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A double-edged sword: does highly active antiretroviral therapy contribute to syphilis incidence by impairing immunity to *Treponema pallidum*?

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Received 28 August 2016

Revised 17 October 2016

Accepted 29 October 2016

Published Online First

30 November 2016

ABSTRACT

Background and hypothesis Recently, the world has experienced a rapidly escalating outbreak of infectious syphilis primarily affecting men who have sex with men (MSM); many are taking highly active antiretroviral therapy (HAART) for HIV-1 infection. The prevailing hypothesis is that HAART availability and effectiveness have led to the perception among both individuals who are HIV-1 infected and those who are uninfected that HIV-1 transmission has become much less likely, and the effects of HIV-1 infection less deadly. This is expected to result in increased sexual risk-taking, especially unprotected anal intercourse, leading to more non-HIV-1 STDs, including gonorrhoea, chlamydia and syphilis. However, syphilis incidence has increased more rapidly than other STDs. We hypothesise that HAART downregulates the innate and acquired immune responses to *Treponema pallidum* and that this biological explanation plays an important role in the syphilis epidemic.

Methods We performed a literature search and developed a mathematical model of HIV-1 and *T. pallidum* co-infection in a population with two risk groups with assortative mixing to explore the consequence on syphilis prevalence of HAART-induced changes in behaviour versus HAART-induced biological effects.

Conclusions and implications Since rising syphilis incidence appears to have outpaced gonorrhoea and chlamydia, predominantly affecting HIV-1 positive MSM, behavioural factors alone may be insufficient to explain the unique, sharp increase in syphilis incidence. HAART agents have the potential to alter the innate and acquired immune responses in ways that may enhance susceptibility to *T. pallidum*. This raises the possibility that therapeutic and preventative HAART may inadvertently increase the incidence of syphilis, a situation that would have significant and global public health implications. We propose that additional studies investigating the interplay between HAART and enhanced *T. pallidum* susceptibility are needed. If our hypothesis is correct, HAART should be combined with enhanced patient management including frequent monitoring for pathogens such as *T. pallidum*.

INTRODUCTION

STDs, HIV-1 and men who have sex with men

In British Columbia (BC), Canada, from 2005 to 2014, infectious syphilis case reports (primary, secondary and early latent) rose 90.6% (288–549), chlamydia 39.9% (9540–13 348) and gonorrhoea 63.8% (1100–1802), corresponding to rate changes

per 100 000 population of +72.4%, +33.9% and +47.6%, respectively.¹ Female syphilis cases decreased while male cases jumped from 202 to 524, accounting for 95% of all 2014 cases. Men who have sex with men (MSM) accounted for 60.4% (122) of cases in 2005, rising to 88.9% (466) in 2014. There was a fourfold increase in MSM syphilis from 2010 to 2014 (115–466 cases), including 112 reinfections (24%) in 2014. The HIV-1 coinfection rate in MSM during this period was 50%–75%. From 2005 to 2014, the male infectious syphilis rate increased 235% (9.7–22.8) compared with a much smaller increase for chlamydia (56.9%; 141.7–222.4) and gonorrhoea (42.1%; 39.7–56.4) in men.

Comparatively larger increases in syphilis cases were also observed in the USA from 2005 to 2014. Primary and secondary syphilis cases rose 128.1% (8724–19 999), chlamydia 47.7% (976 445–1 441 789) and gonorrhoea 3.1% (339 593–350 062), corresponding to rate changes of +117.2%, +38.5% and –3.4%, respectively.² Males contributed an increasing proportion of syphilis cases, accounting for 91% in 2014. From 2007 to 2014, among the 27 US states that collected sex partner data for ≥70% of males, MSM cases increased steadily to 82.9%. In Los Angeles County between January and May, 2010, 76% of 537 early syphilis cases were MSM and ≥58% of these were HIV-1 positive.³ HIV-1 infection in US MSM has also been statistically associated with repeat syphilis infection.⁴

In the UK from 1998 to 2013, new syphilis cases in MSM rose from 23 (26.0% of all cases) to 2546 (71.3% of all cases). From 2009 to 2013 in England, the odds of being diagnosed with syphilis increased from 2.71 (95% CI 2.41 to 3.05, $p < 0.001$) to 4.05 (95% CI 3.70 to 4.45, $p < 0.001$) in HIV-1 positive relative to HIV-1 negative/undiagnosed MSM.⁵

RESULTS

Highly active antiretroviral therapy and syphilis

First-line highly active antiretroviral therapy (HAART) regimens may comprise (1) two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), commonly tenofovir (TDF) and emtricitabine (FTC) or lamivudine (3TC), plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), commonly efavirenz, (2) two NRTIs and an integrase strand-transfer inhibitor (InSTI) or (3) two NRTIs and a boosted protease inhibitor (PI). PIs, InSTIs and fusion/entry inhibitors are used as



► <http://dx.doi.org/10.1136/sextrans-2016-052893>

► <http://dx.doi.org/10.1136/sextrans-2016-052940>



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To cite: Rekart ML, Ndifon W, Brunham RC, et al. *Sex Transm Infect* 2017;**93**:374–378.

second-line and third-line alternative agents. In BC, 86.1% of patients take two NRTIs with a boosted PI (34%), NNRTI (30%), InSTI (19%) or fusion/entry inhibitor (1%).⁶ Common NRTIs include TDF (64%), FTC (59%) and 3TC (40%). An additional 11% (741 patients) take InSTIs in other HAART combinations. In total, 30% (2056) take InSTIs. HAART usage has grown steadily including a 288% increase in InSTI usage from 2010 to 2015 (530–2056 patients).

Because HAART stimulates and supports immune system recovery from HIV-1-related immunosuppression, one might expect HAART to be associated with declining infection rates for most pathogenic organisms. However, several studies support the hypothesis that HAART may be associated with syphilis acquisition. Receiving HAART (adjusted HR=1.81 (95% CI 1.25 to 2.62, $p<0.002$)), older age and MSM status were independent risk factors for syphilis seroconversion by multivariate logistic regression analysis in 1010 people who were infected with HIV in Northeast China from 2009 to 2013.⁷ Using Poisson regression analysis, Park and coauthors⁸ found that the period-specific incidence rate of early syphilis in 539 patients receiving HAART in Korea significantly increased in proportion to the years after starting HAART ($p<0.001$). These two studies were conducted in stable cohorts but they did not control for specific sexual risk behaviours.

Additional studies have reported a significant proportion of new syphilis cases in persons receiving HAART, including 32.7% of all 1089 new syphilis cases in France from 2000 to 2003 and 71% of the 502 cases who knew their HIV-1 positive status.⁹ Among 104 early syphilis and 36 late or indeterminate latent syphilis cases in a Malaga study from 2004 to 2011, 65 of 85 (76.4%) with prior known HIV-1 infection were taking HAART.¹⁰ A retrospective, descriptive study at the University of Alabama found 40 incident syphilis cases from 2004 to 2007 in 1544 patients who were HIV-1 positive.¹¹ Two-thirds were receiving HAART when syphilis was diagnosed including all five patients with primary syphilis. The proportion of the entire cohort on HAART was not reported. Among 3448 patients followed in a Parisian Hospital Infectious Disease Service from January 2000 to December 2002, 48 of 71 (67.6%) patients with a new diagnosis of syphilis were taking HAART.¹² For BC, over 8000 males have tested HIV-1 positive, and HAART usage in MSM is more than 80%.^{1 6} However, the percentage taking HAART when syphilis was diagnosed is unknown.

Behavioural change

One explanation for high rates of syphilis in MSM is increased risky sex, often in the context of optimistic risk perception. Similarly, any association between syphilis and HAART might be a surrogate marker for risky sex in individuals treated with HAART rather than an effect of HAART itself. Seroadaptive behaviours to prevent HIV-1 transmission, such as serosorting (ie, selective unprotected sex with partners of the same HIV status), have also been implicated in increasing STD incidence including syphilis.¹³ What then is the evidence for HIV-1 treatment optimism and behavioural change in MSM and persons on HAART?

Several studies support treatment optimism including a 2013 literature review, which concluded that quantitative studies were 'largely in support' of an association between optimistic beliefs and HIV-1 transmission risk.¹⁴ However, other studies have shown no change or decreased risky behaviour and/or no lessening of risk perception, as discussed later in this section.

Many HIV-1-infected MSM believe they have a responsibility to protect their sex partners,¹⁵ and many eliminate or reduce

HIV-1 transmission behaviours after HIV-1 diagnosis. A 2005 US meta-analysis concluded that high-risk sexual behaviour with partners who were HIV-1 negative was significantly reduced (68%, 95% CI 59% to 76%, $p<0.001$) after HIV-1 diagnosis.¹⁶ Persson used the Swiss Consensus Statement that people on effective HIV-1 treatment cannot transmit HIV-1 as a surrogate for HIV-1 treatment optimism in interviews of HIV-1 discordant couples. Participants were highly sceptical of the Statement's prevention message and not one described it as having any direct relevance to their sexual decision making.¹⁷

Much of the HIV-1 treatment optimism literature focuses on behavioural change in persons on HAART and subsequent to HAART initiation. In 512 patients receiving HAART in Bangkok, unprotected sex risk was found in only 27 patients (5%) and multivariate analysis showed no association with beliefs about HIV-1 transmission while taking HAART.¹⁸ A 2009 meta-analysis of unprotected anal intercourse (UAI) among HIV-1 diagnosed US MSM found no association with HAART¹⁵ and a cross-sectional study of 420 London men who were HIV-1 positive showed that men on HAART had fewer sexual partners and less UAI.¹⁹ Among 456 HIV-1 positive US MSM, Remien *et al*²⁰ found no increased sexual risk behaviour and substantial ongoing perception of HIV-1 transmission risk while on HAART. Using data from a prospective behavioural study nested in a randomised controlled trial of early HAART (Temprano), Jean *et al*²¹ found significant decreases over 24 months in sexual activity (OR 0.72, 95% CI 0.57 to 0.92), multiple partnerships (OR 0.57, 95% CI 0.41 to 0.79), unprotected sex (OR 0.59, 95% CI 0.47 to 0.75) and risky sex (OR 0.58, 95% CI 0.45 to 0.76).

We could find only one study that found a link between increasing syphilis incidence and seroadaptive behaviours such as serosorting in individuals treated with HAART with unsuppressed viral load, but this would not explain rising syphilis incidence out-of-proportion to other STDs.¹³

Some studies have implicated core groups in this syphilis outbreak,²² while other studies have shown little or no significant increase in risky sex, number of contacts or concurrency among core group members. In a retrospective study of syphilis among MSM in San Francisco, number of sex partners, illicit substance use, partner meeting venues and commercial sex were not associated with repeat syphilis infection.⁴ In the Alabama, Bangkok and Temprano cohorts referenced earlier, similar core group characteristics were not associated with incident syphilis, unprotected sex risk or multiple partnerships, respectively.^{11 18 21} Finally, a mathematical model of behaviour in a core group predicted a transient spike in unprotected sex that was counteracted by other pathways on longer timescales, leading to lower rates of unprotected sex on the whole.²³

Modelling studies conducted herein to test our hypothesis are in support of both behavioural change and HAART treatment being able to increase syphilis prevalence, with the combined effect being more than additive (figure 1). Specifically, we developed a mathematical model of HIV-1 and *Treponema pallidum* coinfection in a population with two risk groups and assortative mixing between groups. Susceptible individuals acquire infection from a partner who is infected with a fixed probability per sexual encounter. In the case of HIV-1, the infection probability is lower if the partner who is HIV-1 positive is on HAART versus untreated, but it is higher if the partner who is either HIV-1 negative or HIV-1 positive is already infected with *T. pallidum* versus uninfected. Individuals who are infected receive treatment at a constant rate dependent on the pathogen. Individuals lose their treated status at a disease-dependent rate.

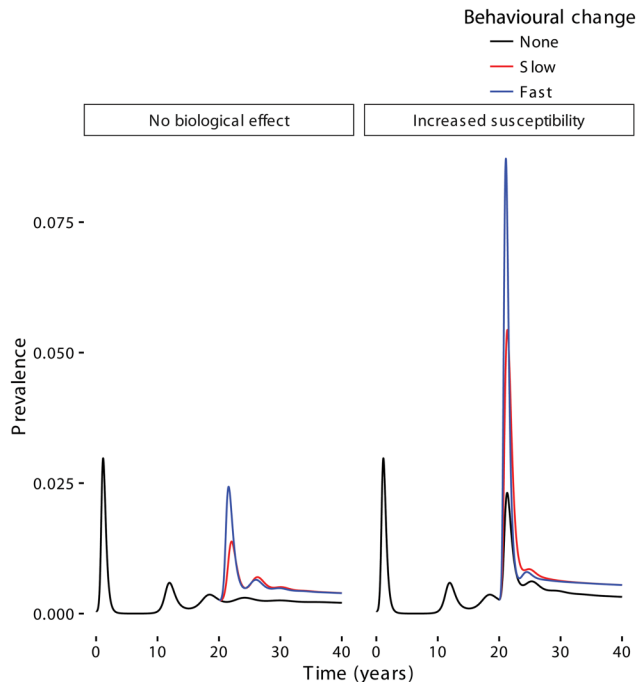


Figure 1 A susceptible-infective-treated model of HIV-1 and *Treponema pallidum* epidemiology predicts that both highly active antiretroviral therapy (HAART) and behavioural change substantially boost syphilis prevalence above baseline. The model used two risk groups and assortative mixing between groups. Using baseline parameters from the literature,²⁴ we varied parameters quantifying HAART effects and partnership formation rates on susceptibility to and transmission of *T. pallidum*. We introduced HAART at 20 years and plotted syphilis prevalence without (left panel) and with (right panel) a threefold effect of HAART on susceptibility to *T. pallidum*, under different assumptions about the effect of HAART on partnership formation rates (for details and code, see https://github.com/dushoff/Syphilis_and_ARVs). Compared with the baseline of no effect (left panel, black line), the combined effect of increased susceptibility and behavioural change (right panel, coloured lines) is larger than the sum of the effects of behavioural change alone (left panel, coloured lines) and increased susceptibility alone (right panel, black line).

Individuals infected with HIV-1 have a disease-imposed mortality rate that is lower for individuals on HAART.

We numerically simulated the model using baseline parameters taken from the literature.²⁴ We initialised each simulation with a small number of individuals who are infected and introduced HAART 20 years later. We explored effects on syphilis prevalence of HAART-induced changes in behaviour versus immunology. For behavioural change, we assumed that individuals on HAART adopt more risky sexual behaviours by increasing their partnership formation rates, which increases their ability to transmit *T. pallidum*. For immunological change, we assumed that individuals on HAART have a higher susceptibility to *T. pallidum* than individuals who are untreated. The simulation results show that either behavioural (figure 1, left panel, blue and red lines) or immunological (figure 1, right panel, black line) change alone can produce syphilis outbreaks with peak prevalence that is substantially higher than baseline. Strikingly, the peak prevalence of the syphilis outbreak produced by both behavioural and immunological changes (figure 1, right panel, blue and red lines) is larger than the sum of the peaks of outbreaks produced independently by either type of change (figure 1, left panel, blue and red lines; right panel, black line). Therefore, the immunological effects of HAART and

HAART-induced behavioural change can in principle act synergistically to increase syphilis prevalence by amounts comparable with that observed in the ongoing outbreak.

DISCUSSION

Biological plausibility

Protection against the extracellular pathogen *T. pallidum*, the causative agent of syphilis, is dependent upon T cell expansion and the generation of an early Th1-stimulating, interferon γ (IFN γ)-producing host proinflammatory response that potentiates the primary clearance mechanism of *T. pallidum*, macrophage-mediated opsonophagocytosis.²⁵ The latter process is dependent on unperturbed mitochondrial function to ensure peak metabolic activity within macrophages,²⁶ opsonic antibody production and IFN γ -mediated macrophage activation.²⁷ Opsonic antibody quality is reduced in individuals infected with HIV-1²⁸ and certain HAART agents significantly suppress mitochondrial function,²⁶ the proinflammatory response²⁹ and macrophage activation,³⁰ leading to reduced treponemal clearance via opsonophagocytosis. InSTIs have been shown to suppress the proinflammatory response in cohort studies²⁹ and opsonophagocytosis is reduced in vitro following treatment of macrophages with NRTIs, consistent with mitochondrial damage.²⁶

Further, the well-documented depletion of CD4⁺ memory T cells in individuals infected with HIV-1³⁰ would enhance their susceptibility to syphilis reinfection. NRTIs, especially TDF, have been shown to inhibit telomerase activity leading to accelerated shortening of telomerase length in peripheral blood mononuclear cells (PBMCs),³¹ which may lead to the accumulation of replicative senescent cells³² with limited ability to protect against pathogens such as *T. pallidum*. Reciprocally, upregulation of monocyte expression of CCR5 receptors by treponemal lipoproteins enhances the susceptibility of monocytes to HIV-1 infection,³³ further weakening the innate and adaptive immune responses to *T. pallidum*.

Collectively, these observations provide viable explanations for (1) an enhanced susceptibility of individuals infected with HIV-1, especially those on HAART, to syphilis infection and reinfection and (2) higher syphilis incidence among individuals treated with HAART compared with chlamydia and gonorrhoea, infections caused by pathogens that are less reliant on opsonophagocytosis for clearance.

Potential approach for hypothesis testing

HAART decreases the proinflammatory response in patients infected with HIV-1,²⁹ but this may result from an HAART-induced reduction of lymphocytes' ability to upregulate inflammatory markers, in line with our hypothesis, or from the disappearance of a major cause of inflammation (ie, a fall in HIV-1 viral load). These different effects can be teased apart using experiments in macaques, which have been used as models for human infection with *T. pallidum*³⁴ and develop AIDS-like disease following simian immunodeficiency virus (SIV) infection. *T. pallidum* challenge after specific HAART administration with or without prior SIV infection can provide insight into how HAART affects the proinflammatory response and syphilis susceptibility in the absence or presence of retrovirus.

Prospective cohort studies can compare opsonophagocytic activity of macrophages and susceptibility to syphilis among healthy individuals who are HIV-1 negative receiving preventative pre-exposure prophylaxis (PrEP), healthy controls, untreated patients with HIV-1 and patients with HIV-1 receiving

the same HAART as healthy individuals. To determine the effect of HAART on CD4⁺ memory T cells, one can measure the number of CD4⁺ memory T cells by flow cytometry in PBMCs of persons on and off HAART with particular attention to TDF.

A retrospective case-control and/or a prospective cohort study comparing the prevalence and epidemiological features of infectious syphilis cases among patients who are HIV-1 positive and treated with HAART, patients who are HIV-1 positive and untreated and patients who are HIV-1 negative, including the usage of specific HAART agents, would be enlightening. Syphilis databases without HAART information could be linked to treatment databases to delineate overlapping factors including HAART usage.

CONCLUSION

Clinicians and researchers typically view HAART suppression of the proinflammatory response positively because it decreases HIV-1-associated pathological sequelae. However, this immune dampening may have detrimental effects including enhanced susceptibility to infection with *T. pallidum* and the occurrence of unusual clinical manifestations such as ocular syphilis. The possibility also exists that HAART-mediated immune dampening may predispose an individual to other conditions that are non-infectious in origin and depend upon a particular immune response for control, including certain types of cancer. In this regard, it is of interest to note that HAART treatment has been suggested to be associated with a higher risk of anal cancer and, potentially, other non-AIDS-defining cancers.³⁵ Overall, these findings suggest a possible link between HAART and an increased risk for selected diseases of infectious and non-infectious origin, a potential unforeseen consequence that warrants further study. If borne out, it will be imperative that the highly exciting and efficacious global implementation of PrEP be carried out with awareness towards the potential need for enhanced patient management.

Key messages

- ▶ The number of new syphilis cases has risen dramatically worldwide in recent years, with repeat infections within a single individual a frequent occurrence.
- ▶ The syphilis outbreak has outpaced new cases of chlamydia and gonorrhoea and is primarily affecting men who have sex with men and who are taking highly active antiretroviral therapy (HAART).
- ▶ Mathematic modelling suggests both behavioural change and HAART contribute to the increasing syphilis prevalence, with the combined effect being more than additive.
- ▶ If experimentally confirmed, HAART administration and pre-exposure prophylaxis implementation will require enhanced patient management guidelines to mitigate the increased risk of developing selected infectious and non-infectious diseases.

Handling editor Jackie A Cassell

Contributors MLR: conceptualised the original hypothesis, analysed and interpreted the literature, drafted a significant portion of the manuscript and reviewed the rest for intellectual content, coordinated coauthor input, approved the final version, agrees to be the corresponding author and to be accountable for all aspects of the work. WN: helped refine the hypothesis, analysed and interpreted the literature, drafted a significant portion of the manuscript, contributed significantly to

the modelling presentation, reviewed the manuscript for intellectual content, approved the final version and agrees to be accountable for all aspects of the work. RCB: helped refine the hypothesis, analysed and interpreted the literature, revised the manuscript critically for intellectual content, contributed to the modelling section, approved the final version and agrees to be accountable for all aspects of the work. JD: helped refine the hypothesis, analysed and interpreted the literature, revised portions of the manuscript and reviewed the rest for intellectual content, drafted the section on mathematical modelling, approved the final version and agrees to be accountable for all aspects of the work. SWP: developed and fine-tuned the model, reviewed the manuscript for intellectual content, approved the final version and agrees to be accountable for all aspects of the work. SR: conducted the initial literature review and analysed the results, reviewed the manuscript for intellectual content, approved the final version and agrees to be accountable for all aspects of the work. CEC: helped refine the hypothesis, analysed and interpreted the literature, drafted a significant portion of the manuscript and reviewed the rest for intellectual content, contributed to the modelling, approved the final version and agrees to be accountable for all aspects of the work.

Funding This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award numbers R01AI015334 and R01AI123196 (CEC). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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