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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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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?