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«ΔΙΕΘΝΗΣ ΙΑΤΡΙΚΗ-ΔΙΑΧΕΙΡΙΣΗ ΚΡΙΣΕΩΝ ΥΓΕΙΑΣ»

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ: “Use of PrEP in MSM and observed modification of sexual behaviour in real life settings”

ΜΕΤΑΠΤ. ΦΟΙΤΗΤΗΣ: ΚΕΛΑΠΟΣΤΟΛΟΥ ΔΗΜΗΤΡΗΣ

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THESIS

SUBJECT: “Use of PrEP in MSM and observed modification of sexual behaviour in real life settings”

MSc STUDENT: KELAPOSTOLOU DIMITRIS

ATHENS

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ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ

ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ

ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

Του Μεταπτυχιακού Φοιτητή Κελαποστόλου Δημήτρη

Εξεταστική Επιτροπή

- ....., Επιβλέπων
- ....., Μέλος
- .....,Μέλος

Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε απο την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της ..... / ..... 2018 για την αξιολόγηση και εξέταση του υποψηφίου κου Κελαποστόλου Δημήτρης, συνεδρίασε σήμερα .../.../....

Η Επιτροπή **διαπίστωσε** ότι η Διπλωματική Εργασία ΤΟΥ ΚΟΥ Κελαποστόλου Δημήτρη με τίτλο: “Use of PrEP in MSM and observed modification of sexual behaviour in real life settings”, είναι πρωτότυπη, επιστημονικά καιτεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπ’ όψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης

(Master's). Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ....., και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «(Αριστα/Λίαν Καλώς/Καλώς)& (Βαθμός).....».

Τα Μέλη της Εξεταστικής Επιτροπής

□ ....., Επιβλέπων (Υπογραφή)

□ ....., Μέλος (Υπογραφή)

□ ....., Μέλος (Υπογραφή)

Περίληψη – Summary

Στόχοι: Στόχος αυτής της συστηματικής ανασκόπησης είναι η διερεύνηση της πιθανής σχέσης μεταξύ χρήση προφυλακτικής αγωγής για τον HIV (PrEP) και της αναφερόμενης αύξησης κρουσμάτων σεξουαλικώς μεταδιδόμενων νοσημάτων

Μεθοδολογία: Οι μελέτες που συμπέριλήφθηκαν στην ανασκόπηση είναι είτε κλειστές τυχαιοποιημένες μελέτες είτε ανοιχτές μελέτες σε περιβάλλον δομής υγείας σε πραγματικές συνθήκες. Μόνο μελέτες που αφορούν τους άνδρες που κάνουν σεξ με άνδρες συμπεριλήφθηκαν όπως και μόνο μελέτες στην αγγλική ή ελληνική γλώσσα.

Αποτελέσματα: Δεν βρέθηκε σύνδεση μεταξύ χρήσης PREP και αυξησης στα σεξουαλικώς μεταδιδώμενα νοσήματα και στις μη ασφαλείς σεξουαλικές πρακτικές στα ελεγχόμενα περιβάλλοντα των κλινικών δοκιμών.

Συμπερασμα: Όσο η PrEP δίνεται σε ελεγχόμενα περιβάλοντα σε συνδιασμό με αρωγή υγείας, μπορεί να έχει πολλάπλά οφέλη για την δημόσια υγεία. Αντιθέτως η άτυπη χρήση PrEP εγκυμονεί πολλούς κινδύνους καθώς γίνεται χωρίς καθοδήγηση, συχνά από πλυθησμό που κάνει κατάχρηση ουσιών εν γένει.

Objectives: This systematic review's objective is to assess if there is any correlation between the implementation of PrEP and modifications in sexual behavior, in the target population (MSM) that could be linked with the reported rise of HCV and other STI's.

Methods: We conducted a systematic review of studies of implementation of PrEP either in RCT environment or in real life settings through Health Clinics. Only data regarding MSM were included as it is the target population and literature only in English was used due to lack of sufficient knowledge, of other languages, of authors.

Results: PrEP uptake was not correlated with rise of STI's and high risk behavior in the controlled environment of RCT's and OLT's, where safe sex counseling was provided.

Conclusion: As long as PrEP is given as part of a comprehensive HIV prevention strategy it will have multiple benefits for the population with no increase in high risk behaviors and STI incidence. Informal use of PrEP can lead to substance abuse because of qualitative characteristics of the MSM population interested in PrEP and must be countered through formal provision with no barriers to access.

Λέξεις κλειδιά: Προφυλλακτική αγωγή για τον ιό ανοσολογικής ανεπάρκειας, Άνδρες που κάνουν σεξ με άνδρες, Ιός ανοσολογικής ανεπάρκειας, Ηπατίτιδα C, Σεξουαλικώς μεταδιδόμενα νοσήματα

Keywords: PrEP, MSM, HIV, HCV, STIs

CONTENTS

ACRONYM TABLE

MSM: Men having Sex with Men
TRG: Transgender Women
PrEP: Pre Exposure Prophylaxis
HIV: Human Immunodeficiency Virus
HCV: Hepatitis C
STI's: Sexually Transmitted Infections
RCT: Randomized Control Trial
OLT: Open Label Trial
OLR: Open Label Research
PHC: Public Health Clinic
UAI: Unprotected Anal Intercourse
CIAI: Condomless Insertive Anal Intercourse
CRAI: Condomless Receptive Anal Intercourse
ncRAI: Non Condom Receptive Anal Intercourse
RAS: Receptive Anal Sex

METHODS

Background – Study Rationale

PrEP has been promoted as a basic tool in struggle to curd the HIV epidemic. MSM are a main group targeted for PrEP implementation. Guidelines from USA, Europe and WHO recommend the use of PrEP in various settings. Results have been excellent in RCTs. However, there is an anticipation that widespread roll out of PrEP in MSM populations could be linked with modification of sexual behavior.

In USA and many other developed nations there is already a steady increase in Sexually Transmited Infections (STI's) and reported rates of condomless anal sex among MSM. The present review will attempt to look into the relation of this trend with the upcoming roll out of PrEP use in real life settings. Efficacy of PrEP is extremely high if adherence is optimum. The question remains as to what will be the net effect of long term effectiveness of PrEP in the efforts to decrease HIV incidence among MSM, the prevalence of other STIs and the epidemic of HCV infection. "Anecdotal epidemiologic observations of declining new HIV infections have buoyed PrEP supporters and the ecological observation of increasing rates of 400 bacterial STIs have galvanized PrEP detractors."(Landovitz et al., 2017)

Study Objective

Primary endpoints

1. Is PrEP linked with increase in STIs and/or HCV incidence of acute infection among MSM in implementation studies or settings with growing roll out?
2. Is PrEP linked with modification in sexual behavior, among MSM in real life settings (either observed or anticipated according to attitudes of HIV positive and negative MSMs)?

Secondary endpoints

3. What are the sub populations of MSM that are more prone to exhibit higher rates of condomless anal sex when using PrEP?
4. What are the factors linked with unsafe sexual practices?

5. What are the time, socioeconomical and race factors that have impact in the rates of adherence?

Explicit questions formed

P= The population to be studied is MSM (Men having Sex with Men)

I= The intervention is the implementation of PrEP

C= The comparison is with the “non implementation of PrEP”

O= Is the implementation of PrEP increasing, the rates of condomless anal sex, the incidence of STI’s, the incidence of HCV?

Hypothesis

- Use of PrEP by MSM does not lead to increase in the rate of observed STIs and/or HCV
- Use of PrEP by MSM does not lead to increase in the rates of reported condomless anal sex

Definitions

MSM Epidemiological Profile:

MSM (Men having Sex with Men) is a subpopulation of general male population that, includes any male that has passive or / and active anal intercourse. It is not a term to describe sexual preference. Trans females are sometimes included as a subpopulation of MSM, because sexual practices, and thus infection risk are identical. Epidemiologically, MSM are more vulnerable against blood-transmitted diseases, because anal intercourse is much more traumatic comparing to other mainstream ways of having sex (Oral & Vaginal) and thus blood-transmitted diseases have high rates of infectivity.

Traditionally, MSM is the main target group of interventions to counter HIV, since the beginning of HIV epidemic, at least in developed countries. The fact that the biggest percentage of MSM population is gay in terms of sexual orientation and by extension vulnerable to social exclusion, reduces the effectiveness of interventions mostly because of the interrupted access to that specific population. It will take many years, from the

beginning of the epidemic, until the “peer to peer” approach is widely used in public health interventions. This inability of the public health system of developed countries to approach effectively the MSM population is a factor which multiplied incidence and prevalence in each nation-wide setting. Additionally late response in HIV epidemic with preventive methods (since effective medication was not available until 1987) formed the current epidemiological profile of MSM.

In addition, high rates of HCV infection are observed in recent years among the MSM population, at the major developed countries contexts such as USA, Europe and Australia. As Chan et al note in their review: “HCV transmission is increasing within the specific core group of MSM because of increased sexual risk behaviors including sero-sorting on the basis of HIV-positive status, chemsex, and intense mucosally traumatic sexual practices.”(Chan et al., 2016) Moreover high rates of HCV re-infection have been observed in the specific population (re-infection incidence of 7.3/100 py) with estimation that re-infection will occur 5 years after treatment in almost one third of the HCV treated population.(Ingiliz et al., 2017)

HIV (Human Immunodeficiency Virus)

“The Human Immunodeficiency Virus (HIV) targets the immune system and weakens people's defense systems against infections and some types of cancer. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient. Immune function is typically measured by CD4 cell count. Immunodeficiency results in increased susceptibility to a wide range of infections, cancers and other diseases that people with healthy immune systems can fight off. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS), which can take from 2 to 15 years to develop depending on the individual. AIDS is defined by the development of certain cancers, infections, or other severe clinical manifestations.”(Organization, 2016) The counter of the HIV epidemic is included in the first two targets (6A & 6B) of the 6th Millennium Developmental Goal of W.H.O. “Target 6A. Have halted by 2015 and begun to reverse the spread of HIV/AIDS. Target 6B. Achieve, by 2010, universal access to treatment for HIV/AIDS for all those who need it.”(WHO, n.d.)

HCV (Hepatitis C)

“Hepatitis C virus (HCV) causes both acute and chronic infection. Acute HCV infection is usually asymptomatic, and is only very rarely (if ever) associated with life-threatening disease. About 15–45% of infected persons spontaneously clear the virus within 6 months of infection without any treatment. The remaining 60–80% of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis of the liver is between 15–30% within 20 years.”(World Health Organization et al., 2017)

PrEP (pre-exposure prophylaxis):

“Pre-exposure prophylaxis or PrEP is the use of an antiretroviral medication to prevent the acquisition of HIV infection by uninfected persons. PrEP may either be taken orally, using an antiretroviral drug available for treatment of HIV infection (tenofovir plus emtricitabine), or topically as a vaginal gel containing tenofovir. The efficacy of oral PrEP has been shown in four randomized control trials and is high when the drug is used as directed. The efficacy of gel has been shown in one trial and is moderate. Making these drugs available for safe, effective prevention outside the clinical trial setting is the current challenge. As of September 2015, WHO recommends that people at substantial risk of HIV infection should be offered PrEP as an additional prevention choice, as part of comprehensive prevention.”(WHO, n.d.)

The efficacy of PrEP in Humans was determined by three large randomized placebo-controlled trials. Iprex(Grant et al., 2010), PROUD(McCormack et al., 2016a) and Ipergay(Molina et al., 2015b) trials were conducted in US, UK and Canada & France respectively. Iprex & PROUD trials used a daily medication regimen based its effectiveness in adherence(Haberer, 2016). Particularly in the Proud trial, “The PrEP regimen was a single daily tablet containing 245 mg of tenofovir disoproxil fumarate and 200 mg ofemtricitabine (Truvada; Gilead Sciences, Foster CityCA, USA).”(McCormack et al., 2016a) In the Iprex trial, “We randomly assigned 2499 HIV-seronegative men or transgender women who have sex with men to receive a combination of two oral antiretroviral drugs, emtricitabine and tenofovir disoproxil fumarate (FTC–TDF), or placebo once daily. All subjects received HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections.”(Grant et al., 2010) On the other hand the Ipergay research team having concerns about the adherence of the treatment in real life settings designed an on demand regimen which is described as follows: “TDF-FTC was given as a fixed-dose combination of 300 mg of TDF and 200 mg of FTC per pill.

Participants were instructed to take a loading dose of two pills of TDF-FTC or placebo with food 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later. In case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then to Take the two post-exposure pills."(Molina et al., 2015b)

Methodology

A systematic review was carried out using PRISMA methodology protocol. The study designs that are considered eligible are: Journal articles, Systematic Reviews, Meta – Analysis. A combination of strong evidence and recent evidence is the target. Even though the journal articles are not of high credibility comparing to the other two designs, it is the type of study design that combines the two pre-mentioned characteristics. As far as concerns the study language, only papers in English and were taken onto account due to the lack of knowledge of other language from the part or the researcher. Inclusive publication dates of the studies are from 2010 until today (last search conducted 10/01/2018). 2010 was the year that the first RCT regarding PrEP("The iPrex trial") was published.

Literature Search Strategy

A combined search was performed in the PubMed Database on February 2018. Term "PrEP" was used as a "Mesh" term in addition with "HIV" and "MSM" terms which were used as plain search terms. The search result amounted to 147 articles.

The search filters that got implemented were:

Publication dates: Published from 2010 – present.

Articles Type: Review, Systematic Review, Journal article, Meta – Analysis, Clinical trial, Implementation studies, Practical – observational studies, Cohort studies.

Species: Humans.

Search fields: Title / Abstract.

The limited search returned with 112 results:

""Pre-Exposure Prophylaxis"[Mesh] AND HIV[Title/Abstract] AND MSM[Title/Abstract] AND ((Clinical Trial[ptyp] OR Journal Article[ptyp] OR Meta-Analysis[ptyp] OR Review[ptyp] OR systematic[sb]) AND ("2010/01/01"[PDAT] : "2018/02/10"[PDAT]) AND "humans"[MeSH Terms])"

Study Selection Criteria

Only studies and papers regarding the implementation of PrEP will be considered. Including Randomized Control Trial environment, Public Health interventions, self reported PrEP taking with unspecified conditions (includes informal PrEP use) and reviews including the studies above.

Only studies and papers with a minimum sample of 70 will be considered. In order to achieve 80% power with 95 CI, alpha= 0.5, the sample should be near 385. A sample size that high would exclude many recent trials that may be not of strong evidence but they may show a trend worth investigating. Furthermore, in the rational of MacCormack et al on why to design an OLT instead of another RCT: “First, the open-label rather than placebo-controlled design enabled us to capture the outcome that is most relevant for assessing PrEP within a public health prevention programme: the combination of the direct biological efficacy of the drug and the indirect effect of altered sexual behaviour among individuals who knew they were taking PrEP. Placebo-controlled trials may underestimate actual adherence because there is less incentive to take a tablet when the participant knows that it might be a placebo.” In the same rational, we decided to include papers that show informal PrEP use because we believe it is a factor worth investigating. Furthermore, an RCT was found regarding adolescent MSM and PrEP use with sample of n=78 and adds the adolescent vulnerability factor in the review. Knowing that the addition of studies with sample size <385 would decrease the credibility of this review, any contradicting results between studies of the same design will be applied the minimum size of n=385 filter.

Records identified through database searching: 112 (10/02/18)

Additional records identified through other sources: 42

Records after duplicates removed: 154

Records after non relevant entries removed: 95

Records after removal of entries with non implementation of PrEP: 22

Records after removal of studies of <70 sample size: 21

Records chosen for further investigation: 21

(TABLE 1 - BIBLIOGRAPHY TREE)

21 papers were chosen to be included in the systematic review. These papers include Randomized Control Trials (RCT’s), implementation of PreP in the context of public health

clinics (PHC) in the form of Open Label Trial (OLT) and Open Label Researches (OLR) which are open behavioural researches and include data of informal use of PrEP. RCT's and OLT's can be included in more than one paper and several of the papers chosen are reviewing more than one of the pre mentioned study design. Furthermore, have been identified that include other studies which do not meet the criteria of this review. Such studies were excluded from the review. The unique studies are presented in TABLE 2 – STUDIES INCLUDED IN THE REVIEW – BEHAVIORAL ALTERATION FACTORS.

Reviews

In the papers chosen for further investigation, 5 reviews were included. Some of these reviews include studies with sample that does not meet the criteria of our review, such as pregnant women and / or heterosexual couples. References to studies that have sample other than MSM, are not to be taken into consideration. iPREX, IPERGAY and the PROUD are the studies included in the Spinner et al, Pialoux et al and Mayer and Ramjee, reviews(Mayer and Ramjee, 2015; Pialoux et al., 2016; Spinner et al., 2016). The Scott et al review(Scott and Klausner, 2016) includes iPREX and PROUD. While the Cairns et al review(Cairns et al., 2016), includes IPERGAY and PROUD studies. As it is rational the three reviews including the same studies have the same eligible sample of 3458. The Cairns et al and the Scott et and Klausner reviews have eligible sample of 959 and 3044 respectively. TABLE 3 – REVIEWS

Data Extraction

The data extraction methodology was designed to have three pillars. First pillar has to do with data regarding the incidence and prevalence of STI's; before, during and after the implementation of PrEP, high risk behavior and anything that has relation with the questions of this review. Second pillar is about any factor that could alter the sexual behavior. The indicators collected for the second pillar are: The type of the PrEP uptake (on demand / consistent) If counseling for safe sexual practices was given, If Screening and/ or treatment for STI's was provided and if the participants that were found HBV+ and HCV+, were excluded from the research. Third pillar is about the strength of data extracted. The indicators for the third pillar are: the type of study, the sample size and the duration of the research. Any data from the first two pillars of the methodology will be assessed based on the indicators of the third pillar of the data extraction methodology.

Data Synthesis

Data Synthesis is structured based in two indicators. The one is the strength of the study design; and the papers are grouped and analyzed within the following categories (from stronger to weaker): Randomized Control Trials – Open Label Trials – Open Label Researches. The second indicator is the relevance with one of the endpoints (primary and / or secondary) of this study's objective. Data were sorted and grouped as answers to this review's scientific questions based on the study design strength from which the data came from.

RESULTS

Study Characteristics and Limitations

Out of 21 papers that include 11 unique studies, 6 out of 11 are open label trials (OLT), 3 out of 11 are RCT's and 2 out of 11 are Open Label Researches in real life settings. The implementation of PrEP in randomized control trials and open label trials, took place in a structured environment, with pre and post counselling regarding PrEP, STI's, safe sexual practices and with free PrEP provision. On the contrary, the open label research, gathered data from people that reported PrEP uptake in the past or currently with no information about the context. The existence of illicit PrEP markets is commonly acknowledged, the informal uptake of PrEP with absence of supportive services and cost per pill, definitely alters the sexual behavior comparing with the controlled and supportive environment of randomized control trials and open label trials in health clinics.

Regarding the type of PrEP uptake, in 2 out of 3 randomized control trials, it is consistent and in 1 it is on demand. In 5 out of 6 open label trials it is consistent, in 1 both of the approaches are followed (consistent77% - on demand19%) and in the 2 open label researches, the use of PrEP is reported by the subjects and the uptake type is not specified.

In randomized control trials, the duration of the programs is between 48 – 132 weeks. In open label trials, 16 – 96 weeks, while in one open label trial the duration is not specified, the only time wise information is that every subject had up to 48 weeks of PrEP uptake. In one of the open label researches the total duration was 100 weeks, while in the other the

sample was collected within 3 days and no information regarding the duration of the PrEP uptake was given.

In regard with the sample size, the randomized control trials had 2499+414+78= 2991 participants in total. The open label trials have more consistent sample sizes; between 100 – 557 with a median number of participants 357,66 and a total of 2146 participants. The two open label researches have 112 + 92 = 204 participants. In total, 5341 participants are included in this review.

HBV+ status

It must be noted that, in almost all RCT's and OLT's participants that where found HBV+ in the initial screening, were excluded from the sample. Only in the Grant RM RCT(Grant et al., 2010),in the Landovitz OLT(Landovitz et al., 2017) and in the Meireles P OLR(Meireles et al., 2015) HBV+ patients were included in the trial. For the Goedel WC OLR(Goedel et al., 2016) and the Whitlock G. OLT(Whitlock et al., 2017) there are no data regarding the exclusion or not of the HBV+ potential participants.

Behavioural Alteration Factors

Some common elements in majority of the studies were found that it is certain or possible to be behavioural alteration factors. These are: 1-counseling about safe sexual practices, 2-screening for STI's, and 3-treatment for STI's. These three services were provided before or right after the initiation of the study and in many cases in regularly distributed and predefined time points until the end of the study and in some cases in follow up. Besides the counseling about safer sexual studies, which effect is self and name defined, The other two services provided; can have behavioral alteration too. Screening and treating STI's promotes health and safety culture, either by the communion with medical staff or a health promotion center, like the ones most of the studies were conducted.

Only in the Rolle et al study the effect of health promotion in sexual behavior was lesser because of the following design characteristic "Our study differs significantly in that our study recruitment materials did not contain information about PrEP, and we offered non-incentivized PrEP as standard of HIV prevention care to all enrolled YBMSM"(Rolle et al., 2017) On the contrary, "The ANRS IPERGAY trial also proposed individualized risk-reduction and counselling (Molina et al., 2015a) . At each scheduled visit, peer counsellors

offered a comprehensive package of prevention services, including individual-centered interactive risk-reduction counselling according to the Respect model(Kamb et al., 1998). Moreover, they were also available to meet participants between scheduled visits, if the latter desired. This individualized support might have had a positive impact on retention in the study, as illustrated by the low discontinuation rate observed (12%,(Molina et al., 2015a)) but also on the high level of adherence observed, as demonstrated by pill count, plasma drug level dosage(Molina et al., 2015a), and self-reported PrEP use (present results)"(Sagaon-Teyssier et al., 2016)

The same concern is raised and in the Spinner et al review: "In any case, the sexual education programs accompanying PrEP use might have influenced sexual risk behavior."(Spinner et al., 2016)

Strengths and Limitations of Reviewed Studies

In the 2 open label researches, use of PrEP is reported by the subjects and there is no information provided regarding the context, the type and the duration of the uptake. "Secondly, behaviours were assessed with self report measures in our study. While there can be some misclassification in self-report measures, the survey was conducted anonymously, so answers may be more likely to be accurate and honest."(Goedel et al., 2016, p. 139) Over-testing is one of the most common bias factors, because of the inevitable constant screening in the PrEP implementation studies (RCT & OLT) higher rates of infections are presented comparing with real life settings. Moreover, Small sample bias should be concerned to any study included in this review with less than 400 participants.

In the Sagaon -Teyssier et al paper, sample representation bias is presented due to socio-demographic characteristics: "Data on socio-demographic characteristics revealed that most of the MSM enrolled in the ANRS IPERGAY trial(Molina et al., 2015a) had quite a high education level and were employed, suggesting a good level of knowledge about HIV transmission and prevention strategies. Furthermore, given its innovative nature, ANRS IPERGAY may have attracted MSM who were more aware of the debates surrounding PrEP and/or of results from earlier clinical PrEP trials. Accordingly they do not represent the gay community at large. This may be a common feature of people who choose to participate in clinical research trials, and who may not represent the diversity of affected

communities – especially MSM – who might be interested in PrEP use in the real life."(Sagaon-Teyssier et al., 2016, p. 6)

In the McCormack et al trial which is one of the most strong in evidence studies of this review there are no longitudinal data for sexual behaviour as described in the following: "The absence of longitudinal data for sexual behaviour is frustrating, as we cannot assess precisely how participants matched adherence to risk, and insights into risk compensation are limited to a single time point at 1 year."(McCormack et al., 2016b)

Even though the Goedel et al study lacks of sufficient sample size, innovative indicators like, PrEP awareness and risk perception should be evaluated for new trends identification and new perception of the available data "However, this is the first study, to our knowledge, to evaluate HIV risk perception, and testing and PrEP awareness and use in a sample of app-using MSM in the Deep South, an at-risk population in a high-HIV prevalence region"(Goedel et al., 2016, p. 139)

Strengths and Limitations of Our State-of-the Science Review

Almost all studies included in the reviews had high behavioral alteration factors and thus the PrEP effect on sexual behavior cannot be assessed by itself. Most of the studies were conducted in Public Healthcare Clinics. It is only reasonable for such services to be provided in a medical – public health intervention context. But it is definite that their proven, by scientific bibliography worldwide, effectiveness cannot be ignored in the extraction of results.

Sample characteristics

Randomized Control Trial Group – In the 3 RCT's the rates of acquired STI's during the inclusion screening are 15%(Hosek et al., 2017), 28%(Molina et al., 2015b), 51%(Grant et al., 2010). The median ages of each trials sample are 16,5% 34,5%, 27,15% respectively. It must be noted that the Hosek SG study(Hosek et al., 2017), is the only study that includes adolescents in its sample. Regarding substance abuse, in the Hosek SG study(Hosek et al., 2017), 64% of participants reported marijuana use and 67% reported alcohol use. The rate of heavy drinkers is 23% and of any other substance use 44% in the Molina J-M study(Molina et al., 2015b), while in the Grant study(Grant et al., 2010) 81,8%

of the participants reported any substance use during the month. High risk behaviour was one of the eligibility criteria in all 3 of the RCT's, so high rates of unprotected sexual acts or other high risk behaviour are observed. Specifically, in the Hosek SG study(Hosek et al., 2017); 17% had transactional sex in the past, while 60% had unprotected sex with the last partner. In the Molina J-M study(Molina et al., 2015b), high risk behaviour is defined as a history of unprotected anal sex with at least two partners during the past 6 months. The median number of sexual partners for the same period of time is 8. Finally in the Grant study(Grant et al., 2010), 59,5% reported unprotected sex in the past 3 months.

Open Label Study Group – Data in this group lack of homogeneity compared to the RCT group. Measures were converted to be the same where possible. In 3 studies participants reported 13%(Landovitz et al., 2017), 25%(Rolle et al., 2017) and 63%(McCormack et al., 2016b) of STI's infection during the last 12 months. In other studies 20%(Hoagland et al., 2017) and 54,1%(Stephanie E. Cohen, MD, MPH,*† Eric Vittinghoff, PhD,† Oliver Bacon, MD, MPH,*† et al., 2014) of any STI infection were reported during lifetime. The median ages of all studies are between 24 and 34 years. Substance abuse is measured also in the Open Label Study Group, in the Hoagland study (Hoagland et al., 2017), 59% reported combination of mental health medication with alcohol and 29% reported use of illicit drugs in the past 3 months. 58.2% reported poppers, crack, cocaine, methamphetamine, or club drug use in the past 3 months(Stephanie E. Cohen, MD, MPH,*† Eric Vittinghoff, PhD,† Oliver Bacon, MD, MPH,*† et al., 2014). 44% of participants had used one or more drugs associated with sexual disinhibition (γ-hydroxybutyrate, 4-methylmethcathinone, or methamphetamine) in the past 3 months(McCormack et al., 2016b). In the Landovitz study(Landovitz et al., 2017), 77,3% of the participants abused alcohol or other substances in the past month. While in the Rolle C-P study(Rolle et al., 2017), nearly 75% abused alcohol or other substances in the last 6 months. In the Landovitz RJ study (Landovitz et al., 2017), 84% reported unprotected sex during the last month. In the McCormack study(McCormack et al., 2016b) 43% reported participation in chemsex and the inclusion criteria was at least 1 condomless act in the past 3 months. In the Hoagland B study(Hoagland et al., 2017) 67.3% reported more than 2 unprotected anal intercourses and 45,2% reported unprotected receptive anal intercourse in the last 3 months In the same rates the Stephanie E study(Stephanie E. Cohen, MD, MPH,*† Eric Vittinghoff, PhD,† Oliver Bacon, MD, MPH,*† et al., 2014) presents 63.5% reported condomless receptive anal sex in the last 3 months.

Open Label Research Group – As expected data in this group completely lack of homogeneity. Still, the trend of high risk behaviour, observed in the previous two study design groups, is the same in OLR group. In the Goedel WC(Goedel et al., 2016), study respondents reported engaging in condomless insertive anal intercourse (CIAI) with 1,69 partners in the previous 6 months, also respondents reported engaging in condomless receptive anal intercourse (CRAI) with an average of 2.38 partners in the previous 6 months. The median age is 31,1 years and a similar number of 29,5 years is the median in the other OLR of Meireles P study(Meireles et al., 2016). In the same study, only 37.1% of the respondents provided lifetime history of STI and only 9.9 out of them reported STI symptoms / diagnoses in the past 12 months. 21% of the respondents reported unprotected sex with occasional partner in the past 12 months and the median of occasional partners of the same period of time is 4. 66,5% of the correspondents, answered one of the following (Often / occasionally / rarely / never) in the question regarding condom use; Leaving almost one third maximum answering “Always”. Reports for transactional sex was at 6,2% and drug abuse was reported as follows: “Lifetime use of alcohol (regardless of the amount) or drugs before or during intercourse was reported by 69.7%, and 59.5% reported consumption in the previous 12 months. The most frequently reported psychoactive substances were alcohol 57.6% poppers 17.8% and cannabis 15.9%”(Meireles et al., 2016)

Data Analysis

Primary Endpoints

Is PrEP linked with increase in STIs and/or HCV incidence of acute infection among MSM in implementation studies or setting with growing roll out?

Randomized Control Trial Group – 1 Data from all three RCT's show no increase in incidence of STI's. To elaborate, in the IPERGAY trial: "The proportions of participants with a new sexually transmitted infection (of the throat, anus, and urinary tract combined) during follow-up were similar, with 41% in the TDF-FTC group and 33% in the placebo group (P = 0.10). Most of the sexually transmitted infections (39%) were rectal infections. Overall, 81 participants (20%) acquired Chlamydia infections During follow-up, 88 (22%) gonorrhoea, 39 (10%) syphilis, and 5 (1%) hepatitis C virus. No participant Acquired hepatitis B virus infection."(Molina et al., 2015b, p. 5). Also, "There were no significant between-group differences in the numbers of subjects with syphilis (P = 0.49), gonorrhea (P = 0.74), chlamydia (P = 0.43), genital warts P = 0.53), or genital ulcers (P = 0.62) during follow up."(Grant et al., 2010) In the Solomon et al review, is in the same direction as above regarding comparison of the two arms of the trial, but it is noted that there are variations in incidence associated with other factors: "The overall syphilis incidence during the trial was 7.3 cases per 100 person-years, but varied by site, age, condomless insertive anal intercourse in the past 3 months, condomless receptive anal intercourse in the past 3 months, reported STI in the past 6 months, HSV-2 positivity, and syphilis prevalence at screening...There was no difference in syphilis incidence between the study arms (7.8 cases per 100 person-years for FTC/TDF vs 6.8 cases per 100 person-years for placebo, P = .304)."(Solomon et al., 2014, p. 4)

In the same study, a more in depth investigation is being made in the incidence of Syphilis during the PrEP uptake, and HIV acquisition is strongly correlated with syphilis incidence and prevalence: "In this large randomized placebo-controlled clinical trial of oral FTC/TDF for PrEP, HIV acquisition was strongly associated with incident syphilis, and syphilis did not attenuate the protective benefit Syphilis infection was highly prevalent at screening (13.3%). Syphilis incidence during the study period was 7.3 cases per 100 person-years overall, but the rate varied by study site, age, condomless anal intercourse, recent STI, HSV-2 serostatus, and syphilis prevalence at screening. The independent effect of syphilis

on HIV acquisition was affirmed in both study arms and with multivariable analyses that controlled for known predictors of HIV and other STIs. Predictors of syphilis incidence were similar to predictors of syphilis prevalence and did not include randomization group or detectable drug. Even when cases of incident syphilis that coincided with HIV diagnosis were excluded (to exclude HIV occurring prior to syphilis in between study visits), the independent effect of syphilis on HIV acquisition was still affirmed."(Solomon et al., 2014, p. 5) But the study concludes that in the overall syphilis incidence declined over time, even though it started high in both arms, during follow up period.(Solomon et al., 2014, p. 5)
The Hosek et al trial, even though it has a significantly smaller sample comparing to the other 2 RCT's detects no change in STI's incidence: "Before PrEP initiation, 19 prevalent STIs were diagnosed in 14 participants (5 rectal GC, 8 rectal CT, 4 urine CT, and 2 syphilis). Over 48 weeks of PrEP use, 23 STIs were diagnosed in 12 participants... Sexually transmitted infection incidence rates that were estimated based on a Poisson regression model were higher in the first 24 weeks of the study (18.1/100 person-years; 95%CI, 9.734.0) compared with weeks 24 to 48 of the study (9.4/100 person-years; 95% CI, 3.4-25.6), but not significantly so (rate ratio, 1.93; 95% CI, 0.62-5.96; P = .25)."(Hosek et al., 2017, p. 5). On the contrary, the researchers report a decrease in STI's incidence: "The incidence of STIs decreased among participants, but the HIV incidence rate was high compared with other open label clinical trials in the United States(Grant et al., 2010; Liu et al., 2016)"(Hosek et al., 2017, p. 7)

Open Label Study Group – 1 In the PROUD study, a minor number of HCV infections occurred evenly distributed amongst the two groups (immediate vs deferred) with possible route of transmission to be the Injecting drug use.(McCormack et al., 2016b) In a more generalized view of the STI's map the trends are the same with no rise of incidence in both of the control groups: "The randomised comparison was biased by the greater number of screens for sexually transmitted infections in the immediate group versus the deferred group (mean 4·2 vs 3·6), a consequence of more regular study clinic attendance to collect prescriptions in the immediate group. After adjustment for the number of screens, we found no significant difference between the groups, either for individual sexually transmitted infections or overall."(McCormack et al., 2016b) As far as concerns the STI incidence it remained stable.(McCormack et al., 2016b)

The same high but stable over time incidence is presented in the Stephanie et al study (Stephanie E. Cohen, MD, MPH,*† Eric Vittinghoff, PhD,† Oliver Bacon, MD, MPH,*† et al., 2014), through the Liu et al analysis: “Positive findings for rectal and pharyngeal STIs decreased from baseline to week 24, then increased (P < .05). The incidence (95% CI) of STIs per 100 personyears was 48 (42-55) for C trachomatis,43(37-49) for gonorrhoea, 12 (9-16) for syphilis, and 90 (81-99) for any STI; in each case, the incidence was stable across quarterly intervals (all, P > .10).”...“We observed high STI positivity rates at baseline and during follow-up, but the STI incidence was stable over time. The initial decline of rectal and pharyngeal STIs followed by an increase may reflect clearance of prevalent infections at screening, regression to the mean, cohort and seasonal effects, and/or risk compensation. High STI rates were also observed among MSM in the PROUD and IPERGAY studies.(McCormack et al., 2016b; Molina et al., 2015b)” (Liu et al., 2016, p. 5)

Lesser information is given in the Landowitz et al and Rolle et al studies concerning STI’s: “Nearly half (46.4%) of participants were diagnosed with at least one incident STI during 48 weeks of study follow-up.”(Landovitz et al., 2017, p. 4) and “The only factor associated with PrEP initiation was reported STI in the prior year (PR 1.50, 95%CI 1.002-2.25).”(Rolle et al., 2017, p. 3)

Is PrEP linked with modification in sexual behavior, among MSM in real life settings (either observed or anticipated according to attitudes of HIV positive and negative MSMs)?

Systematic Review Group - 2 “A potential increase in risk behaviour owing to an overestimated feeling of safety from PrEP could be a critical problem for implementing PrEP in current HIV prevention strategies. Thus, all studies were accompanied by a concern for changes in sexual risk behavior. All subjects were offered safer sex counseling and free condom use. Subsequently, a decrease in condom use for anal intercourse was not observed—neither in the iPREX nor the IPERGAY trials. Interestingly, the number of sexual partners was also found to decrease within the observation period in some studies (Molina et al., 2015a) and the number of unprotected intercourses decreased within the iPREX and Partners-PrEP study (author: any data coming from the Partners study may not be taken into consideration as the study includes populations other than MSM). In line with

these results, no significant changes in sexual risk behaviour were demonstrated in the PROUD study. The number of sexual partners within the last 90 days was constant from baseline to follow-up 12 at approximately 10 per month. Condomless sex was reported in 3 partners within the last 90 days before and after PrEP intervention. However, an increasing trend towards higher rates of other sexually transmitted infections (STI) was documented. The frequency of sexual risk behaviour in the high-risk MSM groups of the PROUD and IPERGAY study seemed to be hardly gradable."(Spinner et al., 2016, p. 6)

"While there were no increases in sexual risk behavior overall in a recent PrEP demonstration project and report of PrEP implementation in a large healthcare system, some PrEP users did report an increase in risk behaviors, Including a decrease in consistent condom use(Liu et al., 2016; Volk et al., 2015).(Scott and Klausner, 2016, p. 2)

Randomized Control Trial Group – 2 In the iPREX study, no diference between the two groups was observed regarding sexual behaviour. A decline in the number of insertive sexual partners was recorded along with an increased condom use from the behalf of the insertive sexual partners: "Sexual practices were similar in the two groups at all time points (P = 0.97) (Figure 1). The total numbers of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those partners who used condom increased after subjects enrolled in the study."(Grant et al., 2010, p. 4) and "Reported high-risk behaviour decreased substantially After enrolment and remained lower than at baseline during the trial." … "and may reflect the services (e.g., counseling, testing, and dispensing of condoms) that are provided as part of such interventions."(Grant et al., 2010)

On the contrary the IPERGAY trial, does not record change in high risk sexual behaviour nor in the number of sexual partners comparing data collected at the initiation of the trial with data collected during the implementation: "Sexual practices did not change overall among the participants during the study period as compared with baseline. There were no significant between group differences in the total number of episodes of sexual intercourse in the 4 weeks before visits (P=0.07), in the proportion of episodes of receptive anal intercourse without condoms (P = 0.40), or in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse (P =0.90)."(Molina et al., 2015b, p. 4) While in the Sagaon-Teyssier et al study of iPERGAY data find similarities

with an OLT of Volk et al (not included in this review due to failure of acquiring full text of the study): “Numbers of sexual partners and condomless sex acts did not change significantly over time (“The first results from a PrEP trial in a US clinic, outside of a research setting, have shown the absence of new HIV infection in participants – despite a high rate of STIs – as well as a stable or decrease in the number of sexual partners, and stable or increased condom use in a majority of participants(Volk et al., 2015)“(Sagaon-Teyssier et al., 2016)

In the same study a focus in the pooled sample is being made and the sexual behaviour is very similar with the sample taking PrEP, with decreased number of the median number of sexual partners and a steady high prevalence of unprotected intercourse: “The longitudinal analysis of the ... More fluctuating patterns were observed for our pooled sample with respect to the median number of sexual partners, with a tendency to decrease (p = .19) being observed over follow-up, and principally between M2 (10 [4–16]) and M22 (6 [3–17]). We found that condoms were not used in 70.3% (65.3–79.4%) of the most recent episodes of anal intercourse (insertive or receptive). The pooled sample did not show significant trend during follow-up (p = 0.91,). With respect to RAI, condoms were not used in 69.3% (58.3–75.4%) of most recent episodes. This proportion seemed to remain stable during follow-up, as the trend was not significant (p = .71)”(Sagaon-Teyssier et al., 2016, p. 4)

Also, the high rates of unprotected intercourse in iPERGAY study is described with the following indicator: “Overall, participants reported that 42.6% of the total number of most recent episodes of sexual intercourses were protected by PrEP as the unique mode of prevention, irrespective of their sexual partner and sexual behaviour.”(Sagaon-Teyssier et al., 2016, p. 3) Alteration in sexual behaviour was not observed in the Hosek et al study either. “At baseline, study participants reported a median of 1.0 (IQR, 1-3) male sexual partners in the past month. Numbers of sexual partners and condomless sex acts did not change significantly over time (eTable could not be located).”(Hosek et al., 2017, p. 6)

Open Label Study Group – 2 In the PROUD study, no change of behaviour was observed in both groups: “Total number of different anal sex partners varied widely at the two time points, and we detected no significant difference between groups at 1 year (p=0·57; indicator of receptive anal intercourse without a condom, was much the same in the two groups.”(McCormack et al., 2016b)

Almost 60% of the participants in the Stephanie et al study, included the prospect of condomless sex as a reason to take PrEP: “Although only 4.7% reported “to make it safer for me to have sex without condoms” as their main reason for enrolling, 58.9% included it as one of several reasons for enrolling.”(Stephanie E. Cohen, MD, MPH,*† Eric Vittinghoff, PhD,† Oliver Bacon, MD, MPH,*† et al., 2014) relevance can be spotted in the near to 60% rate of CRAI of the same population: “The proportion engaging in condomless receptive anal sex remained stable at 65.5%to 65.6%. “(Liu et al., 2016, p. 1) and the same trend is presented in the Rolle et al OLT “The most popular reason for PrEP interest was the possibility of having sex without condoms in the future; the most common reason for disinterest was consistent condom use.”(Rolle et al., 2017, p. 10)

CRAI rates remain stable in the Stephanie et al study: “Overall numbers of RAS episodes in the past 3 months decreased (P = .007), driven by a decline in episodes with a condom (P < .001), whereas episodes without a condom remained stable (P = .73).”(Liu et al., 2016, p. 5) It must be taken into consideration that the specific study does not provide safe sexual practices counselling to avoid behaviour bias. The same results come from most of the OLT’s, in the Hoagland et al study: “44.7% (n = 201) reported condomless receptive anal intercourse in previous 3 months and these behaviours were not significantly different across sites.”(Hoagland et al., 2017, p. 4) and in the Landovitz et al study the CRAI rates are the same with baseline after a decrease in the first 12 months and stabilization thereafter:“Percentages of participants reporting any ncRAI decreased over the first 12 weeks of study participation but then reverted to baseline levels thereafter; Numbers of episodes of ncRAI per participant decreased over the first 24 weeks of study, and then were stable thereafter”(Landovitz et al., 2017, p. 13)

Whitlock et al study is the only OLT that despite the similarity with the others of stable sexual behaviour (63% of the participants), it presents a significant rate of 30% of the participants that increased the rates of CRAI after 4 months of PrEP uptake.”(Whitlock et al., 2017)

Open Label Research Group – 2 The rates of high risk sexual behaviour are higher in the PrEP user comparing to non PrEP users: “PrEP users reported significantly higher numbers of partners on average for condomless sex across all behaviours. Compared to

nonusers (M 5 1.33, SD 5 2.11), PrEP users reported 4.50 CIAI partners [SD 5 2.17; F(1, 50) 5 15.40, p , .001]. PrEP users reported 7.50 CRAI partners (SD 57.40), while those not using PrEP reported 1.53 CRAI partners [SD 5 3.09; F(1, 40) 5 12.059, p 5 .001]."(Goedel et al., 2016, p. 138)

On the contrary a safer approach in sex is followed from the PrEP users in the Meireles et al study: "Always using condom with an occasional partner were more frequently reported among PrEP users (68% vs 48%, p=0.091)."(Meireles et al., 2016)

Secondary Endpoints

What are the sub populations of MSM that are more prone to exhibit higher rates of condomless anal sex when using PrEP?

Even though some of the studies reviewed were targeted to, or included vulnerable subpopulations (Adolescents, young people, black people) of MSM, no correlations could be made. The lack of homogeneity of data leave no space for direct comparison of unsafe behavior or STI's acquisition and any other vulnerability factor. Moreover any comparison would be not accurate due to high rates of unsafe sexual behavior as fundamental characteristic of the overall sample.

What are the factors linked with unsafe sexual practices?

Randomised Control Trial Group – 4 Solomon et al analyzing iPREX data reports that: "Individuals with prevalent syphilis infection at screening were less educated, were older, and reported having more sexual partners and more episodes of condomless anal intercourse in the previous 3 months."(Solomon et al., 2014, p. 4)

Open Label Study Group – 4

There is a clear association between unsafe sexual practices and drug – substance abuse in 2 of the OLT's. In the Stephanie et al study, participants reported high rates of recreational drug use, condomless receptive anal sex, and had a high prevalence of early syphilis or rectal infections."(Stephanie E. Cohen, MD, MPH,*† Eric Vittinghoff, PhD,†

Oliver Bacon, MD, MPH,*† et al., 2014) and also higher drug levels were correlated with CRAI in the last 3 months in the Hoagland et al study.(Hoagland et al., 2017, p. 8)

Other factors linked with unsafe sexual practices are low education and low risk perception amongst others: “Compared to those enrolled, a higher proportion of eligible but not enrolled individuals was younger, less educated, more frequently self-defined as of mixed race, had lower HIV risk perception, lower prior HIV testing rates, lower PrEP awareness and was less likely to report anal sex with partners of unknown HIV status (all $p < 0.05$).”(Hoagland et al., 2017, p. 4) and regarding the risk perception in the Whitlock et al study: “In our survey of perceptions of the concerns about STI risks in 100 men who have sex with men (MSM) attending for PrEP monitoring at our service, between February and June 2016, we found that although 83% were less concerned about the risk of acquiring HIV, with regard to acquiring other STIs, 20% were more concerned and 78% ‘felt the same’”(Whitlock et al., 2017)

Open Label Research Group – 4 Data from the Goedel et al study, show correlation between risk perception and availability of PrEP.”(Goedel et al., 2016)

What are the time, socioeconomical and race factors that have impact in the rates of adherence?

Randomized Control Trial Group – 5 Low levels of adherence were correlated with social stigma factors in the Hosek et al study: “Compared with participants with protective levels of TFVDP, those without protective levels were more likely to endorse the statement “I worry others will see me taking pills and think I am HIV-positive” (baseline, 4 participants [22.2%]; week 48, 5 participants [29.4%]; P = .03).”(Hosek et al., 2017, p. 5) Also low adherence was correlated with the reduction of scheduled visits over time : “A noticeable trend in the adherence data from this study, also seen in ATN110, is the striking drop in TFV-DP levels once participants began the quarterly visit schedule.”(Hosek et al., 2017, p. 7)

Open Label Study Group – 5 In the Landovitz study, an innovative measure was implemented: “Plasma TFV levels from each PrEP visit assessed as below the limit of quantiatation (<10 ng/mL) triggered increased adherence support.”(Landovitz et al., 2017)

Because of the implementation of this intervention, any results concerning adherence should be critically reviewed, as higher rates of adherence are expected. “Most of those with suboptimal adherence had adherence improvement after brief intervention.”(Landovitz et al., 2017, p. 3)

In the Landovitz study, vulnerability factors were associated with low adherence: “Consistent with previous demonstration projects, we found that younger PrEP-users and African-Americans were less likely to achieve rectally-protective levels of adherence as measured by both DBS TFV-DP and plasma TFV levels, even when controlling for education, income, and other co-morbidities.”(Landovitz et al., 2017, p. 16) and respectively, high adherence was associated with older non Hispanic white men which is an indication of high status quo: “In a multivariable model, older and non-Hispanic White participants had greater odds of having TFV-DP levels commensurate with high levels of rectal protection against HIV acquisition; substance use, insurance status, education, and numbers of partners were not independently associated with increased odds of 342 having protective TFV-DP levels”(Landovitz et al., 2017, p. 12).

In the Stephanie et al OLT, as Liu et al in their study report; high adherence is correlated with high risk behaviour, termination of PrEP uptake is correlated with low perceived risk and no correlation is found between adherence and use of substances, in the references respectively: “ Adherence was higher among those participants who reported more risk behaviors.”(Liu et al., 2016), “Among participants who stopped PrEP owing to low perceived risk, 10 of 16 participants with available data (62.5%)reported ncRAS at that visit.”(Liu et al., 2016, p. 3) and “Adherence to PrEP was not diminished among people using alcohol or other recreational drugs.”(Liu et al., 2016, p. 7) Also there is a clear association between adherence and socioeconomic factors, African American participants and those with unstable housing were more likely to have lower drug levels.”(Liu et al., 2016, p. 7)

Educational level is an adherence factor in the Hoagland et al study as well: “In fact, in the adjusted model schooling was the strongest predictor of the drug level: participants with ≥12 years had 1.9 times the odds of a higher versus lower drug level than participants with <12 years of schooling. “(Hoagland et al., 2017, p. 8)

Open Label Research Group – 5 Economical barriers to access of PrEP are presented in the Goedel et al OLR where almost half of the participants would decline PrEP because of high cost.(King et al., 2014).”(Goedel et al., 2016, p. 138)

Underlying Medical Illnesses

Substance addiction - Polysubstance dependence – “Polysubstance dependence refers to a type of substance dependence disorder in which an individual uses at least three different classes of substances indiscriminately and does not have a favourite drug that qualifies for dependence on its own.” ... “Withdrawal: The individual either experiences the withdrawal symptoms when he or she stops using the drugs or the individual uses drugs in order to avoid or relieve withdrawal symptoms”(*Diagnostic and statistical manual of mental disorders : DSM-5*, 2013)
All the studies reviewed show high rates of drug and alcohol abuse. In many cases polysubstance use was recorded. In one of the studies chem sex was recorded. High risk sexual behavior and substance abuse is strongly correlated in most of the studies.

DISCUSSION

As expected rates of STI’s are very high but, the implementation of PrEP is not correlated with rise of STI’s incidence in none of the three RCT’s. It must be taken into consideration that the controlled supportive environment of the trials have a high impact in the sexual behaviour. Measured by the “behavioural alteration factors” all three of the RCT’s offer, STI's screening, counselling about safe sexual practices, treatment for STI's. High rates of STI’s are also observed in both control groups with no significant difference in the two sufficient sample OLT’s. Results are the same in the <385 participants studies too.

Only in the iPREX trial significant behavioural change was observed, in the other 2 RCT’s behaviour did not change significantly over time even though it remained in high levels. It must be noted that the iPREX study had almost 40% bigger duration (132 weeks - 96 weeks) comparing the next biggest study of Molina et al. Overall no increase in sexual behaviour was observed in most of the OLT’s. In the two OLT that offered no counselling for safer sexual practices, the rates of CRAI and high risk perception about PrEP were

close to each other. High interest is found in the Whitlock OLT where 30% of the participants increased the rates of CRAI after 4 months of PrEP uptake, which can be interpreted as a correlation between long term PrEP use and alteration in risk perception. Contradicting data are presented from the two OLR's. One indicated riskier behaviour in PrEP users while the other indicated safer behaviour. But unfortunately there are no longitudinal data available to assess the effect of PrEP in sexual behaviour over time. It is of importance that the OLR that showed rise of high risk behaviour is the Goedel et al(Goedel et al., 2016) study which did not include counselling in the procedure.

Substance and multi-substance abuse, low risk perception and low education are highly linked with unsafe sexual practices. Also, correlation between risk perception and availability of PrEP was found. Vulnerability factors as the above show the need for free distribution of PrEP in such populations that are in higher risk and yet face barriers in PrEP acquisition.

Low adherence was correlated with low perceived HIV risk, social stigma factors, educational level and socioeconomic status.

Conclusion

It is clear that PrEP use is not correlated with rise of STI's and significant alteration in sexual behaviour. Attention must be given to the fact that the above direction is given by studies that offer safe sex counselling, despite the fact that results are the same in 2 studies that do not offer counselling to avoid such bias. PrEP concerns as it is rational, high risk populations with high rates of CAI and high number of median partners. The effect of the behavioural interventions may not be the reduction of high risk practices as it is already proven and measured(Johnson et al., 2008). In the unique context of PrEP uptake, such interventions act as a compensatory factor and their effect it appears to be the non rise of high risk behavior. Furthermore it must not be ignored that all these PrEP implementation projects regardless their design attracted high risk individuals which were introduced to further prevention measures other than PrEP .

Concerning the informal PrEP use, no sufficient data were found to support the rise or not; of high risk behavior during PrEP uptake. If the behavioral interventions do act as a compensatory factor, as described above, then is there any other factor to play the same

role in the informal PrEP uptake context? If there is not, informal PrEP use should be narrowed and be replaced with structured distribution through medical facilities.

Substance abuse is another common characteristic amongst PrEP users. A combination of more than two drugs is often reported. If PrEP is taken informally, by people who abuse drugs, will be considered by this population as another substance to serve a specific purpose and not as part of a Public Health intervention. PrEP should not be stigmatized as an “immunization pill” and be added in the list of “chemsex parties” drugs, where a combination of drugs is used to achieve the desired effect. As long as Prep is treated as such, even from a minority of the population the results can only be negative in Public Health terms.

The existence of illicit markets, is a proof that there is demand for PrEP and it goes along with the high rates of PrEP awareness in MSM population(Goedel et al., 2016, p. 137). Informal PrEP use can only grow in the future and it can only be countered with quick reflexes and immediate response in offering access to structured PrEP use.

It is very interesting that declined median number of partners over time and PrEP use was correlated in some of the studies. It is possible that PrEP uptake gives the option to individuals to have an HIV+ steady partner and thus to have an impact in HIV+ stigma. There are no sufficient data to support this claim, but for sure this is a trend that is worth investigating in the future.
Overall, PrEP seems to be a very effective intervention, with no counter effects in other interventions that PrEP goes in parallel with. But PrEP owns its effectiveness, as any other drug, in the proper uptake, which is based in official guidelines. Illicit markets cover so far the demand for PrEP, since official distribution is offered only in specific countries or in a trial mode with no continuity. Quick reflexes are required from the national Public Health actors in order to cover the preexisting demand for PrEP in a structured, supportive and controlled way. It is possible that misuse of PrEP can lead to stigmatizing in the eyes of public opinion and so more barriers would be raised.

There is an urgent need in constructing a common PrEP implementation protocol, including standardized data to be collected in a longitudinal way. There are still questions to be answered regarding long term PrEP use. Even though the existing interventions are

effective and harmless, their long term effects are not yet to be seen. Constant and concrete monitoring is essential and proactive actions are required in order PrEP to remain beneficial for the Public Health.

REFFERENCES

Cairns, G., McCormack, S., Molina, J.-M., 2016. The European preexposure prophylaxis revolution: Curr. Opin. HIV AIDS 11, 74–79. https://doi.org/10.1097/COH.0000000000000223

Chan, D.P.C., Sun, H.-Y., Wong, H.T.H., Lee, S.-S., Hung, C.-C., 2016. Sexually acquired hepatitis C virus infection: a review. Int. J. Infect. Dis. 49, 47–58. https://doi.org/10.1016/j.ijid.2016.05.030

Diagnostic and statistical manual of mental disorders : DSM-5, 2013. . American Psychiatric Association, Arlington, VA.

Goedel, W.C., Halkitis, P.N., Greene, R.E., Hickson, D.A., Duncan, D.T., 2016. HIV Risk Behaviors, Perceptions, and Testing and Preexposure Prophylaxis (PrEP) Awareness/Use in Grindr-Using Men Who Have Sex With Men in Atlanta, Georgia. J. Assoc. Nurses AIDS Care 27, 133–142. https://doi.org/10.1016/j.jana.2015.11.005

Grant, R.M., Lama, J.R., Anderson, P.L., McMahan, V., Liu, A.Y., Vargas, L., Goicochea, P., Casapía, M., Guanira-Carranza, J.V., Ramirez-Cardich, M.E., others, 2010. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N. Engl. J. Med. 363, 2587–2599.

Haberer, J.E., 2016. Current concepts for PrEP adherence in the PrEP revolution: from clinical trials to routine practice. Curr. Opin. HIV AIDS 11, 10–17. https://doi.org/10.1097/COH.0000000000000220

Hoagland, B., Moreira, R.I., De Boni, R.B., Kallas, E.G., Madruga, J.V., Vasconcelos, R., Goulart, S., Torres, T.S., Marins, L.M.S., Anderson, P.L., Luz, P.M., Costa Leite, I. da, Liu, A.Y., Veloso, V.G., Grinsztejn, B., for the PrEP Brasil Study Team, 2017. High pre-exposure prophylaxis uptake and early adherence among men who have sex with men and transgender women at risk for HIV Infection: the PrEP Brasil demonstration project. J. Int. AIDS Soc. 20, 21472. https://doi.org/10.7448/IAS.20.1.21472

Hosek, S.G., Landovitz, R.J., Kapogiannis, B., Siberry, G.K., Rudy, B., Rutledge, B., Liu, N., Harris, D.R., Mulligan, K., Zimet, G., Mayer, K.H., Anderson, P., Kiser, J.J., Lally, M., Brothers, J., Bojan, K., Rooney, J., Wilson, C.M., 2017. Safety and Feasibility of Antiretroviral Preexposure Prophylaxis for Adolescent Men Who Have Sex With Men Aged 15 to 17 Years in the United States. JAMA Pediatr. 171, 1063. https://doi.org/10.1001/jamapediatrics.2017.2007

Ingiliz, P., Martin, T.C., Rodger, A., Stellbrink, H.-J., Mauss, S., Boesecke, C., Mandorfer, M., Bottero, J., Baumgarten, A., Bhagani, S., 2017. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J. Hepatol. 66, 282–287.

Johnson, W.D., Diaz, R.M., Flanders, W.D., Goodman, M., Hill, A.N., Holtgrave, D., Malow, R., McClellan, W.M., 2008. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men, in: The Cochrane Collaboration (Ed.), Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, Chichester, UK.

Kamb, M.L., Fishbein, M., Douglas, Jr, J.M., Rhodes, F., Rogers, J., Bolan, G., Zenilman, J., Hoxworth, T., Malotte, C.K., Iatesta, M., Kent, C., Lentz, A., Graziano, S., Byers, R.H., Peterman, T.A., for the Project RESPECT Study Group, 1998. Efficacy of Risk-Reduction Counseling to Prevent Human Immunodeficiency Virus and

Sexually Transmitted Diseases: A Randomized Controlled Trial. JAMA 280, 1161. https://doi.org/10.1001/jama.280.13.1161

King, H.L., Keller, S.B., Giancola, M.A., Rodriguez, D.A., Chau, J.J., Young, J.A., Little, S.J., Smith, D.M., 2014. Pre-Exposure Prophylaxis Accessibility Research and Evaluation (PrEPARE Study). AIDS Behav. 18, 1722–1725. https://doi.org/10.1007/s10461-014-0845-5

Landovitz, R.J., Beymer, M., Kofron, R., Amico, K.R., Psaros, C., Bushman, L., Anderson, P.L., Flynn, R., Lee, D.P., Bolan, R.K., Jordan, W.C., Tseng, C.-H., Dierst-Davies, R., Rooney, J., Wohl, A.R., 2017. Plasma Tenofovir Levels to Support Adherence to TDF/FTC Preexposure Prophylaxis for HIV Prevention in MSM in Los Angeles, California: JAIDS J. Acquir. Immune Defic. Syndr. 76, 501–511. https://doi.org/10.1097/QAI.0000000000001538

Liu, A.Y., Cohen, S.E., Vittinghoff, E., Anderson, P.L., Doblecki-Lewis, S., Bacon, O., Chege, W., Postle, B.S., Matheson, T., Amico, K.R., Liegler, T., Rawlings, M.K., Trainor, N., Blue, R.W., Estrada, Y., Coleman, M.E., Cardenas, G., Feaster, D.J., Grant, R., Philip, S.S., Elion, R., Buchbinder, S., Kolber, M.A., 2016. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. JAMA Intern. Med. 176, 75. https://doi.org/10.1001/jamainternmed.2015.4683

Mayer, K.H., Ramjee, G., 2015. The current status of the use of oral medication to prevent HIV transmission: Curr. Opin. HIV AIDS 10, 226–232. https://doi.org/10.1097/COH.0000000000000170

McCormack, S., Dunn, D.T., Desai, M., Dolling, D.I., Gafos, M., Gilson, R., Sullivan, A.K., Clarke, A., Reeves, I., Schembri, G., 2016a. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet 387, 53–60.

McCormack, S., Dunn, D.T., Desai, M., Dolling, D.I., Gafos, M., Gilson, R., Sullivan, A.K., Clarke, A., Reeves, I., Schembri, G., 2016b. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet 387, 53–60.

Meireles, P., Lucas, R., Martins, A., Carvalho, A.C., Fuertes, R., Brito, J., Campos, M.J., Mendao, L., Barros, H., 2015. The Lisbon Cohort of men who have sex with men. BMJ Open 5, e007220–e007220. https://doi.org/10.1136/bmjopen-2014-007220

Meireles, P., Rocha, M., Campos, M.J., Barros, H., 2016. PrEP use in Portugal while waiting for a policyTITLE.

Molina, J.-M., Capitant, C., Spire, B., Pialoux, G., Chidiac, C., Charreau, I., Delfraissy, J.F., 2015a. On demand PrEP with oral TDF-FTC in MSM: results of the ANRS Ipergay trial, in: Conference on Retroviruses and Opportunistic Infections. pp. 23–26.

Molina, J.-M., Capitant, C., Spire, B., Pialoux, G., Cotte, L., Charreau, I., Tremblay, C., Le Gall, J.-M., Cua, E., Pasquet, A., Raffi, F., Pintado, C., Chidiac, C., Chas, J., Charbonneau, P., Delaugerre, C., Suzan-Monti, M., Loze, B., Fonsart, J., Peytavin, G., Cheret, A., Timsit, J., Girard, G., Lorente, N., Préau, M., Rooney, J.F., Wainberg, M.A., Thompson, D., Rozenbaum, W., Doré, V., Marchand, L., Simon, M.-C., Etien, N., Aboulker, J.-P., Meyer, L., Delfraissy, J.-F., 2015b. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N. Engl. J. Med. 373, 2237–2246. https://doi.org/10.1056/NEJMoa1506273

Organization, W.H., 2016. Global health sector strategy on HIV 2016-2021. Towards ending AIDS.

Pialoux, G., Delaugerre, C., Cotte, L., Raffi, F., Cua, E., Molina, J.-M., 2016. Pre-exposure prophylaxis: a useful tool to prevent human immunodeficiency virus infection? Clin. Microbiol. Infect. 22, 757–767. https://doi.org/10.1016/j.cmi.2016.08.029

Rolle, C.-P., Rosenberg, E.S., Siegler, A.J., Sanchez, T.H., Luisi, N., Weiss, K., Cutro, S., del Rio, C., Sullivan, P.S., Kelley, C.F., 2017. Challenges in Translating PrEP Interest Into Uptake in an Observational Study of Young Black MSM: JAIDS J. Acquir. Immune Defic. Syndr. 76, 250–258. https://doi.org/10.1097/QAI.0000000000001497

Sagaon-Teyssier, L., Suzan-Monti, M., Demoulin, B., Capitant, C., Lorente, N., Préau, M., Mora, M., Rojas Castro, D., Chidiac, C., Chas, J., Meyer, L., Molina, J.-M., Spire, B., for the ANRS IPERGAY Study Group, 2016. Uptake of PrEP and condom and sexual risk behavior among MSM during the ANRS IPERGAY trial. AIDS Care 28, 48–55. https://doi.org/10.1080/09540121.2016.1146653

Scott, H.M., Klausner, J.D., 2016. Sexually transmitted infections and pre-exposure prophylaxis: challenges and opportunities among men who have sex with men in the US. AIDS Res. Ther. 13. https://doi.org/10.1186/s12981-016-0089-8

Solomon, M.M., Mayer, K.H., Glidden, D.V., Liu, A.Y., McMahan, V.M., Guanira, J.V., Chariyalertsak, S., Fernandez, T., Grant, R.M., Bekker, L.-G., Buchbinder, S., Casapia, M., Chariyalertsak, S., Guanira, J., Kallas, E., Lama, J., Mayer, K., Montoya, O., Schechter, M., Veloso, V., for the iPrEx Study Team, 2014. Syphilis Predicts HIV Incidence Among Men and Transgender Women Who Have Sex With Men in a Preexposure Prophylaxis Trial. Clin. Infect. Dis. 59, 1020–1026. https://doi.org/10.1093/cid/ciu450

Spinner, C.D., Boesecke, C., Zink, A., Jessen, H., Stellbrink, H.-J., Rockstroh, J.K., Esser, S., 2016. HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. Infection 44, 151–158. https://doi.org/10.1007/s15010-015-0850-2

Stephanie E. Cohen, MD, MPH,*† Eric Vittinghoff, PhD,† Oliver Bacon, MD, MPH,*†, Susanne Doblecki-Lewis, MD,‡ Brian S. Postle, BS,§ Daniel J. Feaster, PhD,‡ Tim Matheson, PhD,*, Nikole Trainor, MPH,* Robert W. Blue, MSW,* Yannine Estrada, PhD,‡ Megan E. Coleman, FNP,k, Richard Elion, MD,k Jose G. Castro, MD,‡ Wairimu Chege, MD, MPH,¶ Susan S. Philip, MD, MPH,*†, Susan Buchbinder, MD,*† Michael A. Kolber, PhD, MD,‡ and Albert Y. Liu, MD, MPH*†, 2014. 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.

Volk, J.E., Marcus, J.L., Phengrasamy, T., Blechinger, D., Nguyen, D.P., Follansbee, S., Hare, C.B., 2015. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting: Figure 1. Clin. Infect. Dis. 61, 1601–1603. https://doi.org/10.1093/cid/civ778

Whitlock, G., Boccino, S., Kanagalinghan, U., Nwokolo, N., 2017. Risk perception in MSM taking prep: a survey. Sex. Transm. Infect. 93, 325–325. https://doi.org/10.1136/sextrans-2016-053050

WHO, n.d. MDG 6: combat HIV/AIDS, malaria and other diseases [WWW Document]. URL http://www.who.int/topics/millennium_development_goals/diseases/en/

WHO, n.d. Pre-exposure prophylaxis [WWW Document]. URL http://www.who.int/hiv/topics/prep/en/

World Health Organization, World Health Organization, Global Hepatitis Programme, 2017. Global hepatitis report, 2017.

ANNEX

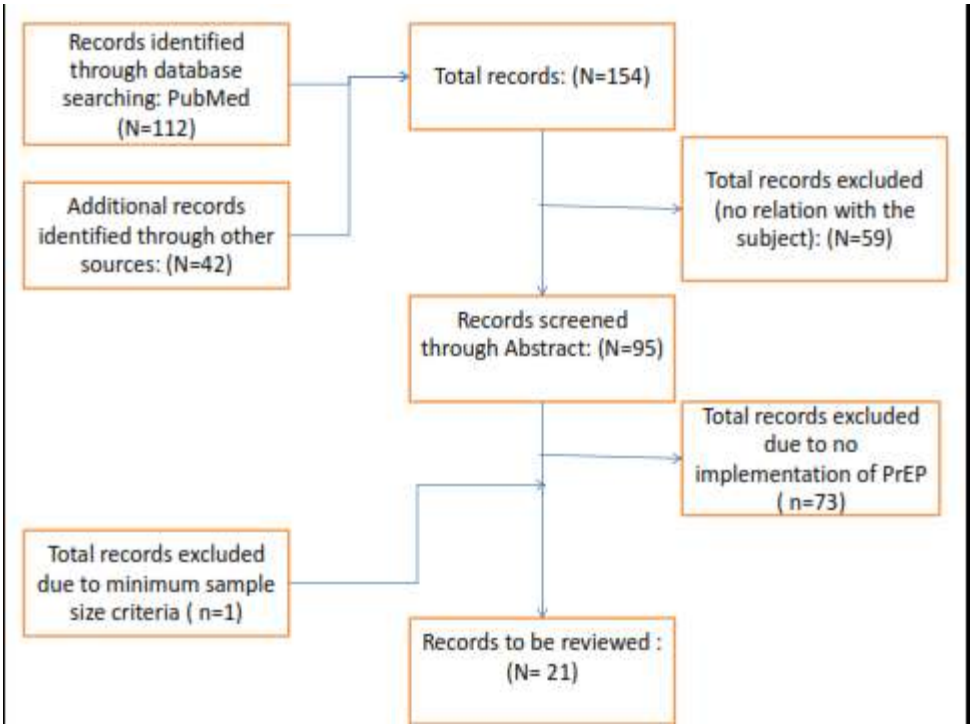

TABLE 1 - BIBLIOGRAPHY TREE

Original paper title	Author	Sample Size	Year of Publication	Type of Study	Uptake Approach	STI's Screening	Counceling about Safe Sexual Practices	Treatment For STI's
Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.	Grant RM	2499	2010	Randomized Control Trial RCT	DAILY	YES	YES	YES
On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection.	Molina J-M	414	2015	Randomized Control Trial RCT	ON DEMAND	YES	YES	YES
Safety and Feasibility of Antiretroviral Preexposure Prophylaxis for Adolescent Men Who Have Sex With Men Aged 15 to 17 Years in the United States.	Hosek SG	78	2017	Randomized Control Trial RCT	DAILY	YES	YES	NO
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.	Stephanie E	557	2014	Open Label Study OLT	DAILY	YES	NO	YES
Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial.	McCormack S	554	2016	Open Label Study OLT	DAILY	YES	YES	YES
High pre-exposure prophylaxis uptake and early adherence among men who have sex with men and transgender women at risk for HIV Infection: the PrEP Brasil demonstration project.	Hoagland B	450	2017	Open Label Study OLT	DAILY	YES	NO	NO
. Plasma Tenofovir Levels to Support Adherence to TDF/FTC Preexposure Prophylaxis for HIV Prevention in MSM in Los Angeles, California	Landovitz RJ	301	2017	Open Label Study OLT	DAILY	YES	YES	YES
Challenges in Translating PrEP Interest Into Uptake in an Observational Study of Young Black MSM:	Rolle C-P	184	2017	Open Label Study OLT	DAILY	YES	YES	YES
Risk perception in MSM taking prep: a survey. Sexually Transmitted Infections.	Whitlock G	100	2017	Open Label Study OLT	77% DAILY 19% ON DEMAND 4% NOT SPECIFIED	?	?	?
PrEP use in Portugal while waiting for a policy.	Meireles P	112	2016	Open Label Reasearch OLR	UNKNOWN	YES	YES	YES
HIV Risk Behaviors, Perceptions, and Testing and Preexposure Prophylaxis (PrEP) Awareness/Use in Grindr-Using Men Who Have Sex With Men in Atlanta, Georgia.	Goedel WC	92	2016	Open Label Reasearch OLR	UNKNOWN	?	NO	?

TABLE 2 – STUDIES INCLUDED IN THE REVIEW – BEHAVIORAL ALTERATION FACTORS

Original paper title	Author	Eligible Sample Size	Year of Publication	Iprex	IPERGAY	PROUD
HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans.	Spinner CD	3458	2016	√	√	√
Pre-exposure prophylaxis: a useful tool to prevent human immunodeficiency virus infection?	Pialoux G	3458	2016	√	√	√
The current status of the use of oral medication to prevent HIV transmission	Mayer KH	3458	2015	√	√	√
Sexually transmitted infections and pre-exposure prophylaxis: challenges and opportunities among men who have sex with men in the US.	Scott HM	3044	2016	√	X	√
The European preexposure prophylaxis revolution	Cairns G	959	2016	X	√	√

TABLE 3 - REVIEWS

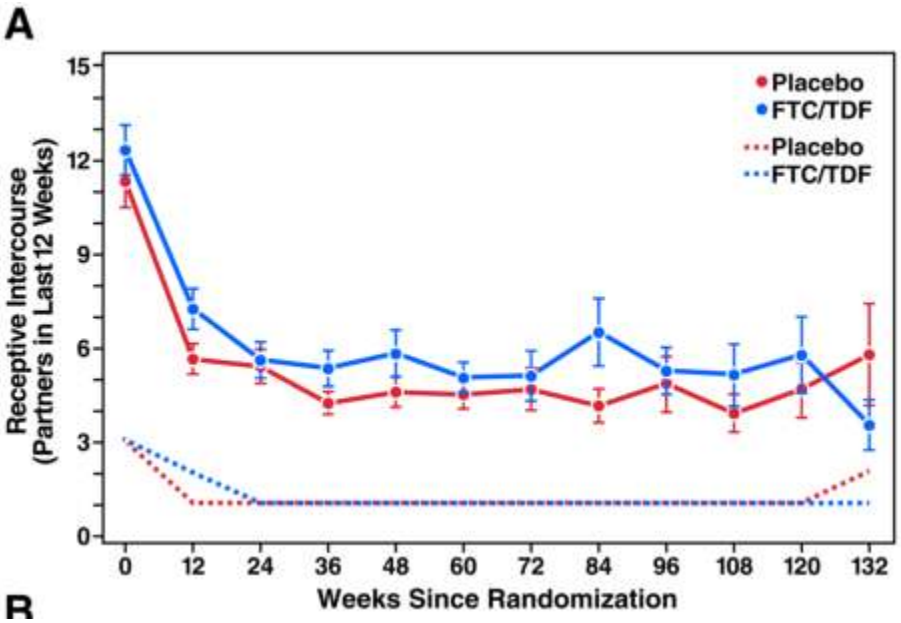

FIGURE 1 - (Grant et al., 2010)

EXTENDED SUMMARY IN GREEK

ΜΕΘΟΔΟΙ

Η χρήση PrEP έχει προωθηθεί ως βασικό εργαλείο για την καταπολέμηση της HIV επιδημίας. Οδηγίες από ΗΠΑ, Ευρώπη και τον Παγκόσμιο Οργανισμό Υγείας (Π.Ο.Υ) συνιστούν την χρήση PrEP σε διάφορες συνθήκες. Στον ανεπτυγμένο κόσμο, η ομάδα στόχος για την παρέμβαση με PrEP είναι οι Άνδρες που κάνουν Σεξ με Άνδρες (ΑΣΑ). Τα απότελέσματα από τις τυχαιωποιημένες Μελέτες κλειστού τύπου είναι ενθαρυντικά. Παρόλ' αύτά υπάρχει μεγάλος προβληματισμός για το κατά πόσο η ευρεία παροχή και χρήση PrEP μπορεί να έχει επίδραση στην ασφαλή σεξουαλική συμπεριφορά της συγκεκριμένης ομάδας στόχου (ΑΣΑ) Το ερώτημα που παραμένει είναι το ποια θα είναι η επίδραση της μακροχρόνιας χρήσης PrEP στην επίπτωση και τον επιπολασμό των Σεξουαλικά Μεταδιδόμενων Νοσημάτων (ΣΜΝ)

Αντικείμενο μελέτης

Κύρια ερωτήματα

1. Συνδέεται η χρήση PrEP με άυξηση των ΣΜΝ ή / και Ηπατίτιδας Γ εντός του πληθυσμού ΑΣΑ σε δομημένο ή ελέυθερο / αδόμητο πλαίσιο;
2. Συνδέεται η χρήση PrEP με αλλαγές στη σεξουαλική συμπεριφορά των ΑΣΑ (Είτε μέσω παρατήρησης είτε μέσω της ανάλυσης τάσεων σχετικά με την αντίληψη του συγκεκριμένου πληθυσμού);

Δευτερεύοντα ερωτήματα

1. Ποιες είναι οι υποκατηγορίες των ΑΣΑ που είναι πιθανότερο να παρουσιάσουν υψηλότερα ποσοστά απροφύλακτου σεξ ενώ κάνουν χρήση PrEP;
2. Ποιοι είναι οι παράγοντες που συνδέονται με μη ασφαλείς σεξουαλικές πρακτικές;
3. Ποιοι είναι οι κοινωνικο/οικονομικοί και φυλετικοί παράγοντες που έχουν επίδραση στα ποσοστά της συνεχόμενης / αδιάκοπης χρήσης PrEP;

Ερευνητική υπόθεση

- Η χρήση PrEP δεν οδηγεί στην αύξηση των ποσοστών ΣΜΝ και ηπατίτιδας Γ
- Η χρήση PrEP δεν οδηγεί στην αύξηση των ποσοστών αναφερόμενης απροφύλακτης σεξουαλικής πράξης

ΜΕΘΟΔΟΛΟΓΙΑ

Για την συγγραφή αυτής της συστηματικής ανασκόπησης χρησιμοποιήθηκε το πρωτόκολλο μεθοδολογίας PRISMA. Τα είδη μελετών που θεωρούνται επιλέξιμα είναι: άρθρα επιστημονικών περιοδικών, συστηματικές ανασκοπήσεις, μετα-αναλύσεις. Ο στόχος είναι ο συνδυασμός ισχυρών και πρόσφατων στοιχείων. Παρόλο που τα άρθρα περιοδικών δεν έχουν μεγάλη αξιοπιστία σε σύγκριση με τα άλλα δύο είδη, είναι ο τύπος μελέτης που συνδυάζει τα δύο προαναφερθέντα χαρακτηριστικά. Σε ό, τι αφορά τη γλώσσα της μελέτης, μόνο δημοσιέυσεις στην αγγλική γλώσσα λήφθηκαν υπόψη. Μελέτες που δημοσιέυθηκαν από το 2010 έως σήμερα (τελευταία αναζήτηση πραγματοποιήθηκε στις 10/01/2018). Το 2010 δημοσιεύθηκε η πρώτη τυχαιωποιημένη μελέτη κλειστού τύπου σχετικά με την χρήση PrEP ("iPrex") όποτε και αποδείχθηκε η αποτελεσματικότητά της

Αναζήτηση βιβλιογραφίας

Έγινε συνδυαστική αναζήτηση στη βάση δεδομένων «PubMed» τον Φεβρουάριο του 2018. Ο όρος "PrEP" χρησιμοποιήθηκε ως όρος "MESH" μαζί με όρους "HIV" και "MSM" οι οποίοι χρησιμοποιήθηκαν ως απλοί όροι αναζήτησης. Το αποτέλεσμα της αναζήτησης ανήλθε σε 147 άρθρα. Τα φίλτρα αναζήτησης που εφαρμόστηκαν ήταν:

- Ημερομηνίες δημοσίευσης: Δημοσιεύθηκε από το 2010 έως σήμερα.
- Τύποι άρθρων: Ανασκόπηση, Συστηματική ανασκόπηση, άρθρο επιστημονικού περιοδικού, Μετα-ανάλυση, Κλινική δοκιμή, Μελέτες εφαρμογής, Πρακτικές - παρατηρησιακές μελέτες, Μελέτες κοόρτης.
- Είδος: Άνθρωποι.
- Πεδία αναζήτησης: Τίτλος / Περίληψη.

Η αναζήτηση με φίλτρα είχε 112 αποτελέσματα.

Κριτίρια επιλογής μελετών

Θα ληφθούν υπόψη μόνον μελέτες και ανασκοπήσεις σχετικά με την χρήση PrEP. Συμπεριλαμβανομένων τυχαιωποιημένων μελετών κλειστού τύπου, δράσεις δημόσιας υγείας, αυτοαναφερόμενη χρήση PrEP κάτω από αδιευκρίνηστες συνθήκες (συμπεριλαμβανεται η ανεπίσημη χρήση PrEP) καθώς και ανασκοπήσεις που περιλαμβάνουν τις παραπάνω μελέτες.

Θα ληφθούν υπόψη μόνον μελέτες και δημοσιέυσεις με ελάχιστο δείγμα 70. Για να επιτευχθεί 80% ισχύς με 95 CI, alpha = 0,5, το δείγμα θα πρέπει να είναι κοντά στο n=385. Εάν επιλεχθεί να εφαρμοστεί ένα τόσο μεγάλο ελάχιστο δείγμα, πολλές από τις πρόσφατες μελέτες θα αποκλείστούν από την παρουσα ανασκόπηση. Ακόμα και αν δεν έχουν την ίδια ισχύ με τις ανω του 385 δείγματος μελέτες, ενδέχεται να συμπεριλαμβάνουν μία ή περισσότερες τάσεις που να αξίζει να διερευνηθούν περαιτέρω. Στην ίδια λογική αποφασίστηκε να συμπεριληφθούν δημοσιέυσεις με συμπεριφοριστικές ερευνες που παρουσιάζουν την ανεπίσημη χρήση PrEP, επειδή είναι ένας παράγοντας που αξίζει να διερευνηθεί εις βάθος.

21 δημοσιέυσεις επιλέχθηκαν για να συμπεριληφθούν σε αυτή τη συστηματική ανασκόπηση. Αυτές οι δημοσιέυσεις περιλαμβάνουν τυχαιοποιημένες μελέτες κλειστού τύπου , παροχή PreP στα πλαίσια κλινικών υγειονομικής περίθαλψης με τη μορφή ανοιχτής μελετης και συμπεριφορικές έρευνες ανοιχτού τύπου που περιλαμβάνουν δεδομένα ανεπίσημης χρήσης PrEP. Οι ίδιες μελέτες μπορούν να συμπεριλαμβάνονται σε περισσότερες από μία δημοσιέυσεις με τη μορφή ανασκοπήσεων. Αρκετές από τις ανασκοπήσεις που εν τέλει συμπεριλήφθηκαν στην παρούσα ανασκόπηση συμπεριλαμβάνουν περισσότερα από ένα είδος μελετης. Επιπλέον, εντοπίστηκαν άλλου τύπου μελέτες που δεν πληρούν τα κριτήρια αυτής της ανασκόπησης. Αποτελέσματα από τέτοιες μελέτες αποκλείστηκαν από την παρούσα ανασκόπηση. Οι πρωτότυπες μελέτες παρουσιάζονται στον πίνακα 2, TABLE 2.

Ανασκοπήσεις

Στις δημοσιέυσεις που επιλέχθηκαν για περαιτέρω διερεύνηση, συμπεριλαμβάνονται 5 ανασκοπήσεις. Ορισμένες από αυτές τις ανασκοπήσεις αυτές, περιλαμβάνουν μελέτες με δείγμα που δεν πληρεί τα κριτήρια της παρούσας ανασκόπησης, όπως οι έγκυες γυναίκες και / ή τα ετεροφυλόφιλα ζευγάρια. Δεν λαμβάνονται υπόψη οι αναφορές σε μελέτες που έχουν δείγμα διαφορετικό από τους ΑΣΑ.

Εξαγωγή δεδομένων

Η εξαγωγή δεδομένων σχεδιάστηκε να έχει τρείς πυλώνες. Ο πρώτος πυλώνας έχει να κάνει με δεδομενα που αφορούν τα ποσοστά ΣΜΝ, πρίν, κατά τη διάρκεια και μετά την χρήση PrEP, τη συμπεριφορά υψηλού κινδύνου και οτιδήποτε έχει να κάνει με τα ερωτήματα αυτής της ανασκόπησης. Ο δεύτερος πυλώνας έχει να κάνει με τους

παράγοντες που θα μπορούσαν να επηρεάσουν την σεξουαλική συμπεριφορά. Οι δείκτες που αφορούν τον δεύτερο πυλώνα είναι αν η χρήση PrEP ήταν συνεχόμενη ή κατά περιστατικό, εάν δόθηκε συμβουλευτική για ασφαλέστερες σεξουαλικές πρακτικές, και αν έγινε εξέταση και θεραπεία για ΣΜΝ. Ο τρίτος πυλώνας, αφορά την ισχύ των δεδομένων που ηξήχθησαν και εξετάζονται οι εξής δείκτες: το είδος της μελέτης, το μέγεθος του δείγματος και η διάρκεια της μελέτης. Δεδομένα από τους δύο πρώτους πυλώνες θα αξιολογούνται βάσει των δεικτών που συμπεριλαμβάνονται στον τρίτο πυλώνα.

Σύνθεση Δεδομένων

Η σύνθεση των δεδομένων θα γίνει βάσει δύο δεικτών. Ο ένας είναι η ισχύς του τύπου της μελέτης από την οποία προκύπτουν τα δεδομένα και ο δευτερος είναι η σχετικότητα με κάποιο από τα εσρευνητικά ερωτηματα αυτής της ανασκόπησης.

ΑΠΟΤΕΛΕΣΜΑΤΑ

Χαρακτηριστικά και περιορισμοί μελετών

Οι 21 δημοσιέυσεις περιλαμβάνουν 11 μοναδικές μελέτες, 6 από τις 11 είναι ανοικτές μελέτες, 3 από τις 11 είναι μελέτες κλειστού τύπου και 2 από τις 11 είναι έρευνες ανοιχτού τύπου σε πραγματικές συνθήκες. Η εφαρμογή της PrEP, σε τυχαιοποιημένες μελέτες ελέγχου και ανοιχτές μελέτες, πραγματοποιήθηκε σε δομημένο περιβάλλον, με συμβουλευτική πριν και μετά την παροχή PrEP για, τα ΣΜΝ, ασφαλείς σεξουαλικές πρακτικές και η παροχή της PrEP ήταν χωρίς κόστος για το υποκείμενο. Αντίθετα, στις ανοιχτές μελέτες, συγκεντώθηκαν δεδομένα από άτομα που ανέφεραν ότι είχαν κάνει χρήση PrEP στο παρελθόν ή και επί του παρόντος, αλλά δεν δίνονται πληροφορίες σχετικά με το πλαίσιο ληψης. Η ύπαρξη μάυρης αγοράς PrEP είναι γεγονός, η ανεπίσημη χρήση PrEP με απουσία παράλληλων υποστηρικτικών υπηρεσιών, αλλάζει σίγουρα τη σεξουαλική συμπεριφορά συγκριτικά με το ελεγχόμενο και υποστηρικτικό περιβάλλον των τυχαιοποιημένων δοκιμών ελέγχου και ανοιχτών δοκιμασιών σε κλινικές υγείας.

Όσον αφορά τον τύπο της πρόσληψης PrEP, σε 2 από τις 3 τυχαιοποιημένες μελέτες, είναι συνεχόμενη και σε 1 είναι κατ 'απαίτηση. Σε 5 από τις 6 ανοικτές μελέτες είναι συνεχόμενη ενώ σε 1 από τις 6 και οι δύο προσεγγίσεις ακολουθούνται (συνεχόμενη77% - κατ 'απαίτηση 19%) και στις 2 ανοιχτές έρευνες, η χρήση PrEP αναφέρεται από τα άτομα και ο τύπος λήψης δεν διευκρινίζεται.

Στις κλειστές μελέτες, η διάρκεια των προγραμμάτων είναι μεταξύ 48 και 132 εβδομάδων. Στις ανοικτές μελέτες, 16-96 εβδομάδες, ενώ σε μία ανοιχτή έρευνα η διάρκεια δεν διευκρινίζεται, η μόνη σχετική πληροφορία με την διάρκεια είναι ότι κάθε άτομο είχε έως 48 εβδομάδες πρόσληψης PrEP. Σε μία από τις ανοικτές έρευνες η συνολική διάρκεια ήταν 100 εβδομάδες, ενώ στην άλλη το δείγμα συλλέχθηκε εντός 3 ημερών και δεν δόθηκαν πληροφορίες σχετικά με τη διάρκεια της πρόσληψης PrEP.

Όσον αφορά το μέγεθος του δείγματος, οι κλειστές μελέτες είχαν συνολικά 2499 + 414 + 78 = 2991 συμμετέχοντες. Οι ανοιχτές μελέτες έχουν πιο ομοιογενή μεγέθη δειγμάτων. μεταξύ 100 - 557 με μέσο όρο συμμετεχόντων 357,66 και συνολικά 2146 συμμετέχοντες. Οι δύο ανοικτές έρευνες έχουν 112 + 92 = 204 συμμετέχοντες. Συνολικά, σε αυτή την ανασκόπηση περιλαμβάνονται 5341 συμμετέχοντες.

Παράγοντες αλλαγής συμπεριφοράς.

Κάποια κοινά στοιχεία στην πλειοψηφία των μελετών που διαπιστώθηκαν είναι πιθανό ή και βέβαιο ότι είναι παράγοντες αλλαγής συμπεριφοράς. Αυτά είναι: 1-συμβουλευτική σχετικά με τις ασφαλείς σεξουαλικές πρακτικές, 2-εξέταση για ΣΜΝ και 3-θεραπεία για τα ΣΜΝ. Αυτές οι τρεις υπηρεσίες παρασχέθηκαν πριν ή αμέσως μετά την έναρξη της μελέτης και σε πολλές περιπτώσεις σε τακτικά χρονικά διαστήματα μέχρι το τέλος της μελέτης και σε μερικές περιπτώσεις στην μεταπαρακολούθηση. Ο έλεγχος και η θεραπεία των ΣΜΝ προωθεί κουλτούρα υγείας και ασφαλούς συμπεριφοράς, είτε με την επαφή με ιατρικό προσωπικό είτε με το κέντρο προαγωγής υγείας. Αυτά τα χαρακτηριστικά συναντιόνται στις περισσότερες από τις μελέτες.

Περιορισμοί και ισχυρά σημεία των μελετών

Η πολύ συχνή εξέταση είναι ένας από τους πιο συνηθισμένους παράγοντες λάθους. Λόγω της αναπόφευκτης συνεχούς εξέτασης στις μελέτες εφαρμογής PrEP παρουσιάζονται υψηλότερα ποσοστά μολύνσεων συγκριτικά με τις πραγματικές συνθήκες.

Περιορισμοί και ισχυρά σημεία της παρούσας μελέτης

Σχεδόν όλες οι μελέτες που συμπεριλήφθηκαν στην παρούσα ανασκοπήση είχαν εφαρμόσει παράγοντες αλλαγής συμπεριφοράς και έτσι η επίδραση της PrEP στη σεξουαλική συμπεριφορά δεν μπορεί να εκτιμηθεί από μόνη της.

Ανάλυση δεδομένων

Τα δεδομένα και από τις τρεις κλειστές μελέτες δεν δείχνουν αύξηση της συχνότητας εμφάνισης ΣΜΝ. Το ίδιο παρατηρείται και στις ανοιχτές μελέτες με ασήμαντες αυξομειώσεις με την πάροδο του χρόνου. Όσον αφορά την αλλαγή της σεξουαλικής συμπεριφοράς στην πλειοψηφία των μελετών δεν υπήρξε κάποια σημαντική αλλαγή, αν και σε περιπτώσεις υπήρξε τάση είτε προς ασφαλέστερη είτε προς πιο επικίνδυνη συμπεριφορά.

ΣΥΖΗΤΗΣΗ

Σε συμφωνία με την αρχική υπόθεση, η χρήση PrEP δεν συσχετίζεται με την αύξηση της συχνότητας εμφάνισης των ΣΜΝ σε καμμία από τις τρείς κλειστές δοκιμές. Πρέπει να ληφθεί υπόψη ότι το ελεγχόμενο και υποστηρικτικό περιβάλλον των δοκιμών έχει μεγάλη επίδραση στη σεξουαλική συμπεριφορά. Όσον αφορά τους παράγοντες αλλαγής συμπεριφοράς, και στις τρεις κλειστές δοκιμές έγινε έλεγχος για ΣΜΝ, παροχή συμβουλευτικής για ασφαλείς σεξουαλικές πρακτικές και θεραπεία για τα ΣΜΝ. Υψηλά ποσοστά ΣΜΝ παρατηρούνται επίσης και στις δύο ομάδες ελέγχου χωρίς σημαντική διαφορά στις δύο ανοιχτές μελέτες με επαρκές δείγμα. Τα αποτελέσματα είναι τα ίδια και στις μελέτες <385 συμμετεχόντων.

Μόνο στη μελέτη iPREX παρατηρήθηκε σημαντική αλλαγή συμπεριφοράς, στις άλλες 2 κλειστές δοκιμές η συμπεριφορά δεν άλλαξε σημαντικά με την πάροδο του χρόνου, παρόλο που παρέμεινε σε υψηλά επίπεδα. Πρέπει να σημειωθεί ότι η μελέτη iPREX είχε σχεδόν 40% μεγαλύτερη διάρκεια (132 εβδομάδες - 96 εβδομάδες) συγκρίνοντας την επόμενη μεγαλύτερη μελέτη των Molina et al. Γενικά δεν παρατηρήθηκε αύξηση της σεξουαλικής συμπεριφοράς στις περισσότερες από τις ανοιχτές μελέτες. Στις δύο ανοιχτές μελέτες που δεν προσέφεραν συμβουλευτική για ασφαλέστερες σεξουαλικές πρακτικές, τα ποσοστά CRAI και η αντίληψη υψηλού κινδύνου για την PrEP ήταν κοντά το ένα στο άλλο. Υψηλό ενδιαφέρον εντοπίζεται στην μελέτη του Whitlock et al, όπου το 30% των συμμετεχόντων αύξησε τα ποσοστά CRAI μετά από 4 μήνες πρόσληψης PrEP, το οποίο μπορεί να ερμηνευθεί ως συσχετισμός μεταξύ της μακροχρόνιας χρήσης του PrEP και της μεταβολής της αντίληψης κινδύνου. Αντικρουόμενα αποτελέσματα παρουσιάζονται από τις δύο ανοιχτές έρευνες. Η μία έδειξε πιο επικίνδυνη συμπεριφορά σε χρήστες PrEP, ενώ η άλλη έδειξε ασφαλέστερη συμπεριφορά. Δυστυχώς όμως δεν υπάρχουν διαθέσιμα

δεδομένα σε βάθος χρόνου για την εκτίμηση της επίδρασης της PrEP στη σεξουαλική συμπεριφορά με την πάροδο του χρόνου. Είναι σημαντικό ότι η ανοιχτή έρευνα που έδειξε αυξημένη συμπεριφορά υψηλού κινδύνου είναι η μελέτη των Goedel et al η οποία δεν περιλάμβανε συμβουλευτική στη διαδικασία.

Η κατάχρηση ουσιών και πολυχρήση ουσιών, η χαμηλή αντίληψη κινδύνου και η χαμηλή εκπαίδευση σχετίζονται σε μεγάλο βαθμό με τις μη ασφαλείς σεξουαλικές πρακτικές. Επίσης, βρέθηκε συσχέτιση μεταξύ της αντίληψης κινδύνου και της διαθεσιμότητας του PrEP. Οι παραπάνω παράγοντες ευαλωτότητας, δείχνουν την ανάγκη για δωρεάν διανομή της PrEP σε τέτοιους πληθυσμούς, που βρίσκονται σε υψηλότερο κίνδυνο και εξακολουθούν να αντιμετωπίζουν εμπόδια στην πρόσβαση PrEP.

Η μη τακτική λήψη PrEP, συσχετίστηκε με χαμηλή αντίληψη κινδύνου για τον ιό HIV, τους κοινωνικούς παράγοντες στίγματος, το χαμηλό εκπαιδευτικό επίπεδο και την χαμηλή κοινωνικοοικονομική κατάσταση.

Συμπεράσματα

Είναι σαφές ότι η χρήση PrEP δεν συσχετίζεται με την αύξηση των ΣΜΝ ή και με σημαντική αλλαγή της σεξουαλικής συμπεριφοράς. Πρέπει να δοθεί προσοχή στο γεγονός ότι η παραπάνω κατεύθυνση δίνεται από μελέτες που παρέχουν συμβουλευτική για ασφαλέστερες σεξουαλικές πρακτικές, παρά το γεγονός ότι τα αποτελέσματα είναι τα ίδια σε 2 μελέτες που δεν προσφέρουν συμβουλευτική για την αποφυγή λάθος αποτελεσμάτων. Η PrEP αφορά καθώς είναι λογικό πληθυσμούς υψηλού κινδύνου με υψηλά ποσοστά απροφύλακτου πρωκτικού σεξ και υψηλό μέσο όρο αριθμού συντρόφων. Η επίδραση των συμπεριφορικών παρεμβάσεων μπορεί να μην είναι η μείωση των επικίνδυνων σεξουαλικών πρακτικών, όπως έχει ήδη αποδειχθεί και μετρηθεί (Johnson et al., 2008). Στο μοναδικό πλαίσιο της πρόσληψης του PrEP, οι παρεμβάσεις αυτές λειτουργούν ως αντισταθμιστικός παράγοντας και το αποτέλεσμά τους φαίνεται να είναι η μη αύξηση της συμπεριφοράς υψηλού κινδύνου. Επιπλέον, δεν πρέπει να αγνοηθεί ότι όλα αυτά τα προγράμματα εφαρμογής PrEP, ανεξάρτητα από το σχεδιασμό τους, προσέλκυσαν άτομα υψηλού κινδύνου τα οποία εκτέθηκαν και σε άλλα μέτρα πρόληψης εκτός του PrEP.

Όσον αφορά την ανεπίσημη χρήση PrEP, δεν βρέθηκαν επαρκή στοιχεία που να υποστηρίζουν την αύξηση ή όχι της συμπεριφοράς υψηλού κινδύνου κατά την πρόσληψη PrEP. Εάν οι συμπεριφορικές παρεμβάσεις λειτουργούν ως αντισταθμιστικός παράγοντας, όπως περιγράφεται παραπάνω, τότε υπάρχει κάποιος άλλος παράγοντας για να παίξει τον ίδιο ρόλο στο άτυπο πλαίσιο πρόσληψης PrEP; Εάν δεν υπάρχει, η άτυπη χρήση PrEP πρέπει να περιοριστεί και να αντικατασταθεί από δομημένη διανομή μέσω ιατρικών δομών.

Η κατάχρηση ουσιών είναι ένα άλλο κοινό χαρακτηριστικό μεταξύ των χρηστών του PrEP. Συχνά αναφέρεται ένας συνδυασμός περισσότερων από δύο φαρμάκων. Εάν το PrEP λαμβάνεται ανεπίσημα, από άτομα που καταχρώνται φάρμακα, θα θεωρείται από αυτόν τον πληθυσμό ως άλλη μία ουσία που εξυπηρετεί έναν συγκεκριμένο σκοπό και όχι ως μέρος μιας παρέμβασης για τη δημόσια υγεία. Το PrEP δεν θα πρέπει να στιγματιστεί ως «χάπι προσωρινής ανοσίας» και να προστεθεί στον κατάλογο των ναρκωτικών των chemsex parties, όπου ένας συνδυασμός ουσιών χρησιμοποιείται για την επίτευξη του επιθυμητού αποτελέσματος. Εφόσον η Prep αντιμετωπίζεται ως τέτοια, ακόμη και από μια μειοψηφία του πληθυσμού τα αποτελέσματα μπορεί να είναι μόνο αρνητικά με όρους δημόσιας υγείας.

Η ύπαρξη μαυρης αγοράς αποτελεί απόδειξη ότι υπάρχει ζήτηση για PrEP και συμβαδίζει με τα υψηλά ποσοστά γνώσης της PrEP στον πληθυσμό MSM (Goedel et al., 2016, σελ. 137). Η άτυπη χρήση του PrEP μπορεί να μόνο αυξηθεί στο μέλλον και μπορεί να αντιμετωπιστεί μόνο με γρήγορα αντανακλαστικά και άμεση ανταπόκριση στην ανεμπόδιστη, δωρεάν πρόσβαση στην PrEP σε δομημένο πλαίσιο.

Είναι πολύ ενδιαφέρον το γεγονός ότι μειώθηκε ο μέσος όρος ερωτικών συντρόφων με την πάροδο του χρόνου και η χρήση του PrEP συσχετίστηκε με αυτό σε ορισμένες από τις μελέτες. Είναι πιθανό η πρόσληψη PrEP να δίνει τη δυνατότητα στα άτομα να έχουν σταθερό οροθετικό σύντροφο και επομένως η PrEP να έχει θετικό αντίκτυπο στο στίγμα ενάντια στα οροθετικά άτομα. Δεν υπάρχουν επαρκή στοιχεία για την υποστήριξη αυτού του ισχυρισμού, αλλά σίγουρα πρόκειται για μια τάση που αξίζει να διερευνηθεί στο μέλλον.

Συνοψίζοντας, η PrEP φαίνεται να είναι μια πολύ αποτελεσματική παρέμβαση, χωρίς αρνητικές συνέπειες σε άλλες παρεμβάσεις με τις οποίες πηγαίνει παράλληλα. Αλλά η PrEP στηρίζει την αποτελεσματικότητά της, όπως και κάθε άλλο φάρμακο, στην ορθή πρόσληψη, η οποία βασίζεται σε επίσημες οδηγίες. Οι μάυρη αγορά καλύπτει μέχρι στιγμής τη ζήτηση για PrEP, δεδομένου ότι η επίσημη διανομή προσφέρεται μόνο σε συγκεκριμένες χώρες ή σε περιβάλλον δοκιμών, χωρίς βάθος χρόνου. Γρήγορα αντανακλαστικά απαιτούνται από τους εθνικούς φορείς Δημόσιας Υγείας για την κάλυψη της προϋπάρχουσας ζήτησης για PrEP με δομημένο, υποστηρικτικό και ελεγχόμενο τρόπο. Είναι πιθανό ότι η κατάχρηση του PrEP μπορεί να οδηγήσει σε στιγματισμό της στα μάτια της κοινής γνώμης και έτσι θα δημιουργηθούν περισσότερα εμπόδια στην αναπόφευκτη μελλοντική της εφαρμογή.

Υπάρχει επείγουσα ανάγκη για την εκπόνηση ενός κοινού πρωτοκόλλου εφαρμογής PrEP, συμπεριλαμβανομένων των κοινών δεδομένων που θα συλλέγονται σε βάθος χρόνου. Υπάρχουν ακόμη ερωτήσεις που πρέπει να απαντηθούν σχετικά με τη μακροπρόθεσμη χρήση του PrEP. Παρόλο που οι υπάρχουσες παρεμβάσεις είναι αποτελεσματικές και ακίνδυνες, οι μακροπρόθεσμες επιπτώσεις τους δεν είναι ακόμη εμφανείς. Η συνεχής παρακολούθηση είναι ουσιαστικής σημασίας και απαιτούνται προληπτικές ενέργειες για να παραμείνει η PrEP ευεργετική για τη δημόσια υγεία.