Summary Overview

Project Title:	Developing a training curriculum for primary care doctors on how to increase Pre-exposure prophylaxis (PrEP) screening, uptake, and adherence among men who have sex with men (MSM) and transgender (TG) patients
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Project Description: This research project will examine the efficacy of PrEP and identify best practices in screening, uptake, and adherence (i.e. PrEP cascade) to MSM, TP, and vulnerable subpopulations in the United States. We will conduct a systematic review of best practices and employ meta-analyses where data is available to identify the elements of an evidence based PrEP cascade curricula for primary care doctors. Our intent is to use the reviews and meta-analysis to identify best practice approaches for pre- and post-graduate trainees and practicing physicians at every point in the PrEP cascade.

Research Description and Policy Relevance

Gay, bisexual and transgendered individuals (GBT) have much higher rates of HIV infection in the United States than their heterosexual counterparts[1-5] While accounting for only 2% of the US population, MSM (including bisexual and MSM/bisexual injection drug users) make up 58.32% of persons with HIV in the country and there continues to be a trend toward increase in this population and a trend toward decrease in the heterosexual population[6]. There is much less data on transgender individuals' HIV disparities, however two studies found elevated rates among the trans-female population (assigned male at birth but whose gender identity is that of a woman)[4,5]. While behavioral prevention intervention has been effective, more is needed to prevent HIV infection among these populations.

PrEP has been tested in multiple studies[7-13], and meta-analyses[14,15] have found that PrEP, when used consistently, significantly decreases HIV infection rates. While empirical support for this intervention is well established adherence to the medication

varies widely across studies[16]. The adherence rates when measured through blood concentrations of Tenofovir range from 26 to 81% and the corresponding efficacy of the intervention varied accordingly[17]. In three studies where drug levels were examined in case controlled sub-studies the difference in infection rates was striking (84-92%) over placebo[18]. While some factors such as heavy alcohol use and younger age tend to decrease adherence[18], other factors including partner support and increased perception of risk are associated with increased adherence.[19] While there remain questions to be addressed in regard to PrEP efficacy, the evidence for effectiveness is fairly clear.

The strong evidence supporting PrEP efficacy indicates that further development and dissemination of evidence based guidelines for screening, uptake, and adherence into clinical settings is the next step[20]. Several studies cite primary care physician discomfort in addressing sexual behavior, particularly among LGBT populations, lack of medical information about PrEP, poor adherence by patients, logistical concerns around lab testing and monitoring, and lack of time for retention counseling as barriers to prescribing PrEP.[25] This lack of clarity is mirrored by potential patients that could benefit from PrEP. These patients are either unaware about PrEP, unsure of its efficacy, confused about its use, and/or unaware of how to obtain it. [21-25] Patient knowledge/interest regarding PrEP is one germane issue to effective screening for PrEP use, as well as identifying strategies to identify those potential MSM and TG patients that could benefit from this prevention method.

Rationale

PrEP has been found in several studies to be efficacious in halting the transmission of HIV. This is of particular importance in regards to young Black MSM and transgender females in that it is estimated that 1 in two will develop HIV in their lifetime. Additionally, this project is directly in line with the National HIV/AIDS prevention strategy in that findings will better equip doctors to reduce incidence of HIV particularly among populations identified as at elevated risk for infection including bi-sexual men, Black and Latino MSM, and transgender persons. Finally, while our findings and subsequent curriculum development will be national in scope, our own experience in providing PrEP education to both physicians and prospective consumers in the Southern United States in Memphis and Nashville, TN as well as Jackson, MS will also be included as this region is one noted in the National Strategy as having the highest prevalence of HIV in the nation, among the aforementioned populations.

Adherence to anti-retroviral therapies (ART) has been shown to result in viral suppression and reduced transmission risk**.** However, HIV treatment providers have met many barriers to treatment adherence among patients that face real and tangible risk as a result of being infected with HIV. Persons recommended for PrEP engage in similar behaviors and face similar barriers to their infected counter parts, while lacking a diagnosable disease that is the impetus for treatment adherence for many persons living with HIV (PLH). The known factors associated with ART adherence, stigma, lack of resources, drug and alcohol use, may all play a role in PrEP non-adherence. Questions regarding barriers to initiating and remaining adherent to PrEP clinical guidelines will be examined in the literature as well as effective interventions for increasing PrEP screening, uptake and adherence.

Physician attitudes and implicit bias regarding MSM and TG patients also have been shown to affect health outcomes. Our accompanying research project will study the impact of teaching medical students how to recognize and address implicit bias in working with LGBT patients on patient care and health outcomes. These findings will inform this present work and be included in the dissemination materials developed as a part of this research project.

Finally, epidemiological data regarding HIV transmission and treatment outcomes show stark differences in infection rates and treatment outcomes between different racial and ethnic groups, as well as patients who have lower access to resources and/or are exposed to adverse social determinants. More comparative studies are needed to understand the effects of these factors on practice**.** We will analyze the existent literature to identify differences in PrEP uptake and preventive outcomes between demographic groups.

Research Project Goals

We will use the findings from this review to:

1. Link the core components of effective PrEP screening, delivery, and adherence training to present AAMC and ACGME competencies.
2. Develop a model PrEP educational curriculum for training pre- and post-graduate trainees and primary care providers with PrEP screening, uptake, and adherence strategies for MSM and TG persons and other high risk populations.

Hypotheses/Research Questions

We plan to address these two research project goals using a combination of meta-analysis when data is available and systematic literature review when sufficient secondary data is not available. Finally, should neither sufficient secondary data nor information in the literature be available to accomplish either of these strategies we will propose additional studies to fill gaps in the research.

Research questions will be posed that correspond to each to the following domains:

<u>Efficacy</u>

1. What demographic and behavioral factors are associated with effective PrEP uptake and adherence outcomes for MSM/TG?
2. Are strategies needed to increase the PrEP cascade cost effectiveness?

<u>Recruitment</u>

3. What PrEP screening strategies are most effective in identifying appropriate patients?

<u>Monitoring</u>

4. What PrEP monitoring protocols are most effective in identifying non-adherence?
5. What PrEP monitoring protocols are most effective in identifying HIV seroconversion?

<u>Adherence</u>

6. What PrEP adherence interventions are most effective?
7. What PrEP adherence interventions are most effective in preventing seroconversion among LGBT and other high risk populations?

8. What PrEP adherence interventions are most effective in preventing seroconversion among sero-discordant MSM?
9. What barriers affect patient uptake and adherence to PrEP?

Physician attitudes and knowledge

10. What are physicians' attitudes and knowledge regrading PrEP delivery?
11. What are physicians' screening, prescribing and adherence practices regarding PrEP?
12. What educational practices change physician PrEP attitudes/knowledge?

Geographic Coverage: Our research will be national in scope, covering the entire United States.

WORK PLAN

Goal 1: Link the core components of effective PrEP screening, delivery, and adherence training to present AAMC and ACGME competencies.

Methodology

1. We plan to conduct systematic reviews and meta-analyses on PrEP screening, uptake, and adherence in pre- and post-doctoral medical education. Full text articles will be assessed by the two independent reviewers and included based on several criteria including: (a) being published in English; (b) address the topic of PrEP implementation with GBT; (c) conducted with a population from the US; and (d) medical resident and student training in PrEP implementation. Addressing the need for PrEP implementation among medical residents and students will require the collection of studies using a range of methodologies.
2. We will conduct an exhaustive search of the literature from 2006 until present using Scopus, PubMed, EBSCOhost, Web of Science, Ovid, and Google Scholar. We will begin this search with the terms: pre-exposure prophylaxis; men that have sex with men; MSM; transgender; trans female; HIV infection; risk reduction; relative risk; training; and efficacy. Should additional search terms relevant to the above questions be identified during the search, they will be added in subsequent searches.
3. We will review the references of each of the selected articles to identify additional articles that may have been missed in the initial search.
4. We will target MSM and TG of all races and ethnicities, and also delineate other vulnerable populations within the larger population of Black and Latino MSM and TG persons and those living in the South. Other vulnerable populations may include homeless persons and migrant workers.
5. We will conduct a web-based scan of medical education and primary care residency training programs of curriculum to increase PrEP screening, uptake and adherence.

6. We will identify model curricula and content experts to participate in a community of practice to help develop recommendations to increase the PrEP cascade among medical students and residents.
7. We will submit a questionnaire to all 141 medical schools to obtain information on how they are educating students to increase PrEP screening, uptake and adherence.
8. We will compare the effectiveness of training methods reported by schools currently providing the PrEP cascade in their curricula to the best evidence that is amassed through the meta-analysis and narrative review.
9. We will use the meta-analytic approach to address research questions 1 and 2, and relevant studies while articles that do not meet the guideline criteria will be summarized narratively. We recognize that meta-analyses offer the most conclusive evidence on effectiveness, but also acknowledge that important clinical training material may come from studies that cannot be included in meta-analysis.
10. We will code all studies meeting inclusion criteria for demographic characteristics, socioeconomic factors, and sexual orientation. Reliabilities will be calculated using intra-class correlations (r_1) for continuous variables and kappa for categorical variables[26]. Coding disparities will be resolved by consensus.
11. We will disseminate the evidence base we compile to the medical schools and primary care residency training programs to ensure these educators have the most up to date data on the efficacy of interventions to increase PrEP screening, uptake, and adherence.

In table one we estimate the likely available data and types of studies and link these to research questions and likely search terms. Table 1. Illustrates the domains, research questions, likely studies to be reviewed, and search terms to be used to answer each research question.

Table 1. Research Questions and Search Strategy

PrEP Component	Research questions	Types of Studies	Search Terms
Efficacy	1,2	Meta-analysis	PrEP AND efficacy; outcomes;
		RCT	
		Cost effectiveness	
Recruitment	3	Prospective risk analyses	PrEP AND outreach; social networking; screening;
		RCT	
		Meta-analysis	
		Quasi-experimental	
		Qualitative	
Monitoring	4	RCT	

	5	Meta-analysis	PrEP AND monitoring; self-report; DBS; HIV screening
Adherence	6,7,8,9	Meta-analysis	(PrEP AND adherence) AND case-management; counseling; risk reduction; patient navigation
		RCT	
		Quasi-experimental	
Physician attitudes/knowledge	10,11,12	Surveys	PrEP AND physician attitudes; physician knowledge; educational intervention; training
		Qualitative studies	
		Quasi-experimental	
		RCT	

Goal 2: Develop a model PrEP educational curriculum for training pre- and post-graduate trainees and primary care providers with PrEP screening, uptake, and adherence strategies for MSM and TG persons and other high risk populations.

Methodology

1. We will disseminate the curriculum to increase PrEP screening, uptake, and adherence to LGBT populations to AAMC, ACGME and other appropriate audiences at professional conferences.
2. We will disseminate the results of the curriculum to increase PrEP screening, uptake, and adherence to LGBT populations through a minimum of two scholarly publications.
3. We will provide training and technical assistance to schools implementing the recommended curriculum.

Limitations

The main limitation of this project will be any lack of available data or literature describing best practices in the various aspects of PrEP delivery noted in the research questions above. While this is an initial limitation, the systematic reviews of the literature we conduct will illuminate the gaps in the literature and suggest needed research that our team will seek to fill through additional research we ourselves will conduct.

Evaluation Plan:

1. Develop a structured format for conducting a systematic review of the literature
    a. Identify key search “mesh” terms.
    b. Identify repositories to be searched.
    c. Identify timeframe for search.
2. Conduct systematic review of literature.
3. Finalize list of articles to be included in report
4. Apply evidence-based review criteria to analyze final list of articles.
5. Establish a community of practice on PrEP uptake and adherence.
6. Summarize evidence base for increasing PrEP uptake and adherence by medical student and physician residents.

7. Summarize evidence base for physician bias training for post-graduate primary care education.
8. Identify gaps in the literature.
9. Conduct a survey of medical education programs about coverage of PrEP uptake and adherence in medical school curricula.
10. Conduct a survey of primary care resident physicians on prescribing PrEP and monitoring adherence.
11. Develop a report of the need, evidence base, and current status of medical school and post graduate primary care residency training program curricula on prescribing PrEP and monitoring adherence.
12. Disseminate report findings on prescribing PrEP and monitoring adherence to medical school curriculum committees.
13. Disseminate report findings on prescribing PrEP and monitoring adherence to graduate medical education primary care program directors.
14. Disseminate findings to general audience of primary care providers about prescribing PrEP and monitoring adherence.

Human Subjects Research: This project does not involve human subjects.

Key Staff Qualifications and per cent of time on research project:

R. Lyle Cooper, PhD (PI), has been a Licensed Clinical Social Worker since 2005. Dr. Cooper has worked with the LGBT population since 1999 when he began his work as an HIV outreach worker funded through the NIDA Indigenous Street Outreach Worker Model Study. He presently serves as PI on an NIAID sub award from the Tennessee Center for AIDS Research examining the role of stress (as measured through salivary cortisol) related to racial and sexual orientation discrimination and HIV related stigma among Black men that have sex with men (MSM), and the role of this stress in HIV disease progression. He is also the PI on a SAMHSA funded study to reduce HIV risk behaviors and substance abuse among young Black MSM. He is also an experienced educator with 14 years of teaching experience. He has served on curriculum committees, and developed two specializations, the Spalding University Alcohol and Drug Counseling Specialty Certificate, and the University of Tennessee, College of Social Work's Doctorate in Clinical Social Work program, where he worked on the committee that developed the program.

Matthew Morris, PhD (Co-PI)**,** has been licensed as a clinical psychologist with Health Service Provider designation in the state of Tennessee since 2013. Dr. Morris is PI of an ongoing NIMH-funded project examining neuroendocrine and psychosocial risk factors for posttraumatic stress disorder and major depressive disorder in young adult women recently exposed to physical or sexual assault (K01 MH10143). He has expertise in the assessment of trauma exposure and trauma-related psychopathology through semi-structured psychiatric interviews and in the measurement of hypothalamic-pituitary-adrenal axis and sympathetic nervous system diurnal secretion and stress reactivity through saliva (i.e., cortisol and alpha-amylase levels) and hair samples (i.e., cortisol concentrations). In addition, Dr. Morris has conducted health disparities research on racial

differences in pain sensitivity in African-American and Non-Hispanic White youth and has expertise in the implementation of experimental pain protocols.

Paul D. Juarez, PhD, Program Director is Vice Chair for Research in the Department of Family and Community Medicine and Director of the Health Disparities Research Center of Excellence at Meharry Medical College and serves as the Director of the Tennessee Area Health Education Center (AHEC). Dr. Juarez also is PI of a research grant to increase PrEP uptake and adherence among young black MSM in Memphis, TN and previously served as the PI of the Nashville Urban Partnership Academic Center of Excellence to Prevent Youth Violence.

Mohammad Tabatabai, PhD, Director, Statistical Methods, is a Professor of Biostatistics at Meharry Medical College. Dr. Tabatabai current research is in cancer modelling, premature death, diabetes in Mid-Cumberland region of Tennessee, and HIV/HCV co-infection. He is a member of the research team preparing to analyze the combined Meharry-Vanderbilt data on HIV/HCV coinfection. He is also a member of the Biostatistics and Biomedical Informatics Core (BBIC) for the Tennessee Center for AIDS Research (TN-CFAR) assisting HIV researchers with the design and analysis of their research proposals. The BBIC provides statistical and biomedical informatics support to HIV/AIDS investigators at Meharry Medical College, Vanderbilt University, and the Tennessee Department of Health. He has recently joined the Research Design, Biostatistics and Clinical Research Ethics (DBRE) Core of the Meharry Clinical and Translational Research Center (MeTRC). He has done extensive research in breast, brain, prostate cancer as well as modeling tumor growth such as glioblastoma multiform type IV, hypertabastic survival analysis and their applications in medical genomics, robust linear and nonlinear regression models including logistic, probit and multinomial regression models and cellular growth models. Dr. Tabatabai has recently been honored with the prestigious Professor of the Year Award by the Meharry Medical College pre alumni association

Content Expert Consultants:

Leandro Mena, MD, Associate Professor, Internal Medicine, University of Mississippi and Jackson State University.

Tom Arcury, PhD, Professor and Vice Chair for Research, Family and Community Medicine, Wake Forest University

Beth Shinn, PhD, Professor, Vanderbilt University

Other resources needed to carry out the research. None identified

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Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. *Journal of Acquired Immune Deficiency Syndrome, 59*(5):463– 468.

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There may be useful resources on the TARGEt site for Ryan White grantees. For example:
https://careacttarget.org/library/prep-real-world-clinical-case-studies