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Moving the bar to the right place: Positioning interventions in HIV prevention

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In their article titled “Setting the Bar High or Setting Up to Fail?: Interpretations and Implications of the EXPLORE Study”, Kalichman and colleagues (1) discuss the positive and negative interpretations in the research literature about the effectiveness of the EXPLORE behavioral intervention in reducing HIV incidence. They conclude that the preponderance of negative interpretations has had a consequential negative impact on policy decisions about the role of behavioral counseling in HIV prevention in the United States (US). Kalichman et al. go on to discuss that the 35% benchmark for a reduction in HIV incidence in the EXPLORE Study was “setting the bar too high.” (1) We believe that while the role of behavioral counseling is critical for HIV prevention, the HIV prevention intervention “bar” needs to move to a different location altogether.

The EXPLORE behavioral counseling intervention was “plausibly efficacious”. Many, if not most, commentators on the EXPLORE Study have failed to recognize the subtleties of the results and, as Kalichman et al. point out, positive and negative interpretations of the trial have proliferated and have not done the study justice. (1) The EXPLORE Study was the first, and only behavioral counseling intervention for men who have sex with men (MSM) tested against an HIV infection outcome. The EXPLORE Study was designed as a Phase IIb screening proof-of-concept trial (as opposed to a Phase III definitive efficacy trial), a prudent approach given the resources and time needed to conduct a trial with an incident HIV endpoint. Using the screening trial approach, the study protocol included decision points to identify a highly effective intervention, rule out a totally ineffective intervention or consider the intervention to be plausibly efficacious. (2)

The results actually fell into the range of plausible efficacy, according to the *a priori* analysis decision points with the modest efficacy of 18.2% (95% CI –4.7% to 36.0%). (2)

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The potential intervention effect was supported by post-hoc examination suggesting that the intervention reduced HIV infection rates by 33% at the 6-month visit and 39% at the 12-month visit. It is also important to note that the intervention arm did not revert back to baseline levels of risk. Rather, the control group decreased risk, albeit more slowly but eventually almost to the levels of the intervention group, thereby reducing the difference in HIV incidence between the two groups at the end of the study. Thus, there was not a problem of regression of benefits from intensive behavioral counseling, but a decrease in risk in the control group, perhaps due to semi-annual HIV counseling and testing, intensive behavioral questionnaires drawing attention to specific risk-reduction practices, and numerous phone contacts throughout the study for reminders and scheduling of study visits.

We conclude that behavioral counseling is useful, but not sufficient to produce lasting reductions in HIV incidence. (3) Just as clinicians must parse out the “clinical significance” of statistically significant medical research findings, we, as public health researchers and practitioners, need to consider the “prevention significance” of our research findings. Meta-analyses have demonstrated that behavioral interventions alone significantly reduce self-reported risk behaviors over those reported in control conditions, in the range of 10–30%. (4–10) Considering the potential limitations of meta-analyses (11), including potential bias toward reporting positive effects and underreporting of null effects in the published literature, these reviews likely present an optimistic role of behavioral interventions alone. For the behavioral intervention trials that have found significant effects on self-reported behaviors, are these effects sufficient to have an impact on HIV incidence? Probably not, as larger changes in reported risk behaviors are needed to create a significant reduction in HIV incidence.

Where do we think that the HIV prevention intervention “bar” needs to move? First, regular HIV testing and feedback to the individual remains an important intervention approach, albeit in a cost-efficient and scalable way (12). A range of options are now available for HIV testing for individuals, couples and communities, including self-testing, and couples-based, community-based and traditional clinic-based testing (13–15). The more options for knowing HIV status--and the more options for effective prevention--the better.

Second, the HIV prevention tool box has expanded significantly, as have the modes of prevention information delivery (e.g., social media)(16). For those found to be HIV uninfected, daily use of oral pre-exposure prophylaxis (PrEP) can be highly effective. (17–19) Those who are HIV infected can benefit from antiretroviral treatment and when on treatment, are less likely to transmit HIV to others. (20) While condoms remain an important intervention for both HIV-uninfected and infected persons, recent analyses suggest that the efficacy of PrEP and antiretroviral therapy (ART) may exceed that of condoms used during anal sex. (21) To strengthen these approaches, multi-level, multi-component and longer-term intervention approaches are needed to address the effect of structural factors on the lives of persons at risk. It is important to note that all biomedical interventions, even an HIV preventive vaccine, will require attention to behavioral factors such as uptake and adherence. Thus, similar to behavioral interventions alone, biomedical interventions alone are not sufficient to produce lasting reductions in HIV incidence and require attention to behavior.

Third, alternative study designs are needed for future research. Given the prevention options available and the likelihood that these enhance overall prevention efforts, the reliance on standard randomized controlled trials with assignment to a limited number of static options is neither optimal nor generalizable. Given the range of unanswered questions about behavioral intervention limitations (e.g., extent of the impact of regression to mean, choice of control group, study/staff attention to control participants), it would serve the field well to

invest in methodology studies to help sort out the relative impact of these limitations on intervention effects. Studies could adopt designs which include multiple control groups to parse out effects and lag periods to address regression to the mean of self-reported behaviors. Furthermore, the validity of self-reported behaviors has been challenged recently as a result of the significant over-reporting of PrEP and microbicide adherence compared to objective drug levels in clinical trials (22, 23). While we caution against broad judgments about the validity of self-reported risk behaviors based on self-reported drug adherence, existing datasets with HIV incidence endpoints (e.g., the EXPLORE public use dataset) can be mined to better understand self-reported behaviors and develop new approaches to analyzing self-report data.

Finally, results of recent trials indicate that the commonly framed dualism of biomedical and behavioral prevention approaches works against the goal of ending this epidemic. (22, 23) While we agree that proper interpretation of the EXPLORE Study requires setting the bar at the right height, we also argue that the “bar” needs to move to a place of interdisciplinary, comprehensive, and tailored prevention approaches that are cost efficient and scalable: (a) interdisciplinary – by fully utilizing the expertise in basic science, clinical research, behavioral research, psychology, anthropology, sociology, epidemiology, biostatistics, geography, medicine, community and others to understand the biological, dyadic, cultural and social systems within which individuals and groups operate (24–27); (b) comprehensive – by utilizing the tools available in the HIV prevention toolbox in an expanded model for HIV prevention and treatment as recently presented by Coates, 2013 (3) and addressing gaps along the HIV prevention, care and treatment continuum (28, 29); (c) tailored – by choosing among the HIV prevention tools available by taking into account individual life circumstances (e.g., primary partner, substance use during sex) and periods of risk that may change over time ; and (d) cost efficient and scalable – by focusing on individuals at high risk for HIV infection or transmission, combined with social marketing and social media approaches (16) in the context of limited HIV prevention funding (30). All of these components can help to create the intervention approaches that have the highest probability of effectiveness.

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References

1. Kalichman SC, Zohren L, Easton LA. Setting the bar high or setting up to fail: Interpretations and implications of the EXPLORE Study (HPTN 015). *Aids and Behavior*. 2013
2. Koblin B, Chesney M, Coates T, Team ES. Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomised controlled study. *Lancet*. 2004 Jul 3–9; 364(9428):41–50. [PubMed: 15234855]

3. Coates TJ. An Expanded Behavioral Paradigm for Prevention and Treatment of HIV-1 Infection. *J Acquir Immune Defic Syndr*. 2013 Jul; 63(Suppl 2):S179–82. [PubMed: 23764633]
4. Johnson BT, Scott-Sheldon LA, Smoak ND, Lacroix JM, Anderson JR, Carey MP. Behavioral interventions for African Americans to reduce sexual risk of HIV: a meta-analysis of randomized controlled trials. *J Acquir Immune Defic Syndr*. 2009 Aug 1; 51(4):492–501. [PubMed: 19436218]
5. Johnson WD, Diaz RM, Flanders WD, Goodman M, Hill AN, Holtgrave D, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. *The Cochrane database of systematic reviews*. 2008; (3):CD001230. [PubMed: 18646068]
6. Scott-Sheldon LA, Huedo-Medina TB, Warren MR, Johnson BT, Carey MP. Efficacy of behavioral interventions to increase condom use and reduce sexually transmitted infections: a meta-analysis, 1991 to 2010. *J Acquir Immune Defic Syndr*. 2011 Dec 15; 58(5):489–98. [PubMed: 22083038]
7. Henny KD, Crepaz N, Lyles CM, Marshall KJ, Aupont LW, Jacobs ED, et al. Efficacy of HIV/STI behavioral interventions for heterosexual African American men in the United States: a meta-analysis. *AIDS Behav*. 2012 Jul; 16(5):1092–114. [PubMed: 22234436]
8. Scott-Sheldon LA, Fielder RL, Carey MP. Sexual risk reduction interventions for patients attending sexually transmitted disease clinics in the United States: a meta-analytic review, 1986 to early 2009. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*. 2010 Oct; 40(2):191–204. [PubMed: 20652778]
9. Crepaz N, Marshall KJ, Aupont LW, Jacobs ED, Mizuno Y, Kay LS, et al. The efficacy of HIV/STI behavioral interventions for African American females in the United States: a meta-analysis. *American journal of public health*. 2009 Nov; 99(11):2069–78. [PubMed: 19762676]
10. Darbes L, Crepaz N, Lyles C, Kennedy G, Rutherford G. The efficacy of behavioral interventions in reducing HIV risk behaviors and incident sexually transmitted diseases in heterosexual African Americans. *AIDS*. 2008 Jun 19; 22(10):1177–94. [PubMed: 18525264]
11. Bornstein, M.; Rothstein, HR.; Hedges, LV.; Higgins, JPT. *Introduction to Meta-Analysis*. West Sussex, GB: John Wiley & Sons, Inc; 2009.
12. The White House Office of National AIDS Policy. *National HIV/AIDS Strategy for the United States*. 2010.
13. OraSure Technologies Inc. [Accessed 28 Nov 2012] Oraquick In-home HIV test. 2012. Available from: <http://www.oraquick.com/>
14. Wagenaar BH, Christiansen-Lindquist L, Khosropour C, Salazar LF, Benbow N, Prachand N, et al. Willingness of US men who have sex with men (MSM) to participate in Couples HIV Voluntary Counseling and Testing (CVCT). *PloS one*. 2012; 7(8):e42953. [PubMed: 22905191]
15. Stephenson R, Sullivan PS, Salazar LF, Gratz B, Allen S, Seelbach E. Attitudes towards couples-based HIV testing among MSM in three US cities. *AIDS Behav* 2011. Apr; 2011 15(Suppl 1):S80–S7.
16. Wei C, Herrick A, Raymond HF, Anglemyer A, Gerbase A, Noar SM. Social marketing interventions to increase HIV/STI testing uptake among men who have sex with men and male-to-female transgender women. *Cochrane Database Syst Rev*. 2011; 2011(9):CD009337. [PubMed: 21901734]
17. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010. Dec 30; 2010 363(27):2587–99.
18. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *The New England journal of medicine*. 2012 Aug 2; 367(5):399–410. [PubMed: 22784037]
19. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013 Jun 15; 381(9883):2083–90. [PubMed: 23769234]
20. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011. Aug 11; 2011 365(6):493–505.

21. Smith, D.; Herbst, J.; Zhang, X.; Rose, C. Condom Efficacy by Consistency of Use among MSM:US. 20th Conference on Retroviruses and Opportunistic Infections; March 3–6, 2013; Atlanta, GA. 2013.
22. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine*. 2012 Aug 2; 367(5):411–22. [PubMed: 22784040]
23. Marrazzo, J.; Ramjee, G.; Nair, G. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine or vaginal tenofovir gel in the VOICE study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections; March 3–6, 2013; Atlanta, GA. p. Abstract 26LB
24. Koblin BA, Andrasik M, Austin J. Preparing for the Unexpected: The Pivotal Role of Social and Behavioral Sciences in Trials of Biomedical HIV Prevention Interventions. *J Acquir Immune Defic Syndr*. 2013 Jul; 63(Suppl 2):S183–6. [PubMed: 23764634]
25. Lau CY, Swann EM, Singh S, Kafaar Z, Meissner HI, Stansbury JP. Conceptual framework for behavioral and social science in HIV vaccine clinical research. *Vaccine*. 2011 Oct 13; 29(44): 7794–800. [PubMed: 21821083]
26. MacQueen KM. Framing the social in biomedical HIV prevention trials: a 20-year retrospective. *Journal of the International AIDS Society*. 2011; 14(Suppl 2):S3. [PubMed: 21968079]
27. Aral SO, Blanchard J. Biomedical and social dimensions of HIV prevention. *American journal of public health*. 2012 Sep.102(9):e9. author reply e-10. [PubMed: 22813470]
28. Hall, HI.; Frazier, EL.; Rhodes, P.; Holtgrave, DR.; Furlow-Parmley, C.; Tang, T., et al. Continuum of HIV care: differences in care and treatment by sex and race/ethnicity in the United States. XIX International AIDS Conferences; July 22–27, 2012; Washington, DC. 2012.
29. Mugavero, MJ.; Amico, KR.; Horn, T.; Thompson, MA. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013 Jun 23. The State of Engagement in HIV Care in the United States: From Cascade to Continuum to Control.
30. Centers for Disease Control and Prevention. [Accessed 14 Aug 2013] Strategic Plan, Division of HIV/AIDS Prevention 2011–2015 2011]. Available from: http://www.cdc.gov/hiv/pdf/policies_DHAP-strategic-plan.pdf