HIV treatment as prevention

HIV PREVENTION ENGLAND

Introduction

The demonstration by the PARTNER and Opposites Attract studies that people with HIV who are on antiretroviral therapy (ART) and have fully-suppressed viral loads cannot transmit HIV sexually has revolutionised HIV prevention, especially in conjunction with pre-exposure prophylaxis (PrEP) for HIV-negative people.

This briefing paper describes the scientific evidence for the efficacy of treatment as prevention for individuals, and the evidence for its public health effectiveness in reducing HIV incidence on a population level, and considers its implications for the UK. It does not consider PrEP or post-exposure prophylaxis (PEP) and only covers antiretrovirals taken by people with diagnosed HIV, as treatment.

Scientific evidence

HIV treatment reduces the risk of transmission by reducing the quantity of HIV circulating in the body. When there is so little HIV in a person's blood that their viral load is 'undetectable', or they are 'fully virally suppressed', the risk of sexual transmission is effectively zero.

As early as the year 2000, the Rakai study in Uganda demonstrated that HIV was rarely transmitted by people with low viral loads. That study found no instance of a transmission by the HIV-positive partner in 415 serodiscordant couples if they had a viral load below 1500 copies/ml, allowing the authors to describe such an event as "rare".

The evidence from Rakai and similar studies allowed the Swiss Federal Commission for HIV/AIDS to make its statement in 2008 that people who have had an undetectable viral load for over six months and no sexually transmitted infections "do not transmit" HIV. The doctors who wrote the Swiss Statement were proved to be largely correct, but it took another ten years for enough evidence to be collected for the idea to be generally accepted by HIV experts.

HPTN 052, whose first results were announced in 2011, was the first randomised controlled trial to conclusively demonstrate that HIV treatment profoundly reduced the risk of sexual transmission.

It's important to note that this study measured the impact of putting people on treatment, not of their becoming virally suppressed. Viral loads were not routinely measured in subjects throughout the study. Nonetheless, it found that transmissions between serodiscordant couples were reduced by 96%, simply by putting the HIV-positive partner on ART.

The trial recruited 1763 couples in which an HIV-positive person had a CD4 cell count between 350 and 550 cells/mm^3 and had an HIV-negative partner. Almost all the couples were heterosexual and most were living in African or Asian countries. The HIV-positive participants were randomised either to start treatment immediately, or to defer treatment until their CD4 count fell below 250 cells/mm^3.

Twenty-eight individuals acquired HIV from their primary partner during the trial, one in the immediate-treatment arm and 27 in the deferred-treatment arm. This amounts to 96% fewer transmissions occurring.

The single transmission in the immediate-treatment arm took place a few days either before or after the person starting HIV treatment, that is, before full viral suppression had been achieved.

HPTN 052 was followed by two observational studies – PARTNER and Opposites Attract – which directly measured the effect of viral suppression.

PARTNER was an observational study whose primary endpoint was the number of transmissions seen within serodiscordant couples where the couple had condomless anal or vaginal sex, and the HIV-positive partner was fully virally supressed (defined as having a viral load below 200 copies/ml.) PARTNER's headline finding was that the number of transmissions seen was zero.

The study recruited over 1110 couples of differing HIV status, nearly 40% of them gay couples. At the start of the study, the HIV-positive partners had been on ART for five years in the gay couples and for 7-10 years in the heterosexuals. An undetectable viral load was reported by 94% of the gay men and 85-86% of the heterosexuals.

By 2014, no transmissions had occurred within couples, from a partner with an undetectable viral load, in what was estimated as 22,000 occasions of sex in the gay men and 36,000 in the heterosexuals.

The PARTNER researchers determined that they required further data for gay couples regarding anal sex. They recruited a second wave of couples to add to the existing couples. This second wave of recruitment and observation was called PARTNER 2.

Its results were announced in July 2018. The study found no transmissions between gay couples where the HIV-positive partner had a viral load under 200 copies/ml – even though there were nearly 77,000 acts of condomless sex between them. There **were** 15 new infections – but three-quarters of those infected reported recent condomless sex with a different partner, and genotyping of the HIV transmitted showed that not one infection came from the regular partner.

Confidence intervals are a statistical calculation used to determine researchers' certainty that what was observed in the study would be true in the real world. For a 95% confidence interval,this means that reserchers are 95% certain that the maximum likelihood of what was observed in the study is true in the real world.

The Partner 1 and 2 study results combined gave great certainty that virally suppressed couples would have zero transmissions. The 95% confidence interval was only 0.23% for all condomless sex.

The researchers were in little doubt what the results signified: principal investigator Alison Rodger said that the study result showed that there was "A precise rate of within-couple transmission of zero" for the risk of someone with a fully suppressed viral load transmitting HIV.

PARTNER was not the only study about viral load and infectiousness. In 2017 the Opposites Attract study also found zero transmissions in nearly 17,000 acts of condomless anal sex between serodiscordant gay male partners, meaning that no transmission has been seen in about 126,000 occasions of sex, if you combine this study with PARTNER 1 and 2.

Reaching and maintaining viral suppression

There may be concerns about circumstances in which transmission could still occur, despite the person with HIV taking treatment.

The first months of taking treatment

In the first few months of a person taking treatment, before the achievement of full viral suppression, transmission could still occur.

However, how long does it usually take for a person to become undetectable? A 2017 study from the US (where viral suppression rates tend to be lower) found that patients starting integrase-inhibitor based ART (the most potent class of modern ART) took a median of 63 days (two months) to achieve viral suppression, with 93% virally suppressed within six months.

Virological failure

After initiating ART and achieving viral suppression, there remains the possibility of adherence difficulties, treatment failure and viral load becoming detectable. In these circumstances, the individual may become infectious.

A couple of large cohort studies have looked at how often this occurs. A 2017 study of 16,000 people from the UK CHIC cohort who started ART between 1998 and 2013 found that 8.1% (one in 12) of people who achieved viral suppression (defined as a viral load below 200 copies/ml) experienced a 'viral rebound', meaning a return of their viral load to above that figure, within the first year on ART. The likelihood of viral rebound during the second year after starting ART was 5.8% and after seven years of therapy, had settled down to a steady state of 1.4% a year, or one person in 71.

In 2019, the European COHERE cohort examined the virological rebound data of over 19,000 people starting the efavirenz/tenofovir/emtricitabine combination that is familiar as the branded single-pill combination **Atripla**. This found roughly similar rebound rates of 6.3% in the first year, 3.5% in the second year, and 1.7% after the seventh year.

These two studies gathered data on viral failure over considerable lengths of time, and include a lot of people who started on what would now be regarded as sub-standard regimens. Virological failure rates in people starting modern regimens today would likely be considerably lower.

Infectiousness after virological failure

Even after virological failure, viral load does not rebound immediately to infectious levels.

Although French researchers who asked patients to interrupt their treatment found that viral load became detectable after just two weeks in most people and in all of them by four weeks, viral rebound might not be as rapid in situations of poor adherence or resistance than after completely stopping therapy.

In addition, a proportion of detectable viral load tests on people on ART are single 'blips', whether caused by adherence problems, natural variance or laboratory error; the UK CHIC study found that in 29% of detectable tests, the viral load in the subsequent test was below 50 copies/ml.

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Nonetheless, although the risk of viral failure in people taking long-term ART is low, it is not insignificant in the first couple of years and never declines to zero. This is an argument for the maintenance of regular viral load testing for people with HIV. Also, serodiscordant couples considering condomless sex may be advised to wait for at least two undetectable viral load results in the HIV-positive partner.

Other body fluids

Studies have sometimes found that individuals have had an undetectable viral load in blood, but not in other body fluids. Nonetheless most people who have an undetectable viral load in blood are also undetectable in their semen or vaginal fluids, as well as in their rectal mucosa and (in the case of women) vaginal mucosa. Even when there are so-called discordant viral loads and someone has detectable HIV in their genital tract but not in their blood, the viral loads detected are rarely high enough to pose a strong risk of transmission.

Sexually transmitted infections

It was thought that inflammatory STIs would raise the viral load and the risk of transmission, even in people on fully-suppressive ART. It is certainly the case that in people not on ART, STIs such as syphilis and herpes magnify the risk both of transmitting and acquiring HIV.

However, the PARTNER study found that even though STIs were common in their participants (especially gay men), there were zero transmissions from couples were one partner had an STI and the HIV-positive partner was virally suppressed.

Undetectable = untransmittable

It was the personal experience of not being told by doctors that viral undetectability means zero risk of transmission which spurred Bruce Richman, a gay man with HIV to set up the Prevention Access Campaign in 2016. Richman's view was that the knowledge of treatment as prevention is a neutral piece of scientific information which all people with HIV needed to be aware of and allowed the autonomy to use it.

Prevention Access Campaign created the slogan "U=U" (undetectable equals untransmissible). It quickly became one of the phrases that will evoke the history of the HIV epidemic (along with "silence equals death", "safer sex" and others). It has helped consolidate a consensus that universal treatment access and helping people achieve viral undetectability is both good medical practice and an important contribution to reducing the global burden of HIV infection.

The principle of U=U has been endorsed by treatment guidelines, public health organisations and HIV experts around the world. The British HIV Association (BHIVA) encourages universal promotion of U=U as explained by Professor Chloe Orkin, BHIVA's chair in 2017: "As the UK's leading voice for HIV health professionals, our backing for U=U is unequivocal. There should be no doubt about the clear and simple message that a person with sustained, undetectable levels of HIV virus in their blood cannot transmit HIV to their sexual partners."

BHIVA treatment guidelines recommended that HIV treatment should be offered to all people living with HIV. The scientific evidence about the effect of HIV treatment on onward sexual transmission should be discussed with all patients as a part of safer sex messages. The guidelines add that "For individuals with a high CD4 cell count, the impact of treatment on the risk of transmission may be an additional factor to aid their decision-making".

The public health impact

Since treatment as prevention unquestionably works at the individual level, it follows that it would have prevention benefits at the population level. Namely, increasing the number of HIV-positive people on treatment lowers the total amount of virus circulating in a community and leads to a reduction in the number of new HIV infections.

Trends in HIV diagnoses in gay and bisexual men in 13 countries in western Europe, North America and Australasia support this. Between 2000 and 2005, HIV diagnoses increased in most countries. There were increases in diagnoses of sexually transmitted infections at the same time, suggesting that the key factor was changing sexual behaviour.

Between 2008 and 2014, diagnoses continued to increase in five countries (including the UK), whereas they either decreased or were stable in eight countries. Importantly, STI diagnoses and reports of condomless sex in community surveys continued to increase. HIV testing rates were also on the rise, showing that the lower number of diagnoses in those countries was not simply due to fewer people being tested.

The researchers who analysed the data from these 13 countries therefore argued that "increased effective use of antiretroviral therapy during the 2000s may have led to stable and decreasing HIV rates among men who have sex with men". More men living with HIV had an undetectable viral load, leading to reductions in HIV incidence in the wider community.

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The 90-90-90 targets, set by the United Nations agency UNAIDS, are global targets aimed at maximising the public health effect of reducing undiagnosed HIV and scaling up HIV treatment. They are:

- To diagnose 90% of people living with HIV
- For 90% of diagnosed people to have initiated treatment
- For 90% of people who have initiated treatment to be virally suppressed

This sequence of actions, or 'treatment cascade' is calculated to result in overall viral suppression (undetectable viral load) of 73% of all people living with HIV, which would greatly reduce HIV transmissions, and, over time, HIV prevalence. If this target is achieved or surpassed, it will also greatly reduce the healthcare, economic and societal costs of HIV to the world.

These targets have been surpassed in the United Kingdom. This is probably the key factor which explains the dramatic decline in HIV diagnoses and HIV incidence in recent years. The 2018 data, reported in January 2020, show that in the UK:

- 93% of people with HIV were diagnosed
- 97% of diagnosed people were on treatment
- 97% of people on treatment were virally suppressed

As a consequence, 85.7% of all people with HIV were virally suppressed.

It was estimated that London had reached the milestone of having over 90% of HIV-positive people virally suppressed (95% diagnosed, 98% of those on treatment, 97% of those virally suppressed = 90.3%).

Between 2014 and 2018, the annual figure for HIV diagnoses in the UK fell by 29%, from 6,728 to 4,453. The decline was most marked in gay and bisexual men (35%).

Diagnoses of recent infection fell even faster. These figures enabled Public Health England to estimate that HIV incidence – the real annual rate of new infections, whether diagnosed that year or not – decreased by 65% in gay and bisexual men between 2014 and 2018. Incidence in heterosexual men and women was estimated to fall by 55% and 22% respectively in the same time period.

While PrEP could make a significant contribution to reducing incidence in the future, in 2018 not enough people were taking PrEP for it to have had such a large effect, especially in heterosexual men and women.

Public Health England's interpretation of these data is that the use of combination prevention tools (condom use; expanded HIV testing;, prompt ART initiation and ongoing adherence; PrEP availability) are working in the UK.

Key points

- HIV treatment reduces the amount of virus in the body to such low levels that it can't be transmitted sexually.
- An individual must maintain good adherence in order to ensure their viral load remains undetectable, or <200 copies/ml.
- STIs have no effect on transmission risk when individuals are taking HIV treatment and are virally supressed.
- The individual-level benefits of treatment as prevention are clear, sharing the science has increased HIV knowledge and challenged HIV-related stigma in key populations. People living with HIV can enjoy sexua relationships without fear of HIV transmission.
- Benefits for the populations affected by HIV of treatment as prevention include lower HIV incidence in conjunction with other prevention tools, and a reduction in the healthcare, societal and economic burden of HIV.

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