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Treatment to Prevent Transmission of HIV-1

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Abstract

Antiretroviral agents (ART) have the potential to prevent HIV transmission by reducing the concentration of HIV in blood and genital secretions. Indeed, mathematical models with favorable assumptions suggest the potential of ART to stop the spread of HIV. Empirical results from ecological and population based studies, and several short term observational studies involving HIV discordant heterosexual couples suggest that ART reduces HIV transmission. A multinational randomized controlled trial (NIH NPTN052) also examining the reliability and durability of ART as prevention in HIV discordant couples is underway. The latter and other studies also consider sexual risk taking behavior, and transmission of HIV resistant variants when ART is used as prevention. Early HIV detection and treatment ("test and treat") are being considered as an important prevention strategy. In this article, we review the data supporting the use of ART to prevent HIV transmission, and critically examine the public health implications of this strategy.

Keywords

HIV; transmission; antiretroviral therapy; prevention; modeling

Introduction

For every individual who receives HIV treatment it is estimated that 4 more require treatment [1]. HIV prevention efforts have lagged behind advances in treatment, and the development of a preventive vaccine has proven to be a truly daunting challenge. Intense interest has developed in the usage of antiretroviral drugs to prevent transmission [2]. Indeed, the belief in the power of HIV suppression to stop secondary transmission (from an infected index case to a sexual partner) is so strong that the Swiss AIDS Commission issued a "declaration" indicating that under some circumstances discordant couples might engage in unprotected intercourse with minimal risk [3]. Mathematical models argue that we can simply treat our way out of the epidemic [4]. Early HIV detection and treatment (test and treat strategies) are being considered as an important prevention strategy [5]. The purpose of

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this article is to review the data that support the belief that ART may serve to prevent transmission, and to critically examine the public health implications of this strategy. This article is meant to provide a sober view of the actual potential of ART for prevention.

HIV transmission

Each HIV transmission event results from exposure to blood, a blood product or bodily secretions contaminated with HIV-1 [6]. The probability of a transmission event whether from blood, sex, or vertical transmission broadly correlates with the concentration of HIV-1 in the host secretion. The most widely cited transmission study entailed a retrospective analysis of nearly 15,000 people living in the Rakai district of Uganda [7]. HIV transmission was studied in couples retrospectively assembled through careful analysis of the data. The probability of an HIV transmission reflected the blood viral burden of the index case with no transmission events occurring among individuals with a blood viral burden less than 3,500 HIV RNA copies/ml. Nearly half of transmission events could be traced to infected subjects with blood viral burden exceeding 35,000 copies/mL. These results have been confirmed in prospective studies of discordant couples [8, 9].

However, the limitations of these results are generally overlooked. First, the number of transmission events reported in these studies is very unlikely to be correct as HIV transmission was not defined by matching viral sequences between the index case and seroincident partner. When viral sequences have been analyzed in studies of transmission in discordant couples 9-13% of transmission events prove to involve a second, unsuspected sexual partner [10, 11]. Second, transmission events followed prospectively in studies of discordant couples are not representative of the general epidemic because the very efficient transmission during acute HIV infection is not observed. Indeed, it is precisely because the Rakai, Uganda study was not a prospective discordant couples study that transmission during acute and early HIV infection was captured [7], and demonstrated the most efficient transmission of HIV [10]. Finally, sexual transmission must reflect HIV-1 in the genital secretions, not the blood, and the correlation between blood and genital secretions is poor [12] except when subjects are given ART [13].

Effects of ART on Viral Load in the blood and genital tract

There are now twenty-five antiretroviral agents available for the treatment of HIV-1 infection. Through the use of triple antiretroviral combinations, HIV-1 replication can be effectively suppressed to <50 copies in most people over several weeks [14]. However, even after suppression very low level viremia persists, integrated HIV can be detected in cellular DNA [15], and the latent pool of HIV renders HIV incurable [16].

Antiretroviral therapy reduces the likelihood of HIV RNA recovery from cervical secretions. HIV-1 RNA levels in plasma and genital secretions declined rapidly and in parallel in a study among Kenyan female sex workers initiating non-nucleoside reverse transcriptase inhibitor-based ART [17]. However, the suppression of HIV-1 in the genital tract is incomplete; intermittent shedding of HIV-1 in genital secretions during apparent complete suppression of blood viral replication is to be expected. In the prior study of 20 women, HIV RNA was recovered in cervical and vaginal secretions through 28 days of treatment in half

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of subjects [17]. In another study of women starting ART, the detection of HIV RNA in genital secretions decreased from 51% before ART to 15% following treatment initiation [18]. In general, suppression of HIV in blood does not assure that HIV will not be recovered from female genital secretions among women with undetectable plasma viral load [19, 20]. In addition, the concentration of HIV in female genital secretions recovered is greatly affected by the collection method used, [21-23], and by menses [24].

HIV shedding in semen has also been extensively studied [21, 25, 26]. The concentration of HIV in semen is generally lower than in plasma [21, 25], but can equal or exceed blood in the setting of inflammation as seen with sexually transmitted diseases (STDs) [26]. Suppression of HIV in blood does not assure that replicative HIV will not be recovered in semen [27-30]. Most recently, Sheth *et al.* studied HIV shedding in 25 men with durable suppression of HIV-1 in blood [31]. HIV RNA was detected in semen in 12 of 25 (48%) participants, and in 4 of 25 (16%) with more than 5000 copies/mL recovered in semen. HIV was detected in semen at 19 of 116 clinic visits when blood viral load was less than 50 copies/ml.

The choice of antiviral agents makes a difference. While most antiretrovirals can penetrate the genital tract, protease inhibitors achieve limited concentration in genital secretions [30, 32-35], and distinct resistant HIV-1 variants in blood and seminal plasma from individuals on therapy with protease inhibitors supports their limited penetration into the genital tract [32, 34].

In addition, STDs can increase shedding of HIV-1 during ART therapy [36]. Sadiq *et al.* demonstrated that treatment of STDs decreased seminal plasma HIV levels, more than 20-fold in the case of gonococcal urethritis [37]. Nagot *et al.* reported better suppression of HIV-1 in the female genital tract only when twice daily valacyclovir was added to an ART [38], but herpes simplex virus (HSV) suppression does not prevent HIV transmission (see below). These results emphasize the compartmentalization of HIV-1 reflected in discordant viral RNA levels [39, 40], different viral phenotypes and genotypes recovered from blood and the genital tract [39, 41, 42] and local replication of HIV in the genital tract [43].

HIV RNA has also been evaluated in rectal specimens during treatment [44], and these results are extremely important for HIV prevention among men who have sex with men (MSM), as well as many heterosexual couples. Among 233 MSM in Seattle, HIV RNA could be detected in anorectal mucosal swab specimens in 49% of the men who were not receiving therapy, 30% of men receiving therapy that did not include a protease inhibitor, and 17% of men on triple drug therapy that included a protease inhibitor [44]. HIV DNA was recovered from 58% of specimens harvested from men not receiving therapy and 43% of men taking triple drug therapy including a protease inhibitor.

ART and Suppression of HIV Transmission

It seems clear that current ART suppresses but does eliminate shedding of HIV in genital secretions. Accordingly, the magnitude of HIV transmission during therapy is impossible to estimate. Three lines of evidence have been used to determine the prevention benefits of

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ART: retrospective and prospective observational studies of couples, ecologic community studies and an ongoing randomized trial.

Observational results

Musicco and coworkers conducted a retrospective study of HIV transmission among 436 HIV discordant couples [45]. Among the fifteen percent of men with more advanced disease who took zidovudine, a decrease in the relative risk of HIV transmission to a female sexual partner (O.R =0.5, 95% CI 0.1-0.9) was noted. Castilla *et al*. retrospectively compared HIV transmission in 386 serodiscordant couples in the pre-HAART, early HAART and post-HAART periods (1991-2002), and reported an 80% reduction in HIV transmission following the implementation of HAART [46].

More recently, results from HIV discordant couples in Uganda, Zambia and Rwanda have been reported. [47, 48]. Working in Uganda, Were and colleagues conducted a household survey and found an HIV prevalence of 37.1% among adults aged 25 to 44; 43% of spouses of patients eligible for ART were HIV negative [47], emphasizing the frequency of discordant couples and the potential to prevent transmission. The apparent low rate of transmission reported reflects the complexity of HIV transmission within couples, but does not assure that future HIV transmission will not occur [49]. Using a model which incorporated partner HIV status and viral load in the index partner, these same investigators estimated that the risk of HIV transmission decreased from 45.7 to 1.0 transmission per 1000 person-years in 454 of 926 participants over 24 months when the infected partner was provided ART [50]. Sullivan *et al.* (2009) followed 2993 discordant couples in Zambia and Rwanda for a median of 512 days [48]. Subjects who required ART for falling CD4 counts were less likely to transmit HIV to their sexual partners than those who remained untreated (hazard ratio [HR] = 0.21, CI 0.09 to 0.52). It should be noted that 4 transmission events occurred in participants on therapy which has major implications for counseling (see below) since the provision of ART does not eliminate the risk of transmitting to a partner. This finding raises real concern regarding the Swiss Declaration which assumed extremely low HIV transmission risk [3].

The effects of ART on HIV transmission have also been assessed by statistically analyzing population-level trends. In San Francisco, Porco *et al.* noted a 48% decline in predicted incidence of HIV in a large closed MSM cohort ascribed to availability of ART [51]. In Taiwan, a 48% reduction in expected HIV cases was noted after the introduction of free ART in 1997, where country-wide surveillance has occurred since 1989 [52]. In a study of 1062 MSM (the Amsterdam Cohort Study), Couthino *et al.* reported that the introduction of ART in Amsterdam in 1996 was associated with increased risky sexual behaviors [53] and STDs [54]. However, a large decrease in HIV incidence was observed between 1985 and 1993, and HIV incidence has fluctuated at low levels since that time [53]. In contrast, Katz *et al.* reported that widespread use of ART had not reduced incident HIV infections in San Francisco [55].

While population/epidemiologic studies are interesting, they are greatly limited by the data collected and several kinds of bias. In none of the studies described above could the exact

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risk of HIV exposure be characterized, so it is impossible to prove that people receiving ART actually encountered the subjects included in surveillance.

HPTN052: A Randomized Controlled Trial

HPTN052 is a study supported by NIH through the prevention trials network. The study is designed to examine several linked questions. First, can ART prevent sexual transmission to a discordant partner over 5 years? The duration of benefit is extremely important. To examine this question, infected index subjects are randomized to immediate versus delayed ART based on clinical history and CD4 counts. To measure a 30% reduction in HIV transmission ascribed to ART 1750 couples must be followed. Because participants must be treated at high CD4 counts (350-550) and ART started before CD4 counts fall to low levels (<250), this study can also determine whether earlier ART will offer clinical benefit. Recent observational studies from developed countries suggest that earlier therapy reduces HIV-related morbidity [56] and mortality [57]. However, it is not known whether the benefits of earlier therapy (CD4 >350 cells/mm^3) extend to subjects living in developing countries because cardiovascular disease was so commonly observed in those for whom therapy was delayed in the US/European study [56]. It is entirely clear that CD4 count should not be allowed to fall below 200 cells/ mm^3 [58]. To date, HPTN052 is following more than 1500 couples and enrollment will be complete in 2010. The majority of index cases have HIV viral load > 5000 copies/ml blood and 30% have >50,000 copies/ml blood at enrollment emphasizing the risk for HIV transmission (reviewed at www.hptn.org).

Other Considerations: Newer thinking about the HIV infected subject

Stage of HIV Infection

Patients with acute HIV infection represent a very high risk for transmission [10]. However, the detection of acute HIV requires specific testing for HIV RNA or p24 antigen, not available in many resource poor settings as well as a high clinical suspicion given protean symptoms [59]. There are no data to support emergent treatment of patients with AHI [60], although it appears that earlier treatment of HIV may reduce the pool of latently infected cells [16].

ART Impact on Sexual Behavior

The impact of ART on sexual behavior among HIV-infected individuals remains critical but studies to date have produced variable results [61]. A meta-analysis of the effect of ART on sexual behavior in developed countries did not find an increase in high risk sexual behavior between treated and untreated HIV-infected persons [62]. However, unprotected sex was reported more often by HIV-infected individuals who perceived that therapy prevented transmission or who expressed less HIV threat given the availability of ART.

Other studies have suggested that advances in HIV treatment have resulted in sexual disinhibition [63-66]. Among intravenous drug users on ART, a 3-fold increase in unprotected sex following ART initiation was observed [66]. Studies among HIV-infected MSM have found that HIV-infected MSM less concerned about transmitting HIV to sexual partners due to ART availability were more likely to engage in unprotected anal intercourse

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[63, 67]. In Canada, risk behavior was associated with the perception that ART reduced HIV transmission risk and that increased unsafe sex was related to advances in HIV treatment; however, other factors such as safer sex fatigue, use of poppers and serosorting were more strongly correlated with unsafe risk behavior [68]. In an Australian cohort, frequent unprotected anal intercourse with casual partners was reported more often by HIV- infected MSM on ART; although 70.7% of unprotected anal intercourse with casual partners was reported by a minority (10%) of participants [69]. In contrast, another study of MSM found no increase in risk behavior for those on ART [70].

In a study of HIV positive men and women, only HIV treatment beliefs were associated with unprotected intercourse with serodiscordant partners [61]. Among a study focused on HIV positive women, study participants who felt that ART was associated with reduced HIV transmission were more likely to report less consistent condom use [71] .

Studies have also produced discrepant data on the association between HIV viral load suppression and risky sexual behavior. Some studies have suggested that undetectable viral loads were associated with increased sexual risk behaviors [53, 62, 72, 73]. However, one study among HIV-infected MSM found that even with detectable viremia unprotected anal intercourse transpired [74]Other studies found no association between viral load and increased sexual risk behavior [75, 76].

Kennedy and colleagues conducted a systematic review on the impact of ART on sexual behavior in people living in developing countries [77]. Only three studies [50, 78, 79] conducted in Africa met criteria for inclusion, and each found that approximately half of HIV-infected participants reported sexual abstinence. The review concluded that access to ART was not associated with high risk sexual behavior, but in some cases, with reduced sexual risk behavior. Subsequent studies in Uganda, Kenya and Brazil have found that participants on ART were more likely to report protected sex compared with untreated participants [80-82]. One study in Cape Town, South Africa found no difference in reported unprotected sex at last encounter between 520 participants who recently initiated ART and 404 participants waiting to start ART [83]. However, a recent study in Cŏte d'Ivoire reported that unprotected sex among participants starting ART increased from 20.4% to 30.1% ($p<0.0001$) at 6 months compared with stable risk behavior among untreated participants [84]. It bears noting that only a few studies [50, 66, 78, 84] on the affects of ART on sexual behavior were prospective cohort studies which adjusted for baseline sexual behavior before the initiation of ART, and results from these studies were conflicting as above. In addition, very little research has been done on MSM in resource constrained countries, limiting the ability to apply findings from studies of MSM living in developed countries to such populations.

The Public Health Implications of ART: Modeling

An extensive group of models have been developed (**Table 1**). Inevitably, the models are bounded by assumptions about the number of people to be treated, the degree and durability of suppression, and adherence to therapy. The more optimistic the assumptions applied to the models, the greater the benefits of ART for a community (**Table 1**). Several

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mathematical modeling studies have suggested that widespread use of ART could substantially reduce HIV incidence [85, 86], but that any possible preventative benefit of ART could be undermined by behavioral disinhibition [85, 87-89]. Baggaley and colleagues concluded that ART is unlikely to reduce HIV transmission due to the limited ability of ART to prevent HIV transmission, widespread emergence of ART resistance and significant increases in HIV risk-taking behavior [87]. However, in a recent more "utopian" model Granich *et al.* argued that the HIV epidemic in Africa could be ended with universal annual HIV testing and immediate treatment [4]. In a model constructed by Lima and colleagues, increasing ART coverage beyond the current 50% of those with a CD4 count less than 200 cells/mm^3 to 75%, 90% and 100% in the setting of stable adherence would decrease HIV incidence by 37%, 54% and 62%, respectively, as well as per capita lifetime treatment costs [90]. Obviously, empiric data is absolutely required to demonstrate a public health benefit from ART. To date, no community randomized clinical trials of ART for public health benefit have started, although such studies are necessary to determine the validity and cost-effectiveness of such an approach [5]. The broadest coverage would result from initiation of ART regardless of CD4, and this approach is currently being described as "Test and Treat." A very detailed discussion on this topic can be reviewed at the World Health Organization (WHO) website at http://www.who.int/hiv/events/artprevention/en/index.html.[91]

Transmitted antiviral resistance

The success of ART for prevention will undoubtedly be limited by the development of resistance. Recent studies demonstrate considerable HIV resistance in newly diagnosed patients [92, 93]. However the rates of resistant HIV may actually be lower than expected suggesting reduced viral fitness or other antiviral effects. In addition, resistant HIV isolates have been detected in genital secretions [32, 34] and sexual transmission of such resistant variants has been demonstrated [94-96].

HSV-2 suppression and HIV transmission

Among the STDs, HSV-2 has been considered particularly important because of widespread world-wide infection and documented effects on HIV genital tract shedding [97]. More than one meta-analysis has ascribed significant HIV transmission to HSV as a co-factor [98-100]. However, recent clinical trials designed to suppress HSV-2 in HIV negative subjects at risk [101], and HSV in HIV-infected subjects [102] failed to reduce transmission of HIV-1. Such findings were unexpected and it seems likely that acyclovir used in these trials was not sufficiently suppressive to override other factors. In addition, acyclovir has a weak direct effect on HIV that might help account for partial reduction in blood viral load [103].

Conclusion

Literally days after zidovudine (AZT) was described in the late 1980s, the public health implications of ART were considered. A series of studies demonstrated the ability of antiviral agents to concentrate in genital secretions [104], and to reduce recovery of HIV [28, 105, 106]. These results provided the biological plausibility for the belief that HIV treatment can serve as prevention. Enthusiasm for this approach has recently been driven by:

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i) the failure of other behavioral and biological prevention efforts to end the epidemic [107]; ii) cheaper, safer and simpler ART regimens; iii) the widespread availability of ART in developing countries; iv) the optimism of mathematical modelers (see above) and some policy makers [108]. Accordingly, the public health benefits of ART have now taken center stage, not just for treatment of the infected subject, but as pre-and post exposure prophylaxis well [2, 109]. While this momentum is exciting, threats must also be weighed. Use of ART for prevention will require much wider usage of drugs in much healthier people. Clinical and community randomized trials are absolutely necessary to determine the actual feasibility and benefit of this approach.

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Table 1

Modeling the effect of antiretroviral therapy on HIV transmission.

Author	Model	Assumptions	Conclusions
Baggaley, RF, et al, 2006[87]	Deterministic model of HIV transmission using ART and stratification of HIV progression.	• Existence of only one sensitive and one ART-resistant HIV strain with a fixed infectiousness for each group determined by treatment and resistance status. • ART resistant strain is resistant to all three drugs in the triple regimen. • No pre-existing background ART resistance; ART failure precedes resistance evolution. • Availability of only one, standard triple-drug ART regimen, with no second-line therapy for those failing the first line regimen. • All sexual relationships are heterosexual and characterized by immediate transmission if determined to occur. • Four sexual activity classes: 0.1% with the highest activity followed by 26%, 59% and 15% with lower activity rates associated with partner change rates of 153, 13.6, 0.5 and 0.2 partners per year, respectively. • Sexual activity of pre-AIDS clients drops to next lowest class following diagnosis and counseling and 85% of AIDS patients increase sexual activity after ART initiation. • A defined proportion of patients stop ART due to side effects or illness, dies following ART initiation and fails treatment each year. • HIV prevalence based on data from antenatal clinics in Malawi. • Availability of CD4 testing determines if patients with pre-AIDS and/or AIDS-defining illnesses begin treatment. • Only a one month delay from determination of ART eligibility to ART initiation. • Model tested with variable partner change rates, levels of ART coverage, ability to initiate ART prior to AIDS-defining illnesses and ability to detect treatment failure. • ART has a limited effect on HIV transmission in the setting of ART failure and no effective second line regimen.	• The most optimistic impact of ART involving treatment of all pre-AIDS and AIDS patients, decreased risk-taking following ART initiation and an epidemic with a low case reproduction number, would not change HIV prevalence. • Number of life-years saved per person-year of treatment for pre-AIDS and AIDS exceeded that for AIDS-only treatment by 2029 with coverage of 30,000 patients and best-case scenario parameters. • HIV prevalence is likely to increase in the absence of behavior change following ART initiation and effective prevention counseling. • Increasing ART coverage does not increase life-years gained per person-year of treatment because of limited effect of ART on treatment, but does increase the prevalence of ART resistance.
Blower S, et al.[110]	Uncertainty analysis/ Monte Carlo sampling techniques.	• ART reduces per partnership infectivity by up to 60%. • 25- 28 million HIV-infected people in Sub-Saharan Africa. • 15-20% of HIV+ population eligible for treatment. • 10% of HIV-infected people will be treated. • 3 million new infections in Sub-Saharan Africa per year.	• 5% incidence decrease results in 143,296-473,598 new infections prevented over 5 yrs. • Change in incidence will be undetectable over following decade. • Transmission of ART resistance will be below WHO surveillance threshold of 5%. • Majority of ART resistance will be acquired not transmitted. • Large-scale ART resistance surveillance unnecessary. • Sentinel surveillance sites should be based in large urban areas where treatment coverage rates likely >10%.
Granich, RM, et al, 2009[4]	Deterministic transmission model of the effect of universal voluntary HIV testing and immediate ART.	• Test community has a generalized epidemic like South Africa with only heterosexual HIV transmission. • HIV elimination defined as reduction in incidence to less than one case per 1000 people. • CD4 count decreases 25% immediately following HIV infection and linearly thereafter. • Mean survival following HIV infection without ART is 11 (SD 0.5) years. • Acute phase lasts 2 months when infectivity is ten times higher than in the chronic phase. • End stage phase lasts 5% of survival time without ART during which infectivity is five times higher than during the chronic phase. • HIV tests are 100% sensitive and specific for the detection of HIV.	• To decrease the case reproduction number to less than 1 would require annual HIV testing and immediate ART initiation for those testing HIV positive. • Annual universal testing and immediate ART could decrease HIV incidence and mortality to less than one case per 1000 per year by 2016, or within 10 years of full implementation. • This test and treat strategy could reduce HIV prevalence to less than 1% within 50 years. • The strategy would reduce HIV-related mortality by an estimated 55% up to 2050 in comparison with starting ART with a CD4 count less than 350 cells/mm^3.

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Author	Model	Assumptions	Conclusions
		• All persons tested and with a CD4 count below a specific threshold are offered ART. • All persons tested and with a CD4 count below a specific threshold are offered ART. • Based on data from Malawi, assumed long term drop-out rate of 1.5% per year and first-line treatment would fail in 4% of individuals per year. • ART coverage would increase to 50% by 2012 and to 90% by 2016. • Infectiousness on ART decreases to 1% of the baseline infectiousness prior to ART. • Case reproduction number (R_0) during the chronic phase is equal to 7 with a doubling time of 1.25 years, to match data from South Africa. • HIV prevalence taken from South African 2005 national antenatal survey. • In comparison of immediate versus CD4 count threshold for ART initiation, all infected individuals present prior to CD4 decline below 350 and start ART at this threshold. • Forty percent reduction in HIV transmission via combined HIV prevention programs. • Seventeen percent of estimated yearly global funding for HIV/AIDS up to 2008, and 17% of UNAIDS projected yearly needs for universal access up to 2015.	• The yearly cost of the strategy is higher than the current strategy, but would decrease after 2015 to less than the cost of ART initiation after CD4 counts fall below 350 cells/mm^3. • Full implementation of the strategy would allow the epidemic to shift from an endemic phase to an elimination phase in 2010.
Law MG, et al, 2001[85]	Mathematical model of HIV transmission in homosexual men in Australia.	• 9300 HIV-infected homosexual men of whom 80% diagnosed and 70% on ART in 1996. • 56% of HIV-infected men receiving ART. • 400 new HIV infections in homosexual men in Australia if combination ART has no effect on infectiousness and prevalence of unsafe sex. • ART uptake and increases in unsafe sex were instantaneous and coincident. • ART administered independent of viral load.	• Decreased infectiousness and incidence of HIV due to ART could be counterbalanced by increases in unsafe sex. • Decreased infectiousness due to ART was non-linearly associated with decreased HIV incidence. • Decreases in infectiousness of two-, five- and 10-fold would be counterbalanced by increases in unsafe sex of 40, 60 and 70% respectively.
Lima, VD, et al, 2008[90]	Semi-deterministic dynamic transmission Semi-deterministic dynamic transmission	• HIV progression defined via four categories including susceptible, primary infection, symptomatic phase defined by HIV RNA strata (<3, ≥3 and <4, ≥4 and <5, and ≥5 $\log_{10}$ copies/mL) and late stage (with opportunistic diseases). • Key eligibility for ART defined as CD4 count ≤200 cells/mm^3. • Cost of first-line ART in 2006 was estimated to be Can$17,288.22; cost for years 2007-2030 assumed a discounting of the future health rate equal to 3%. • Lifetime individual treatment cost was based on an estimated life expectancy of 22.9 years at 30 years of age.	• The continued HAART coverage rate of 50% for those with a CD4 count ≤200 cells/mm3 with 78.5% adherence levels would results in an increase in the number of new diagnosed HIV cases in British Columbia. • Increased HAART coverage to 75%, 90% and 100% for those with CD4 counts ≤200 cells/mm3 and stable adherence would result in a decline in the annual number of newly diagnosed HIV positive individuals of 37%, 54% and 62%, respectively. • Increase HAART coverage from 50% to 75% could translate into total per capita lifetime treatment cost savings of Can$95 million.
Wilson, DP, et al, 2008[89]	Mathematical model of cumulative risk of HIV transmission from effectively treated HIV-infected individuals.	• Each ten-fold increase in viral load carries a 2.45 fold increase in the risk of HIV transmission per sexual encounter[10]. • Association between viral load and HIV transmission risk did not vary for female to male, male to female or male to male transmission, regardless of treatment status of the infected partner. • HIV transmission probability per sexual act in absence of ART is 0.0005 for receptive penile-vaginal intercourse, 0.001 for insertive penile-vaginal intercourse and 0.01 for penile-anal intercourse between men. • Heterosexual couples do not engage in penile-anal intercourse. • MSM engage in insertive and receptive sex acts in equal proportions. • Baseline viral load of infected partner assumed to be 10^4-10^5 copies/mL. • Effective ART reduced viral load to less than 10 copies/mL. • Risk of HIV transmission per sexual act among monogamous, serodiscordant couples was independent over n acts.	• Cumulative probability of HIV transmission to the serodiscordant partner of an effectively treated HIV-infected patient per 100 sexual contacts per year was 0.0022 for female-to-male transmission, 0.0043 for male-to-female transmission and 0.043 from male-to-male transmission. • Among 10,000 serodiscordant couples over 10 years, 215 female-to-male, 425 male-to-female and 3524 male-to-male transmissions would occur with effective ART and no condom use. • If condom use declined due to perceived non-infectiousness with effective ART, HIV incidence could increase four-fold.

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