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Sexually transmitted infections among high-risk populations that use treatment as prevention or pre-exposure prophylaxis: a protocol for a systematic review

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ABSTRACT

Background Among men who have sex with men, pre-exposure prophylaxis (PrEP) reduces the risk of HIV by 95%. Based on the documented benefits, the Centre for Disease Control and Prevention has recommended PrEP as a prevention method for high-risk groups. Moreover, for those HIV-infected individuals, antiretroviral therapy has been shown to serve as both as a treatment and prevention method for HIV.

Methods and analysis This systematic review protocol was reported according to the Preferred Reporting Items for Systematic reviews and Analyses (PRISMA) P framework. Medline (1980–present), Embase (1980–present), CINAHL (1980–present), Cochrane Central Register of Controlled Trials and clinicaltrials.gov will be used to identify relevant articles based on a piloted search strategy. Peer-reviewed observational and experimental studies will be included. A narrative style will be used to describe descriptive data. A meta-analysis will be conducted if heterogeneity is not significant.

Ethics and dissemination Recent evidence suggests that there is an increased risk of sexually transmitted infections (STIs) among high-risk persons that use PrEP. Furthermore, there is a paucity of data on the relationship of treatment as prevention and incidence of STIs. The findings of this review will assess this emerging public health phenomenon and serve to inform future public health policy. No formal ethical review is required for this protocol. All findings will be published in a peer reviewed journal.

PROTOCOL registration number CRD42019128720.

Strengths and limitations of this study

- This protocol was registered with PROSPERO, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) P guidelines were followed for reporting.
- Two reviewers will conduct screening and data extraction to reduce bias.
- Heterogeneity of results will be assessed.
- Grey literature will be excluded.

INTRODUCTION

According to the United Nations (UNAIDS), as of 2017, there were 36.9 million people living with HIV globally.[1] About 21.7 million of them were on antiretroviral therapy (ART).[1] Advances in preventive measures for HIV have led to the use of ART by HIV-uninfected persons to prevent the acquisition of HIV, which is known as pre-exposure prophylaxis (PrEP).[2] PrEP consists of a daily oral regimen of tenofovir alafenamide and emtricitabine.[3–5] PrEP has been shown to reduce the risk of acquisition of HIV.[2 4] Among men who have sex with men, PrEP reduced the risk of HIV by 95%.[3 6] The documented benefits of PrEP resulted in the Centre for Disease Control and Prevention (CDC) guidelines, which recommend PrEP as a prevention method for persons at high-risk for HIV.[4] PrEP is recommended for all populations; however, efficacy is influenced by the differential adherence among groups.[2]

Among HIV-infected individuals, ART has been shown to serve as both a treatment and prevention method for HIV. ART effectively decreases the viral load among HIV-infected persons who are adherent to treatment to an undetectable level, which prevents the transmission of HIV, also known as treatment as prevention (TasP).[7] This phenomenon has been coined U=U, that is, undetectable=untransmittable. TasP has been shown to reduce the risk of mother-to-child transmission of HIV and HIV transmission between HIV discordant couples.[7 8] The risk of HIV transmission can be considered negligible among HIV-infected individuals with an undetectable

viral load adherent to ART who are not coinfected with a sexually transmitted infection (STI).[7]

Literature illustrates that both PrEP and TasP decrease the risk of acquisition and transmission of HIV.[6 9] High incidence rates of STIs among persons receiving PrEP and TasP are also documented.[6] Jenness and colleagues suggest that elevated STI incidence among PrEP users is due to behavioural risk compensation and that PrEP use reduces the use of other disease prevention strategies.[6] Current CDC guidelines recommend biannual screening for STIs among PrEP users.[6] The use of PrEP has no biological effect on the risk of acquiring a bacterial STI.[6] Literature is also unclear with respect to the relationship between PrEP and viral, bacterial and protozoal STIs. Marcus *et al* determined that PrEP was not a protective factor for herpes simplex virus 2 (HSV-2) acquisition, while Celum *et al* determined PrEP provided moderate protection against HSV-2.[10 11] There is a need to explore the behavioural predictors of increased STI incidence among PrEP users. There is a paucity of data with respect to TasP and STI incidence and testing among HIV-infected individuals. Consequently, the current systematic review aims to comprehensively assess available literature to elucidate the relationship between PrEP and TasP and the incidence of STIs.

OBJECTIVES

The objectives of this systematic review are as follows:

- To examine the use of TasP among HIV-infected persons and its associated risk of acquisition of STIs.
- To examine the use of PrEP among high-risk persons for HIV and the associated risk of acquisition of STIs.
- To compare the difference of the associated risk of acquisition of STIs between TasP and PrEP users.

METHODS AND ANALYSIS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) P guidelines were used to report this protocol.[12] This systematic review will be reported according to the PRISMA guidelines.[13]

Protocol registration

This systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019128720 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019128720).

Study selection

Types of studies

Both observational and experimental study designs will be included (cohort, case-control, cross-sectional, case series, case reports and clinical studies).

Types of participants

Persons 12 years and older who are at-risk of transmitting HIV or becoming infected with HIV will be included in the study. Adolescents will be included since the Food and Drug Administration (FDA) has approved the use of PrEP by adolescents.[14]

Types of interventions

- TasP
- PrEP

Types of outcome measures

- Laboratory confirmed or self-reported, incident or prevalent STIs (*Chlamydia trachomatis*, *Neisseria gonorrhoea*, HSV-2, syphilis, human papillomavirus, hepatitis C virus, *Trichomonas vaginalis*).

Eligibility criteria

- Inclusion criteria
  - Research findings published in peer-reviewed journals.
  - Literature published since 2005.
- Exclusion criteria
  - Animal studies
  - Children (11 years and under)
  - Grey literature
  - Dissertations/theses
  - Conference abstracts
  - Studies without reported estimates (risk ratio, OR, CIs, point prevalence)
  - Unpublished studies
  - Protocols

Search strategy

The search strategy will include key-terms and database-specific terminology, for example, Medical Subject Headings (MeSH). We will be using databases including: Medline (1980–present), Embase (1980–present), CINAHL (1980–present), Cochrane Central Register of Controlled Trials and clinicaltrials.gov. We will modify the search strings based on the selected databases. Only studies that occurred since 2005 will be included. The first study which indicated that TasP was effective to reduce the transmission of HIV was published in 2011.[9] PrEP was approved by the FDA in 2012.[15] As such only articles published since 2005 will be included in the review to capture research most relevant to TasP and PrEP interventions. The final PRISMA diagram will be presented. The general search strategy includes: PrEP or TaSP, STIs and HIV. Abbreviations used are included in table 1 We have included the overall search strategy in box 1. Boolean operators AND/OR will be included in the search strategy for the key terms and the MeSH words. The detailed strategy for MEDLINE is included in box 2. No language restrictions will be applied. The search strategy will be pilot tested and finalised.

All three independent reviewers (SK, MC and FS) will meet to identify the screening and data extraction process and conduct the literature search of all databases. The results of each database specific search strategy will be downloaded from the respective databases. We will then import the combined search results into Covidence, a reference software for full screen review and

Table 1 List of abbreviations

ART	Antiretroviral therapy
CDC	Center for Disease Control and Prevention
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HSV-2	herpes simplex virus 2
MeSH	Medical Subject Headings
MSM	men who have sex with men
PrEP	Pre-exposure prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
STI	Sexually transmitted infection
TAF	Tenofovir alafenamide
TasP	Treatment as prevention
UNAIDS	United Nations

citations screening.[16] Duplicates will be checked for and removed. An automated check for duplicate titles and year of publication will be applied. The authors will manually check each possible duplicate before removal to decrease error. The updated library will then be saved. Using Covidence, two independent reviewers (from among SK, MC and FS) will screen the titles and abstracts based on the eligibility criteria identified to determine which studies should be included for full text screening. If any disagreement occurs, two authors will discuss and resolve any issues. If no consensus is reached, the third author will arbitrate. Next, eligible full text articles will be screened by two independent reviewers (from among SK, MC and FS) for inclusion in the data extraction process. If any disagreement occurs, two authors will discuss and resolve any issues. If no consensus is reached, the third author will arbitrate. Reasons for exclusion will be referenced for each article at each stage.

Box 1 Search strategy

Search query

#1 "treatment as prevention" OR TasP OR "pre-exposure prophylaxis" OR PrEP OR Tenofovir OR "emtricitabine-tenofovir" OR truvada OR descovy OR Emtriva OR FTC OR viread OR "tenofovir disoproxil fumarate" OR TDF OR coviracil OR PMPA OR TAF OR "tenofovir alafenamide"
#2 "sexually transmitted infection" OR "sexually transmitted infections" OR STI OR STIs OR "sexually transmitted disease" OR "Sexually transmitted diseases" OR STD OR STDs OR "venereal disease" OR "venereal diseases" OR chlamydia OR syphilis OR "herpes simplex virus type 2" OR HSV2 OR gonorrheagonorrhoea OR trichomoniasis OR "trichomonas vaginalis"
#3 "Human Immunodeficiency VirusHIV" OR HIV OR "human immunodeficiency virusHIV infection" OR "acquired immunedeficiency syndrome" OR AIDS
OR "acquired immuno-deficiency syndrome" OR "human immunedeficiency virus" OR "human immune-deficiency virus"
#4 Search (#1 AND #2 AND #3)

Box 2 Medline search strategy

#1 "treatment as prevention" OR TasP OR "pre-exposure prophylaxis" OR PrEP OR Tenofovir OR "emtricitabine-tenofovir" OR truvada OR descovy OR Emtriva OR FTC OR viread OR "tenofovir disoproxil fumarate" OR TDF OR coviracil OR PMPA OR MESH.EXACT("Pre-Exposure Prophylaxis") OR TAF OR "tenofovir alafenamide"
#2 "sexually transmitted infection" OR "sexually transmitted infections" OR STI OR STIs OR "sexually transmitted disease" OR "Sexually transmitted diseases" OR STD OR STDs OR "venereal disease" OR "venereal diseases" OR chlamydia OR syphilis OR "herpes simplex virus type 2" OR HSV2 OR gonorrheagonorrhoea OR trichomoniasis OR "trichomonas vaginalis" OR MESH.EXACT("Sexually Transmitted Diseases") OR MESH.EXACT.EXPLODE("Chlamydia") OR MESH.EXACT("Syphilis") OR MESH.EXACT("Herpes Genitalis") OR MESH.EXACT("GonorrheaGonorrhoea") OR MESH.EXACT("Trichomonas Infections") OR MESH.EXACT("Trichomonas Vaginitis")
#3 "Human Immunodeficiency VirusHIV" OR HIV OR "human immunodeficiency virusHIV infection" OR "acquired immunedeficiency syndrome" OR AIDS
OR "acquired immuno-deficiency syndrome" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR MESH.EXACT("HIV") OR MESH.EXACT("Acquired Immunodeficiency SyndromeAIDS")
#4 Search (#1 AND #2 AND #3)

Data extraction

Two independent reviewers (from among SK, MC, FS) will independently extract data using a piloted data extraction table from Microsoft Excel. The table will include study details such as title of the study, study design, study setting (including country), publication year, sample size, the intervention details and the outcome details such as HIV and STI incidence or prevalence (with types of laboratory tests to confirm HIV and STI diagnosis). Furthermore, the type of sampling techniques implemented by the study (convenience, snowball, trial and so on), the context of PrEP provision (informal or formal), condom use (before and after PrEP or TasP initiation) and PrEP regimen (daily, on-demand, event-based dosing, the Ts and Ss) will be assessed. These factors will be assessed to adequately evaluate factors which may moderate the association between treatment intervention and the acquisition of STIs.

The two reviewers will meet to resolve and discuss any disagreements. However, if disagreements persist, the third reviewer will arbitrate. For any missing information, the reviewers will contact the corresponding authors to request any updates on the missing items. Authors will be contacted a maximum of three times via email and/or phone. Email will be the first form of contact. If unsuccessful, three attempts will then be made to call the authors.

Data management

Covidence will be used for title and abstract screening and full-text screening. After each round of screening, a backup database will be saved. Reasons for exclusion of articles at each stage will be documented in Covidence.

Data synthesis

All data will be stratified by intervention type. TasP and PrEP populations will not be mixed. Findings for TasP and PrEP populations will be presented independently. Descriptive data will be summarised using a narrative style. A meta-analysis will be conducted if heterogeneity is not a major concern. The I^2 statistic will be used to assess heterogeneity where 25%, 50% and 75% will represent low, moderate and high heterogeneity, respectively.[17] Additionally, the χ^2 test for heterogeneity will also be used. P<0.1 will indicate significant heterogeneity. If heterogeneity is found, p values less than or equal to 0.05 will be considered statistically significant. A Forest plot will be used to graphically assess heterogeneity. The RevMan software will be used to generate the Forest Plot. Measures of association reported by studies to be included in the meta-analysis will be summarised using the random effects model for meta-analysis. If heterogeneity is found, sensitivity and subgroup analyses will be performed. The R Project for Statistical Computing will be used to conduct analyses.

Quality assessment

The Quality Assessment Tool for Quantitative Studies will be used to assess the quality of articles to be included in the systematic review. Deeks *et al* determined this to be an effective assessment tool.[18] Two reviewers (from among SK, MC and FS) will assess the quality of each of the included studies including items on selection bias, randomisation, participation, data collection and intervention integrity. If there are significant differences in scores, raters will discuss and resolve any differences. If differences cannot be resolved, a third rater will arbitrate. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation.

Bias assessment

Risk of bias will be assessed for each of the included studies using the Cochrane Collaboration's tool for the assessment of the risk of bias.[19] RevMan will then be used to develop a funnel plot to graphically assess bias. Two independent reviewers (from among SK, MC and FS) will review each article with the tool including random sequence generation and allocation concealment (for selection bias), participant and personnel blinding (for performance bias), blinding of outcomes assessment (detection bias), incomplete data (attrition bias), selective reporting (reporting bias), as well as any other potential sources of bias. If there are disputes about a bias rating, raters will discuss and resolve any differences. If differences cannot be resolved a third rater will arbitrate.

TIMELINE FOR SYSTEMATIC REVIEW

Pilot screening was initiated from 14 March 2019. We anticipate that data extraction will begin December 2019. Our preliminary manuscript will be completed by July 2020.

Patient and public involvement

No patient involved.

ETHICS AND DISSEMINATION

There are no formal ethics approvals needed for this review because we will only use data that is publicly available. The findings of this review will be published in a peer-reviewed journal. These findings will also be presented at relevant conferences. The PRISMA-P guidelines were used to report this protocol. Findings, as well as any amendments made, will also be reported using the PRISMA guidelines.

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