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Commentary

Study designs for identifying risk compensation behavior among users of biomedical HIV prevention technologies: Balancing methodological rigor and research ethics

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ABSTRACT

The growing evidence base for biomedical HIV prevention interventions – such as oral pre-exposure prophylaxis, microbicides, male circumcision, treatment as prevention, and eventually prevention vaccines – has given rise to concerns about the ways in which users of these biomedical products may adjust their HIV risk behaviors based on the perception that they are prevented from infection. Known as risk compensation, this behavioral adjustment draws on the theory of "risk homeostasis," which has previously been applied to phenomena as diverse as Lyme disease vaccination, insurance mandates, and automobile safety. Little rigorous evidence exists to answer risk compensation concerns in the biomedical HIV prevention literature, in part because the field has not systematically evaluated the study designs available for testing these behaviors. The goals of this Commentary are to explain the origins of risk compensation behavior in risk homeostasis theory, to reframe risk compensation as a testable response to the perception of reduced risk, and to assess the methodological rigor and ethical justification of study designs aiming to isolate risk compensation responses. Although the most rigorous methodological designs for assessing risk compensation behavior may be unavailable due to ethical flaws, several strategies can help investigators identify potential risk compensation behavior during Phase II, Phase III, and Phase IV testing of new technologies. Where concerns arise regarding risk compensation behavior, empirical evidence about the incidence, types, and extent of these behavioral changes can illuminate opportunities to better support the users of new HIV prevention strategies. This Commentary concludes by suggesting a new way to conceptualize risk compensation behavior in the HIV prevention context.

Introduction

Recent advances in biomedical HIV prevention science have galvanized the HIV/AIDS field, generating enthusiasm for combination prevention approaches, treatment as prevention, and the expansion of prevention services to groups in which behavioral interventions have had limited effect. In several short years, HIV prevention technologies have expanded to include an efficacious vaginal microbicide (Abdool Karim et al., 2010) oral antiretroviral pre-exposure prophylaxis (PrEP) (Baeten et al., 2012; Grant et al., 2010; Thigpen et al., 2012), male circumcision for preventing heterosexual acquisition of HIV in men (Siegfried et al., 2009), and firm evidence for the effectiveness of antiretroviral treatment as prevention (Cohen et al., 2011). Alongside these advances, however, has emerged uncertainty about the behavioral impacts of new prevention technologies, which will mediate the effects of biomedical prevention outside trial settings. Uptake of new technologies and adherence to dosing regimens will be important factors in real-world effectiveness, but this Commentary is concerned primarily with risk compensation behavior—a cognitive-behavioral process by which individuals may take more behavioral risks based on the belief that they are protected from adverse consequences (Eaton & Kalichman, 2007; Hogben & Liddon, 2008).

Many have expressed the concern that users of biomedical prevention technologies will expect to be protected from HIV, and will then respond by taking more behavioral risks (e.g., reducing condom use, increasing numbers of partners) (Eaton & Kalichman, 2007). These concerns have also found their way into regulatory processes; for example, risk compensation questions played a role in discussions about approving tenofovir-emtricitabine for use as

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oral PrEP. The Antiviral Drugs Advisory Committee of the FDA considered the need for postmarketing studies to identify behavioral changes associated with PrEP use (FDA Center for Drug Evaluation and Research, 2012), and the Risk Evaluation and Mitigation Strategy for Truvada® requires the manufacturer to inform prescribers and users that "TRUVADA… must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used" (FDA, 2012; Gilead Sciences Inc., 2012, p. 1). Questions about risk compensation behavior have arisen for each of the emerging HIV prevention technologies (Crosby, Ricks, & Young, 2012; Eaton & Kalichman, 2007), and they will persist as the field progresses to study new drug candidates, delivery strategies, and mechanisms for preventing infection.

Also known as behavioral disinhibition (Hogben & Liddon, 2008; Paltiel et al., 2009), offsetting behavior (Peltzman, 1975), or moral hazard (Malani, 2008), the dynamic of risk compensation behavior is not unique to the biomedical HIV prevention context. Studies of this phenomenon have focused on behavioral reactions to such disparate interventions as auto safety equipment (McCarthy, 1989; Mackay, 1985; Peterson, Hoffer, & Millner, 1995; Streff & Geller, 1988), bicycle helmets (Adams & Hillman, 2001), children's safety gear (Morrongiello, Lasenby, & Walpole, 2007; Morrongiello, Walpole, & Lasenby, 2007), diet soda (Fowler et al., 2008), low-tar cigarettes (Institute of Medicine, 2001), Lyme disease vaccination (Brewer, Cuite, Herrington, & Weinstein, 2007), and mandated insurance coverage for diabetes (Klick & Stratmann, 2007) or substance use (Klick & Stratmann, 2006), to name a few studies. Among HIV prevention scientists, risk compensation—also called condom migration (Crosby et al., 2012)—has provoked some to advise caution in the dissemination of new prevention strategies, while others dismiss the idea as improbable or scientifically unfounded (Grady, 2012; Grant & McConnell, 2008). Despite these debates, however, the behavioral analyses accompanying trials of biomedical prevention interventions can say little to confirm or dispel risk compensation concerns.

An important reason for this information deficit is the lack of accepted study designs for the identification of risk compensation behavior. To date, there has not been a focused inquiry into the study designs available for assessing this phenomenon. The goals of this Commentary are to describe the mechanism of risk compensation behavior, to identify shortcomings of current study designs for evaluating the existence and extent of this behavior, and to explore alternative study designs for accessing risk compensation effects. IRB approval was not needed for this Commentary because it does not meet the definition of research involving human subjects.

Characterizing the phenomenon

Descriptions of risk compensation behavior originate in the theory of "risk homeostasis" (Adams, 1995; Hedlund, 2000; Wilde, 2001) which proposes that for every activity, "people accept a certain level of subjectively estimated risk to their health…in exchange for the benefits they hope to receive from that activity" (Wilde, 2001, p. 5). To the extent that we control our behaviors, this theory suggests that each of us continually adjusts our risk-taking so that our perceived risk approaches a "target risk level": the level at which we see the most acceptable trade-off between risks and benefits. This level need not be static, and it may change due to factors such as time or social influences. But at any given point, our target risk level represents what we perceive to be the optimal balance between risk-taking (e.g., sex without condoms) and the potential benefits of risky behavior (e.g., intimacy, sexual pleasure).

When we perceive that our risks or potential benefits have changed, risk homeostasis theory suggests that we respond by altering our behavior in a direction that brings the perceived balance closer to our target risk level (Wilde, 2001). This adjustment is "risk compensation," and although most discussions of this behavior are concerned with *increases* in risk-taking, this phenomenon also encompasses *decreases* in risk-taking when we perceive that our risks are unacceptably high. For example, knowing that one's partner is HIV-positive may make someone more likely to use a condom or to avoid unprotected receptive sex (Carballo-Dieguez, Balan, Frasca, Dolezal, & Valladares, 2012). Usually, however, discussions of risk compensation behavior focus on ways in which increased behavioral risk-taking may undermine the effectiveness of new health and safety interventions.

Risk homeostasis theory and its corollary mechanism of risk compensation have been criticized, often on the basis that people are not sufficiently rational to calculate their risks or calibrate their behaviors in response to a preventive intervention (McKenna, 1985; O'Neill & Williams, 1998). The mechanism of risk compensation, however, accommodates irrationality at every stage. Individuals' perceptions of risks and benefits need not be accurate for them to know that they are balancing risks and benefits, or to adjust their behavior *to some extent* when they perceive (however accurately) that the balance has shifted. The theory further does not demand that an individual's actual risk level remain constant over time; rather, it stipulates only that changes in risk perceptions will predictably prompt behavioral adjustments in the direction of one's preferred balance of risks and benefits. These adjustments may be modest, or they may be entirely absent if individuals do not have the opportunity or motivation to behave more riskily (e.g., decreased condom use is irrelevant for individuals with no sexual partners, or for individuals who never used a condom in the first place). But even minimal behavioral changes may influence the effectiveness and cost-effectiveness of new HIV prevention technologies. For example, one mathematical model of PrEP's cost-effectiveness among US men who have sex with men (MSM) suggested that a 4.1% increase in the annual number of new sexual partners could fully offset the population-level benefit of a PrEP drug with 50% efficacy, assuming that PrEP is used by 25% of the population with 50% adherence (Desai et al., 2008).

In a summary of risk compensation research, Hedlund has identified four preconditions for an individual risk compensation response: 1) the intervention must be visible to the individual, 2) the intervention must have an effect on the individual that gives rise to the perception of protection, 3) the individual must have a motivation to increase his risk-taking, and 4) the individual must have control and opportunity to adjust his behavior (Hedlund, 2000). These preconditions are fulfilled for HIV prevention technologies such as PrEP, microbicides, and vaccines. For instance, individuals who take oral PrEP will be aware of their product use, and they will expect the pills to reduce their HIV risk. They may desire to have more partners or to use condoms less frequently (but previously did not due to HIV concerns), and they may have opportunities to take these actions while using PrEP. Surveys and qualitative data suggest that some MSM may indeed take more behavioral risks while using PrEP (Brooks et al., 2012; Golub, Kowalczyk, Weinberger, & Parsons, 2010; Krakower et al., 2012; Tripathi, Whiteside, Scanlon, & Duffus, 2012; Underhill et al., 2012), although analyses of actual user behavior are still unavailable.

To facilitate the study of risk compensation behavior, it is helpful to consider it as the effect of a psychological stimulus. That is, an individual's increase in risk-taking behaviors is a response to the belief that he or she is protected (to any extent) from harm. In biomedical HIV prevention, this perception has two components: the individual must believe that she is receiving a preventive intervention, and she must believe that the intervention works to reduce her HIV risk. For the ensuing discussion, this two-part