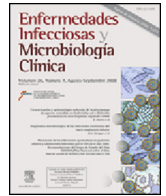




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Review article

Can we rely on the antiretroviral treatment as the only means for human immunodeficiency virus prevention? A Public Health perspective



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ABSTRACT

The evidence that supports the preventive effect of combination antiretroviral treatment (cART) in HIV sexual transmission suggested the so-called 'treatment as prevention' (TAP) strategy as a promising tool for slowing down HIV transmission. As the messages and attitudes towards condom use in the context of TAP appear to be somehow confusing, the aim here is to assess whether relying on cART alone to prevent HIV transmission can currently be recommended from the Public Health perspective.

A review is made of the literature on the effects of TAP strategy on HIV transmission and the epidemiology of other sexual transmitted infections (STIs) in the cART era, and recommendations from Public Health institutions on the TAP as of February 2014. The evolution of HIV and other STIs in Barcelona from 2007 to 2012 has also been analysed.

Given that the widespread use of cART has coincided with an increasing incidence of HIV and other STIs, mainly amongst men who have sex with men, a combination and diversified prevention methods should always be considered and recommended in counselling. An informed decision on whether to stop using condoms should only be made by partners within stable couples, and after receiving all the up-to-date information regarding TAP.

From the public health perspective, primary prevention should be a priority; therefore relying on cART alone is not a sufficient strategy to prevent new HIV and other STIs.

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¿Podemos confiar en el tratamiento antirretroviral como único método para la prevención del virus de la inmunodeficiencia humana? Una perspectiva de Salud Pública

RESUMEN

La efectividad del tratamiento antirretroviral (TAR) combinado en la reducción de la transmisión del VIH ha impulsado la estrategia «tratamiento como prevención» (TcP) como herramienta prometedora para controlar la epidemia del VIH. Debido a que los mensajes y actitudes respecto al uso del preservativo en el contexto del TcP pueden parecer confusos, en este trabajo se evaluó si usar únicamente TAR como estrategia de prevención puede ser recomendado desde una perspectiva de Salud Pública.

Se hizo una revisión de la literatura sobre la efectividad del TAR en la transmisión del VIH y epidemiológica de otras infecciones de transmisión sexual (ITS). También se realizó una revisión de las recomendaciones vigentes (febrero 2014) sobre TcP desde diferentes instituciones de Salud Pública. Asimismo, se analizó la evolución del VIH y otras ITS en Barcelona durante el periodo 2007–2012.

Palabras clave:

Virus de la inmunodeficiencia humana
Infecciones de transmisión sexual
Tratamiento antirretroviral
Prevención

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Dado que el amplio uso del TAR ha coincidido con un aumento en la incidencia del VIH y otras ITS, especialmente entre hombres que tienen sexo con hombres, en el consejo asistido se contempla la utilización combinada de diferentes métodos de prevención. La decisión sobre el uso del preservativo se debe tomar en el seno de las parejas estables serodiscordantes, con pleno conocimiento de los riesgos y limitaciones del TAR cuando se utiliza como único medio de prevención. Desde la perspectiva de la Salud Pública, la prevención primaria debe ser una prioridad. Confiar en el TAR solamente como una estrategia de prevención de nuevas infecciones por el VIH y otras ITS no sería suficiente, ya que el éxito del TcP depende no solo de diagnosticar y tratar adecuadamente, sino también de mantener conductas de sexo seguro para evitar la transmisión de ITS, de realizar controles clínicos adecuados y de tener acceso continuado al TAR.

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Background and rationale

Antiretroviral therapy in post-exposure prophylaxis (PEP) and in pre-exposure prophylaxis (PrEP) is effective,¹ and a Cochrane review of 25 clinical trials documented the benefits of the combination antiretroviral treatment (cART) in limiting the risk of mother-to-child transmission of HIV infection.² These findings have served as a basis for recommendations regarding prevention of vertical HIV transmission and helped to formulate algorithms for PEP protocols and approved PrEP use for certain high-risk groups.³ An observational study published in 2010⁴ and a clinical trial⁵ demonstrated also the role of cART in the prevention of HIV transmission from HIV-infected persons to their sexual partners.

A mathematical model presented in 2006 predicted that providing cART to every HIV-positive person in the world would stop the HIV epidemic within 50 years.⁶ Since then, extensive efforts have been made in the province of British Columbia, Canada, to support the test-and-treat strategy, including expanding HIV testing by implementing the programme of routine testing in emergency departments for individuals with no prior risk factors or indications for HIV testing, and promoting earlier access to cART. As a result, the proportion of HIV-infected people with undetectable viral load increased and that has been accompanied by substantial reduction in new diagnoses of HIV in this province.⁷ Several attempts to analyse the cost-effectiveness of the treatment as prevention (TAP) strategy strongly indicated cost-saving effect of early initiation of cART over time.^{8,9}

However, other studies indicate that even in the communities where a high proportion of HIV-infected persons receive cART and have undetectable viral loads, the incidence of HIV is similar to estimates reported from developed country settings in the pre-cART era.¹⁰ Furthermore, the changing perception of the risk of transmission from HIV-positive persons on cART may influence the frequency of high-risk sexual behaviour.¹¹

The aim of this paper is to assess whether relying on cART alone is a sufficient strategy in preventing HIV in the community and individual level, based in existing evidence and recommendations from national and international public health institutions; and reviewing the evolution of HIV and other STIs during the period 2007–2012 using surveillance data from a large city (Barcelona) where cART is universally provided. For the literature review, we searched PubMed electronic database for original articles and reviews published in English and Spanish from 2008–2013 on cART in the context of prevention of sexual HIV transmission, challenges of HIV prevention strategies based on condom and reemerging STI since the introduction of cART. As well, we have identified important relevant publications published before 2008 using the snowball method by checking the references of selected papers, and finally included most recent publications as of June 2014.

Impact of cART on sexual HIV transmission – current evidence

The idea that cART might decrease the spread of the HIV infection by reducing the infectivity of treated HIV-positive persons has been considered since the late 1990s. A clear association between the plasma viral load and the risk of onwards transmission of HIV was identified already in 2000, indicating that transmission is rare among persons with less than 1500 copies of HIV-1 RNA per millilitre.¹²

Several independent systematic reviews of the observational studies and randomised control trials conducted among heterosexual serodiscordant couples have been published recently. In three studies where the virologic suppression by cART was documented, the rate of transmission was 0 per 100 person-years with a 95% confidence interval (CI): 0 to 0.05.¹³ The Cochrane review in 2013¹⁴ and the review conducted by Attia and colleagues in 2009 similarly suggested that the risk of sexual transmission for heterosexual serodiscordant couples when the HIV-positive partner was on suppressive treatment was minimal.¹⁵

The strongest evidence gained in a clinical trial regarding the protective effect of the cART on HIV transmission in serodiscordant couples came from the HPTN-052 study.⁵ It included 1763 serodiscordant couples divided into two groups based on the timing of the cART initiation: receiving cART either immediately (early therapy) or after a decline in the CD4 count or the onset of HIV-1-related symptoms (delayed therapy). Importantly, all couples received counselling on every visit and were provided with free condoms. Overall 39 HIV-1 transmissions were observed (incidence rate: 1.2 per 100 person-years; CI: 0.9 to 1.7). Of these, 28 were virologically linked to the infected partner (incidence rate: 0.9 per 100 person-years, CI: 0.6 to 1.3). Only one of the 28 linked transmissions was reported in the early-therapy group (hazard ratio: 0.04; CI: 0.01 to 0.27; $p < 0.001$). Based on these findings, the authors concluded that early initiation of cART reduced linked transmissions by 96%. The only genetically confirmed transmission from an HIV-positive participant on cART happened at the early stage of the treatment; before achievement of an undetectable viral load.

Concerns have been raised about the external validity the results of the HPTN-052 trial among those engaging in anal intercourse, including MSM and transgendered persons (among its 1763 serodiscordant couples, only 37 were MSM) as the rate of transmission per-act associated with anal intercourse in persons who are not on suppressive cART is greater than the rate associated with penile-vaginal intercourse.¹⁶ However, interim results of an ongoing observational study among serodiscordant MSM couples, presented in March 2014, suggested that cART may substantially reduce the risk of HIV transmission also during anal sex.¹⁷

In the same time, many investigators have pointed on the fact that still there is not enough scientific evidence to state that the risk of the HIV transmission from the person on effective cART is practically zero, because there is evidence that plasma viral load

does not always correlate with the viral load in the semen and genital fluids.^{18,19} Moreover, shedding of HIV viral particles in the genital fluids has been repeatedly detected when the viral load is undetectable in the plasma, though the transmission potential of these particles remains unclear.²⁰ Finally, there was at least one case report of HIV sexual transmission from a person on treatment with undetectable plasma viral load.²¹

Challenges of the HIV prevention strategies based on the behavioural changes and condom use

Evidence from numerous studies²² documents the effectiveness of condoms in preventing both HIV and other STIs and reducing the spread of infections within populations. Still, the 2002 Cochrane review indicated that real-life effectiveness of condom use to prevent HIV transmission only reached 80% in self-reported consistent condom users.²³ This probably reflects the frequency of condom failure or incorrect use and also possibly social desirability bias in self-reporting.

Many researchers also noticed that since the advent of the cART in the 1996, an increasing trend in the incidence of high risk sexual behaviour, especially among MSM, both in USA and in Europe has been observed. In the USA, self-reported unprotected anal sex at least once in the past 12 months among MSM increased from 48% in 2005 to 57% in 2011 ($p < 0.001$).²⁴ Similar findings were reported in France²⁵ and Denmark.²⁶ Data from behavioural surveillance in Catalonia, Spain, suggest that the trend of the risk behaviours associated with HIV transmission is increasing both among MSM²⁷ and among female sex workers.²⁸

Several studies found that among MSM unprotected anal sex was associated with drug abuse (particularly methamphetamine and sildenafil (Viagra®)),²⁹ lack of knowledge about HIV transmission, low self-esteem, 'condom fatigue,' stigma or lack of incorporation of the social norm of condom use.^{30–33} However, other factors including 'HIV optimism'³⁴ and adoption of presumed risk-reduction strategies, amongst them, engaging in unprotected sex only with partners perceived to have the same HIV status as one's own (serosorting) or adapting sexual practices based on knowledge or perceptions about one's own and his partner's HIV status (sero-adapting) also have contributed to the increase of unsafe sexual behaviour.³⁵

Re-emerging STIs in the era of cART

While cART may be effective in reducing the risk of HIV transmission, several other STIs, including gonorrhoea, syphilis remain common especially amongst MSM.^{36–40} In England in 2011, reported rates of gonorrhoea among MSM increased by 61% while syphilis increased by 28%.⁴¹ Some of the increase might be secondary to improved testing, but the increase in syphilis where there have been no changes in testing practice suggests that the rises in STIs are at least partly due to ongoing risky sexual behaviours.⁴² Similarly, increasing rates of self-reported STIs were observed among female sex workers from 2005 to 2011, while HIV prevalence remained stable in the same population.²⁸

Other diseases like viral hepatitis, whereas it is A, B or C, have been observed to increase in MSM across Europe.⁴³ Hepatitis C is posing an important threat especially amongst HIV-positive MSM, because its incidence is higher in this group than in HIV-negative MSM.⁴⁴ HIV-HCV co-infection worsens the evolution of both diseases, with higher rates of fibrosis, chronic hepatitis and hepatocellular carcinoma.^{45,46}

Another disease that has increased among HIV-positive males in the cART era is anal cancer, linked to human papilloma virus (HPV) infection. Cases of cancer rates increased 5-fold when it was

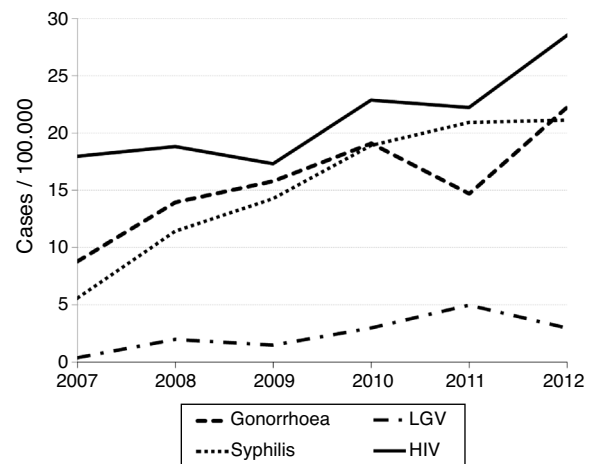


Fig. 1. Annual overall incidence of newly diagnosed cases of gonorrhoea, syphilis, LGV and HIV. Barcelona, 2007–2012.

compared to pre-cART era in the US. Longer duration of HIV infection is associated with higher rates of anal cancer, which could be caused by a decrease in other death causes.⁴⁷ Lymphogranuloma venereum (LGV), once a rare STI in the European context, now is considered an emerging STI in Europe and in North America, mostly affecting HIV-infected MSM.⁴⁸

Recent trends in the epidemiology of HIV and other STIs in Barcelona

In 2007–2012, Barcelona faced increasing trend in the reported incidence of syphilis, gonorrhoea, LGV and HIV (Fig. 1). During that five-year period, the incidence of syphilis rose by 276%, the incidence of gonorrhoea rose by 153% and the incidence of LGV rose by 650%. The incidence of new HIV diagnoses rose by 63%, in spite of high cART coverage in Catalonia – according to the 2011 report from the PISCIS Cohort study, among people living with HIV (PLWH) retained in care, 92.4% of eligible persons received cART and, among them, 94.9% achieved undetectable viral load 6 months after starting the cART. However, taking into account the number of PLWH who are not aware of their diagnosis, and those who are not linked to care, the proportion of PLWH who have achieved undetectable viral load is estimated to be 48% of all HIV-infected people.⁴⁹

The majority of the STIs cases were attributable to men 25–34 years of age and, among them, up to 80% of cases of syphilis and HIV infection and, in 2011–2012, almost 100% of LGV cases were MSM. The increase in the number of cases of HIV and other STIs was mainly explained by MSM (Fig. 2), that is consistent with the results of a study based on the data from the sentinel network of Spanish STI clinics, where more than a half of gonorrhoea cases were diagnosed among MSM, and this was the only sub-population where increasing trend of gonorrhoea was observed between 2006 and 2010.⁵⁰ For comparison, the rates of new HIV cases on the national level appeared to be slowly decreasing from 2010 to 2012 in all transmission groups, still, with 51% of new HIV cases diagnosed among MSM in 2012,⁵¹ and, to confirm whether the incidence is truly decreasing among in group, further surveillance is needed, taking into account that the number of cases among MSM has increased by 35% in Barcelona during the same period of time.

The first outbreak of acute hepatitis C among HIV-infected MSM occurring from 2003 to 2010 was reported by the team of researchers from one of the Barcelona's hospitals.⁵² On the community level, an ongoing hepatitis C outbreak was being under investigation as of beginning of 2014. In 2011, of 70 reported

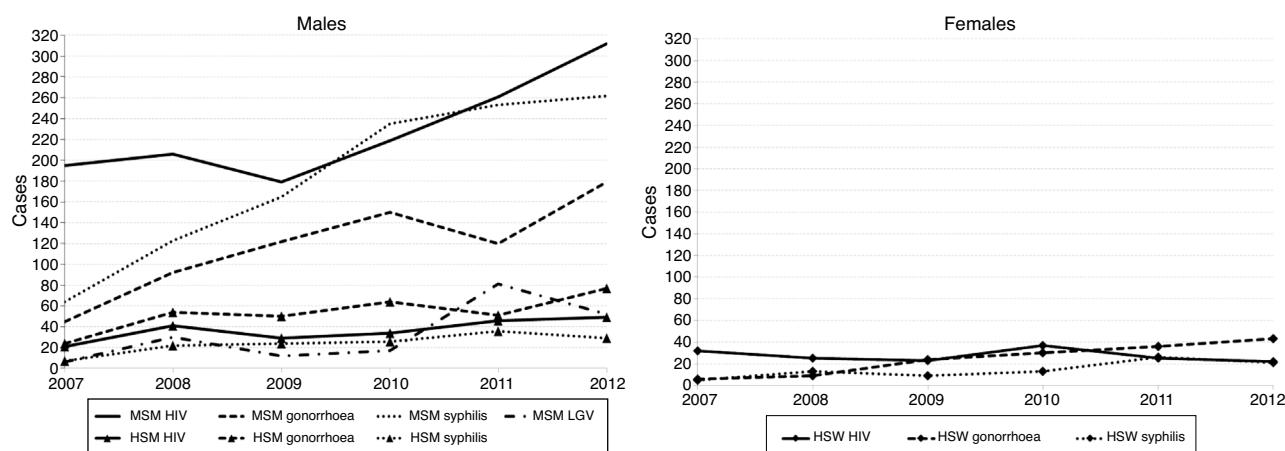


Fig. 2. Evolution of cases of HIV, gonorrhoea, syphilis and LGV by sex and transmission route (MSM–men who have sex with men; HSM–heterosexual men; HSW–heterosexual women). Barcelona, 2007–2012.

cases of LGV all occurred among MSM, 94% of which also had HIV infection.⁵³

Our surveillance data also indicate that, in 2010–2012, a high proportion of gonorrhoea and syphilis cases also had HIV infection (16–17% and 31–33%, respectively). This, and also the fact that relative increase in the incidence of other STIs appears to be notably higher than one of HIV (Fig. 1), indicate that also in Barcelona some HIV-positive persons who are on cART might engage in high risk sexual behaviour relying on protective effects of cART in terms of sexual transmission of HIV. Still, other factors may play an important role in the increase of STIs, including a developed entertainment industry, which makes Barcelona one of the most popular tourism and sex-tourism destinations in Europe, growing popularity of smartphone based on-line dating applications for MSM that promote a larger number of casual sexual partners,⁵⁴ harmful alcohol consumption patterns⁵⁵ and increasing use of recreational drugs during sex and partying among some parts of the MSMs community.⁵⁶

Public Health recommendations regarding the use of cART in HIV prevention

We could not identify recommendations that supported the use of cART alone to prevent new infections on the population level. However, most guidelines advise suppressive cART as a means of reducing the risk of sexual transmission of HIV among individual serodiscordant couples.

In 2008 the Swiss Federal Commission for HIV/AIDS issued a statement claiming that ‘an HIV-positive individual not suffering from any other STIs and adhering to cART with a completely suppressed viraemia does not transmit HIV sexually.’ This was valid under specific conditions, namely: (a) the HIV-positive individual fully complied with the cART therapy and was monitored by an attending physician; (b) the viral load should be undetectable for at least six months and (c) the HIV-positive individual did not have any other STI. The authors made also clear that mutual agreement was needed between serodiscordant partners.⁵⁷

In January 2013, the British HIV Association and the Expert Advisory Group on AIDS published their position statement on the use of cART to reduce HIV transmission. It specified that the viral load testing should be undertaken every 3–4 months and that none of the partners should have an STI. It emphasised that no single prevention method could completely prevent HIV transmission.⁵⁸

The United States CDC in its ‘Guidance on ART and its Effect on Sexual Transmission of HIV’ acknowledges the potential benefit of

cART on substantial reduction of the risk of sexual HIV transmission in serodiscordant couples. However, since HIV transmission can still occur when the infected partner is on effective cART, in February 2008 it reiterated its 2003 recommendations that sexually active people living with HIV should use condoms consistently and correctly with all partners.⁵⁹

In Spain, the latest recommendations of the National AIDS Plan/GeSIDA (January 2014) advise earlier start of cART in asymptomatic patients to reduce sexual transmission of HIV in serodiscordant couples who wish to minimise the risk of transmission.⁶⁰

Similarly, the WHO guidelines recommend offering cART to the HIV positive partner, regardless of his/her own immune status (CD4 count) to reduce the risk of HIV transmission. However, it stated that whenever possible, cART should be used for HIV prevention in combination with other proven methods of sexual risk reduction, including use of male or female condoms, partner number reduction and male circumcision.⁶¹

Conclusions

The ability of suppressive cART to reduce the risk of sexual transmission between individual serodiscordant couple is documented in observational studies and in HPTN-052 trial, but available data do not support zero risk of HIV transmission under cART.⁶² HIV incidence depends not only on the per-act transmission risk reduction by effective cART, but also of the strategic use of other preventive measures.⁶³ No single prevention method can be 100% effective and combination prevention strategies, especially those that include cART, targeted both on HIV-infected and HIV-non infected individuals should be always recommended and encouraged.⁶⁴

On the individual level, in the context of counselling serodiscordant couples, full and evidence-based information regarding the risk of HIV transmission and all available prevention measures must be provided to both partners to let the couple make informed decisions about whether to continue to use condoms or to rely on protective effect of the suppressive cART only, including when there is an intention to conceive naturally. The importance of adherence, consistent use of protection measures outside the relationship and regular STIs and viral load check-ups has to be stressed on every visit.

On the community level, the benefits of the TAP strategy are still debated.⁶⁵ Growing rates of other STIs and emergence of new infections reported in the literature in the last decade, such as hepatitis C, highlights the importance of primary prevention measures, such as

condom use and behavioural change oriented interventions. Moreover, newly infected individuals not aware of their HIV status may account for the majority of new infections,⁶⁶ and increase in high-risk sexual behaviour among undiagnosed individuals may offset the benefits offered by enhanced testing and treatment.⁶⁷ From the public health perspective, avoiding new infections is a priority. TAP strategy implies very high coverage with adequate treatment and adherence levels, which apparently still is not feasible in many settings, therefore relying on cART alone, unless combined with frequent HIV testing alongside primary prevention programmes,⁶⁸ is not sufficient strategy to avoid transmissions of HIV and other STIs.

Conflict of interest

The authors declare no conflict of interest.

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