic review of empirical research on syndemics, all studies demonstrated statistically significant associations between co-occurring psychosocial problems and one or more (typically HIV-related) outcomes. However, fewer than one in three studies used an empirical specification that appropriately assessed the extent to which psychosocial problems *interact* to magnify HIV risk. Therefore, the extent to which the literature supports the concept of disease interaction, a central aspect of the theory of syndemics, is unclear. Our findings have important implications both for academic research as well as for HIV prevention programs.

The most commonly employed specification in this literature was the count of psychosocial problems. In many ways this specification resembles a comorbidity index, without the weighting functions and/or supporting psychometric analyses that typically support such indices (de Groot et al., 2003). When the range of predicted probabilities is between 0.3 and 0.7, or when the range of predicted probabilities is small (e.g., between 0.05 and 0.1), then -- assuming the values of other covariates are held constant -- the relationship between the outcome and the count of psychosocial problems is approximately linear (Long, 1997). Under these conditions, the effect on the outcome of an increase from 1 psychosocial problem to 2 psychosocial problems is equal to the effect on the outcome of an increase from 2 psychosocial problems to 3 psychosocial problems, and incremental changes in the number of psychosocial problems might be said to have an “additive” impact on the outcome. Some researchers have specified the number of psychosocial problems as a categorical variable (Stall et al., 2003); the extent to which ascending odds ratios across exposure categories can be interpreted as evidence of an “additive” impact on the outcome would again be contingent on the pattern of predicted probabilities, assuming the values of other covariates are held constant. However, it should also be emphasized, as discussed previously, that, in a linear model with no product terms, *by definition* the explanatory variables have additive effects on the outcome. Therefore it is mathematically unclear what additional information a count variable would add to this interpretation.

The count variable approach has received muted criticism in the syndemics literature for being too “simplistic” (Gebrekristos, 2010; Halkitis et al., 2013). Such specifications assume that each psychosocial problem has an equally weighted effect on the outcome (Guadamuz et al., 2014; Sibley, 2011), e.g., the impact of a positive screen for depression is assumed to be equal to the impact of having a history of victimization by an intimate partner. When specified as a categorical variable, each psychosocial problem still receives equal weighting in that incremental changes in the number of exposures are interpreted as having effects on the outcome that are independent of the type of exposure. These assumptions are likely untenable. For example, in a reanalysis of data from Parsons, Grov, and Golub (2012) (who themselves had employed the count variable approach), Starks et al. (2014) highlighted these and other psychometric assumptions and used latent factor analysis to demonstrate that the assumption of equal factor loadings reduced model fit. Latent factor approaches, such as those employed by Starks et al. (2014) and two other studies included in our review (Halkitis et al., 2013; Mustanski et al., 2014), may suggest ways to improve models in settings where this assumption is unwarranted. For example, researchers planning to adopt

the count variable approach in an intended analysis may wish to first conduct a latent factor analysis to confirm that a single parameter model would yield adequate fit.

Most importantly, the total count of psychosocial problems does not assess the extent of deviation from additivity of the risk differences of the causal exposures under investigation and therefore *does not shed light on the extent of disease interaction*. When Singer and Clair (2003) reported data on counts of psychosocial problems from a study of persons who inject drugs living in three New England cities, they specifically noted this limitation, stating, “While the data do not enable an assessment of disease interaction, collecting biological and health data that would allow such an assessment with this population seems warranted” (p. 433). In the studies included in our systematic review, this notable limitation was highlighted only by Batchelder (2012) (“The additive conceptualization of syndemics does not enable the assessment of interactions between variables” [p.44]) and Guadamuz et al. (2014) (“a count variable does not consider potential interactions between its components” [p.2094]) but has otherwise been largely ignored in the literature. In a regression framework, assessing deviation from additivity requires the use of product terms between the two or more exposures being considered. However, only a minority of studies used a product term to assess for disease interaction.

If the majority of studies motivated by the theory of syndemics are utilizing the count variable approach to estimate associations between psychosocial problems and HIV risk, what are the principal challenges to future studies incorporating tests of the disease interaction concept into their analyses? First, we believe future studies have an opportunity to extend the findings of Stall et al. (2003) by not only considering the extent to which psychosocial problems in the aggregate are associated with HIV risk but also considering the extent to which psychosocial problems *interact* to intensify HIV risk. Second, an important challenge is that estimation of statistically significant product terms may, under certain conditions, require large sample sizes. For example, a Cox proportional hazards regression model fitted to the data used in Mimiaga et al. (2015), with 259 seroconversions during study follow-up, would have permitted approximately 25–50 covariates under assumptions of differing conservatism (Peduzzi et al., 1995; Peduzzi et al., 1996; Vittinghoff & McCulloch, 2007). A fully saturated model would have required a total of 120 covariates, easily exceeding what this specific dataset could reasonably be expected to bear. Even if a dataset could incorporate a full set of product terms, the issue of multiple comparisons may need to be considered. Problems with statistical power may be especially severe if the explanatory variables are collinear with each other (Pitpitan et al., 2013) -- which is likely to be the case in this literature, given that collinearity is implied by the concept of disease concentration. Unfortunately, implementing large studies of syndemics and incident HIV infection may not be feasible given current funding constraints. Furthermore, given the scope of the various syndemics and the vulnerable populations involved, it would be inadvisable, from a public health perspective, to recommend inaction until definitive studies are published. However, it is also important to note that the data requirements are not excessively burdensome: our calculations, based on study sample sizes and event counts, and drawing on generally accepted rules of thumb, suggest that nearly one-half of the studies included in our review would have permitted a fully saturated model. Investigators can also

make decisions -- based on theoretical models or previously published empirical findings -- about excluding certain product terms from the regression models (thereby reducing the degrees of freedom), and prospectively registering their analysis plans in the interest of transparency (Dal-Re et al., 2014). Third, while the use of the count variable approach appears to be unique to this literature, unclear understanding of the distinctions between causal vs. statistical interaction is not unique to the field of HIV prevention. Even though multiplicative models do not have direct relevance for assessing departures from additivity (VanderWeele & Knol, 2014), most studies assessing for interactions simply include a product term in a multiplicative model without undertaking the additional computation that is required; departures from additivity are rarely assessed (Knol et al., 2009). For example, in a study published in the *American Journal of Kidney Diseases*, Weiner et al. (2006) included a product term in a multivariable Cox proportional hazards regression model. Observing the estimated regression coefficient on the product term between chronic kidney disease and cardiovascular disease to lack statistical significance, the authors concluded that the interaction “was only additive and not synergistic” (p.398) -- when their model in fact only tested for a departure from multiplicativity, not a departure from additivity.

5.1 Public health relevance

The public health relevance of the above discussion can be understood by considering a simple syndemic model in which two conditions (depression and substance abuse) co-occur, are determined by poverty, and interact synergistically to increase HIV risk (Figure 2a). Both depressive and substance abuse disorders are highly prevalent among persons at risk for HIV acquisition and among persons with HIV (Bing et al., 2001; Riley et al., 2014; Tsai et al., 2013a; Tsai, 2014; Tsai et al., 2015; Weiser et al., 2006; Weiser, Wolfe, & Bangsberg, 2004), and the need for effective dual diagnosis interventions for both primary and secondary HIV prevention is widely acknowledged (Batki, 1990; Fisher & Smith, 2009; Sikkema et al., 2010; Walkup et al., 2008). General consensus in the field (Blot & Day, 1979; Kupper & Hogan, 1978; Rothman, 1986; Rothman, Greenland, & Walker, 1980; Saracci, 1980) suggests that an analysis that assesses for departures from additivity would more appropriately reflect the causal structure of the interaction between depression and substance use. Such an analysis would also be more relevant from the perspective of public health and/or clinical decision making (Vandenbroucke et al., 2007): a departure from additivity would imply that a person with both depression and substance use has a risk of HIV that is greater than what would be predicted from the independent effects of the two exposures alone. By implication, it is possible that ameliorating depression may have a greater impact on reducing HIV risk than would otherwise be predicted in a model where no synergistic effects were observed. Such a finding would be of substantive interest to public health practitioners faced with important decisions about allocating scarce resource across multiple sectors. It is also apparent that knowing whether an increase from 1 psychosocial problem to 2 psychosocial problems has an equal effect on HIV risk compared to an increase from 2 psychosocial problems to 3 psychosocial problems (i.e., knowing whether incremental changes in the number of psychosocial problems have -- to adopt the terminology that is typically used in the literature -- an “additive” impact on HIV risk) provides less valuable information from a public health perspective. A second reason for why interaction on the additive scale should be of primary concern is that, in a multiplicative

model, the effect of a risk factor on the outcome cannot be understood without knowing the values of all of the other covariates (Ai & Norton, 2003). This concern would be particularly acute when it comes to making decisions based on observational studies where many covariates (e.g., confounders) are included in the regression models. As was aptly summarized by Greenland and Rothman (1998): “if the excess case loads produced by each factor are not additive, one must know the levels of all the factors in order to predict the public-health impact of removing or introducing any one of them” (p.341).

An entirely separate concept that has concerned many investigators in the field, frequently implied in the literature on syndemics but not formally stated, is *not* that psychosocial problems have synergistic adverse effects but that they may be *mutually causal* (Figure 2b). In their discussion, for example, Guadamuz et al. (2014) state that, “While current prevention approaches tend to focus on one health issue, integration and simultaneous implementation of prevention programs for multiple conditions needs serious consideration” (p.2094). This orientation does not necessarily follow from the theory of syndemics as elaborated by Singer (1994, 1996, 2006), nor does an analysis that relies on the count variable approach yield useful evidence to motivate this concern. However, it is consistent with clinical thinking on the etiology of dual diagnosis and the reciprocal associations between mental and substance use disorders (Kessler, 2004; Mueser, Drake, & Wallach, 1998). There is widespread consensus in the field that treatment in the setting of dual diagnosis should be coordinated and integrated (Drake et al., 2004; Horsfall et al., 2009), because depression cannot be ameliorated without also reducing substance abuse and vice versa if the two conditions are mutually causal. However, it is worth emphasizing that depression and substance abuse may each potentiate the effect of the other without being mutually causal (Figure 2a), or depression and substance abuse may be mutually causal without exerting synergistic adverse effects (Figure 2b) (and there is also a third possibility: that they may both act synergistically and be mutually causal).

Finally, it should also be noted that both models (Figures 2a and 2b) imply that -- assuming the causal pathway between poverty and HIV risk is not fully mediated by depression and substance use -- an intervention addressing either depression or substance use, or a combination of both together, might be ineffective in reducing HIV risk unless the intervention also addressed poverty as the causative factor of both psychosocial problems as well as of HIV risk. Instead, interventions targeting the structural factors conditioning people’s risk for HIV would be needed (Tsai, 2012). These simple models are consistent with the fundamental cause concept elaborated by Link and Phelan (1995). In brief, a fundamental social cause influences multiple risk factors and disease outcomes, enables some people to leverage their resources to either avoid risk factors or minimize the adverse health impacts of disease, and reproduces health disparities over time through the organic production of new pathways to disease (Link & Phelan, 1995; Phelan et al., 2004). (Although the bodies of literature on fundamental causes and syndemics seem to have evolved independently of each other, a reasonable synthesis of the two concepts would state that syndemics are rooted in fundamental causes.) Thus, interventions focused solely on mediating mechanisms such as depression or substance abuse -- even if they are targeted at all of the exposures in concert -- may fail to reduce health disparities by leaving the

fundamental cause unaddressed. Even if the causal pathway between the fundamental cause and HIV risk is fully mediated by the intervening mechanisms and these mechanisms were to be blocked by effective integrated treatment, it is possible that new mechanisms may unfold over time to open up additional pathways to disease. While we are unaware of studies providing empirical support for this hypothesis in the context of the literature on HIV risk, Hatzenbuehler, Phelan, and Link (2013) offer an illuminating conceptual discussion on fundamental causes of disparities in population health and provide a concrete example of how racism remains a fundamental cause of health disparities in the U.S. due to the changing mechanisms of slavery, Jim Crow laws, aversive racism, and stereotype threat.

5.2 Recommendations

Our recommendations for the syndemics literature can be summarized in Table 2. While the count variable approach may be useful in generating findings about how multiple exposures are associated with HIV risk in the aggregate (subject to the limitations as noted previously), the use of product terms in multivariable regression models has greater utility for advancing our understanding about how exposures *interact* to produce excess HIV risk. Regarding studies that employ the product term specification, epidemiologists have called for an end to the practice of assessing interactions based purely on product terms in multiplicative models (Greenland, 2009; Rajaleid, Janszky, & Hallqvist, 2011). With additional computation a multiplicative model like the logit regression model can yield output that is useful for assessing departures from additivity, as was done in the study by Herrick (2011). These measures include the RERI; the attributable proportion due to interaction (AP), which is a derivative measure of the RERI; and the synergy index (S) (Rothman, 1974, 1976b; Rothman, 1986). Computation of standard errors for the RERI is straightforward and can be done using many standard software packages (Andersson et al., 2005; Assmann et al., 1996; Kallberg, Ahlbom, & Alfredsson, 2006; Lundberg et al., 1996; Richardson & Kaufman, 2009; VanderWeele & Knol, 2014). Finally, inclusion of a product term in an additive model can straightforwardly evaluate for a departure from additivity. The linear probability model (Angrist & Pischke, 2009; Wooldridge, 2010) with heteroskedasticity-consistent robust estimates of variance (Huber, 1967; White, 1980) is easily employed for this purpose.

These recommendations necessarily raise further questions about the persuasiveness of varying levels of evidence, how to interpret potentially divergent findings in the literature, and how to effectively address an important public health issue with some urgency. The well-known hierarchy of evidence, in which randomized studies occupy a position of privilege (Atkins et al., 2004; Canadian Task Force on the Periodic Health Examination, 1979; Guyatt et al., 2002; Sackett, 1986), certainly applies to the literature on syndemics. Among observational studies, longitudinal studies are generally privileged over cross-sectional studies, although analyses of cross-sectional data that employ robust econometric methods to address unobserved confounding (Altonji, Elder, & Taber, 2005; Angrist, Imbens, & Rubin, 1996; Gormley et al., 2005) can often be more compelling than conventional analyses of longitudinal data. Ultimately, in the (appropriate) absence of a study that randomizes individual participants to be “treated” with co-occurring syndemic conditions and then follows them to observe for synergistic effects on the incidence of HIV acquisition, the most persuasive evidence for the concept of disease interaction would

probably be derived from the reverse: a study that randomized participants with co-occurring syndemic conditions to receive effective treatment for one or more of these conditions and then followed them to assess the extent to which the treatments synergistically improved HIV-related health behaviors or subsequent psychosocial outcomes of interest, or were synergistically protective against future HIV acquisition. A similar strategy has been employed in an attempt to validate conceptual models of depression and HIV transmission risk behavior (Tsai et al., 2013b). Such intervention studies would, assuming clinical equipoise, also have the benefit of providing the field with rigorous data to inform clinical and programmatic decisions to address an urgent public health issue instead of delaying action until the academic debate is settled. At the population level, experimental evidence will be hard to come by, and the strongest levels of support will likely be obtained through quasi-experimental designs (Meyer, 1995). Large-scale surveillance programs that incorporate both survey and biomarker data collection (Tanser et al., 2013) may provide the most promising settings in which to explore these issues at the population level in more detail.

5.3 Limitations

Interpretation of our findings is subject to three important limitations. First, while we attempted to conduct a comprehensive literature search, it is possible that we may have missed some relevant records. While our search strategy would have successfully identified records in which the authors failed to cite Singer's work if the concept of syndemics was invoked in a searchable field (e.g., Safren et al. (2010)), our search strategy would *not* have identified records where the authors did not use the term "syndemic" in a searchable field and *also* failed to cite Singer's work. The previously-cited commentary by Gerberding (2005) is a relevant example of such a record (although it would have been excluded from our analysis due to lack of original data). Second, while there was remarkable consistency across the studies included in our review in that all demonstrated statistically significant associations between one or more psychosocial problems and the outcomes of interest, our summary conclusions could have been driven by non-publication of non-statistically significant findings (Rosenthal, 1979; Sterling, 1959). However, due to heterogeneity in the study designs employed, we did not attempt to formally assess for publication bias. Third, despite the consistency with which studies estimated statistically significant associations between co-occurring psychosocial problems and HIV risk, the robustness of the evidence base supporting the concept of disease interaction in the field of HIV prevention is relatively limited. Most studies were conducted in the U.S., were based on cross-sectional designs, and were focused on men who have sex with men. While qualitative studies exploring psychosocial health problems in sub-Saharan Africa have been informed by the theory of syndemics (Daftary, 2012; Hatcher et al., 2014; Mendenhall & Norris, 2015), only two studies included in our review were conducted in sub-Saharan Africa -- home to more than two-thirds of the 35.3 million persons living with HIV worldwide (Joint United Nations Programme on HIV/AIDS, 2013). More research, preferably using longitudinal study designs, is needed to better understand the role of syndemics in sustaining health disparities among vulnerable populations around the world. Fourth, for the studies that employed a product term in the context of a multiplicative model but nonetheless employed the language of synergy, some of these conclusions may have been correct. Under certain conditions, a

deviation from multiplicativity may imply a deviation from additivity (VanderWeele, 2009b), and the absence of a deviation from multiplicativity may imply a deviation from additivity (Greenland & Rothman, 1998).

6 Conclusions

In this systematic review, we found that most studies in the syndemics literature have not employed product terms to document the manner in which multiple psychosocial problems exert synergistic influences on HIV risk. While a variable denoting the total count of psychosocial problems does not formally test the disease interaction concept in syndemic theory, it does speak to the importance of considering multiple simultaneous health risks in vulnerable populations. From a public health perspective, these are missed opportunities: future studies have an opportunity to substantially extend the literature by assessing the extent to which multiple psychosocial problems *interact* to worsen HIV risk. In doing so, they will generate evidence to support appropriate interventions to improve the health and psychosocial wellbeing of vulnerable populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the following individuals for responding to our queries for additional information about their work: Sonya Arreola, Helen Bates, Star Chen, Typhanye Dyer, Mackey Friedman, Abbey Hatcher, Seth Kalichman, Glenn-Milo Santos, and Soraya Seedat. We also thank Ingrid Katz, Mark Siedner, Sheri Weiser, and participants at the weekly work-in-progress seminar sponsored by the Harvard University Center for AIDS Research (U.S. National Institutes of Health [NIH] P30AI060354) for their thoughtful and constructive comments on earlier drafts of this manuscript. Our acknowledgment of their assistance should not be construed as suggesting their endorsement of any manuscript contents or conclusions. No specific funding was received for the conduct of this study, but salary support was provided through NIH K23MH096620 and the Robert Wood Johnson Health and Society Scholars Program.

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Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting the number of reports screened and included in the systematic review.

* Includes Anthropological Index Online, Anthropological Literature, and AnthroSource
 § Commentary (N=88), empirical but not relevant to syndemics (N=111), qualitative (N=126), review (N=54)

¶ Commentary (N=1), empirical but not syndemic (N=91), mapped to published journal (N=2), qualitative (N=8)

Figure 2.
(A) Simple model of syndemics depicting synergistic interactions between psychosocial problems and (B) simple model depicting mutually causal psychosocial problems.

Table 1

Summary characteristics of included studies

	No. (%)
Year of publication	
2003–2008	3 (8)
2009–2013	18 (45)
2014–2015	19 (48)
Study design	
Experimental or quasi-experimental	0 (0)
Observational	40 (100)
Cross-sectional	32 (80)
Longitudinal	8 (20)
Study setting	
U.S.	32 (80)
Other	8 (20) ^a
Study population	
Men who have sex with men	21 (53)
Women	7 (18)
General	4 (10)
Persons with HIV	5 (13)
Other	3 (8)
Sample size	
Psychosocial problems	
Substance use	36 (90)
Mental health	33 (83)
Violence	27 (68)
Other	23 (58) ^b
Outcomes of interest	
HIV transmission risk behavior	29 (73)
HIV infection	9 (23)
HIV-related health outcome	6 (15)
Mental health	4 (10)
Substance use	2 (5)

^a Includes Belgium (N=1), Canada (N=1), China (N=1), Ghana (N=1), South Africa (N=1), Thailand (N=1), and Vietnam (N=1)

^b Includes homelessness (N=6), poverty (N=5), sexual compulsivity (N=4), social isolation (N=5), food insecurity (N=4), HIV seropositivity (N=3), incarceration (N=2), caregiving responsibility (N=1), HIV transmission risk behavior (N=1), housing insecurity (N=1), internalized homophobia (N=1), lack of health insurance (N=1), low educational attainment (N=1), racism (N=1), residential mobility (N=1), and sexual stigma (N=1)

Table 2
Recommendations for using regression modeling to test the concept of disease interaction in the theory of syndemics

Specification	Conditions	Example from Systematic Review	Can Estimate Associations between Psychosocial Problems and HIV risk	Can Assess for Departures from Additivity in Interactions between Psychosocial Problems
Count of psychosocial problems	As a continuous variable	Moeller, Halkitis, and Surrence (2011)	Yes	No
Product term between psychosocial problems	As a categorical variable	Stall et al. (2003)	Yes	No
	In a multiplicative model with no further computation	Garcia et al. (2013)	Yes	No
	In a multiplicative model with additional computation	Herrick (2011)	Yes	Yes
	In an additive model	None identified	Yes	Yes