HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2017 December 15.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2016 December 15; 73(5): 547–555. doi:10.1097/QAI.0000000000001140.

Enhancing PrEP Access for Black and Latino Men Who Have Sex with Men

Corina Lelutiu-Weinberger[1] and **Sarit A. Golub**[1,2]

[1] Department of Psychology, Hunter College of the City University of New York (CUNY), New York, NY, USA

[2] Department of Psychology, Basic and Applied Social Psychology PhD program, The Graduate Center of the City University of New York (CUNY), New York, NY, USA

Abstract

Objective—Implementation of HIV pre-exposure prophylaxis (PrEP) programs for populations with highest incidence is critical to reducing new infections in the United States. Black and Latino men who have sex with men (BLMSM) are disproportionately burdened by HIV. We examined differences in perceived barriers and facilitators to PrEP access for BLMSM compared to other MSM.

Method—MSM who met CDC criteria for PrEP (n = 491) completed measures of barriers and facilitators to PrEP at the systems-, provider-, and individual-levels. Multivariate analyses examined differences by race/ethnicity, adjusting for other sociodemographic factors.

Results—Compared to other MSM, BLMSM (56% of the sample) were more likely to have public insurance and access health care via public clinics (aOR 3.2, p< 0.001; aOR 2.4, p< 0.01). BLMSM were more likely to regard having to talk to their doctor about their sex life as a barrier to PrEP (aOR 3.7, p< 0.001), and less likely to endorse agency in medical decision-making (aOR .58, p< 0.001). BLMSM were more likely to report PrEP stigma (aOR 2.3, p< 0.001) and concerns regarding PrEP efficacy (aOR 1.6, p< 0.05). BLMSM were more likely to consider access to free sexual health care (aOR 2.1, 95% CI: 1.3-3.3; p< 0.01) and additional supportive services, e.g., counseling (aOR 3.1, p< 0.001) or text-based support (aOR 2.9, p< 0.001), to be significant facilitators of PrEP use.

Conclusions—Findings suggest specific points of multi-level intervention to increase PrEP access for BLMSM and increase representation of BLMSM along the PrEP continuum of care.

Keywords

pre-exposure prophylaxis (PrEP); implementation; HIV; men who have sex with men; Black/African American MSM; Latino MSM

Correspondence regarding this article should be addressed to Sarit A. Golub, Department of Psychology, Hunter College of the City University of New York, 695 Park Avenue, New York, NY 10065. sarit.golub@hunter.cuny.edu.

Conflicts of Interest

The authors have no conflict of interest to declare.

Data from this manuscript were presented at 11th International Conference on HIV Treatment and Prevention Adherence, IAPAC, May 9 – 11, 2016, Fort Lauderdale, Florida.

INTRODUCTION

Daily oral use of anti-retroviral medications as pre-exposure prophylaxis (PrEP) has been demonstrated to be an extremely effective biomedical HIV prevention tool.[1-4] The challenge now is implementation – how to ensure genuine access to PrEP for individuals who would most benefit from it.[5,6] In considering lessons learned from implementation of antriretrovirals for HIV *treatment,* comprehensive access is still lacking; data from the widely used HIV treatment "cascade," or continuum of care, indicate that only 33% of those infected in the United States (U.S.) have been prescribed antiretroviral therapy.[7] Research on barriers along the treatment cascade can inform PrEP implementation efforts, but there are unique dynamics inherent in PrEP uptake and persistence that have yet to be fully understood.

In an effort to shed light on these dynamics, several researchers have proposed a PrEP continuum of care, which, analogous to the treatment cascade, draws attention to the specific steps necessary for identifying, engaging, and retaining patients on PrEP.[8,9] The proposed PrEP cascades begin with patients who are interested in PrEP[10] or aware of and willing to take PrEP,[9] and then moves to the subset of those patients who can be linked to/access PrEP-related care, and then the subset of patients who receive a PrEP prescription. Retention and adherence are the ultimate goal of successful PrEP implementation, but engaging highest priority individuals in PrEP programs is a necessary first step toward prevention goals.

To date, this engagement, i.e., uptake of PrEP by highest priority populations, has been slow. And perhaps more concerning, early indications suggest that awareness and uptake of PrEP are lowest among Black men who have sex with men (MSM),[11-14] and adherence seems to be lower among young Black MSM compared to white and Latino youth.[15] While uptake of PrEP has increased by over 500% between 2013 and 2015, recent data suggest that 75% of all prescriptions were filled by Whites, with only 10% and 12% being filled by Blacks and Hispanics, respectively.[16] Differences in PrEP uptake by race/ethnicity are important because Black and Latino MSM bear a disproportionate burden in terms of HIV incidence in the United States.[17-21] In fact, the Centers for Disease Control and Prevention (CDC) recently reported that the lifetime risk of HIV infection among Black MSM is one in two, and the lifetime risk of infection for Latino men is one in four, compared to a lifetime risk among White MSM of one in eleven.[22] Intervention at every level of the prevention and treatment continuum is needed immediately to address such unacceptable disparities, and increasing access to effective biomedical prevention is a critical component of any such action.

As part of these efforts, research is urgently needed to better understand differential PrEP uptake among Black and Latino MSM. In studies that ask participants about PrEP interest and acceptability, reported willingness to adopt PrEP among Black and Latino MSM is as high (if not higher) than that reported by white and other MSM.[13,23-25] However, we know that hypothetical interest is not the same as real-world willingness, which is impacted not only by "objective" factors such as PrEP awareness/knowledge, but also by underlying attitudes and beliefs that influence comprehension and interpretation of any PrEP education.

In addition, we know that PrEP *availability* is not the same as access. In order to be truly accessible, PrEP programs must be available to highest priority individuals within the settings in which they are most likely to receive care and in a manner that is financially affordable. Emerging research also points to the important role of providers in PrEP implementation. Meaningful PrEP access for patients happens both before and after they express interest in PrEP. Many patients learn about PrEP for the first time from their medical providers, while others report that their providers have been a barrier to PrEP prescription.[26-28] Comprehensive PrEP implementation requires increasing patient-provider communication about HIV prevention and ensuring that providers serving highest priority populations are willing and able to offer PrEP to them.

This paper analyzes data collected from MSM of varying race/ethnicity regarding potential barriers to PrEP implementation relevant to these first three steps of the PrEP cascade – interest, access, and prescription. These levels may be mapped onto what has been termed the social-ecological model,[29] which treats individuals as embedded within larger environments and social systems, and acknowledges that these multiple levels of influence are interactive and reinforcing.[30] Application of social-ecological models to program implementation is recommended by both the CDC and the Institute of Medicine, and several such models have been developed specifically to understand the HIV prevention context.[31,32] As such, we applied these cascade steps to factors at the patient-, provider, and systems-levels, positing that both risk and health behaviors are "generated and perpetuated through socially or environmentally structured social interactions."[32] We operationalized interest barriers at the *patient-level*, examining attitudes and beliefs that might discourage uptake. We operationalized prescription barriers at the *provider-level*, examining dynamics of patient-provider interaction. In these analyses, we are particularly interested in differences in barriers at each level by race/ethnicity. Finally, we operationalized access barriers at the *systems-level*, examining the type of setting in which patients are more likely to access PrEP and the ways in which they may be able to pay for it. In a previous paper analyzing a portion of this sample[34] [blinded for review], we reported that there were differences in a subset of these barriers by race/ethnicity. However, that analysis included only 184 participants, did not include BLMSM-specific analyses, was not sufficiently powered to adjust for the role of socioeconomic status, and did not examine systems- or provider-level barriers. These analyses build on and clarify these previous findings. A better understanding of the ways in which Black and Latino MSM differ from their White counterparts may allow us to identify potential targets for intervention to meaningfully increase PrEP access across the continuum of care for these high priority individuals.

PARTICIPANTS AND METHODS

Between January 2012 and June 2014, 500 participants were enrolled in a cross-sectional study examining the impact of PrEP messaging and communication strategies on PrEP knowledge and adoption intentions. Participants were recruited in the New York City area [blinded for review] using passive recruitment (i.e., display of study flyers and cards in local venues catering to our target populations; placement of study ads on websites and mobile applications used by MSM to seek partners, such as Grindr, Adam4Adam, or Craigslist), active recruitment (i.e., outreach at bars, events, community-based organizations), and

participant referral. Eligible individuals were born male (regardless of current gender identity), aged 18 years or older, self-reported an HIV-negative serostatus, and reported at least one act of condomless anal sex with a male partner in the past 30 days, consistent with CDC's guidelines for PrEP eligibility for MSM.[35] Although current CDC guidelines do not recommend PrEP for MSM in monogamous HIV-negative partnerships, we decided to include men who reported recent condomless sex regardless of partner type, because modeling data suggest that between one-third and two thirds of infections among gay and bisexual men result from sex with main partners [36,37] and surveys of gay couples suggest that some couples have discrepancies in their beliefs about monogamy agreements and/or may break such agreements.[38-40] After providing informed consent, participants received information about PrEP, completed a self-administered computer survey, and an interviewer-administered semi-structured Timeline Follow-Back assessment[41] of sexual behavior in the past 30 days. All procedures were reviewed and approved by the Human Research Protections Program at the City University of New York [blinded for review].

Measures

Sample Characteristics—We collected information on the sample's characteristics, including age, race/ethnicity, education, income, sexual identity, and relationship status. Race/ethnicity was asked using a two-part question consistent with federal reporting requirements[42]: 1) Do you consider yourself Hispanic or Latino (yes/no); and 2) How would you describe your race (including the five racial categories defined by OMB, plus the option of “multiracial” and “other.”). Individuals who chose “multiracial” or “other” were asked to check as many of the OMB racial categories as they liked and were given the ability to self-report a race not listed. While we acknowledge that any classification of participants’ race/ethnicity into discrete categories for analysis is inherently problematic,[43] we operationalized race/ethnicity for the purposes of this study according to the definitions in the most recent NIH diversity statement, which defines five racial and ethnic categories, and classifies individuals as Hispanic or Latino if they have a “Spanish culture or origin, regardless of race.”[44] As such, we examined the data for each person who reported being Hispanic or Latino, “multiracial” and “other”, given that some participants who identified as Hispanic or Latino used at least one of these categories for self-classification. If Hispanic or Latino appeared in any of these fields, these participants were classified accordingly. Further, any participant who chose Black, African American, Caribbean, or West-Indian was classified as Black. Based on these classifications, a third of the sample (n = 163; 33%) identified as Black/African American, nearly a quarter (n = 114; 23%) identified as Latino, 37% (n = 183) identified as white, and 7% (n =31) as “other” (including “multiracial” individuals who did not indicate anything else). Therefore, over half of the sample (56%) identified as Black or Latino, and the vast majority of other MSM (183 of 214; 86%) identified as white. Finally, participants were asked whether they were currently taking PrEP; nine participants were excluded for this reason from the current analysis.

HIV Risk and Prevention Behavior: Sexual and substance use behavior in the past 30 days was assessed with a modified version of the semi-structured Timeline Follow-Back interview. [41] Using a calendar, interviewers asked participants to report the type of sexual activity (anal or vaginal intercourse; with or without a condom) by partner type (primary or

casual) on each of the prior 30 days. Participants were also asked to report any substance use and heavy episodic alcohol use (five or more standard drinks). For the current analyses, we examined total number of partners, number of condomless anal sex acts, percent of anal sex acts that were condomless, number of heavy drinking days, and number of substance use days. Participants were asked when they were last tested for HIV, and responses were dichotomized into within the past 6-months or over 6 months ago.[45] Consistent with our previous work,[34] [blinded for review] PrEP adoption intentions were assessed using a single item dichotomized to reflect whether or not the participants would "definitely or probably" take PrEP if it were available for free.

Barriers to PrEP Access and Uptake—We examined specific factors that might impact PrEP access and uptake at three levels. **At the systems-level**, we asked participants about insurance type (public, private, uninsured) and point of health care access (private doctor, community health center, public clinic or hospital/emergency room).

At a provider level, we asked participants whether or not they: 1) had a specific provider they saw regularly (yes/no), and 2) considered having to talk to their doctor about their sex life to be an important barrier to PrEP use (5-point scale, dichotomized into 1-3 (not important) versus 4-5 (important)). Third, we asked participants a single item[46] to assess patient preferences for participation in treatment decision-making. Participants were asked to choose one of five "ideal" preferences, ranging from 1 "the doctor should make the decisions using all that's know about the treatments" to 5 "I should make the decisions using all I know or learn about the treatments." We dichotomized this item to represent either "high" (a value of 3 or above) or "low" (a value of 2 or lower) desire for agency in medical decision-making, with 3 representing equal involvement of doctor and patient in decisions making.

At a **patient level**, we asked participants five questions about the importance of specific barriers to PrEP, each rated on a five-point scale (1 = not at all important; 5 = extremely important). Barriers included concerns that: a) I have to take a pill every day; b) people will see me taking the medication and will want to know why I'm taking it; c) people will see me taking the medication and think that I have HIV; and d) PrEP does not provide complete protection against HIV infection. For analysis, each barrier was dichotomized into 4-5 "important" versus 1-3 "not important." Finally, participants were presented with a list of sexual behaviors and asked to rate whether taking PrEP would make these behaviors more or less risky (5 point scale, 1 = much less risky; 3 = no change; 5 = much more risky). In order to assess whether participants believe that sexual behavior is less risky on PrEP, we chose three behaviors -- condomless anal insertive sex, condomless anal receptive sex, and sex with an HIV-positive partner – and coded whether the participant believed that this behavior was less risky on PrEP (i.e., 3 or below).

Finally, we asked several questions ascertaining potential factors that might catalyze PrEP adoption intentions (e.g., "Not having to pay for PrEP"; "Access to text-based support on PrEP use"). These factors, which we explored previously in our work,[34] [blinded for review] were informed by literature reviews and consultation with PrEP experts; the response

options were on a 5-point Likert scale which we dichotomized for analyses into low versus high scores.

Statistical Analysis—Analyses were conducted in using SPSS software 22 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). As these data are drawn from a larger study of PrEP messaging factors, we first verified that there were no differences by study condition on any of the variables included in these analyses. Initial bivariate analyses examined demographic and behavioral differences between the Black, Latino, and other MSM in our sample, using chi-square for categorical variables, t-tests for continuous variables, and non-parametric tests for count variables. Then, logistic regression models were used to examine differences by race/ethnicity on variables within each of the three types of barriers to PrEP access – system, provider, and patient. We calculated both crude odds ratios (ORs) and ORs adjusted for socioeconomic status (SES) by including education and income (whether or not participants held a Bachelor's degree or earned $10,000 or less annually). In preliminary analyses, there were no significant differences between Black and Latino MSM on the variables of interest; rather, MSM from each of the two racial/ethnic groups demonstrated the same pattern of difference from the rest of the sample. As such, our final analyses below combine Black and Latino participants (BLMSM) and compare them with other MSM. This analytic decision was made for parsimonious reporting; however, the limitations of this approach and the importance of further data collection on Black and Latino MSM separately are discussed below.

RESULTS

Table 1 outlines the characteristics of the sample and compares BLMSM to other MSM in terms of demographic factors and HIV risk and prevention behavior. BLMSM were significantly more likely than other MSM to make less than $10,000/year and were less likely to have a bachelor's degree. BLMSM were also more likely to be between the ages of 18 and 29 and were less likely to identify as gay. There were no differences in race/ethnicity by relationship status, frequency of last HIV test, or reported willingness to use PrEP. Black and Latino participants reported a greater number of sexual partners in the past 30 days; however, there were no differences in the number of condomless sex acts. Black and Latino participants reported that a significantly smaller percentage of their total anal sex acts were condomless (56% compared to 66% for other MSM, $p < .001$). There were no differences in substance use or heavy drinking days by race/ethnicity.

Barriers to PrEP Access and Uptake

Table 2 displays odds ratios and adjusted odds ratios for each potential PrEP barrier, comparing BLMSM to the rest of the sample. Even after adjusting for education and income, BLMSM were significantly less likely to have private health insurance and more likely to have public insurance (aOR .45, 95% CI: .29-.68; $p< 0.001$; and aOR 3.2, 95% CI: 1.9-5.2; $p< 0.001$, respectively). Further, BLMSM were significantly more likely to access health care via public clinics (aOR 2.4, 95% CI: 1.2-4.7; $p< 0.01$). Identification as gay was included as a systems-level barrier, because many PrEP programs are being implemented through gay-focused health centers. Although BLMSM were significantly less likely to

identify as gay in bivariate testing, this difference was no longer present after adjusting for SES.

In terms of provider level barriers to PrEP, BLMSM were significantly more likely to regard having to talk to their doctor about their sex life as a barrier to seeking PrEP (aOR 3.7, 95% CI: 2.1-6.6; $p< 0.001$). Additionally, BLMSM scored lower on desire for agency in participating in medical decisions (aOR .58, 95% CI: .38-.87; $p< 0.001$). A high percentage of participants (75%) reported having a regular provider (369/491), and this factor did not differ by race/ethnicity.

At the patient level, BLMSM were significantly more likely to endorse stigma-related concerns related to PrEP, including concerns that others will notice they are taking a pill and want to know why (aOR 2.3, 95% CI: 1.5-3.8; $p< 0.001$) and people will see them taking a pill and think they are HIV-positive (aOR 2.1, 95% CI: 1.3-3.3; $p< 0.01$). Having to take a pill a day was more likely to be a concern for BLMSM than for the rest of the sample (aOR 2.4, 95% CI: 1.6-3.7; $p< 0.001$). BLMSM had consistently lower beliefs regarding PrEP efficacy. As such, they were significantly less likely than the rest of the sample to believe that PrEP would reduce the risk of HIV acquisition during anal condomless receptive (aOR .61, 95% CI: .40-.92; $p< 0.05$), insertive sex (aOR .51, 95% CI: .33-.80; $p< 0.01$), or sex with an HIV-positive partner (aOR .61, 95% CI: .40-.91; $p< 0.01$). Lastly, BLMSM were significantly more likely to indicate concerns that PrEP does not provide complete protection against HIV (aOR 1.6, 95% CI: 1.1-2.4; $p< 0.05$).

Facilitators to PrEP Access and Uptake

Table 3 presents results from comparisons between the two groups of interest regarding facilitators of PrEP adoption. BLMSM, even after adjusting the models for SES, differed significantly from the rest of the sample in the importance they attributed to the following facilitators of PrEP uptake at the systems level: having access to free HIV testing and counseling (aOR 2.1, 95% CI: 1.3-3.3; $p< 0.01$); having access to free sexual health care while on PrEP (aOR 2.1, 95% CI: 1.3-3.3; $p< 0.01$); at the provider level: access to support or counseling about their sex life (aOR 2.5, 95% CI: 1.7-3.7; $p< 0.001$); access to one-on-one counseling and support for PrEP use (aOR 2.6, 95% CI: 1.6-3.9; $p< 0.001$); and at the patient-level: access to text-based support for PrEP use (aOR 2.4, 95% CI: 1.6-3.7; $p< 0.001$); and access to group adherence PrEP support (aOR 2.4, 95% CI: 1.6-3.6; $p< 0.001$). Finally, there were no differences between the groups in how important it would be not to pay for PrEP (Table 3).

DISCUSSION

This analysis was designed to identify differences between Black and Latino MSM (BLMSM) and other MSM (who were predominantly White) that are most relevant to the first three steps of the PrEP cascade – interest, access, and prescription. Our goal was to identify key factors that might be integrated into PrEP uptake and sustainability strategies for MSM of color in the United States. Although they were similar to other MSM in terms of sexual behavior, HIV testing patterns and stated intentions to adopt PrEP, BLMSM demonstrated significant and distinct multilevel barriers to PrEP adoption that may disrupt

their ability to access and engage with PrEP programs. At the patient level, BLMSM were significantly more likely to endorse stigma-related barriers to PrEP use (i.e., concerns about others seeing them taking the medication) and were significantly less likely to believe in the efficacy of PrEP (i.e., that taking PrEP reduces the risk associated with condomless sex), compared to other MSM. At the provider-level, BLMSM were more likely to report that talking to their provider about sex is a barrier to PrEP and expressed lower agency for medical decision-making. At the systems-level, BLMSM were less likely to identify as gay, more likely to receive care at a public clinic and more likely to be publically insured.

These findings suggest a complex set of barriers to BLMSM's interest/engagement in PrEP, including a potential skepticism of the medical establishment in general[47,48] (by being apprehensive about discussing their sex lives with their doctors, lacking a sense of agency in their own medical decision power, and not trusting the proven efficacy of PrEP.) These barriers are similar to those identified for HIV treatment among individuals of color, including a lack of trust in HIV-related care [49,50] and the efficacy of anti-retroviral medication in particular,[47] fueled by the awareness that optimal courses of treatment are at times not offered by racist and homophobic providers.[34,51,52] Our failure to adequately address inequity and discrimination in HIV prevention and care has the potential to further exacerbate disparities in the epidemic, and evidence is emerging showing that young BMSM are often not offered the option of PrEP.[14]

Not surprisingly, our BLMSM participants isolated having to talk to their doctor about their sex life as a significant barrier to PrEP compared to the rest of the sample. These findings are disconcerting given the CDC PrEP guidelines recommending discussing patient's sexual patterns in the context of PrEP education and counseling.[35] However, such discussions will likely not be initiated by patients, nor are they normatively practiced by providers, especially in HIV testing contexts,[35,53-55] where PrEP introduction may be ideal yet curtailed due to potential provider homophobia.[56] As one intervention step for the immediate future, providers may wish to purposefully incorporate the opening of such discussions into their routine practice, and in such a way that it is culturally sensitive to the patient and agentic in lowering their own and patient's discomfort around having these conversations. In fact, there is evidence that LGBT-affirmative training for medical providers has the potential to lower stigmatizing attitudes and increase cultural competency,[57,58] including towards treating sexual and gender minorities equitably.[59] Exposure to such trainings for all level medical staff would be ideal.

Even for BLMSM who may be as ready to adopt PrEP as their counterparts, the ways in which PrEP programs are currently configured may not be meeting their needs.[60] The fact that significantly fewer BLMSM identify as gay leads to the inference that they might also be less likely to present for care at an LGBT-based health centers or programs, where PrEP is currently primarily promoted. This finding leads us to suggest that public-based facilities where BLMSM may utilize for routine check-ups (such as STD or primary care clinics), should actively promote PrEP via displayed waiting and exam room brochures, pamphlets and posters, as well as during provider interactions, just as HIV testing was not long ago routinely introduced in these practices. Further, programs that provide PrEP but do not include access to facilitators such as supportive services or free sexual health care may not

be truly “available” for BLMSM. PrEP programs must be actively developed with redress of these problems and in response to them. Importantly, BLMSM in our sample were more likely to rate the availability of enhanced services (e.g., access to free sexual health care while on PrEP, access to one-on-one counseling) as important facilitators of PrEP use, compared to their counterparts. These data suggest that BLMSM may want and be receptive to programs that concretely increase health care access in the context of PrEP. The PrEP uptake facilitators suggested by our analyses align with recent encouraging findings of HPTN 073 showing that adherence among BMSM in three cities was high when participants received client-centered care coordination. [61] These procedures, similar to support facilitators found important by our BLMSM sample, entailed tailored coordination of services, including service referrals, linkage and individually tailored follow-up strategies to uphold psychosocial needs that may otherwise pose barriers to PrEP uptake and adherence. Additionally, qualitative data on PrEP facilitator for African-American youth suggest the importance of PrEP provision in settings that are familiar and can provide services without long waits.[62] Text-based adherence supports have been used in PrEP research[63,64] but not integrated into practice. Our findings contribute to a growing body of data suggesting that MSM of color are receptive to mobile health technologies for HIV prevention.[65-67]

Limitations

These findings should be considered in the context of several limitations. Perhaps the most important limitation is that this study was not designed to examine racial/ethnic differences in PrEP-related barriers, and therefore did not include specific questions that might better elucidate culturally competent models for intervention. This lack of culturally-specific barriers is evinced by the fact that Black and Latino MSM did not differ significantly from each other in endorsement of barriers; rather they differed only from their predominately white counterparts. These analyses are not meant to suggest that the specific dynamics of PrEP engagement for Black and Latino MSM are the same, or that strategies to enhance engagement for these groups should be similar. However, these analyses do suggest that MSM of color may face a significantly different set of barriers along the PrEP cascade, and underscore the importance of better understanding how to ameliorate these barriers with culturally-competent and specific strategies. The systemic racism and historic discrimination encountered in medical settings may increase medical mistrust for MSM of color in general, but modes of redress must be examined with an appreciation of the unique cultural contexts in which they may be experienced for Black and Latino MSM separately.

Second, participants in this study were enrolled on a PrEP messaging study, and therefore were interested, at some level, in learning about PrEP, and might be more open to PrEP adoption than the general population of MSM. However, this increased interest would be true for participants regardless of race/ethnicity and so would be unlikely to influence the differential findings presented above. Third, study data were collected from 2012 to 2014, and increased knowledge about and shifting attitudes toward PrEP may influence these barriers and attempts to reduce them. However, given persistent disparities in PrEP adoption, it seems critical to consider these differences in cascade-focused barriers as they relate to enhanced implementation efforts.

CONCLUSIONS

Despite these limitations, this analysis informs a broader understanding of efforts to increase representation of BLMSM along the PrEP continuum of care. Increasing interest in PrEP may involve high-quality education about PrEP efficacy, and increased engagement by trusted community members and representatives. Current PrEP messaging focuses on what PrEP is (i.e., an HIV prevention pill), but less on how we know it works. Increasing access may require ensuring that there are multiple entry points for PrEP services, provided in the settings BLMSM already visit, rather than where we hope to recruit them. Lastly, increasing prescription may require enhancing patient-provider communication about sexual health and involving BLMSM in a meaningful way in their medical decision-making more generally.

ACKNOWLEDGEMENTS

This project was funded by Grant R01MH095565 from the National Institute of Mental Health (S.A. Golub, PI). We gratefully acknowledge the hard work of Anthony Surace, Kailip Boonrai, Inna Saboshchuk, and Dr. Kristi Gamarel. We also thank the participants who gave their time and energy to this study, and Dr. Willo Pequegnat for her support. [blinded for review]

REFERENCES

1. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New Eng J Med. 2010; 363:2587–2599. [PubMed: 21091279]
2. Bangsberg, D.; Haberer, J.; Psaros, C.; Baeten, J.; Katabira, E.; Tumwesigye, E. High adherence and high effectiveness observed in HIV discordant couples: Partners PrEP Study, adherence monitoring and counseling substudy.. Paper presented at: The Conference on Retroviruses and Opportunistic Infections (CROI); Seattle. 2012;
3. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New Eng J Med. 2012; 367:423–434. [PubMed: 22784038]
4. Choopanya K, Martin M, Suntharasamai P, 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; 381:2083–2090. [PubMed: 23769234]
5. Mayer KH, Hosek S, Cohen S, et al. Antiretroviral pre-exposure prophylaxis implementation in the United States: a work in progress. J Int AIDS Soc. 2015; 18:19980–19987. [PubMed: 26198345]
6. Mayer KH, Krakower DS. Editorial Commentary: Scaling Up Antiretroviral Preexposure Prophylaxis: Moving From Trials to Implementation. Clin Infect Dis. 2015; 61:1598–1600. [PubMed: 26270688]
7. Centers for Disease Control and Prevention. [March 31, 2016] Key graphics from CDC analysis showing proportion of people engaged in each of the five main stages of HIV care. 2013. http://www.cdc.gov/nchhstp/ux-test-2015/newsroom/2012/continuum-of-care-graphics.html.
8. Bowers, P. [March 31, 2016] Improving the HIV pre-exposure prophylaxis (PrEP) cascade. 2015. Available at: http://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2015/improving-the-hiv-pre-exposure-prophylaxis-prep-cascade.shtml.
9. Kelley CF, Kahle E, Siegler A, et al. Applying a PrEP continuum of care for men who have sex with men in Atlanta, Georgia. Clinl Infect Dis. 2015; 61:1590–1597.
10. Liu, A.; Colfax, G.; Cohen, S., et al. The spectrum of engagement in HIV prevention: Proposal for a pre-exposure prophylaxis (PrEP) cascade.. Paper presented at: 7th International Conference on HIV Treatment and Prevention Adherence; Miami. 2012;
11. Galindo GR, Walker J, Hazelton P, Lane T, Steward WT, Morin SF. Community member perspectives from transgender women and men who have sex with men on pre-exposure prophylaxis as an HIV prevention strategy: implications for implementation. Implement Sci. 2012; 7:116–129. [PubMed: 23181780]

12. Eaton LA, Driffin DD, Bauermeister J, Smith H, Conway-Washington C. Minimal awareness and stalled uptake of pre-exposure prophylaxis (PrEP) among at risk, HIV-negative, black men who have sex with men. AIDS Patient Care and STDs. 2015; 29:423–9. [PubMed: 26083143]
13. Cohen SE, Vittinghoff E, Bacon O, et al. High interest in preexposure prophylaxis among men who have sex with men at risk for HIV infection: baseline data from the US PrEP Demonstration Project. J Acquir Immune Defic Syndr. 2015; 68:439–448. [PubMed: 25501614]
14. Highleyman, L. [June 30, 2016, 2016] PrEP use is rising fast in the US, but large racial disparities remain.. aidsmap. 2016. http://www.aidsmap.com/PrEP-use-is-rising-fast-in-US-but-large-racial-disparities-remain/page/3065545/.
15. Cairns, G. [April 5, 2016] Gay youth PrEP study finds good retention and reasonable adherence.. aidsmap. 2015. Available at: http://www.aidsmap.com/Gay-youth-PrEP-study-finds-good-retention-and-reasonable-adherence/page/2987813/.
16. Bush, S.; Magnuson, D.; Rawlings, M.; Hawkins, T.; McCallister, S.; Mera Giler, R. Racial characteristics of FTC/TDF for pre-exposure prophylaxis users in the US.. Paper presented at: ASM Microbe 2016; Boston, MA. June 16-20, 2016; 2016.
17. Centers for Disease Control and Prevention. [April 22, 2013] HIV Incidence. 2013. Available at: http://www.cdc.gov/hiv/statistics/surveillance/incidence/index.html.
18. Centers for Disease Control and Prevention. [December 12, 2011] HIV surveillance in adolescents and young adults. 2010. Available at: http://www.cdc.gov/hiv/pdf/statistics_surveillance_adolescents.pdf.
19. Centers for Disease Control and Prevention. [December 12, 2011] HIV surveillance in men who have sex with men. 2010. Available at: http://www.cdc.gov/hiv/pdf/library/slidesets/cdc-hivsurveillance-slides-msm.pdf.
20. Centers for Disease Control and Prevention. [April 22, 2013] HIV among African Americans. 2013. Available at: http://www.cdc.gov/hiv/topics/aa/pdf/HIV_among_African_Americans_final.pdf.
21. Centers for Disease Control and Prevention. [May 5, 2014] Today's HIV/AIDS epidemic. 2013. Available at: http://www.cdc.gov/nchhstp/newsroom/docs/HIVFactSheets/TodaysEpidemic-508.pdf.
22. Hess, KL.; Hu, X.; Lansky, A.; Mermin, J.; Hall, HI. Estimating lifetime risk of a diagnosis of HIV infection in the United States.. Paper presented at: CROI; Boston, MA.. February 22-25, 2016;
23. Sullivan, P.; Liu, A.; Fuchs, J.; Irby, R.; Tarver, R.; Buchbinder, S. Awareness of and intention to use PrEP: a post-iPrEX survey of US MSM.. Paper presented at: National HIV Prevention Conference; Atlanta. 2011;
24. Cohen, S.; Vittinghoff, E.; Anderson, P.; Doblecki-Lewis, S.; Bacon, O.; Chege, W. Implementation of PrEP in STD Clinics and a Community Health Center: High Uptake and Drug Levels among MSM in the Demo Project.. Paper presented at: The Conference on Retroviruses and Opportunistic Infections (CROI); Boston. 2014;
25. Mansergh G, Koblin BA, Sullivan PS. Challenges for HIV pre-exposure prophylaxis among men who have sex with men in the United States. PLoS Med [serial online]. Aug.2012 9:e1001286. [March 1, 2016] Available from: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001286.
26. Taylor SW, Mayer KH, Elsesser SM, Mimiaga MJ, O'Cleirigh C, Safren SA. Optimizing content for pre-exposure prophylaxis (PrEP) counseling for men who have sex with men: perspectives of PrEP users and high-risk PrEP naive men. AIDS and Behav. 2014; 18:871–879.
27. Karris MY, Beekmann SE, Mehta SR, Anderson CM, Polgreen PM. Are we prepped for preexposure prophylaxis (PrEP)? Provider opinions on the real-world use of PrEP in the United States and Canada. Clin Infect Dis. 2013; 58:704–12. [PubMed: 24319083]
28. Ayala G, Makofane K, Santos G-M, et al. Access to basic HIV-related services and PrEP acceptability among men who have sex with men worldwide: barriers, facilitators, and implications for combination prevention. J Sex Transm Dis. 2013; 2013:1–11.
29. Bronfenbrenner, U. The Ecology of Human Development : Experiments by Nature and Design. Harvard University Press; Cambridge: 1979.

30. Golden SD, Earp JA. Social ecological approaches to individuals and their contexts: twenty years of health education & behavior health promotion interventions. Health Educ Behav. Jun; 2012 39(3):364–372. [PubMed: 22267868]
31. Baral S, Logie CH, Grosso A, Wirtz AL, Beyrer C. Modified social ecological model: a tool to guide the assessment of the risks and risk contexts of HIV epidemics. BMC Public Health. 2013; 13:482–490. [PubMed: 23679953]
32. Latkin CA, Knowlton AR. Micro-social structural approaches to HIV prevention: a social ecological perspective. AIDS Care. Jun; 2005 17(Suppl 1):S102–113. [PubMed: 16096122]
33. Golub SA, Gamarel KE, Rendina HJ, Surace A, Lelutiu-Weinberger CL. From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and Mmtivations for adherence among MSM and transgender women in New York City. AIDS Patient Care and STDs. 2013; 27:248–254. [PubMed: 23565928]
34. Centers for Disease Control and Prevention. [December 4, 2015] Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014 Clinical practice guidelines. 2014. Available at: http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf.
35. Sullivan PS, Salazar L, Buchbinder S, Sanchez TH. Estimating the proportion of HIV transmissions from main sex partners among men who have sex with men in five US cities. AIDS. 2009; 23:1153–1162. [PubMed: 19417579]
36. Goodreau SM, Carnegie NB, Vittinghoff E, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? PLoS One. 2012; 7:e50522. [PubMed: 23209768]
37. Mitchell JW, Harvey SM, Champeau D, Seal DW. Relationship factors associated with HIV risk among a sample of gay male couples. AIDS Behav. 2012; 16(2):404–411. [PubMed: 21614560]
38. Hoff CC, Beougher SC, Chakravarty D, Darbes LA, Neilands TB. Relationship characteristics and motivations behind agreements among gay male couples: differences by agreement type and couple serostatus. AIDS Care. 2010; 22:827–835. [PubMed: 20635246]
39. Gomez AM, Beougher SC, Chakravarty D, et al. Relationship dynamics as predictors of broken sexual agreements about outside sexual partners: implications for HIV prevention among gay couples. AIDS Behav. 2012; 16:1584–1585. [PubMed: 22020757]
40. Sobell, LC.; Sobell, MB. Timeline FollowBack user's Guide: A Calendar Method for Assessing Alcohol and Drug Use. Addiction Research Foundation; Toronto: 1996.
41. National Institutes of Health. [March 31, 2016] Reporting race and ethnicity data. 2013. Available at: http://grants.nih.gov/grants/funding/women_min/race_ethnicity_qa.htm#3735.
42. Schneider J, Bouris A, Smith D. Race and the public health impact potential of PrEP in the United States. J Acquir Immune Defic Syndr. 2015; 70:e30–2. [PubMed: 25950209]
43. National Institutes of Health. [March 31, 2016] Racial and ethnic categories and definitions for NIH diversity programs and for other reporting purposes. 2015. Available at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-089.html.
44. Centers for Disease Control and Prevention. [August 20, 2014] Gay and bisexual men's health. HIV/AIDS. 2014. Available at: http://www.cdc.gov/msmhealth/HIV.htm.
45. Sutherland HJ, Llewellyn-Thomas HA, Lockwood GA, Tritchler DL, Till JE. Cancer patients: their desire for information and participation in treatment decisions. J R Soc Med. 1989; 82:260–263. [PubMed: 2754680]
46. Bogart LM, Thorburn S. Are HIV/AIDS conspiracy beliefs a barrier to HIV prevention among African Americans? JAIDS Journal of Acquired Immune Deficiency Syndromes. 2005; 38(2):213–218. [PubMed: 15671808]
47. Bogart LM, Thorburn S. Are HIV/AIDS conspiracy beliefs a barrier to HIV prevention among African Americans? J Acquir Immune Defic Syndr. 2005; 38:213–218. [PubMed: 15671808]
48. Gwadz MV, Colon P, Ritchie AS, et al. Increasing and supporting the participation of persons of color living with HIV/AIDS in AIDS clinical trials. Curr HIV/AIDS Rep. 2010; 7:194–200. [PubMed: 20737252]
49. Gwadz M, Leonard N, Nakagawa A, et al. Gender differences in attitudes toward AIDS clinical trials among urban HIV-infected individuals from racial and ethnic minority backgrounds. AIDS Care. 2006; 18:786–794. [PubMed: 16971289]

50. Christopoulos K, Das M, Colfax G. Linkage and retention in HIV care among men who have sex with men in the united states. Clin Infect Dis. 2011; 52:214–222.
51. Voisin DR, Bird JD, Shiu C-S, Krieger C. “It's crazy being a Black, gay youth.” Getting information about HIV prevention: a pilot study. J Adolesc. 2012; 36:111–119. [PubMed: 23218485]
52. Metsch LR, Pereyra M, del Rio C, et al. Delivery of HIV prevention counseling by physicians at HIV medical care settings in 4 US cities. Am J Public Health. 2004; 94:1186–1192. [PubMed: 15226141]
53. Laws MB, Bradshaw YS, Safren SA, et al. Discussion of sexual risk behavior in HIV care is infrequent and appears ineffectual: a mixed methods study. AIDS Behav. 2011; 15:812–822. [PubMed: 20981480]
54. Wimberly YH, Hogben M, Moore-Ruffin J, Moore SE, Fry-Johnson Y. Sexual history-taking among primary care physicians. J Natl Med Assoc. 2006; 98:1924–1929. [PubMed: 17225835]
55. Bernstein KT, Liu K-L, Begier EM, Koblin B, Karpati A, Murrill C. Same-sex attraction disclosure to health care providers among New York City men who have sex with men: Implications for HIV testing approaches. Arch Intern Med. 2008; 168:1458–1464. [PubMed: 18625927]
56. Beach MC, Price EG, Gary TL, et al. Cultural competency: A systematic review of health care provider educational interventions. Med Care. 2005; 43:356–373. [PubMed: 15778639]
57. Drain PK, Primack A, Hunt DD, Fawzi WW, Holmes KK, Gardner P. Global health in medical education: A call for more training and opportunities. Academic Medicine. 2007; 82:226–230. [PubMed: 17327707]
58. Lelutiu-Weinberger C, Pollard-Thomas P, Pagano W, et al. Implementation and evaluation of a pilot training to improve transgender competency among medical staff in an urban clinic. Transgender Health. 2016; 1:45–53.
59. Mays VM, Cochran SD, Zamudio A. HIV prevention research: Are we meeting the needs of African American men who have sex with men? J Black Psychol. 2004; 30:78–105. [PubMed: 20041036]
60. Wheeler, D. [June 27, 2016] HPTN 073 demonstrates client-centered care coordination attains high uptake for PrEP among U.S. BMSM. 2016. Avaialble at: https://www.hptn.org/news-and-events/press-releases/hptn-073-demonstrates-client-centered-care-coordination-attains-high. 2016
61. Smith DK, Toledo L, Smith DJ, Adams MA, Rothenberg R. Attitudes and program preferences of African-American urban young adults about pre-exposure prophylaxis (PrEP). AIDS Educ Prev. 2012; 24:408–21. [PubMed: 23016502]
62. Curran K, Mugo NR, Kurth A, et al. Daily short message service surveys to measure sexual behavior and pre-exposure prophylaxis use among Kenyan men and women. AIDS Behav. 2013; 17:2977–2985. [PubMed: 23695519]
63. Haberer JE. Current concepts for PrEP adherence in the PrEP revolution: from clinical trials to routine practice. Curr Opin HIV AIDS. 2016; 11:10–17. [PubMed: 26633638]
64. Sullivan PS, Grey JA, Rosser BRS. Emerging Technologies for HIV Prevention for MSM: What We have Learned, and Ways Forward. J Acquir Immune Defic Syndr. 2013; 63:S102–S107. [PubMed: 23673879]
65. Muessig KE, Pike EC, Fowler B, et al. Putting prevention in their pockets: developing mobile phone-based HIV interventions for black men who have sex with men. AIDS Patient Care STDs. 2013; 27:211–222. [PubMed: 23565925]
66. Hightow-Weidman LB, Fowler B, Kibe J, et al. HealthMpowerment. org: development of a theory-based HIV/STI website for young black MSM. AIDS Education Prev. 2011; 23:1–12.

Table 1

Sample Characteristics (N=491).

	Total	Black and Latino MSM (n = 277)	Other MSM (n =214)	
	***N*(%)**	**n(%)**	**n(%)**	**Significance**
Age				$p < 0.05$
18-29	233 (47)	144 (52)	89 (42)	
30-49	216 (44)	115 (42)	101 (47)	
50 and above	42 (9)	18 (7)	24 (11)	
Education				$p < 0.001$
Does not have a BA	274 (56)	204 (74)	70 (33)	
BA or more	217 (44)	73 (26)	144 (67)	
Income				$p < 0.001$
<$10,000	151 (31)	113 (41)	38 (18)	
$10,000 to $49,000	255 (52)	142 (51)	113 (53)	
$50,000 to $75,000	42 (8)	15 (5)	27 (13)	
> $75,000	43 (9)	7 (3)	36 (17)	
Sexual Identity				$p < 0.01$
Gay	357 (73)	188 (68)	254 (78)	
Not gay	134 (27)	89 (32)	45 (21)	
Relationship Status				*n.s.*
Single	251 (51)	149 (54)	102 (48)	
In a relationship	240 (49)	128 (46)	112 (52)	
HIV Testing				*n.s.*
Past 6 months	346 (70)	200 (72)	146 (68)	
Over 6 months ago	145 (30)	77 (28)	68 (32)	
Likelihood of taking PrEP				*n.s.*
Maybe or definitely not	162 (33)	84 (30)	78 (36)	
Probably or definitely	329 (67)	193 (70)	136 (64)	
		Mean (SD)	Mean (SD)	
Number of sexual partners		5.1 (6.6)	3.7 (4.0)	$p < 0.01$
Number of condomless anal sex acts		4.88 (5.7)	4.81 (5.4)	*n.s.*
Percent of condomless anal sex acts		55.7 (30.0)	65.7 (31.4)	$p < 0.01$
Days of substance use past month		14 (10.9)	14 (9.3)	*n.s.*
Heavy drinking days past month		3.6 (5.7)	3.3 (4.7)	*n.s.*

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2017 December 15.

Table 2

Race-Ethnicity as Determinant of System-, Provider-, and Patient-Level Barriers to PrEP Access

	BLMSM		Other MSM		Crude Analysis		Adjusted for SES	
	% Yes	95% CI	% Yes	95% CI	OR	95% CI	aOR	95% CI
Systems-Level Barriers								
Insurance Type								
Public	45.6	38.9-50.7	13.1	8.5-17.6	5.4***	3.4-8.6	3.2***	1.9-5.2
Private	35.7	30.0-41.4	67.2	60.9-70.6	.27***	.19-.39	.45***	.29-.68
Uninsured	19.5	14.8-24.2	19.6	14.2-24.9	.99	.63-1.6	.91	.55-1.5
Point of Health care Access								
Private doctor's office	44.2	38.3-50.2	58.8	52.0-66.0	.56**	.39-0.80	.78	.52-1.2
Community Health Center	9.2	5.8-12.7	11.0	6.5-15.0	.84	.46-1.5	.70	.36-1.4
Public Clinic	16.2	11.8-21.1	7.3	3.7-11.1	2.4**	1.3-4.5	2.4**	1.2-4.7
Hospital Clinic or ER	30.2	24.8-35.8	23.0	17.2-28.9	1.4	.96-2.2	1.03	.65-1.6
Identify as gay	68.4	62.3-73.4	78.0	73.4-84.5	.56**	.37-.85	1.01	.63-1.6
Provider-Level Barriers								
Have a regular provider	72.8	67.6-78.1	78.5	73.6-84.1	.73	.48-1.1	.88	.55-1.4
Having to talk to my doctor about my sex life	33.5	28.8-39.2	8.98	5.04-12.7	5.2***	3.0-8.8	3.7***	2.1-6.6
Desire for agency in medical decisions	56.5	50.1-62.4	69.6	63.4-75.8	.55**	.38-.81	.58***	.38-87
Patient-Level Barriers								
Having to take a pill a day	63.1	57.1-68.5	38.5	31.3-44.4	2.7***	2.1-4.0	2.4***	1.6-3.7
People seeing me take it will want to know why	35.5	29.0-40.3	17.2	12.7-21.9	2.6***	1.7-4.1	2.3***	1.5-3.8
People seeing me take it will think I have HIV	33.2	28.3-39.9	18.2	13.0-23.4	2.2***	1.5-3.4	2.1**	1.3-3.3
Efficacy Concerns								
PrEP does not provide complete protection	61.7	56.7-67.5	48.1	41.4-54-9	1.8**	1.2-2.5	1.6*	1.1-2.4
CAR is less risky on PrEP	58.5	52.6-64.3	79.1	73.6-84.1	.52**	.36-.77	.61*	.40-.92
CAI is less risky on PrEP	66.1	60.5-71.7	75.2	70.4-79.9	.53**	.35-.80	.51**	.33-.80

	BLMSM		Other MSM		Crude Analysis		Adjusted for SES	
	% Yes	95% CI	% Yes	95% CI	OR	95% CI	aOR	95% CI
Sex with an HIV+ partner is less risky on PrEP	49.0	43.2-55.0	66.4	60.7-72.7	.22***	.34-.70	.61**	.40-.91

† $p < 0.057$

CAR = condomless anal receptive sex

CAI = condomless anal insertive sex

BLMSM = Black and Latino MSM

SES = socioeconomic status (includes whether or not the participant had a Bachelor's degree, and earned above or below $10,000 annually)

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 3

Racial-Ethnic Differences in System-, Provider-, and Patient-Level Facilitators of PrEP adoption among PrEP-Eligible MSM

	BLMSM		Other MSM		Crude Analysis		Adjusted for SES	
	% Yes	95% CI	% Yes	95% CI	OR	95% CI	aOR	95% CI
Systems-Level Facilitators								
Access to free HIV testing	84.5	79.4-88.1	65.9	59.5-72.3	2.7**	1.7-4.1	2.1*	1.3-3.3
Access to free sexual health care while on PrEP	83.7	78.2-87.2	68.2	62.4-74.5	2.2**	1.5-3.4	2.1*	1.3-3.3
Not having to pay for PrEP	84.5	79.1-88.1	80.1	74.5-85.3	1.3	.82-2.1	1.5	.95-2.7
Provider-Level Facilitators								
Access to one-on-one counseling and support for PrEP use	82.1	77.0-86.1	60.0	53.1-66.4	3.1**	2.1-4.5	2.6**	1.6-3.9
Access to support or counseling about my sex life	62.8	57.1-68.5	40.1	30.4-43.4	2.9**	2.1-4.2	2.5**	1.7-3.7
Patient-Level Facilitators								
Access to text-based support for PrEP use	71.5	65.3-76.1	45.3	38.6-52.1	2.9**	2.0-4.2	2.4**	1.6-3.7
Access to group adherence PrEP support	60.2	54.1-66.3	30.1	23.7-36.1	3.5**	2.4-5.1	2.4**	1.6-3.6

BLMSM = Black and Latino MSM

SES = socioeconomic status (includes whether or not the participant had a Bachelor's degree, and earned above or below $10,000 annually)

* $p < 0.01$

** $p < 0.001$