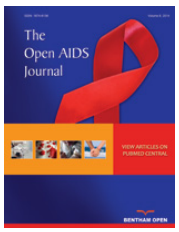

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RESEARCH ARTICLE

To Run with the Hares and Hunt with the Hounds: How to get HIV Transmission Reduced in MSM Using PrEP without Increasing STI Incidence?

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HIV pre-exposure prophylaxis (PrEP) refers to a primary prevention strategy aimed to reduce the risk of HIV acquisition through sexual contacts that consists in administering antiretroviral drugs to uninfected individuals belonging to high-risk populations, in particular men who have sex with men (MSM), not compliant to regular condom use and nonetheless engaging in high risk promiscuous sexual activities.

It is an acceptable, accessible and effective prevention package for HIV infection prevention in high-risk populations: daily PrEP, with good adherence, can reduce the risk of HIV infection by over 90% among various risk group, even with the occasional missed doses [1].

Undoubtedly, the introduction of PREP in the HIV prevention in clinical setting had dramatic effects on HIV transmission in at risk categories: several studies demonstrated significant decreases in HIV infection incidence in cohorts subjected to PrEP administration [2] and this leads health authorities to promote implementation of PrEP use worldwide.

There are, however, some concerning aspects that deserve consideration: the populations included in PrEP plans are "per se" not regularly using the condom (otherwise they would not need PrEP). Once they enter the PrEP program they may start to adopt "risk compensation" behaviours: this term refers to an increase in risk-related behaviors when an intervention reduces perceptions of risk among individuals or a population. In the HIV transmission setting, this includes a possible increased number of partners, condom-less anal sex, increased use of alcohol or recreational drugs, including chem-sex. Although these behaviors may not hamper the effects of PreP in HIV transmission prevention nonetheless, of course, this does not apply to other STI.

We are now facing a growing epidemic of STI among MSM, both bacterial (syphilis, gonorrhea, clamydia, enteric bacteria) and viral (HCV), that had started before PrEP introduction and was most probably correlated to an antiretroviral treatment optimism caused by the evidence that subjects virologically suppressed did not transmit the virus: U=U (Undetectable equals Untrasmittable) was a very popular and mediatic sentence. In addition, the evidence that antiretrovals reduced morbidity and mortality of HIV infection made individuals look less scared at a possible acquisition of the infection [3].

The subsequent decline in condom use caused a dramatic increase of bacterial STI in the last 20 years, with a rise of incidences of gonococcal and chlamydia infections, LGV, syphilis, especially at extragenital sites, such as the rectum and pharynx [4].

One could argue that the introduction of PrEP in the clinical practice and the adoption of risk compensation behaviours could produce a dramatic further increase of STI incidence especially in the MSM.

Although there is a general agreement that in MSM populations, this risk compensation occurs [4], studies aimed to address the question of whether MSM taking PreP experience more STI events gave quite contradictory results: in fact, while some studies demonstrated a clear increase, nevertheless others failed to confirm these findings.

Two reviews of the literature on this issue [5, 6], covering articles published until March 2010, although highlighting the dramatically high incidence of STI among PrEP users, were nevertheless unable to demonstrate a clear correlation between PrEP use and STD incidence increase while in another PrEP use was associated with a significant increase in rectal chlamydia and an increase in any STI diagnosis [7]

However, more recent studies still seem to confirm PrEP use to be associated with an increase in the number of patients diagnosed with STI and STI diagnoses [8 - 10]

Surely one should consider that PreP administration

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programs also include periodical screening for STI (including examination of extragenital sites): we can argue that otherwise undiagnosed infections are then intercepted. From one side, this will increase the number of (diagnosed) STI in PrEP users. At the same time, the frequent screening, the early diagnosis and treatment and the shorter duration of STI in these individuals may overall cause a reduction of STI incidence in the population.

Another aspect that needs consideration is that certain studies demonstrated gaps in the periodical screening for STI, especially in extra-genital sites, in PreP users [11].

The observation that the association between PrEP use and increased STI frequency is stronger in more recent studies and studies with longer follow-up, possibly reflects more confidence among PrEP users in PrEP efficacy, more widespread use of PrEP and a lower perception of risk [8].

These are some of the factors that may contribute to explain the puzzling issue of STI in MSM using PrEP and justify the fact that in spite of the many studies published till now, we still cannot really state if they are more affected by STI or not.

But, we do believe that neither the studies claiming increased STI in this population nor those showing the contrary, reached the wrong conclusions.

Probably population based behavioral characteristics, size and type of risk compensation, compliance to STI screening visits, health systems organization may heavily influence study findings and cause apparently discordant results.

So why speak about the relationships between PreP MSM users and STI? Because we are facing nowadays an STI epidemic reaching all-time highs that leads to greater health problems and rises concerns about both morbility and issues such as antimicrobial resistance and MSM is the population more heavily affected by the problem.

PrEP and administrations plans may be a valid tool to identify and enroll HIV negative "at risk" individuals, allowing not only HIV prevention but also STI control. But the achievement of these results surely needs the implementation of the strategy [11].

The CDC PrEP clinical guidelines recommend STI screening in PrEP users at three months interval, including extragenital sites and this could be a keystone to reach the goal of STI control.

We should emphasize with PrEP users that antiretrovirals are a complement and not a substitute of common preventive measures and that condom use should not be neglected. Probably subgroups need to be identified as less susceptible to behavioural counselling (younger populations, heavy drinkers or recreational drug users, individuals with repeated diagnosis of STI, especially rectal infections) to study more tailored preventive messages and more frequent STI testing.

STI periodical screening should be carefully planned and organized by health authorities and clinics, to avoid as many gaps as possible: to achieve this, STI screening must be easily accessible and, of course, for free. Care about minorities should be devoted to improving their access to STI prevention plans.

Another aspect that needs consideration is that certain studies demonstrated significant gaps in the periodical screening for STI in PrEP programs especially in extra-genital sites, in PreP users [11]. If STI services will be well integrated within PrEP programs, there will be the potential to also control STI pandemic. Higher coverage and more frequent STI testing among key populations and their sexual partners may reduce STI incidence [11].

A review of the literature in this field underlined the main challenges that influence the efficacy of programs aimed to reduce STI incidence in at high risk populations taking PrEP that are: 1) limited resources for testing 2) logistic aspects of STI testing and PrEP administration sites 3) adequate training of staff involved [11].

In addition, the serogical screening for syphilis, tests for gonorrhea and chlamydia infections (at genital and non genital sites), possibly by means of nucleic acid amplification methods, should be strongly implemented; the use of self-collected swabs can be proposed in certain cases and might help to increase diagnosis.

As a matter of fact, PrEP use may or may not increase STI incidence in MSM. Further analysis may clarify this aspect. But the wide use of PrEP in at-risk populations and the increasing request for PrEP worldwide represents at the moment an exceptional tool we got to work on STI prevention to reduce them if we are able to implement a well cohordinated system aimed to face two issues simultaneously (HIV and STI prevention)

In other words, if we will be able enough to **"**run with the hares and hunt with the hounds**"**

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