

ORIGINAL ARTICLE

The Flawed Reliance on Randomized Controlled Trials in Studies of HIV Behavioral Prevention Interventions for People Who Inject Drugs and Other Populations

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This article discusses ways in which randomized controlled trials do not accurately measure the impact of HIV behavioral interventions. This is because: 1. *Such trials measure the wrong outcomes.* Behavior change may have little to do with changes in HIV incidence since behavior change in events between HIV-concordant people have no impact on incidence. Even more important, the comparison of HIV incidence rates between study arms of individual-level RCTs does not measure the true outcome of interest—whether or not the intervention reduces HIV transmission at the community level. This is because this comparison cannot measure the extent to which the intervention stops transmission by HIV-infected people in the study to those outside it. (And this is made even worse if HIV-infected are excluded from the evaluation of the intervention.) 2. *There are potential harms implicit in most cognitively oriented behavioral interventions that are not measured in current practice and may not be measurable using RCTs.* Intervention trials often reinforce norms and values of individual self-protection. They rarely if ever measure whether doing this reduces community trust, solidarity, cohesion, organization, or activism in ways that might facilitate HIV transmission. 3. *Many interventions are not best conceived of as interventions with individuals but rather with networks, cultures of risks, or communities.* As such, randomizing individuals leads to effective interventions that diffuse protection through a community; but these are evaluated as ineffective because the changes diffuse to the control arm, which leads to systematic and erroneous reductions

in the evaluated effectiveness as RCTs measure it. The paper ends by discussing research designs that are superior to individual-level RCTs at measuring whether an intervention reduces or increases new HIV transmission.

Keywords research design, randomized controlled trials, RCTs, behavioral interventions, HIV transmission, reducing infection, effectiveness

Since the beginning of the study of the HIV epidemic in the early 1980s, many in the field have emphasized randomized controlled trials (RCTs) as the gold standard for studies of HIV behavioral prevention interventions (Anderson, 1991; Padian, McCoy, Balkus, & Wasserheit, 2010). The RCTs in question have almost never been trials with site randomization, but instead have generally focused on randomizing individuals either to receive or not to receive an intervention. Usually, the outcomes of such RCTs are some set of self-reported behaviors. Less frequently, outcomes utilized are proxy infections such as rates of becoming infected with a sexually transmitted infection (STI) or hepatitis, or more rarely, with HIV. In the syringe exchange controversies in the United States, the lack of RCT data to show that syringe exchange was effective in preventing HIV infection was sometimes claimed to be a fatal flaw in the argument for their legalization, implementation and/or funding (Goldstein, 1991). In contrast, some argued (c.f., Hartel & Schoenbaum, 1998; Zaric, Barnett, & Brandeau, 2000), there was

We gratefully acknowledge support from National Institute on Drug Abuse Grants DP1 DA034989 (HIV Transmission by Recently-Infected Drug Users); P30 DA11041 (Center for Drug Use and HIV Research); DA13128 (Networks, Norms and HIV Risk Among Youth); and National Institute of Mental Health Grant R01 MH62280 (Local Context, Social-Control Action, and HIV Risk). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other funding agencies.

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considerable evidence that methadone maintenance programs or outreach programs worked because they had undergone RCTs that showed they reduced drug use, specific risk behaviors, and/or HIV infection.

The logic supporting such claims about individual-level RCTs being the appropriate gold standard for HIV prevention trials, however, is seriously flawed; and the insistence that such RCTs show what does and does not work has probably held the field back considerably. Further, a focus on the lack of RCT data on syringe exchange as an argument to justify bans against the legalization and expansion of syringe exchange has arguably caused thousands of unnecessary deaths. The major reasons that reliance on RCTs as the gold standard for prevention research is flawed are that, as further explained below: (1) risk behaviors (if they could be accurately measured), new STIs, and even incident HIV infections among study participants are not adequate measures of whether or not the intervention reduced HIV transmission; (2) there are potential harms implicit in most cognitively oriented behavioral interventions that are not measured in current practice and may not be measurable using RCTs; and (3) many of the interventions are not best conceived of as interventions with individuals but rather with networks, cultures of risks, or communities. As such, community-randomized trials and longitudinal serial cross-sectional designs, perhaps supplemented by cohort studies, may be more appropriate and informative designs.

The Inadequacy of the Outcome Variables—Including HIV Incidence

The inadequacies of self-reported risk behaviors at follow-up interviews (when the degree of improvement is measured) as a proxy for actual risk behaviors are well known (Darke, 1998; Weinhardt, Forsyth, Carey, Jaworski, & Durant, 1998), so we will not belabor them. The inadequacy of *actual* risk behavior change as a measure of reducing HIV incidence is not so evident, however. There are two basic reasons for this inadequacy: (1) reduction in risk behaviors may be short-lived (El-Bassel et al., 2011; Gagnon, Godin, Alary, Bruneau, & Otis, 2010). A temporary reduction of risk behavior is useful, but it may not prevent many new infections. (2) HIV incidence is only partially a function of risk behavior. As basic epidemiology argues (disregarding issues of being infected with additional strains of HIV in a second infection event), and as we and others have shown (Friedman, Curtis, Neaigus, Jose, & Des Jarlais, 1999; Neaigus et al., 1996), an uninfected person can only be infected by an infected person, and an infected person can only transmit to an uninfected person—and this means that risk network issues, both at the egocentric and sociometric level, are just as important as behavioral issues. Reductions in injecting with shared needles or in unprotected sex thus considerably overstate the impact of an intervention, since a large percent of sexual or injection “risk” events are likely to be

between people with the same infection status—at least for HIV.¹

Of course, it is also true that both for reasons of general health and because STIs make HIV transmission more likely, some of those instances where HIV does not transfer because the partners are both infected or both uninfected cannot be ignored. To the extent that behavioral risk reduction reduces STI transmission, it will tend to reduce transmissions at the community level. Nonetheless, studies that use individual-level RCTs to show that their intervention reduced STI incidence and that this is a good proxy for both behavioral risk reduction and for decreasing the odds of HIV transmission also tend to overstate this case. STI transmission is also a characteristic of partners having different infection status, and thus STI infection is a product of both networks and behavior, so an intervention may reduce STIs without having reduced sexual risk behaviors if the intervention is associated with changes in the networks that participants are part of, or if randomization failed to equalize network characteristics among the different arms of the study.

More important, the use of STIs as a proxy for HIV disregards the fact that STIs have different network and behavioral distributions from each other and from HIV. As we showed in Friedman et al. (2003), HIV, herpes simplex virus type 2 (HSV-2), and perhaps syphilis are more prevalent among people who inject drugs (PWID) than among people who use no drugs or perhaps only marijuana, whereas the prevalence of chlamydia and gonorrhea is not related to drug use (Table 1). In previously unpublished data from our community network study, *Networks, Norms and HIV/STI Risk*, in Brooklyn in 2002–2005 (see Khan et al., 2009 for the methods and sample in this study), we defined a “risk network distance scale” as follows: a core group consisted of 201 people who either injected drugs or were men who had sex with men; a partners group consisted of 67 people who were sex partners of one or more members of the core group (and who thus had distance = 1); a distance = 2 group of 32 people who were sex partners of the “sex partners of the core” group, but who themselves neither reported being a partner of a core group member nor had a core group member name them as a partner; a distance = 3 group who were sex partners of a distance = 2 group member but not of either the core group or the distance = 1 partners; and an “unconnected” group of 94 people who were not linked to the core group by a path of any length. When we treated the risk network distance scale as an ordinal scale and analyzed the data using the chi-squared test for trend, the network distance scale was significantly associated with HIV, hepatitis C, and HSV-2 infection and with induced immunity to hepatitis B. It was not associated with gonorrhea

¹ Efforts to address this weakness by comparing study arms in terms of the extent to which HIV-positive persons report engaging in behaviors that can transmit the virus with people they believe to be uninfected can offer some insight, but are greatly flawed to the extent that infected participants lack knowledge of their partners' serostatus and/or report on only a subset of those with whom they engage in potential transmission behaviors.

TABLE 1. Rates of prevalent infection* among Bushwick young adults in the DUHRAY study†

Hierarchical scale of drug use (ever)	n*	HIV%	HSV2%	GC%	CT%	Syphilis%
Men						
No drug use	30	0	13	7	0	0
Marijuana	65	0	6	3	6	2
Non-injecting cocaine or heroin	114	3	7	3	7	1
Crack smoking	37	5	24	11	5	0
Drug injection	24	8	21	4	4	0
<i>P</i> (Jonckheere–Terpstra test for trend)		0.01	0.034	0.53	0.58	0.60
Women						
No drug use	67	0	13	3	3	0
Marijuana	64	0	27	3	8	0
Noninjecting cocaine or heroin	44	0	39	2	7	0
Crack smoking	21	5	57	5	10	0
Drug injection ever	15	20	67	13	13	13
<i>P</i> (Jonckheere–Terpstra test for trend)		0.0013	0.0001	0.31	0.13	0.018

*Positive responses for HIV, hepatitis C (HCV), herpes simplex virus, type 2 (HSV-2), chlamydia trachomatis (CT), and gonorrhea (GC) indicate ongoing infection. For hepatitis B (HBV), they indicate prior or current infection with the virus. For syphilis, positive responses indicate either that the participant had syphilis and has been treated in the recent past, or that the participant has been infected at some time in her/his life but not been treated.

†Taken from Friedman et al. (2003).

or chlamydia, and there was some tendency for chlamydia to be negatively associated with network distance. This means that an RCT could yield significantly different results for chlamydia or gonorrhea infection by arm if it affects the partnership patterns of participants—but that these changes might be network changes that are not linked to HIV at all. Alternatively, an intervention that is efficacious in reducing risk behaviors might not produce significant differences in incident STI rates if the reductions are concentrated among participants in network or behavioral subgroups in which the STI is less prevalent.

Finally, comparing HIV incidence rates between study arms is less meaningful than might be apparent. This is so because the underlying public health objective of most HIV behavioral interventions is their ability to reduce HIV transmission at the community level. HIV incidence in the study group, however, only measures the extent to which uninfected group members become infected. It does not measure the extent to which previously-infected participants transmit HIV to nonparticipants in the intervention (who normally will far outnumber the study participants). Indeed, prevalent HIV cases are often excluded from RCTs of HIV prevention interventions. This is a potentially major issue. For example, behavioral research has indicated that HIV counseling and testing interventions may be more effective in increasing condom use among the infected participants than among uninfected participants (Allen et al., 2003; Fonner, Denison, Kennedy, O'Reilly, & Sweat, 2012). To the extent to which this is true, then an individual-level RCT study of this intervention might well find little or no difference in HIV incidence between the “treatment” arm of people who get counseled and tested and a control arm of those who do not—in spite of having greatly reduced HIV transmission in the community by reducing HIV transmissions by the infected. This is a potentially severe limita-

tion of RCTs in HIV prevention studies. (We are trying to develop ways to remedy this limitation by combining phylogenetic analysis of HIV infection chains in the community as a whole with mathematical modeling, but these methodological problems remain far from resolved.)

There are Potential Harms Implicit in Most Cognitively Oriented Behavioral Interventions that are Not Measured in Current Practice and may not be Measurable Using RCTs

Cognitively oriented behavioral interventions, including many forms of HIV pre-test counseling, focus on teaching participants either “information,” or “skills” such as how to protect themselves. Often, they even warn that other people may lie about their HIV serostatus or about their risk behaviors, or about having other sexual partners. These behavioral interventions often rely entirely on psychological theory which assumes humans are innately self-serving and ignore the findings of Vygotsky and others that human development occurs through internalized social relations, and that humans are capable of trust and altruism, as well as mistrust and selfishness, depending on social and societal circumstances (Friedman et al., 2013; Vygotsky, 1978). Although this has not, insofar as we are aware, been studied, we hypothesize that the individualistic common cognitively behaviorist interventions which ignore a sociocultural understanding of human behavior, may potentially erode the bonds of trust in communities-at-risk. If this does occur, it may undermine protective intravention and protective normative pressures (Friedman, Bolyard, Maslow, Mateu-Gelabert, & Sandoval, 2005; Friedman, Bolyard, et al., 2007; Friedman et al., 2004; Friedman et al., 2013). It may also erode the sense of collective fate and mutual trust that

form the basis for collective community action and organization that could improve prevention efforts (Adam, 1995; Freire, 1970; Friedman, de Jong, et al., 2007; Friedman, Neaigus, et al., 1999; Friedman, Wiebel, Jose, & Levin, 1993).

RCTs that study behavioral interventions have never, to the best of our knowledge, studied whether the individualizing and egoistic focus of these interventions reduces community trust, solidarity, organization, or activism. To do this is not impossible, but it does mean developing ways to measure these using individual-level data to measure supra-individual social processes that occur around the participants (perhaps using measures like those referred to in Friedman et al (2013) in which respondents report on the normative pressures that community members exert on them and on others). It also may require having one arm of the experiment in which participants are *not* provided with egoistic teaching or counseling and are instead provided with counseling which instead highlights community bonds, social supports, and understandings of collective shared interests.

Many of the Interventions are not Best Conceived of as Interventions With Individuals but Rather with Networks, Cultures of Risks, or Communities

RCTs at the individual level are not an appropriate way to assess the value of interventions that aim at community change whether this be efforts to change the local culture of risk (Friedman et al., 1993) or efforts to reduce HIV transmission through a social intervention like a syringe exchange (*Assessing the Social and Behavioral Science Base for HIV/AIDS Prevention and Intervention: Workshop Summary—Background Papers*, 1995; Friedman, Des Jarlais, & Ward, 1994; Friedman et al., 1992; Friedman et al., 1995; Friedman & Wypijewska, 1995).² Calls to use individual-level RCTs to evaluate syringe exchange conceptualize using a syringe exchange as an intervention that teaches the individual to reduce risk behavior and gives her/him the supplies to do so. This is an inadequate conceptualization of syringe exchange, however. Often the people who get sterile syringes pass them (and perhaps prevention messages) on to other people in what has been called “secondary exchange” (Bryant & Hopwood, 2009; Huo, Bailey, Hershow, & Ouellet, 2005). This can be conceptualized as a diffusion effect—and such diffusion effects are not “contamination of the control group,” as the RCT model generally considers them (because it reduces differentials in outcomes between the experimental and control arms) but instead are an integral part of the intervention. Syringe exchanges also are a “market intervention” in that they aim to reduce the

disparity between the number of sterile syringes available to be stolen or bought on the market by PWID and what PWID need by providing additional sterile syringes (Friedman et al., 1994; Friedman et al., 1992; Friedman et al., 1995; Friedman & Wypijewska, 1995). Market effects of this kind are inherently a group phenomenon and not an individual phenomenon. Thus, without syringe exchanges, an individual PWID might go to her syringe source and find that only used syringes are available, or might find that the price is too high for her to afford. In the presence of a syringe exchange in the neighborhood, however, she might go to the dealer and find that the syringe dealer has several unsold sterile syringes still available at a lower price due to decreased demand. Finally, individual RCTs are not appropriate as a way to evaluate syringe exchanges to the extent that they reduce the number of infected potential HIV transmitters in the community. Put in simple words, if the intervention keeps Alter from becoming infected, then Alter cannot infect Ego (the participant in the RCT experimental or control arm) even though Alter was not himself a participant in the study.

Outreach “bleach and teach” interventions are subject to the same logic as well, to a degree. They were originally conceptualized as a way to diffuse protective cultural innovations (knowledge of the assumed protective effect of bleach, plus bleach containers and bleach itself) through the subculture of street injectors in San Francisco (Newmeyer, 1988a, 1988b). This approach was adapted to include network persuasion elements to assist in the diffusion by an allied project in Chicago (Friedman et al., 1993; Wiebel, 1988). As described above, diffusion projects are systematically mis-evaluated by individual-level RCTs which treat the sought-for diffusion as a reduction in efficacy.

Thus, individual-level RCTs have very limited value as a way to evaluate the full range of impacts of these interventions. Other ways do exist, although all are subject to limitations. Evaluations of syringe exchange, for example, included a combination of serial cross-sectional studies, cohort studies, and comparisons of HIV prevalence trajectories among PWID between cities that did and did not implement syringe exchange (Des Jarlais, Lyles, & Crepaz, 2004; Huo & Ouellet, 2007; Vlahov et al., 2001; West et al., 2008).

DISCUSSION

RCTs are sometimes appropriate, of course. Individual-level RCTs are useful in evaluating whether a given treatment that operates solely at the individual level promotes health. Thus, if the question is whether an antiretroviral medicine may prolong the life and reduce the symptoms of someone who is infected with HIV (or another infection such as hepatitis C or Ebola), an individual-level RCT is appropriate. (Even in these cases, there may be circumstances in which RCTs may not be possible or ethical, and it is possible to derive useful sound information from well-chosen designs other than RCTs (Des Jarlais et al., 2004; West et al., 2008)).

²While effectiveness RCTs, which by virtue of broader inclusion criteria and other aspects of their design, are more predictive of real world outcomes for those in the intervention when the intervention is rolled out in practice, they still ignore any network or community level impact, and usually still rely on outcomes variables with the limitations discussed (Gartlehner, Hansen, Nissman, Lohr, & Carey, 2006; Glasgow, Lichtenstein, & Marcus, 2003; Singal, Higgins, & Waljee, 2014).

Others have of course criticized the use of RCTs in HIV prevention research or more generally for their failure to adjust for clinical reality and for potential bias if the set of practitioners willing to host a given clinical trial leads to loss of external validity; for the inability of the interventions tested in clinical trials to be implemented in real-world settings (i.e., differences between efficacy in trial settings and effectiveness when implemented as public health interventions); and due to the tendency for the behavioral interventions that are tested to be distorted by the needs of testability (Kienle, 2005; Kippax, 2012; Kippax, Reis, & de Wit, 2011; Kippax & Stephenson, 2012; Porzolt & Kliemt, 2008). Kippax and others (Kippax, 2012; Kippax et al., 2011; Kippax & Stephenson, 2012; Manhart & Holmes, 2005) have widely discussed the difference between efficacy and effectiveness. In Kippax (2012), after saying that RCTs determine the efficacy of an intervention, she says that the effectiveness needs to be determined: "In other words, in order for there to be a decline in HIV incidence, not only are efficacious prevention tools necessary, but also the means to ensure that, once provided, people adopt and use them correctly in a sustained manner." In a parallel argument, Sanson-Fisher et al. (2007) describe ways in which RCT methods may facilitate ensuring internal validity and yet may not have adequate approaches to obtain external validity with respect to population health effects.

Though we agree with many of these prior critiques, we go beyond them to argue that RCTs as they have been implemented at the individual level are not adequate even in principal to determine the *efficacy* of the intervention. This is because they can only measure the extent to which participants in the two arms change their behavior and/or differ in the extent to which they become infected. These comparisons between control arms are not adequate to measure: (1) differences in the extent to which those who are infected transmit HIV or other infections to their partners and then throughout their networks; (2) the extent to which the focus of an intervention on self-protection may weaken protective norms of solidarity and group protection in the target population; or (3) differences between arms in the extent to which participants' partners are infected and infectious. (This last item, #3, is in theory controlled for by randomization. Recruitment methods for some trials, however, may inadequately prevent correlations between condition assignment and network characteristics, and we have never seen any empirical evaluations to determine whether such correlations occur.)

For studies of the effects of most HIV prevention interventions, then, individual-level RCTs, even effectiveness RCTs, are not fully adequate, due to these issues. In addition, these and other processes discussed above make the outcomes that are usually relied on in such studies (behavior change; STI incidence as a proxy for HIV incidence; and HIV incidence within the participants in the study) potentially misleading and not sufficient to evaluate the full impact of the intervention.

To a large extent, what we describe here is a paradigm shift. The RCT is enshrined as the "gold standard" for

testing interventions, even for behavioral interventions. Yet, as we describe here, RCTs cannot address key issues related to the performance of a behavioral intervention in a population. So long as funders continue to solicit proposals for RCTs of behavioral interventions among people who inject drugs and other populations, investigators submit such proposals, and reviewers favor RCTs over well-designed alternatives, the status quo will continue.

Many of these limitations of RCTs stem from their restriction of focus only to outcomes measured among those in the study. Impacts of the intervention on any unmeasured variable among the study participants, and, particularly, impacts of the intervention on anyone outside the study arms, are treated as irrelevant externalities—even though these unmeasured outcomes include HIV transmission from participants to nonparticipants and, thus, whether the intervention may have increased community-level infection rates. Thus both potential adverse and beneficial intervention effects are unmeasured and unstudied—and thus are unpredictable when interventions tested solely in RCTs are disseminated. This feature may account for some proportion of the differences observed between intervention effects in trials and in real world settings.

Nonetheless, there are research designs that *are* appropriate. These take the form of community randomized trials, where some communities are randomly assigned to the intervention and others to the control condition. Such studies face what seems to us to be a very tricky statistical issue: that what is often conceived of as a great reduction in statistical power due to cluster-correlation effects (that those in one town have similarities due to their social or other relationships due to being in the same town) is in fact a mixture of such clustering effects together with the mechanisms of the intervention such as social network diffusion effects and the fact that protecting one person from infection then prevents additional transmission from him to his partners, their partners, and so forth. The simple solution—measuring the change in transmissions through serial cross-sectional studies (and maybe cross-sectional measures of recent infection using assays such as LAg (Duong et al., 2012) or of transmission patterns using phylogenetic designs) as a town-level outcome, with the study N = the number of towns, is clearly valid. This approach, however, tends to lead to extremely expensive trials.

In summary, rather than being the gold standard for studies of HIV behavioral prevention interventions, RCTs ignore critical network- and community-level impacts, and frequently rely on inappropriate and/or insufficient outcome variables. Community randomized trials better reflect the full range of relevant impacts and outcomes of candidate and implemented HIV behavioral interventions, and hence should be used when feasible. If they are not feasible, other mechanisms to measure community impacts, such as serial cross-sectional studies, seem essential to assure that interventions that "work" in the two study arms are not increasing risk behavior, leading to in-

creased network-based risk, and/or leading to increased viral transmission.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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GLOSSARY

RCT: Randomized controlled trial.

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