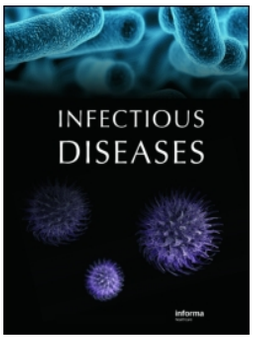

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REVIEW ARTICLE

Risk of HIV transmission from patients on antiretroviral therapy: A position statement from the Public Health Agency of Sweden and the Swedish Reference Group for Antiviral Therapy

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Abstract

The modern medical treatment of HIV with antiretroviral therapy (ART) has drastically reduced the morbidity and mortality in patients infected with this virus. ART has also been shown to reduce the transmission risk from individual patients as well as the spread of the infection at the population level. This position statement from the Public Health Agency of Sweden and the Swedish Reference Group for Antiviral Therapy is based on a workshop organized in the fall of 2012. It summarizes the latest research and knowledge on the risk of HIV transmission from patients on ART, with a focus on the risk of sexual transmission. The risk of transmission via shared injection equipment among intravenous drug users is also examined, as is the risk of mother-to-child transmission. Based on current knowledge, the risk of transmission through vaginal or anal intercourse involving the use of a condom has been judged to be minimal, provided that the person infected with HIV fulfils the criteria for effective ART. This probably also applies to unprotected intercourse, provided that no other sexually transmitted infections are present, although it is not currently possible to fully support this conclusion with direct scientific evidence. ART is judged to markedly reduce the risk of blood-borne transmission between people who share injection equipment. Finally, the risk of transmission from mother to child is very low, provided that ART is started well in advance of delivery.

Keywords: *HIV transmission therapy*

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Introduction

In 2008 the Swiss AIDS Commission announced that people infected with HIV who are on effective antiretroviral therapy (ART) should not be considered infectious through sexual contact, provided that certain criteria are fulfilled [1]. This drew considerable attention to the scientific evidence for the transmission risk from patients on ART. The subject became topical again in 2011 with the release of the results from the HPTN 052 study [2]. This study followed 1763 serodiscordant couples where one partner was HIV-positive and the other HIV-negative at the beginning of the study. The couples were enrolled from 2007 to 2010 and randomized into 2 study groups, one in which the HIV-positive partner immediately received ART irrespective of their immune status, and a second where ART was started later if an indication for treatment developed (i.e. CD4 count <250 cells/μl blood). All participants received advice about the use of condoms. The study demonstrated that early ART was associated with a 96% reduction in the risk of transmission through sexual contact compared with ART started later. This confirmed the results of several previous observational studies. These findings have led to extensive scientific discussions about how ART might be used in the prevention of HIV transmission (so-called treatment as prevention, TasP).

Against a background of recent scientific discoveries and the ongoing discourse, several national expert groups, in addition to the Swiss, have published their opinions. In the United Kingdom, the British HIV Association (BHIVA) and the Expert Advisory Group on AIDS (EAGA) have stated that there is an extremely low risk of transmission through sexual contact from people who are continuously fully suppressed on ART, provided that no other sexually transmitted infections are present [3].

There is also a parallel discussion into the possibility of preventing HIV spread through the large-scale use of post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP). PEP describes the initiation of ART immediately following a single HIV exposure with the aim of preventing transmission, whereas PrEP involves the preventative treatment of HIV-negative people who have an ongoing or recurrent risk of infection.

The Swedish national quality registry InfCare HIV includes more than 99% of all known HIV cases in Sweden. According to the registry, 87% of all HIV-positive patients in Sweden were receiving ART in 2012 (http://infcare.com/hiv/sv/resultat/2012-arsrapport/, in Swedish). Of these, 92% had effective ART, i.e. a plasma viral load <50 HIV RNA copies/ml. In light of this and the findings of the HPTN 052 study, there is great demand for comprehensive information about the most current evidence on the risk of transmission from patients who are on effective ART. There is also a need for knowledge about the risk of HIV transmission from those who are not on ART and about the long-term medical consequences for people living with HIV infection.

This position statement from the Public Health Agency of Sweden and Swedish Reference Group for Antiviral Therapy is based on a workshop organized in the fall of 2012. It summarizes the latest research and knowledge on the risk of HIV transmission from patients on ART, with a focus on the risk of sexual transmission. The risk of transmission via shared injection equipment among intravenous drug users is also examined, as is the risk of mother-to-child transmission. The text was published online in Swedish on the website of the Public Health Agency of Sweden in October 2013, together with 9 background articles (also in Swedish).

Medical consequences of HIV infection

- HIV infection is still a serious, incurable disease that requires lifelong treatment.
- The life-expectancy of people infected with HIV in industrialized countries has increased markedly and is becoming comparable to that of uninfected people.
- In Sweden, HIV infection now very seldom leads to death if the infection is diagnosed in time to start ART before any serious immunodeficiency has developed.

Modern ART was introduced in 1996 and quickly led to a dramatic reduction in both the morbidity and mortality caused by HIV infection. Further improvements have since been made, both in antiviral effect and reduction in adverse effects, with positive implications for the patient's experience of ART and the impact on health-related quality of life [4].

Resistance to the antiretroviral drugs may develop, but, with few exceptions, this can be managed by exchanging all or some of the drugs. Several studies have shown that the life-expectancy of HIV patients in industrialized countries is increasing and is now close to that of the rest of the population [5–7]. An important reason for the remaining shortened life-expectancy is that, aside from factors connected to lifestyle and socio-economic status, some patients are diagnosed at such a late stage that ART cannot be started in time to have an effect [8]. Data from InfCare HIV show that all-cause mortality among HIV patients in Sweden is currently lower than 1% annually (http://infcare.com/hiv/sv/resultat/2012-arsrapport/, in Swedish). However, the mortality is significantly higher among

those diagnosed late in disease progression, i.e. with serious immunodeficiency, and those who were infected through intravenous drug use.

Definition of effective antiretroviral therapy

The following criteria must be fulfilled in order for the antiretroviral therapy of HIV infection to be considered effective:

- The viral load of HIV RNA in the blood plasma must be continuously <50 copies/ml, verified in 2 successive measurements conducted at an interval of 3–6 months.
- The patient must maintain a continuously high adherence to treatment.
- Monitoring of viral load and adherence to treatment must take place regularly in accordance with Referensgruppen för Antiviral Terapi (RAV) guidelines, i.e. 2–4 times per y [9].

In addition, there must not be any clinical or epidemiological reason to suspect the presence of any other ongoing sexually transmitted infection, as this theoretically could increase the risk of transmission even if ART is effective.

Low yet detectable plasma viral loads of up to 500 copies/ml are seen in a limited number of patients with good adherence to treatment and effective ART. When viral loads up to this level are detected on any single occasion, they are referred to as 'blips'. The causes of these blips may be both biological and related to the measurement technique, but they are not usually an indication of increased viral replication. Blips are seen in a majority of patients with effective ART if the viral load is measured sufficiently often. This also applies to the patients who were involved in the HPTN 052 study and other studies that form the basis for the assessment of the risk of HIV transmission during ART. There is no indication that patients receiving effective therapy who have blips are more infectious than patients without documented blips. A small proportion of patients on ART instead have continuously identifiable low-level viraemia, i.e. a low presence of virus in plasma (50–500 copies/ml). There are not yet sufficient data to assess with complete certainty the transmission risk from these patients, but available data indicate that it is very low [10].

Assessment of the risk of transmission through sexual contact

The risks of transmission through vaginal and anal intercourse in cases of effective ART are as follows:

- There is minimal risk of transmission through vaginal and anal intercourse if the HIV-infected partner is on effective ART and a condom is used throughout intercourse.
- There is also a very low risk of transmission through vaginal and anal intercourse if the HIV-infected partner is on effective ART and a condom is not used.
- The above applies for each individual sexual contact and in cases of repeated contact over the course of longer periods (y), regardless of whether the HIV-infected partner is a woman or a man and regardless of whether the HIV-infected partner is penetrative or receptive during the sexual act.

With regard to the risk of transmission through vaginal intercourse, the assessment above is supported primarily by the prospective HPTN 052 study [2], but also by several observational studies. A recently published meta-analysis of the results from 6 different studies covering a total of 6070 heterosexual serodiscordant couples where the HIV-positive partner had effective ART calculated the risk of transmission to be <0.01 per 100 person-y [11].

In the treatment group of the HPTN 052 study there was 1 transmission observed in approximately 1500 person-y, which corresponds to a risk of transmission of approximately 1 per 150,000 sexual contacts. Furthermore, it has been reported that this single observed transmission took place before or very soon after the HIV-infected partner had initiated ART. This means that the available data do not contradict the Swiss statement that there may be a non-existent (zero) risk of transmission through vaginal intercourse when a patient is on effective ART. However, zero risk is impossible to demonstrate scientifically. It is probable that the risk of transmission is also minimal in cases of effective ART even when a condom is not used. However, because condom use was encouraged in the HPTN 052 study, there is insufficient scientific evidence currently available to support such a conclusion. In addition, condoms are recommended because the risk of transmission of other sexually transmitted infections may be present in the absence of symptoms. There is a lack of knowledge about the potential of other barrier methods to reduce the risk of transmission.

Furthermore, the risk of transmission is assessed to be very low even if treatment does not entirely comply with the above criteria of effective ART. This is based on the reduction in the risk of transmission of at least 96% seen in the HPTN 052 study, even though effective ART was defined as a viral load <1000 copies/ml, rather than <50 copies/ml. Furthermore, 5% of patients in the HPTN 052 study had virus levels >1000 copies/ml. This conclusion is also supported by a meta-analysis of the results from several studies, covering a total of 5021 heterosexual

couples and 461 transmission events, in which there were no transmissions observed from patients with a viral load below 400 copies/ml [10].

There are no prospective studies that directly address the risk of transmission through unprotected anal intercourse from patients on effective ART. The assessment above is thus extrapolated from risks that are better understood. For example, in cases of untreated HIV infection the risk of transmission per sexual contact is on average about 10 times higher for the receptive partner in anal intercourse than in vaginal intercourse. The risk of transmission is lower for the penetrative partner than for the receptive partner. It is likely that effective ART reduces the risk of transmission through anal intercourse to about the same degree as through vaginal intercourse. This was also the conclusion recently drawn by an expert committee from the World Health Organization (WHO) [12]. There has only been 1 case described in the literature in which transmission has taken place between 2 men despite the HIV-infected partner being on effective ART [13]. The absence of similar cases in the international medical literature indicates that transmission through vaginal or anal intercourse from patients on effective ART is highly unusual, as such cases would be of great academic, epidemiological, and clinical interest. Furthermore, there have been no known cases in Sweden of sexual transmission from patients who meet the criteria for effective ART.

Risk of transmission through oral sexual contact in cases of effective ART

- The risk of transmission through oral sexual contact is assessed to be minimal if the HIV-infected partner is on effective ART.
- This applies regardless of gender or type of sexual contact (heterosexual or homosexual).

There are no studies on the risk of transmission through oral sexual contact where the HIV-infected partner is on effective ART. However, in cases of untreated HIV infection, the risk of transmission through oral sexual contact is lower than through vaginal intercourse, which provides support for the assessment above.

The significance of HIV RNA in genital secretions in cases of effective ART

- Low levels of HIV RNA are sometimes detected in the genital secretions of patients on effective ART. However, this has not been shown to be of significance to the risk of transmission.

Several studies have reported findings of low, yet detectable, levels of HIV RNA in the semen and cervical secretions of ART-treated patients who do not have detectable levels of HIV RNA in their blood plasma [14,15]. However, it has not been established whether these patients are contagious. Cohen and colleagues maintain that low levels of HIV RNA in genital secretions are unlikely to significantly affect contagiousness, arguing that some participants in the HPTN 052 study and observational studies probably also had low levels of HIV RNA in their genital secretions, but ART was still associated with a dramatically reduced risk of transmission [16].

Assessment of the risk of transmission from intravenous drug users on effective ART

- Based on the available indirect data, the risk of HIV transmission between intravenous drug users is thought to be markedly reduced if the HIV-infected person is on effective ART.

There are no studies that provide a direct answer regarding the risk of transmission via injection equipment that is shared between intravenous drug users when the HIV-infected person is on effective ART. However, 2 observational studies from British Columbia, Canada and Baltimore, USA, indicate that reduced viral load at the population level, as a result of the increased use of ART, is associated with a reduced incidence of HIV infections among intravenous drug users [17,18]. Based on these findings, Wood and colleagues recently concluded that ART is also relevant to the prevention of HIV transmission via shared needles [19]. The risk of transmission of other blood-borne infections such as hepatitis C remains unchanged, even in cases of successful HIV treatment.

In summary, it is highly probable that the risk of blood-borne transmission of HIV between intravenous drug users is significantly reduced if the HIV-infected person is on effective ART, but the magnitude of the reduction is still unclear.

Assessment of the risk of mother-to-child HIV transmission during pregnancy and childbirth

- The risk of HIV transmission from mother to child is less than 0.5% if the pregnant woman has effective ART beginning well in advance of delivery [20].

The very low risk of mother-to-child transmission and recent advances in HIV treatment that have extended life-expectancy and improved quality of life have meant that more HIV-infected women are planning to have children.

Although reduced fertility is probably more common among HIV-infected women, they are not currently offered in vitro fertilization (IVF) in Sweden, in accordance with regulations governing the donation and utilization of organs, tissues, and cells. The opportunity for IVF is now available to HIV-positive women in Denmark and several other countries inside and outside of the European Union.

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