

PrEP and sexually transmitted infections

Gus Cairns, Published June 2019

Concern has been raised that PrEP could lead to, or contribute to, a new epidemic of sexually transmitted infections (STIs) other than HIV.

The questions we will aim to answer in this briefing are:

- > **To what extent have STI infections increased in recent years?**
- > **Are these increases especially concentrated in gay men, especially since PrEP became available? Which are not?**
- > **Are increases in STIs correlated with changes in behaviour such as condom use, or 'seroadaptive' behaviours such as serosorting (preference for sexual partners of the same HIV status) or seropositioning (decisions on sex roles dependent on HIV status)**
- > **Does PrEP directly lead to STI increases? Or are they just happening at the same time?**
- > **Are the observed increases in STIs caused by people taking more tests for them?**
- > **Could increased testing and treatment rates for STIs actually help reduce STIs? Is there any evidence for this already happening and if not, why not?**

To what extent have STI infections increased in recent years?

The truly exceptional period in the epidemiology of STIs both in the UK and globally was the 1990s, when the fear of HIV and the adoption of safer sex led to historic lows in STI diagnoses.

Diagnoses of STIs in general have been increasing since then, and [since well before the advent of PrEP](#).

Diagnoses have yet to reach [the historic highs](#) of the [late 1970s-early 1980s](#).

In recent years, diagnoses of three STIs – HPV/genital warts (due to vaccination), hepatitis B (due to vaccination and treatment), and [HIV itself](#) (for many reasons) have declined in many countries, but all others continue to rise.

The rise in the bacterial STIs gonorrhoea and syphilis are especially marked, and they are also the two bacterial STIs most concentrated among gay and bisexual men.

[In Europe](#), syphilis cases, over 80% of them in gay and bisexual men, have risen 50% since 2020 and gonorrhoea cases, two-thirds of them in gay and bisexual men, have more than doubled, from 35,000 a year to 80,000.

We will look below at the reasons for this and whether PrEP has any influence on increases in the most recent years.

Are increases in STIs correlated with changes in behaviour?

The proportion of people who maintain completely consistent and correct condom use as their primary HIV and STI prevention strategy has been in decline in the UK and other high-income countries since 1998, when antiretroviral therapy first became widely available.

One long-established series of surveys, the UK gay men's sex surveys, has found that, while up till 1997 a third of gay men were not using condoms 100% of the time, by 2014 only a third were using them that consistently.

It is worth noting that condoms are not as effective against other STIs as they are against HIV, partly because they are more contagious and [are often spread via oral sex](#). So, while reductions in condom use will logically lead to rises in most STIs, making condom use routine again might not have the expected impact against other STIs that it might have in HIV.

Using condoms has never been the only measure taken to avoid HIV infection, especially by gay men. As condom use became less frequent, but before biomedical prevention measures including PrEP and treatment-as-prevention ("U=U") were adopted, [people with HIV and at risk of it were using so-called "seroadaptive" behaviours that attempted to minimise the risk of sex if it was condomless](#).

Serosorting (restricting condomless sex to partners of one's own HIV status) was a major behavioural phenomenon in the 2000s. From 2001 onwards, for instance, in San Francisco, while the amount of condomless sex increased in HIV positive gay men, and stayed level in HIV-negative men, there was a sharp drop in reported condomless sex between partners of different HIV status. This trend was especially notable in men with HIV, in whom condomless sex "across the serodivide" fell by two-thirds. Serosorting was not restricted to gay men: [at least one study found similar behavioural trends in women](#).

A meta-analysis of serosorting found that while HIV-negative people who serosorted were half as likely to acquire HIV than ones who did not, [it was the least effective "seroadaptive" behaviour](#). One hundred per cent condom use was more effective, and "seropositioning" was even more effective than that. Seropositioning involves HIV negative men adopting the insertive role in anal sex and HIV-positive men the receptive role.

Since PrEP came along, there has been a change in gay men's ideas of what the safest HIV prevention strategy would be. [A study from New York, for instance, found that PrEP was now regarded as the safest HIV prevention strategy](#).

The fact that gay men are once more willing to "cross the serodivide" may significantly contribute to the increases seen in STIs in the last few years.

One of the most convincing explanations of why HIV rates are exceptionally high in certain communities despite similar or lower rates of risk behaviour, (such as [black gay men in the USA, or African migrants in Europe](#)), is that racism and cultural isolation means that people largely have sex only with other members of their minority group. This creates a tightly-bound network in which most of the sexually-active population is connected closely to other people, including people with HIV – or STIs.

HIV serosorting had a similar effect on STIs in gay men. The HIV-positive population was only 10% the size of the negative population but had exceptionally high rates of condomless sex between each other. This led to a concentration of STIs among HIV positive gay men such that some – such as LGV and sexually-transmitted hepatitis C – were almost exclusively seen in HIV-positive men.

[However as soon as serosorting was relaxed, and more HIV-positive and HIV-negative men started having sex with each other](#), a greater number of infections such as hepatitis C started to occur in HIV-negative men, as has been noted above.

Conclusion:
**STIs and
behaviour change**

A rise in STIs following the historic low of the HIV years was therefore probably inevitable, and the reasons for it unsurprising. The rise started just after the millennium, at the time when the availability of antiretroviral therapy first started to reduce people's fears of the consequences. It has accelerated since 2013-14, when awareness of the efficacy of both PrEP and of treatment as prevention as measures against HIV started to seep into the consciousness of at-risk populations.

The questions to ask now are;

- > **Are these increases all part of an inevitable historic rebound from the days of AIDS?**
- > **Or do PrEP, and treatment as prevention, have causative roles to play in sustaining, and possibly accelerating, the observed increases in STIs?**
- > **If they do, is this due to less condom use increased willingness to have serodiscordant sex – or are other factors at play?**
- > **In particular, do recent increases in the number and frequency of HIV tests and, alongside them, STI tests, have a part to play? Are we seeing more STIs mainly because we are looking for them?**
- > **If PrEP and awareness of the benefits of immediate HIV treatment lie behind increases in the regularity of STI testing, could they in the longer term have a beneficial effect on STI incidence?**

**Does the use
of PrEP lead to
more STIs?**

Whether PrEP actually leads to further increases in STIs, or is instead being adopted by people who would already be likely to get them, is unclear.

Some studies of PrEP have found rises in STIs following the initiation of PrEP. Others have found no increase. And in some, increases in STIs preceded the adoption of PrEP, suggesting STIs may have been motivators for people to seek out PrEP.

People taking part in PrEP studies have certainly had very high rates of STIs. The proportion of subjects diagnosed with a bacterial STI was 43% in the Ipergay study and 57% in the PROUD study. In the DISCOVER study, the annual incidence of bacterial STIs was almost 100% - this does not mean everyone in the study caught an STI but that the annual number of STI diagnoses nearly equalled the number of participants in the study.

[A meta-analysis of PrEP studies and rollout programmes in 2019](#) found that the average annual bacterial STI diagnosis rate among gay and bisexual men taking part in the highest-quality PrEP studies was 84%, with rates of individual conditions of 42% for chlamydia, 40% for gonorrhoea and 9.5% for syphilis.

The first meta-analysis to compare STI rates in studies of gay men taking PrEP and studies of gay men not on PrEP caused considerable concern when researchers reported that [men using PrEP were 25 times more likely to acquire gonorrhoea and 47 times more likely to acquire syphilis](#) than gay men not on PrEP. However, the authors themselves commented that "PrEP studies recruited MSM [men who have sex with men] with high-risk sexual behaviour, whereas MSM in studies not using PrEP may have had different baseline risk behaviour."

Does the use of PrEP lead to more STIs?

In March 2018, a meta-analysis of eight PrEP studies found that the risk of acquiring an STI increased by 25% in the first six months after starting PrEP; the risk of rectal STIs increased by 39% and of rectal chlamydia by 59%. There was also evidence that the increase was greater in more recent studies, with STIs increasing by 47% in the first six months after starting PrEP in studies terminating after 2016. However, there were only two out of the eight studies included in the analysis where the increase in STIs was statistically significant.

In one of these two studies, based on data collected in Seattle in 2014-2016, while chlamydia rates did increase after men started on PrEP, rates of syphilis and gonorrhoea were elevated in the year before men started on PrEP. Rates of gonorrhoea increased no further after starting PrEP, while rates of syphilis declined.

A US study was able to measure STI infections in men before, during and after their time on PrEP. The study found that while the number of condomless sex acts men reported tripled during their time on PrEP, the proportion diagnosed with a rectal STI only increased from 7% before to 10% during, and fell back to 2% after stopping PrEP. The author commented that his study showed association, but not causation. He said: “[Men] are taking PrEP when they are engaging in high risks and they are stopping PrEP at times when they are no longer at high risk.”

Moreover, post-PrEP rises in STIs vary between individuals. An example comes from the PrEPX study in the state of Victoria, Australia. In people who started PrEP for the first time, the annual incidence of STIs in this study increased by 71%, from 69.5 diagnoses per 100 people a year in the year before starting PrEP to 98.4 diagnoses per 100 people a year in the year after. Nonetheless, 52% of men did not have an STI during that year, while 25% had had two or more, accounting for 76% of infections, and 13% had had three or more, accounting for 53%.

The mechanism for the increases in STIs that have been seen does not appear to be a reduction in condom use, at least in people using PrEP, but rather an increase in partners. In the PrEPX study, there was not a statistically significant difference in STI rates according to the frequency of condom use, either with casual or regular partners. The relative lack of significance of condom-use frequency may be due to the fact that condom use was already very low in study participants even before starting PrEP.

The number of receptive anal sex partners was much more significant than condom use. Compared to people who had had one to five such partners in the last six months, people with between eleven and 20 partners were 91% more likely to have an STI, and people with 21-50 partners, 117% more likely.

Are more STIs due to more STI testing?

One significant confounder of the observed rise in sexually transmitted infections is that there has also been a significant increase in testing for them. This is an increase not only in the overall number of tests but in the appropriate testing of all anatomical sites and in screening of people who do not report symptoms.

More testing, especially of asymptomatic STIs, will at least temporarily inflate the number of diagnoses. So it is important to establish the extent to which the rises in STI diagnoses are rises in incidence: are we finding more STIs primarily because we are testing more often for them?

Gonorrhoea and chlamydia are often both asymptomatic and self-limiting; the immune system can eventually get rid of the infection (though not always, which is what can give rise to serious consequences). Syphilis is not self-limiting and can have serious acute symptoms as well as chronic ones, but its early stages can often be missed.

In the UK, the number of STI tests performed at sexual health clinics increased by 17.5% between 2013 and 2017, with the largest increases in women (20%) and gay men (44%).

In gay men especially, part of this increase may have been due to the demand for testing brought on by PrEP: central London clinics had been offering medical support for PrEP users since spring 2016 and saw the first significant decline in HIV incidence a year later. The IMPACT demonstration study, which began in October 2017, would in itself be expected to increase the number of HIV tests performed by gay men by an additional 20-25% if all its participants test quarterly and had not done with the same frequency before.

Furthermore, the UK is one of the few countries in Europe which has tested appropriately in the past for rectal, urethral and pharyngeal (throat) infections. For instance, the first EMIS survey asked its participants if they had had an STI test in the last year, and only 30% had. However many "STI tests" consisted solely of a blood test, which cannot detect chlamydia or gonorrhoea. Fewer than 50% of EMIS's gay and bisexual male respondents had had a urethral swab and only 16% a rectal swab, indicating that about one in 20 of EMIS's 180,000 respondents had had a test in the previous year that could detect two of the most common STIs in gay men in every site.

A PrEP demonstration project in New York City found evidence that increased testing rates were contributing to at least some of the rise in STI diagnoses in gay men on PrEP. In this study, from 68 to 83% of the STIs diagnosed were asymptomatic, and the researchers estimated that 24% of STIs would have been missed even if participants had screened for STIs every six months, as US guidelines recommend, instead of every three months as in the study.

Going back to the PrEPX study in Australia, the observed, large, increases in STI diagnoses became much smaller when testing frequency was controlled for. Among those starting PrEP, the number of clinic visits increased from 3.2 in the year before PrEP to 4.7 in the year after, and tests for individual STIs increased from 8.5 to 12.9. In multivariate analysis, controlling for testing frequency turned the 71% increase in STI diagnoses to a 21% absolute increase in incidence.

Similarly, an observed increase of 84% in chlamydia turned into an absolute increase in incidence of 38%. After controlling for testing, increases in gonorrhoea (at any site) were no longer significant, and there was no increase in syphilis even before controlling for testing.

Might frequent testing and treatment reduce STIs?

It is clear that high rates of testing and treatment for HIV are starting to produce substantial falls in HIV incidence in some countries and communities, as the proportion of people with HIV who are infectious shrinks. Might the same apply to STIs?

There is evidence that this can be achieved with some STIs, notably hepatitis C. One study found that new cases of hepatitis C among HIV-positive gay and bisexual men seen at three clinics in London had declined by nearly 70% since 2015, which was attributed to regular HCV screening and a treatment-as-prevention effect resulting from wider use of direct-acting antiviral (DAA) therapy. A previous study in the Netherlands found the same thing. In Australia, a study among a different population, people who inject drugs, found that testing and DAA treatment had reduced the community prevalence of hepatitis C viremia (a detectable viral load) from 43% in 2015 to 25% in 2017. The British HIV Association has declared that hepatitis C could be eliminated in the UK by 2021 if these trends continue.

Achieving this with the more contagious and often asymptomatic bacterial STIs is more difficult. England has had a national chlamydia screening programme for young people under 25 since 2003. Modelling showed that between 26% and 43% of 16- to 24-year olds would have to be tested and treated for chlamydia yearly to have an effect in infections.

A 2009 report by the National Audit Office found that only 50% of primary care trusts were achieving 26% coverage, and since then coverage has declined and the proportion of young people testing positive for chlamydia has increased, from 7.5% in 2013 to 9% now.

However it is arguable that high rates of testing and treatment might have a more positive effect in smaller, more targeted populations with very high background incidence. At London's 56 Dean St, the largest sexual health clinic in Europe, there was a huge increase in gonorrhoea testing from 3000 in the fourth quarter of 2013 to 11,000 in the third quarter of 2015. This was followed by a decline from 1600 gonorrhoea diagnoses during that quarter to 1100 per quarter for the next seven quarters, despite testing rates staying at the same level. This apparent decline in gonorrhoea infections was to some extent reflected in a national decline in gonorrhoea diagnoses from 22,000 to 17,000 in 2016. However, this decrease was not sustained, and gonorrhoea diagnoses started increasing again in the second half of 2017, possibly due to an increase in resistant infections.

If "test and treat" against STIs is not a complete answer, how about adding in "STI PrEP"? So far there have only been a couple of studies of the idea of giving gay men at very high risk of STIs antibiotic PrEP in the form of the cheap and safe antibiotic doxycycline, already used widely for malaria prophylaxis.

In a pilot study with 30 gay men in the US, there were 70% fewer STIs in the men given doxycycline. In a later study in France, 233 gay men took doxycycline for an average of 8.7 months. There was a fall of 73% in cases of syphilis and 70% in chlamydia - but no fall in gonorrhoea, possibly due to the presence of circulating doxycycline-resistant gonorrhoea.

A note on gonorrhoea resistance

Gonorrhoea resistance causes significant concern and may be one of the most significant medical risks of increased STI prevalence. The *Neisseria gonorrhoeae* bacterium easily becomes resistant to antibiotics. Originally treated with sulphonamides and then penicillin in the 1940s, gonorrhoea became progressively resistant to those drugs and then to tetracycline and ciprofloxacin, which replaced them.

As the proportion of gonorrhoea resistant to ciprofloxacin in the UK climbed to 50% in gay men and 20% in heterosexuals, a switch was made to a whole new class of antibiotics – the cephalosporins. A single drug from this class, cefixime, was used for first-line treatment of gonorrhoea starting in 2006.

However, the proportion of gonorrhoea with resistance to cefixime rapidly increased in gay men from about 5% in 2008 to 31% in 2010. As a result, in 2011 the recommended therapy changed, to dual combination therapy. This combined another cephalosporin, ceftriaxone, with the macrolide drug azithromycin.

Emphasising this as the only approved regimen for gonorrhoea, and guarding against over-treatment, appeared to have positive results both in the US, where rates of resistance to ceftriaxone fell tenfold between 2011 and 2014, and in Europe, where in the UK and Belgium resistance to both drugs halved between 2011 and 2014. No cases of ceftriaxone-resistant gonorrhoea were detected in Europe in 2016, compared with seven in 2013.

Doctors, however, were faced with the dilemma that up to 3% of patients are allergic to ceftriaxone. To preserve the action of azithromycin, the 2019 guidelines in the UK reverted back to solo ceftriaxone. At the moment cases of gonorrhoea resistant to ceftriaxone are rare, but higher levels of resistance in south and south-east Asia have led to predictions that increases over here are likely; it is notable that the first cases of multi-drug-resistant gonorrhoea seen in the UK were in heterosexual men who had acquired it in south-east Asia.

- To summarise:**
- > There is no doubt that there has been a considerable increase in STIs since the historic lows of the 1990s. The exceptions are HIV itself and in the two STIs for which we have vaccines – hepatitis B and HPV.
 - > Gonorrhoea and syphilis, as well as some less common conditions such as LGV, have seen the steepest rises, and have become proportionally more common in gay and bisexual men, in the UK, the US and in western Europe.
 - > A number of influences have contributed to the rises in STIs, together and sequentially.
 - > Firstly, 100% condom use became less often the primary HIV prevention method for gay men.
 - > Then ‘seroadaptive’ methods such as serosorting and seropositioning became more popular. These may have had some efficacy against HIV but less against STIs. They tended to concentrate STIs among HIV-positive people, in the same way that HIV has become concentrated among certain tightly-networked populations that tend mainly to have sex with each other.
 - > While there has been an upward inflection in the already steady increase in diagnoses in gay men since 2010-2013, it is impossible to ascribe this to PrEP. Any PrEP-specific effect would be unlikely to be seen until use became widespread, as it has done only even in the USA only in the last two to four years.
 - > A combination of factors ranging from falls in condom use to a relaxation of seroadaptation and sexual segregation between HIV-positive and HIV-negative gay men is more likely to have been the cause, as these trends have been around for longer.
 - > Another complicating factor is that STI testing rates have increased in all populations and especially in gay men. The PrEPX study found that most – though not all - of the increase in STI diagnoses after men started PrEP was due to more STI testing.
 - > The potential exists for more testing and treatment of STIs to eventually lead to falls in STI infections, as more people get treated sooner after infection. This has already been observed with hepatitis C. Initially, however, more tests will lead to more diagnoses, amplifying the impression of a rise in incidence.
 - > As PrEP use requires engagement with sexual health services, PrEP might facilitate this happening.
 - > Although condoms are not as fully effective against most STIs as they are for HIV, they remain the most effective preventative strategy, at least for rectal and vaginal infections.
 - > However [PrEP’s role in reducing sexual anxiety has been cited as a significant positive effect by PrEP users](#), especially gay men, in a number of studies. We will look at this topic in another factsheet.
 - > Thought needs to be given therefore to how to develop messages that lead to behaviours protective against HIV without re-instating sexual anxiety among people at risk of HIV.
-