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Examining the evidence on the causal effect of HAART on transmission of HIV using the Bradford Hill criteria

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Abstract

In recent years, evidence has accumulated regarding the ability of HAART to prevent HIV transmission. Early supportive evidence was derived from observational, ecological and population-based studies. More recently, a randomized clinical trial showed that immediate use of HAART led to a 96% decrease in HIV transmission events within HIV serodiscordant heterosexual couples. However, the generalizability of the effect of HAART, and the population-level impact on HIV transmission continues to generate substantial debate. We, therefore, conducted a review of the evidence regarding the preventive effect of HAART on HIV transmission within the context of the Bradford Hill criteria for causality. Taken together, we find the accumulated evidence supporting HIV treatment as prevention meets each of the Bradford Hill criteria for causality. We conclude that the opportunity cost of inaction while waiting for additional evidence on the generalizability of effect in other risk groups is too high. Efforts should be redoubled to mobilize the financial capital and political will to optimize implementation of HIV Treatment as Prevention strategies on a wide scale.

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Conflicts of interest

P.C. has declared board membership for GSK/ViiV, Janssen and Merck; pending grants from Abbot, payments for lectures from GSK, Abbott, Janssen and Merck and payment for educational development presentations from ViiV. B.W. has declared WHO consultancy. J.L. declares grants from Abbott, Gilead, Johnson & Johnson, Merck and Mylan. J.M. has also received financial support from the International AIDS Society, United Nations AIDS Program, World Health Organization, National Institutes of Health Research-Office of AIDS Research, National Institute of Allergy & Infectious Diseases, The United States President's Emergency Plan for AIDS Relief (PEPfAR), Bill & Melinda Gates Foundation, French National Agency for Research on AIDS & Viral Hepatitis (ANRS), the Public Health Agency of Canada, the University of British Columbia, Simon Fraser University, Providence Health Care and Vancouver Coastal Health Authority. He has received grants from Abbott, Biolytical, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare.

Keywords

Bradford Hill criteria; causality; HAART; HIV prevention; human immunodeficiency virus

> All Scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.
>
> - Sir Austin Bradford Hill, 'The Environment and Disease: Association or Causation: A Case for Action' (Hill, 1965)

Introduction

HAART stops HIV replication driving plasma viral load (pVL) to undetectable levels [1,2]. This allows immune reconstitution to take place, leading to long-term disease remission and prolonged survival [3,4]. As a result of HAART availability, some 3 million life-years had been saved in the USA from 1996–2006 [5]. Life expectancy of HIV-positive individuals on HAART has increased dramatically in both high-income and low-income countries [6–9].

Viral load has been shown to be the key driver of HIV transmission [10–12]. More recently, a secondary benefit of HAART in preventing HIV transmission has been documented [13–15]. As a result, treatment as prevention (TasP) is now incorporated into antiretroviral treatment guidelines in resource rich [2,16,17] and in resource limited settings [18].

Nonetheless, the generalizability of the effect of HAART on HIV transmission remains a matter of debate [19–21]. Indeed, some have argued for more research to evaluate the generalizability of the relationship before TasP strategies are implemented [22,23]. Our objective, therefore, is to provide a critical review of the evidence supporting the secondary benefit of the use of HAART among HIV-positive individuals on the prevention of HIV transmission in the context of the Bradford Hill criteria for causality (Table 1) [24].

Review of the HIV treatment as prevention evidence using the Bradford Hill criteria

We executed a focused review of experimental, observational, ecological studies and meta-analyses published in the English language peer-reviewed literature on the secondary benefit of the use of HAART among HIV-positive individuals on the prevention of HIV transmission. Additional complementary evidence was drawn from the peer-reviewed literature.

Biological plausibility

This criterion refers to the scientific plausibility of the effect of exposure on outcome. The case for the preventive effect of treatment against HIV transmission is straight forward: HAART-driven undetectable levels in pVL among HIV-infected individuals' can similarly render the viral load in blood and sexual fluids undetectable, and as a result the likelihood of

parenteral or sexual HIV transmission is markedly reduced. Although it has been clear for some time that the use of HAART leads to a marked reduction in pVL in both the female genital tract and in semen [25,26], pVL suppression is not always complete, particularly in rectal fluids [27–31]. Nonetheless, from a public health perspective the association between viral load and other bodily fluids is strong, especially in the setting of long-term, sustained, and effective HAART [25]. From a practical standpoint this serves to emphasize interrelated-ness and indeed the indivisibility of the therapeutic and preventive benefits of HAART. Sustained pVL suppression to undetectable levels is the key driver of the therapeutic benefit of HAART; in the context of HIV transmission, sustained suppression of pVL is also the key driver of the preventive benefit of HAART.

Experimental evidence

The initial human experimental evidence regarding the preventive effect of antiretrovirals on HIV transmission was derived from the vertical transmission setting from mother to child, before the HAARTera [11]. Since then, HAART has been shown to reduce vertical transmission to below 5% [32]. Again, sustained suppression of maternal pVL is the key determinant of efficacy in this setting [32,33].

Experimental evidence supporting the preventive effect of HAART was provided by the HIV Prevention Trials Network (HPTN) 052 trial, which compared immediate versus deferred HAART among HIV serodiscordant couples [13]. Immediate HAART led to a 96% reduction in the number of linked HIV-1 transmissions compared with deferred HAART. The study also reported that immediate use of HAART was associated with a 41% decrease in a combined morbidity and mortality endpoint among HIV-infected participants.

Consistency of the association

Consistency refers to the repeated observation of an association in different study designs, on different populations and under different circumstances. A diverse body of evidence is available in support of the consistency of the association between expanded use of HAART and decreased HIV transmission derived from observational, ecological and population based studies, from a variety of geographic regions, and sub-populations.

A meta-analysis of observational studies among HIV serodiscordant heterosexual couples revealed 11 cohorts reporting on 5021 couples and 461 HIV-transmission events. The overall rate of transmission from HAART-treated patients was 0.46 (95% confidence interval 0.19–1.09) per 100 person-years, based on five events. HAART was associated with a 92% decrease in the rate of heterosexual transmission among serodiscordant couples [34]. This result was supported by a more recent and broader systematic review [15]. Subsequently, Donnell *et al.* [14] reported one out of 103 genetically linked HIV transmissions from an index participant on HAART within a cohort analysis of HIV serodiscordant heterosexual couples, resulting in an estimated 92% (adjusted incidence rate ratio: 0.08 (0.00–0.57; $P = 0.004$)) reduction in HIV transmission with HAART.

Among IDU, a sentinel cohort stratified by baseline HIV status was used to longitudinally characterize the association between community viral load (CVL) and HIV incidence at the

individual-level [12]. Controlling for individual-level injection drug use frequency, unsafe sex, used syringe sharing and other relevant covariates, estimated CVL was independently associated with time to HIV seroconversion, with a $\log_{10}$ decrease in median CVL resulting in a reduction of HIV incidence by a factor of 3.32 (1.82–6.08; P <0.001). These findings have since been independently validated [35].

Further, Das *et al.* [36] reported a decrease in HIV incidence of 74% for each $\log_{10}$ decline in CVL since 1997 in a San Francisco-based cohort. In a separate model, HIV incidence was reported to decrease by 5% for each 1% increase in HAART coverage. Finally, Montaner *et al.* [37] reported an ecological association between increasing HAART coverage, decreased pVL, and decreased number of new HIV diagnoses per year at the population-level in British Columbia, Canada. Between 1996 and 2009, the number of individuals actively receiving HAART increased from 837 to 5413 (547% increase; P = 0.002), and the number of new HIV diagnoses fell from 702 to 338 per year (52% decrease; P = 0.001). Rates of HIV testing increased throughout the study period, whereas rates of other blood-borne disease increased or remained stable.

Although these results have been supported elsewhere [38–40], ecological studies on the HAART – HIV transmission relationship have not consistently been positive [41]; in a study of MSM in San Francisco the early-HAARTera, increased coverage rates among MSM did not result in decreases in HIV incidence – a finding authors attributed to increased rates of unprotected sex [42]. Castel *et al.* [43] found no relationship between what the authors termed CVL and new cases of HIV, however, the CVL definition (measured pVL in a population, amounting to 4.8–33.4% of diagnosed cases) was conceptually different from the initial definition (complete capture of pVL measurements within a sentinel cohort [12]); the latter definition is clearly subject to considerable misclassification, which is unlikely to be consistent over time. Further, an administrative databased study from China did not find a protective effect of HAART on HIV transmission [44], however, a lack of data on drug quality, pVL, CD4 cell count or adherence rendered the findings inconclusive [45,46]. The results of a recently published population-level analysis on serodiscordant heterosexual couples in this setting supported previous studies of similar design [47,48].

Similar limitations are inherent in each of the studies described in this section, detailing observational or ecological associations that may be subject to measurement error and/or unmeasured confounding. Further, relationships revealed in ecological studies may not reflect individual-level associations [49]. Nonetheless, the studies described above support the consistency, and therefore the generalizability of HIV treatment as prevention, crucially, in a range of populations and study designs.

Temporal relationship

Temporality refers to the necessity that the cause precedes the effect in time. Only if it is found that the cause cannot precede the effect can we dispense with the causal hypothesis. In this instance, HAART stops viral replication, as a result it drives pVL in blood and sexual fluids to undetectable levels, which in turn markedly reduces the likelihood of parenteral or sexual HIV transmission. Temporality is clearly established within the experimental and

nonexperimental longitudinal studies on serodiscordant couples described above, where the introduction of HAART predictably precedes the decrease in HIV transmission.

Strength of the association

Bradford Hill argued that strong associations are particularly compelling, as unmeasured confounding would be more likely at play within a weaker association. In the biological experiments, observational studies, randomized control trial and community-based evidence, the association between HAART-induced pVL suppression and the risk of HIV transmission has been found to be strong, and consistent. Indeed, there has been a remarkable consistency among the various studies regarding the fact that HAART is highly protective (over 90%) against HIV transmission. This is in keeping with a review on the hierarchy of research designs by Concato *et al.* [50], which concluded that well designed observational studies do not systematically overestimate the magnitude of the treatment effect established in randomized controlled trials.

Specificity

Specificity relates to both exposure and outcome. Specificity in exposure implies that an outcome is attributed to a single exposure, whereas specificity in outcomes implies that a given exposure leads to a single predictable outcome. In the context of HIV treatment as prevention, this is equivalent to asserting that (a) the use of HAART predictably prevents HIV transmission, and (b) that it is indeed HAART that is independently responsible for preventing HIV transmission.

In the presence of HAART, sexual transmission of HIV can be prevented as a result of condom use and circumcision, whereas sterile needle and syringe provision can prevent transmission through injection drug use. However, evidence on the specificity of the exposure is demonstrable through the use of multivariate regression analysis. To this end, Cohen *et al.* [13] controlled for baseline condom use, among other covariates, in their assessment of the effect of early HAART initiation versus delayed therapy on the risk of linked HIV-1 transmission. Also, Wood *et al.* [12] controlled for relevant illicit drug use-related practices, including used syringe sharing, as well as frequency of heroin and cocaine injection. Both studies, therefore, demonstrated HAART's protective effect against HIV transmission, controlling for other relevant covariates.

Evidence on specificity in outcomes is demonstrated in two ecological studies. In Taiwan, there was a 53% reduction in new positive HIV tests after the introduction of free access to HAART, against a background of stable syphilis rates, as a marker of stable sexual risk behavior [51]. Similarly, in British Columbia, HAART coverage expansion after 1996 was associated with a decrease in new HIV diagnoses per year against a background of stable or increasing rates of syphilis, gonorrhea, chlamydia and HCV infection, as markers of sexual and injection risk behaviors, respectively [37].

In contrast, a cohort-based analysis showed a concurrent decrease in HCV incidence rates alongside decreasing CVL and HIV incidence. The authors considered the uptake of harm reduction strategies and saturation of HCV infection in the population under study as

possible explanations [52]. No doubt, evidence on specificity of effect and outcome are stronger in individual-level rather than aggregate-level measurement, yet evidence on both levels of measurement support this criterion.

Biological gradient

Biologic gradient refers to the presence of a defined dose–response or exposure–response relationship. At a minimum, a monotonic relationship (i.e. a unidirectional gradient) is required. The evidence to satisfy this criterion is particularly strong, as demonstrated by increased preventive efficacy with more effective antiretroviral drug regimens, and at the population level, the direct relationship between HAART coverage and rate of HIV new diagnoses.

Prior to the onset of HAART, Quinn *et al.* [10] demonstrated a dose–response effect between pVL level and the rate of HIV transmission within an observational study of untreated serodiscordant couples in Rakai, Uganda. This result was confirmed in multivariate analysis, in which each $\log_{10}$ pVL increase was associated with an increase in the risk of transmission by a factor of 2.45. A limitation of this study was that all incident cases of HIV were assumed to be linked. A contemporaneous study by Fideli *et al.* [53] confirmed this result with genetic sequencing to refine classification of linked and unlinked cases. This dose–response relationship has been demonstrated elsewhere in observational settings [54], with even small reductions in pVL resulting in reductions in HIV transmission [55].

With regard to the increased preventive efficacy with more effective antiretroviral drug regimens, an increased level of efficacy has been shown when considering zidovudine monotherapy or single-dose nevirapine against HAART in the setting of vertical HIV transmission [56]. Also, a direct relationship has been demonstrated between increasing HAART coverage and decreasing rate of HIV new diagnoses, mediated by decreasing CVL or increasing level of pVL suppression among IDU [12], and at the population level [37], respectively.

Coherence

Coherence implies that a cause-and-effect interpretation for an association does not conflict with what is known of the natural history and biology of the disease. Hill emphasized that the absence of coherent information, as distinguished from the presence of conflicting information, should not be taken as evidence against an association being considered causal. The simplicity and coherence of the argument for the relationship between HAART and HIV transmission is the defining characteristic that has mobilized investigators to assess it on across the globe.

Reasoning by analogy

This criterion requires that the observed association be supported by analogous associations in different diseases. Quite simply, HAART prevents HIV transmission through suppression of the virus. This is analogous to say that treatment of TB prevents airborne transmission of *Mycobacterium tuberculosis* because it sterilizes the sputum of patients with pulmonary

tuberculosis [57]. Likewise, treatment of genital herpes decreases viral burden and potential for transmission [58].

Conclusion

Taken together, the accumulated evidence supports the notion that HIV treatment as prevention meets the Bradford Hill Criteria for the relationship to be deemed causal. While the evidence is clearly strongest in heterosexual serodiscordant couples, the biological evidence, complementary findings in IDU populations, as well as population-level studies in both concentrated and generalized epidemics suggest that this is a consistent and generalizable effect. Considerable challenges may limit the extent to which HIV treatment as prevention may reduce HIV incidence in the real world. Among them, high infectivity during acute HIV infection [59], the potential escalation of antiviral resistance [60], HIV risk compensation [61], and medication shortages [62] have been cited [63].

Nonetheless, the effectiveness of abstinence promotion, condom use and needle exchange programs have been limited [64,65], and in 2010 there were 2.5 million new infections, 1.8 million AIDS-related deaths and 390 000 children infected globally, with disproportionate representation in low-income countries. Only 54% of HIV-infected individuals with severe immunodeficiency are on HAART, and only 20% of people with HIV know their status [66].

Although recent amendments to HIV treatment guidelines [2,16–18,67] are encouraging, the emphasis remains on the use of TasP among stable heterosexual serodiscordant couples. This narrow interpretation of the available evidence seriously limits the potential impact of the HIV treatment as prevention strategy, as a substantial proportion of HIV transmissions occur outside of the stable heterosexual serodiscordant couples setting.

A wide range of research and demonstration projects have been initiated globally to characterize the optimal implementation of TasP [68–70] with an emphasis on efficiency and cost-effectiveness. To this end, the immediate costs of HIV treatment as prevention implementation will undoubtedly be high; however, the long-term financial benefits can be tremendous [71,72]. The current protracted global financial crisis has had a significant impact on the global HAART roll out: UNAIDS recently reported a 10% drop in funding from 2009 to 2010 to support the Universal Access pledge [23]. The US' budgeted contribution to the Global Health Initiative is also projected to fall 10.8% for 2013 [73]. This threatens to reverse the recent gains and undermines the promise of HIV treatment as prevention. The economic argument for HIV treatment as prevention requires reinforcement. Economic modeling studies have evolved to reach beyond the individual benefits of HAART to capture first-order and second-order preventive benefits [71,72]; further advances are needed to capture and quantify economic externalities such as orphanhood, child labor and household expenditures as well as macroeconomic effects in endemic countries [74–77].

Consistent with Bradford Hill's [24] case for action, we propose that the opportunity cost of inaction is simply too high not to mobilize the financial capital and political will toward optimizing implementation of the HIV treatment as prevention strategy.

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References

1. Carpenter CC, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, et al. Antiretroviral therapy for HIV infection in 1996. Recommendations of an international panel International AIDS Society-USA. JAMA. 1996; 276:146–154. [PubMed: 8656507]
2. Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, et al. International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA. 2010; 304:321–333. [PubMed: 20639566]
3. Hogg RS, O'Shaughnessy MV, Gataric N, Yip B, Craib K, Schechter MT, Montaner JS. Decline in deaths from AIDS due to new antiretrovirals. Lancet. 1997; 349:1294. [PubMed: 9142067]
4. The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration and ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. 2006; 367:817–824. [PubMed: 16530575]
5. Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, et al. The survival benefits of AIDS treatment in the United States. J Infect Dis. 2006; 194:11–19. [PubMed: 16741877]
6. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008; 372:293–299. [PubMed: 18657708]
7. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. ATHENA national observational cohort study. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. AIDS. 2010; 24 :1527–1535. [PubMed: 20467289]
8. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, et al. The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration; ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. 2006; 367:817–824. [PubMed: 16530575]
9. Kadhiravan T, Sharma SK. Mortality of HIV-infected patients in low-income countries. Lancet. 2006; 368:2207. [PubMed: 17189025]
10. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. for the RAKAI project study group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med. 2000; 342:921–929. [PubMed: 10738050]
11. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. Lancet. 1999; 354:795–802. [PubMed: 10485720]
12. Wood E, Kerr T, Marshall BDL, Li K, Zhang R, Hogg RS, et al. Longitudinal community plasma HIV-1-RNA concentrations and incidence of HIV-1 among injecting drug users: a prospective cohort study. BMJ. 2009; 338:b1649, 1191–1194. [PubMed: 19406887]

13. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. for the HPTN 052 study team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365:493–505. [PubMed: 21767103]
14. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Partners in Prevention HSV/HIV Transmission Study Team. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet. 2010; 375:2092–2098. [PubMed: 20537376]
15. Anglemyer A, Rutherford GW, Baggaley RC, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane Database Syst Rev. 2011:CD009153.
16. Department of Health and Human Services. [Accessed 12 March 2012] Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Oct 14. 2011 http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
17. [Accessed 14 May 2012] British HIV Association Clinical Guidelines. http://www.bhiva.org/ClinicalGuidelines.aspx
18. World Health Organization. [Accessed 2 May 2012] Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples: Recommendations for a public health approach. Apr. 2012 http://www.who.int/hiv/pub/guidelines/9789241501972/en/index.html
19. Cohen MS. HIV treatment as prevention: to be or not to be? J Acquir Immune Defic Syndr. 2010; 55:137–138. [PubMed: 20798638]
20. Bruhn CA, Gilbert MT. HIV-2 down, HIV-1 to go? Understanding the possibilities of treatment as prevention. Lancet Infect Dis. 2011; 11:260–261. [PubMed: 21453865]
21. Cohen MS, Muessig KE, Smith MK, Powers K, Kashuba ADM. Antiviral agents and HIV prevention: controversies, conflicts and consensus. AIDS. 2012; 26:1585–1598. [PubMed: 22507927]
22. Institute of Medicine of the National Academies. [Accessed 11 April 2012] Preparing for the Future of HIV/AIDS in Africa: A Shared Responsibility. Nov. 2010 http://www.iom.edu/~/media/Files/Report%20Files/2010/Preparing-for-the-Future-of-HIVAIDS-in-Africa-A-Shared-Responsibility/Future%20of%20HIV%20AIDS%202010%20Report%20Brief.pdf
23. Lomborg, B.; Piot, P. [Accessed 27 September 2011] Re-thinking the fight against AIDS. Wall Street Journal Online. Sep 27. 2011 http://online.wsj.com/article/SB10001424053111904194604576583071258290228.html?KEYWORDS=HIV
24. Bradford-Hill A. The environment and disease: assocation or causation? Proc R Soc Med. 1965; 58:295–300. [PubMed: 14283879]
25. Vernazza P, Hirschel B, Bernasconi E, Fiepp M. HIV-infected patients under HAART without any other sexually transmitted infection do not transmit HIV by sexual intercourse. Bull Med Suisse. 2008; 89:165–169.
26. Cu-Uvin S, Caliendo AM, Reinert S, Chang A, Juliano-Remollino C, Flanigan TP, et al. Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA. AIDS. 2000; 14:415–421. [PubMed: 10770544]
27. Brown, L.; Poole, C.; Patterson, K.; Cohen, M. Variability in female genital tract shedding and plasma viral loads: a systematic review. 17th International AIDS Conference; 3–8 August 2008; Mexico City.
28. Chan DJ. Pathophysiology of HIV-1 in semen: current evidence for compartmentalization and penetration by antiretroviral drugs. Curr HIV Res. 2005; 3:207–222. [PubMed: 16022654]
29. Le Tortorec A, Dejucq-Rainsford N. HIV infection in the male genital tract: consequences for sexual transmission and reproduction. Int J Androl. 2010; 33:e98–e108. [PubMed: 19531082]
30. Cu-Uvin S, DeLong AK, Venkatesh KK, Hogan JW, Ingersoll J, Kurpewski J, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. AIDS. 2010; 24 : 2489–2497. [PubMed: 20736815]
31. Baggaley R, White R, Boily M. HIV transmission risk through anal intercourse: systematicreview, meta-analysis and implications for HIV prevention. Int J Epidemiol. 2010; 39:1048–1063. [PubMed: 20406794]

32. World Health Organization. [Accessed 2 May 2012] Programmatic update: Use of Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Executive Summary. Apr. 2012 http://www.who.int/hiv//PMTCT_update.pdf
33. Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Anti-retrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev. 2011:CD003510. [PubMed: 21735394]
34. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009; 23 :1397–1404. [PubMed: 19381076]
35. Kirk, G.; Galai, N.; Astemborski, J.; Linas, B.; Celentano, D.; Mehta, S.; Vlahov, D. Decline in community viral load strongly associated with declining HIV incidence among IDU [abstract]. 18th Conference on Retrovirusses and Opportunistic Infections; Boston, MA. February 27–March 2; 2011; p. 484
36. Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, Colfax GN. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLOS One. 2010; 5:e11068.10.1371/journal.pone.0011068 [PubMed: 20548786]
37. Montaner JSG, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet. 2010; 376:532–539. [PubMed: 20638713]
38. Tanser, F.; Barnighausen, T.; Grapsa, E.; Newell, ML. Effect of ART Coverage on Rate of New HIV Infections in a Hyper endemic, Rural Population: South Africa [abstract]. 19th Conference on Retroviruses and Opportunistic Infections; Seattle, Washington. 2012; p. Abstract 136LB
39. Porco TC, Martin JN, Page-Shafer KA, Cheng A, Charlebois E, et al. Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. AIDS. 2004; 18:81–88. [PubMed: 15090833]
40. Law MG, Woolley I, Templeton DJ, Roth N, Chuah J, Mulhall B, et al. The Australian HIV Observational Database. Trends in detectable viral load by calendar year in the Australian HIV observational datablase. J Int AIDS Soc. 2011; 14:10. [PubMed: 21345234]
41. Smith MK, Powers KA, Muessig KE, Miller WC, Cohen MS. HIV Treatment as Prevention: the utility and limitations of ecological observation. PLoS Med. 2012; 9:e1001260. [PubMed: 22802740]
42. Katz MH, Schwarcz SK, Kellogg TA, Klausner JD, Dilley JW, Gibson S, McFarland W. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. Am J Public Health. 2002; 92:388–394. [PubMed: 11867317]
43. Castel AD, Befus M, Willis S, Griffin A, West T, Hader S, Greenberg AE. Use of the community viral load as a population-based biomarker of HIV burden. AIDS. 2012; 26:345–353. [PubMed: 22008660]
44. Wang LZG, Jing Luo BS, Shan Duo, Gao Xing, Ding Guo-wei, Zhou Jian-ping, et al. HIV transmission among serodiscordant couples: a retrospective study of former plasma donors in Henan, China. J Acquir Immune Defic Syndr. 2010; 55:232–238. [PubMed: 21423851]
45. Montaner J, Hogg R. Implications of the Henan Province report on the treatment as prevention debate [Letter]. J Acquir Immune Defic Syndr. 2011; 56:e101. [PubMed: 21317576]
46. Cohen MS. HIV treatment as prevention: in the real world the details matter [Letter]. J Acquir Immune Defic Syndr. 2011; 56 :e101. [PubMed: 21317576]
47. Jia, Z.; Ruan, Y.; Li, Q.; Xie, P.; Li, P.; Wang, X., et al. Antiretroviral therapy to prevent HIV transmission in serodiscordant couplesin China (2003–11): a national observational cohort study. Lancet. 2012. http://dx.doi.org/10.1016/S0140-6736(12)61898-4[Epub ahead of print]
48. Vermund SH. Treatment as prevention for HIV in China. Lancet. 2012 Epub ahead of print. 10.1016/S0140-6736(12)62005-4
49. Greenland S, Robins J. Invited commentary: ecologic studies-biases, misconceptions, and counterexamples. Am J Epidemiol. 1994; 139:747–760. [PubMed: 8178788]
50. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000; 342:1887–1892. [PubMed: 10861325]

51. Fang CT, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, et al. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. J Infect Dis. 2004; 190:879–885. [PubMed: 15295691]
52. Mehta SH, Astemborski J, Kirk GD, Strathdee SA, Nelson KE, Vlahov D, Thomas DL. Changes in blood-borne infection risk among injection drug users. J Infect Dis. 2011; 203:587–594. [PubMed: 21282191]
53. Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. AIDS Res Human Retrovirus. 2001; 17:901–910.
54. Tovanabutra S, Robinson V, Wngtrakul J, Sennum S, Suriyanon V, Kingkeow D, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. J Acquir Immune Defic Syndr. 2002; 29:275–283. [PubMed: 11873077]
55. Modjarrad K, Chamot E, Vermund SH. Impact of small reductions in plasma HIV RNA levels on the risk of heterosexual transmission and disease progression. AIDS. 2008; 22:2179–2185. [PubMed: 18832881]
56. Senise JF, Castelo A, Martínez M. Current treatment strategies, complications and considerations for the use of HIV anti-retroviral therapy during pregnancy. AIDS Rev. 2011; 13 :198–213. [PubMed: 21975356]
57. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011; 378:57–72. [PubMed: 21420161]
58. Workowski KA, Berman SM. Centers for Disease Control and Prevention Sexually transmitted diseases treatment guidelines 2006. Published correction appears in MMWR Recomm Rep 2006; 55:997. MMWR Recomm Rep. 2006; 55(RR-11):1–94. [PubMed: 16888612]
59. Cohen MS, Dye C, Frasher C, Miller WC, Powers KA, Williams BG. HIV treatment as prevention: Debate and commentary-Will early infection compromise treatment-as-prevention strategies? PloS Med. 2012; 9:e1001232. [PubMed: 22802728]
60. Smith K, Powers KA, Kashuba AD, Cohen MS. HIV-1 treatment as prevention: the good, the bad, and the challenges. Curr Opin HIV AIDS. 2011; 6:315–325. [PubMed: 21646878]
61. Sullivan PS, Drake AJ, Sanchez TH. Prevalence of treatment optimism-related risk behavior and associated factors among men who have sex with men in 11 states. AIDS Behav 2000–2011. 2007; 11:123–129.
62. Schouten EJ, Jahn A, Ben-Smith A, Makombe SD, Harries AD, Aboagye-Nyame F, Chimbwandira F. Antiretroviral drug supply challenges in the era of scaling up ART in Malawi. J Int AIDS Soc. 2011; 14 (Suppl 1):S4. [PubMed: 21967844]
63. Shelton JD. ARVs as HIV prevention: a tough road to wide impact. Science. 2011; 334:1645–1646. [PubMed: 22194560]
64. Crosby R, Bounse S. Condom effectiveness: where are we now? Sex Health. 2012; 9:10–17. [PubMed: 22348628]
65. Underhill K, Operario D, Montgomery P. Abstinence-only programs for HIV infection prevention in high-income countries. Cochrane Database Syst Rev. 2007:CD005421. [PubMed: 17943855]
66. UNAIDS. World AIDS Day Report. UNAIDS; Geneva: 2011. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/20120718_togetherwewillendaids_en.pdf [Accessed 30 September, 2012]
67. World Health Organization. [Accessed 30 September, 2012] ART Guidelines for adults and adolescents – evidence map. 2010. http://www.who.int/hiv/topics/treatment/evidence/en/index.html
68. Granich R, Gupta S, Suthar A, Smyth C, Hoos D, Vitoria M, et al. on behalf of the ART in Prevention of HIV and TB Research Writing Group. ART in prevention of HIV and TB: Update on current research efforts. Curr HIV Res. 2011; 9:446–469. [PubMed: 21999779]
69. Dabis, F.; Newell, M-L. [Accessed 30 October 2012] A cluster randomised trial comparing the impact of immediate versus WHO recommendations guided ART initiation on HIV incidence. The ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, Kwazulu-Natal, South Africa. http://www.africacentre.ac.za/Portals/0/TasP/Protocol/TasPprotocol_20July2012.pdf
70. HIV Prevention Trials Network. [Accessed 30 October 2012] HPTN 071: The PopART Study. http://www.hptn.org/web%20documents/IndexDocs/071StudyAnnouncement14Sep11.pdf

71. Schwartländer B, Stover J, Hallett T, Atun R, Avila C, Gouws E, et al. Investment Framework Study Group. Towards an improved investment approach for an effective response to HIV/AIDS. Lancet. 2011; 377:2031–2041. [PubMed: 21641026]

72. Walensky RP, Paltiel AD, Losina E, Morris BL, Scott CA, Rhode ER, et al. for the CEPAC investigators. Test and treat DC: Forecasting the impact of a comprehensive HIV strategy in Washington DC. Clin Infect Dis. 2010; 51:392–400. [PubMed: 20617921]

73. The Henry J. Kaiser Family Foundation. [Accessed 28 February 2012] US Global Health Policy. http://globalhealth.kff.org/Policy-Tracker/Content/2012/February/13/FY13-Budget-Request.aspx

74. Ventelou B, Arrighi Y, Greener R, Lamontagne E, Carrieri P, Moatti JP. The macroeconomic consequences of renouncing to universal access to antiretroviral treatment for HIV in Africa: A micro-simulation model. PLoS One. 2102; 7:e34101. doi:10/371/journal.pone.0034101. [PubMed: 22514619]

75. Ventelou B, Moatti JP, Videau Y, Kazatchkine M. 'Time is costly': modelling the macroeconomic impact of scaling-up antiretroviral treatment in sub-Saharan Africa. AIDS. 2008; 22 :107–113. [PubMed: 18090398]

76. Meyer-Rath G, Over M. HIV Treatment as Prevention: Modeling the cost of antiretroviral treatment – state of the art and future directions. PLoS Med. 2012; 9:e1001247. [PubMed: 22802731]

77. Bärnighausen T, Salomon JA, Sangrujee N. HIV treatment as prevention: issues in economic evaluation. PLoS Med. 2012; 9 :e1001263. [PubMed: 22802743]

Table 1

Bradford Hill criteria for causality.

Biological plausibility	Does it make sense?
Temporal relationship	Does the cause precede the effect?
Strength of the association	How large is the effect?
Experimental evidence	Are there any clinical studies (ideally double-blinded randomized controlled trials) supporting the association?
Consistency of the association Specificity	Has the same association been observed by others, in different populations, using a different method? Does altering only the cause alter the effect?
Biological gradient	Is there a dose response?
Coherence	Does the evidence fit with what is known regarding the natural history of the outcome?
Reasoning by analogy	Is the observed association supported by similar associations?