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# Impact of Small Reductions in Plasma HIV RNA Levels on the Risk of Heterosexual Transmission and Disease Progression

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## Abstract

**Objective—**To estimate the impact of small changes in plasma levels of HIV-1 RNA on the risk of heterosexual transmission or disease progression to an AIDS-defining event or death.

**Design and methods—**We systematically reviewed the published literature for studies that evaluated small viral load changes among antiretroviral therapy (ART)-naïve, adult populations. We modeled relative risk estimates for viral transmission and disease progression according to 0.3, 0.5, and 1.0 $\log_{10}$ increments of HIV load.

**Results—**We calculated that the likelihood of transmitting HIV by heterosexual contact increased, on average, by 20% and that the annual risk of progression to an AIDS-defining illness or related death increased by 25% with every 0.3 $\log_{10}$ increment in HIV RNA. A 0.5 $\log_{10}$ increment in HIV RNA was associated with 40% greater risk of heterosexual transmission and 44% increased risk of progression to AIDS or death. A 1.0 $\log_{10}$ increment in HIV RNA was associated with 100% greater risk of heterosexual transmission and 113% increased risk of progression to AIDS or death.

**Conclusions—**ART continues to be unavailable or not-yet-indicated for 72% of the world's HIV-infected persons. Mounting evidence that treatment of co-infections may reduce HIV viral load, even modestly, suggests the priority of improved adjunctive care for HIV-infected persons even without ART, both to slow disease progression and to reduce infectiousness.

### Keywords

HIV; Viral Load; Transmission; Disease Progression; Review

## Introduction

The effort to identify low-cost therapeutic and preventive strategies for human immunodeficiency virus (HIV) in Africa and other resource-limited settings is still among the most difficult operational research challenges. Despite recent cost reductions and widespread implementation of antiretroviral therapy (ART) programs, medications continued to be unavailable or not-yet-indicated for 72% of the world's HIV-infected persons in 2007 [1]. ART requires a life-long, daily regimen supported by laboratory tests to monitor the efficacy and toxicity of treatment. Furthermore, persons without opportunistic infections and with $CD4^+$ T-

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Author Contributions

Conceived and designed the study: KM, SHV. Analyzed the data: KM, EC, SHV. Wrote the paper: KM, EC, SHV.

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lymphocyte counts greater than 200–350 cells/μL may not be advised to take ART. Thus, there remains a compelling imperative to identify cheap, implementable, and sustainable approaches to prevent HIV transmission and improve the prognosis of HIV-infected individuals on a large scale when ART is either unavailable or not yet indicated.

Prior to the era of ART, considerable attention was given to HIV co-infections and their impact on host immunity [2]. It was reasoned that down-modulation of the non-specific immune response that many chronic infections elicit might be exploited for therapeutic benefits [3–5]. Subsequent human studies demonstrated that the theoretical gains of clearing co-infections translated into small but consistent viral load reductions. In fact, a growing body of literature reports that elimination or suppression of concurrent infection with pathogens as diverse as herpes viruses, geohelminths, mycobacteria, and *Plasmodia spp.* drop HIV RNA levels by a logarithmic factor of 0.3 to 1.0 [6–15]. Greater focus on co-infections among persons not yet on ART is warranted for at least three reasons: (1) there is a high burden of co-infections in HIV endemic zones; (2) there is evidence that many co-infections non-specifically activate host immunity; and (3) some organisms, notably herpes simplex virus type 2, can specifically facilitate HIV replication.

Despite mounting evidence for its salience to HIV outcomes, this literature has marshaled scant attention in the face of highly potent ART that typically drops HIV RNA copy levels by a logarithmic factor of at least 2 to 5. A large proportion of the world's HIV-infected population, however, is still not being treated either because of logistic impediments and lack of antiretroviral medications or because of a relatively early stage of illness for many infected persons [16]. If small reductions in HIV RNA resulting from relatively simple interventions, such as clearing co-infections, were to translate into large benefits in transmission and survival, then a low-cost, sustainable, therapeutic approach toward assisting HIV-infected persons in resource-limited settings could be implemented to complement ART.

But given the relatively large impact of ART, is there a clinical and public health rationale for interventions that achieve only small reductions in HIV RNA? Would a 0.3 or 0.5 $\log_{10}$ viral load decline be too trivial to be of tangible importance to HIV-infected patients? Will small reductions in viral load be likely to reduce transmission of HIV or slow its progression in any meaningful way? This systematic review seeks to address these questions.

## Methods

We conducted a search of Medline and PubMed databases for studies published from January 1, 1987 to July 1, 2008 that evaluated the association between changes in plasma HIV-1 RNA levels and either risk of HIV transmission by heterosexual contact or the risk of progression to an AIDS-defining event or AIDS related death. In our search we employed permutations of key terms: "HIV-1", "HIV RNA", "viral load", "risk", "heterosexual transmission", and "disease progression". We excluded articles prior to 1987 since reliable and reproducible HIV RNA assays were not yet available. Additional references were identified from bibliographies of published manuscripts. Studies were included in our analysis if they reported incremental risk of HIV-1 heterosexual transmission or disease progression in association with differences in baseline plasma levels of HIV-1 RNA among adult, highly active antiretroviral therapy (HAART)-naïve populations.

We reviewed titles and abstracts of 435 articles and identified 22 articles for full review. Nine studies reported risk estimates of HIV heterosexual transmission or disease progression per-$\log_{10}$ change in viral load. When we relaxed our inclusion criteria to include pediatric and HAART-experienced populations, we found 32 articles were eligible for full review, 17 of which reported per $\log_{10}$ transmission or progression risk estimates. We conducted a sensitivity

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analysis to compare the aggregate estimates of studies identified by the two sets of inclusion criteria. Because the difference in risk estimates was negligible, we report the results of the former review of nine studies, as the implications for small reductions in viral load are most applicable to ART-naïve, adult populations who still constitute the overwhelming majority of persons living with HIV.

We calculated risk estimates of transmission and disease progression for 0.3, 0.5, and 1.0 $\log_{10}$ viral load increments. Four key considerations dictated our choice of these threshold values. First, the positive human studies-to-date on the impact of co-infections on HIV viral load generally report a 0.3 to 1.0 $\log_{10}$ change in plasma HIV RNA levels with either acquisition or clearance of most co-infections [6–15]. Second, the consensus estimate of background fluctuations in viral load biologic and assay variability generally hovers around 0.25 $\log_{10}$ [17–19]. Third, the significant impact of a viral load decrement greater than 1.0 $\log_{10}$ has already been demonstrated numerous times since the advent of antiretroviral monotherapy in the 1980s. Finally, we deemed a 0.5 $\log_{10}$ change in viral load as an appropriate intermediate in our range of values because it exceeds the threshold of biologic assay variability but does not approach the magnitude of impact observed with ART.

We assumed linearity of risk based upon the work of Mellors et al. and Wawer et al. [20–22]. Pooled estimates, weighted by number of transmission or progression events, and corresponding standard deviations were calculated for the three logarithmic values. Data regarding number of events, median baseline $CD4^+$ cell count, HIV RNA quantification assay type, and outcome of interest are presented with relative risk estimates as relevant for each study population. We employed a linear model to assess the contribution of publication bias and found no significant impact on the data for this review (data not shown).

## Results

Nine articles published between January 1987 and May 2008 reported incremental risk estimates per logarithmic unit change (base 10) in plasma levels of HIV-1 RNA among ART-naïve adults. Four assessed the risk of heterosexual transmission as a function of logarithmically transformed increments in plasma viral load. Five reported associations between baseline increments in HIV RNA and risk of progression to an AIDS-defining event or AIDS related death.

### Risk of heterosexual transmission

Several studies from countries with diverse HIV epidemic patterns have suggested that each 1.0 $\log_{10}$ increment in viral load corresponds to a near two-fold or greater risk of viral transmission through heterosexual contact (Table 1). Quinn et al. reported a 2.5 fold greater risk of heterosexual transmission per 1.0 $\log_{10}$ increment in viral load among 415 serodiscordant couples living in the rural Rakai district of Uganda [23]. Over the course of 4 years of follow-up (1994–1998) the Ugandan team identified 90 transmission events. Because tests for seroconversion were performed at 10 month intervals, transmission events were assumed to have occurred at interval midpoints. Investigators used transmitters' HIV RNA measurements five months prior to the presumed date of transmission based on the assumption that HIV RNA levels in asymptomatic HAART-naïve African adults vary little over the course of a half-year, an assumption which has subsequently been shown to be robust [17–19]. No DNA sequencing was reported, such that some transmission events may have been falsely attributed to persons who did not actually transmit the virus to his or her sexual partner.

In 2001, Fideli et al. reported a 2.5-fold increased risk of heterosexual transmission (female-to-male) per 1.0 $\log_{10}$ increment in viral load from a nested case-control study of 1022 discordant couples living in Lusaka, Zambia [24]. During a follow-up period that was nearly

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contemporaneous with that of the Ugandan study, the Zambian team identified 109 transmission events. Viral sequencing was performed, enabling precise epidemiologic linkage of those persons transmitting and acquiring a given HIV strain and, thus, refining transmission estimates. Time of transmission and transmitters' corresponding levels of HIV RNA were estimated by methods similar to those of Quinn et al., except that participants in the Zambian study were evaluated every three months, instead of every ten months, making the extrapolated time of infection more feasible in a narrower time window. Moreover, Fideli et al. reported a slightly lower per $\log_{10}$ increment risk of male-to-female transmission [odds ratio (OR) 1.8, 95% confidence interval (CI) 1.2 – 2.8] compared to female-to-male transmission (OR 2.5, 95% CI 1.5 –4.0), a sex-specific finding that was not noted in the Rakai study, though the Quinn and Fideli studies had identical 2.5-fold increased transmission risk estimates per 1.0 $\log_{10}$ increased viral load. An assertion of gender difference in transmission risk, however, might be viewed with caution as the 95% CI for the two estimates overlapped considerably.

In a nested case-control study of hepatitis C virus (HCV) and HIV co-infected adults in Western Europe and the United States, Hisada et al. found a significantly increased odds of heterosexual transmission of HIV per $\log_{10}$ increment viral load, though of a lower magnitude (OR 1.31, 95% CI 0.94–1.84) than the two African studies [25]. Although 299 serodiscordant couples were included in the analysis, the risk of seroconversion was based on only 9 transmission events. Tovanabutra et al., in a cross-sectional study of 493 discordant couples in Thailand, calculated that the likelihood of an HIV seropositive male's heterosexual partner being infected with HIV per 1.0 $\log_{10}$ increase in plasma HIV RNA levels was intermediate (OR 1.81, 95% CI 1.33–2.48) to those calculated from the African and Western cohorts [26]. This last study differs from the other three in that it did not measure incident infections or control for other possible sources of transmission such as blood transfusion, injection drug use, and sexual intercourse with other partners. Although the study populations varied by host immunity and prevalence of concomitant infection, the transmitters' (4.4 – 5.1 $\log_{10}$) and non-transmitters' (4.0 – 4.8 $\log_{10}$) median HIV RNA levels were reasonably consistent, indicating that participants across studies were likely to be at a similar viral set-point in their latent infections. The mean differential of 0.3–0.4 $\log_{10}$ between transmitters and non-transmitters is notable.

The observations from geographically distinct studies that plasma HIV RNA increments of 1.0 $\log_{10}$ translate to a significant increase in HIV transmission risk by heterosexual contact are in accordance with a number of other studies that did not evaluate the correlation on a log-linear scale. For example, two studies of heterosexual males independently found a 1.0 $\log_{10}$ difference between persons who transmitted infection to their female partners and those who did not [27,28]. In addition, a study from Rakai, Uganda that calculated rates of HIV transmission per coital act from the data of Quinn et al. [20] found that a 0.7 $\log_{10}$ viral load increment corresponded to a two-fold increased risk of heterosexual transmission at intermediate levels of HIV RNA (3.50 – 4.88 $\log_{10}$) [29]. An earlier study from a similar but smaller population found only an 11% rise in the risk of transmission with an average 0.74 $\log_{10}$ increment in viral load [30].

Other prospective studies have found that median HIV RNA levels differed between transmitters and non-transmitters by a range of 0.6 to 1.0 $\log_{10}$ [31–34]. These studies were of relatively small size, investigating no more than a few dozen HIV-infected persons in each case. In aggregate, however, they suggest that the risk of heterosexual transmission of HIV may be influenced, among other factors, by relatively small differences in plasma viral load.

## Risk of progression to AIDS or death

Among studies that reported the time to AIDS or death per $\log_{10}$ increment of viral load in HAART-naïve adults (table 2) [35–39], a 0.3 or 0.5 $\log_{10}$ increment corresponded to relative

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risk estimates of at least 1.14 and 1.24, respectively. The excess annual risk of progression to AIDS or death associated with a 0.3 $\log_{10}$ increment in HIV RNA ranged between 14% and 36%, although all [35,36,38,39] but one study [37] indicated an excess risk of at least 25%. Four of the five studies reported >40% excess annual risk in disease progression with just a 0.5 $\log_{10}$ increase from baseline HIV RNA [35–36,38–39]. Four of five studies reported an excess annual risk of disease progression that was statistically significant at all $\log_{10}$ increments in viral load [35,36,38,39].

Kaplan-Meier plots from the Multicenter AIDS Cohort Study and a French blood donor cohort show that a 0.5 $\log_{10}$ decrement in HIV RNA corresponds to an additional 2 years of AIDS-free survival [17,18,40,41]. The magnitude of these estimates, however, vary according to sex, age, $CD4^+$ T lymphocyte count, time since seroconversion, and other covariates. Arduino et al., for example, found that the excess risk of progressing to an AIDS-defining event or death per $\log_{10}$ increment of plasma RNA was almost 9 times lower (9% vs. 80%) for those who had a $CD4^+$ T lymphocyte count ≥100 cells/μL compared to those with a $CD4^+$ T lymphocyte count <100 cells/μL, although this outcome was determined among adults on ART [42]. Among antiretroviral naïve persons in one study, however, only a 0.5 $\log_{10}$ difference in median HIV RNA separated rapid from non-rapid progressors, as defined by progression to an AIDS-defining event or death within 18 months of infection [43]. An even stronger association of three- to four-fold increased risk per $\log_{10}$ increment viral load was observed when opportunistic infections as a whole (not just AIDS-defining) were the primary endpoint of interest [43,44].

### Aggregate risk of heterosexual transmission and progression to AIDS

We calculated that the likelihood of transmitting HIV by heterosexual contact increased, on average, by 20% with every 0.3 $\log_{10}$ increment [20,24–26] and that a 0.3 $\log_{10}$ increment in HIV RNA corresponded to a mean increased risk of progression to an AIDS-defining illness or related death of 25% [36–40]. A 0.5 $\log_{10}$ increment in HIV RNA was associated with 40% greater risk of heterosexual transmission of HIV and 44% increased risk of progression to AIDS or death. For every 1.0 $\log_{10}$ increase in viral load, the relative risk of HIV heterosexual transmission was 2.0 and progression to an AIDS-defining event was 2.13.

## Discussion

In our review, we found evidence that increments in plasma concentrations of HIV RNA as small as 0.3 to 0.5 $\log_{10}$ are directly proportional to the risk of viral transmission by heterosexual contact and to time to an AIDS-defining event or death. Despite indications for a significant impact of small reductions in viral load on HIV heterosexual transmission and disease progression, our review is limited by a number of factors. These estimates were abstracted from studies that vary according to sample size, study population demographics, viral load assay type, and study design. These differences may bias summary estimates, but they do not affect, we believe, the individual estimates from each study included in our review. Although the magnitude of association between viral load and the risk of transmission or disease progression varied between studies, they were all positive associations, of which most (seven of nine) met statistical significance at an alpha level of 0.05. While we cannot rule out negative publication bias, we think large transmission studies with couples are rare and costly; any results would, therefore, be published. Time to illness studies are more common and if negative publication bias exists, it might be in that venue.

Small reductions in viral load may have practical applications, even in an ART era. Treatment of co-infections prevalent among HIV-infected persons in the developing world, for example, may result in small, sustained drops in plasma levels of HIV RNA. Based upon the principle that efficient HIV replication requires activation of the immune system's cellular compartment

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[45–48], a number of infections endemic to the developing world (i.e. tuberculosis, herpesviruses, malaria, leishmania, helminthes) have been studied and found to upregulate HIV transcription [49,50]. Data are still equivocal, however, with regard to the clinical significance of co-infection clearance on the epidemiology of HIV transmission and progression [51–57]. Ultimately, it may be that the benefits of aggressively and systematically treating co-infections on HIV control may be greatest in concert with other preventive and therapeutic efforts. In fact, multifaceted basic HIV care packages that include opportunistic infection prevention, co-infection clearance, and nutritional support may soon become the idealized standard of care for all HIV-infected persons in the developing world [58–60]. Mathematical models have consistently shown that this combination of targeted interventions can significantly alter or even disrupt established patterns of HIV transmission [61,62], though the magnitude of an expected impact may depend on the maturity of the epidemic, sexual mixing patterns and prevalence of sexually transmittable co-infections. It is probable then, that even partially efficacious HIV vaccines that nonetheless reduce viral setpoint of an infected individual may be able to prevent a large number of new infections through this “small viral load reduction” strategy, if enough persons were vaccinated and the viral load reduction were sustainable [63–65].

Although ART is being introduced in resource-limited settings, basic medical services remain a challenge and preventable, endemic illnesses constitute substantial morbidity among HIV-infected individuals. Small declines in viral load, when introduced on a mass scale, can reduce the likelihood of transmission and slow disease progression. In global efforts to provide ART, good primary care and systematic control of opportunistic and other co-infections should not be neglected for any HIV-infected person as their treatment may provide a hitherto unanticipated HIV-associated boon.

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**Table 1**

Relative risk of heterosexual transmission of HIV between serodiscordant couples per 0.3, 0.5, and 1.0 $\log_{10}$ increment of plasma HIV RNA concentration.

| Reference | No. of discordant couples | No. of events | Viral assay | Risk ratio per $\log_{10}$ Δ HIV RNA | | |
|---|---|---|---|---|---|---|
| | | | | 0.3 | 0.5 | 1.0 |
| Quinn et al. [23][a] | 415 | 90 | RT-PCR | 1.31 (1.20, 1.42) | 1.56 (1.36, 1.80) | 2.45 (1.85, 3.26) |
| Fideli et al. [24][b] | 1022 | | | | | |
| Female-to-Male | | 43 | RT-PCR | 1.3 (1.1, 1.5) | 1.6 (1.2, 2.0) | 2.5 (1.5, 4.0) |
| Male-to-Female | | 66 | RT-PCR | 1.2 (1.0, 1.4) | 1.3 (1.1, 1.7) | 1.8 (1.2, 2.8) |
| Hisada et al. [25][a] | 299 | 9 | bDNA | 1.14 (0.97, 1.36) | 1.19 (0.98, 1.20) | 1.31 (0.94, 1.84) |
| Tovanabutra et al. [26][c] | 493 | 218 | RT-PCR | 1.19 (1.09, 1.31) | 1.34 (1.15, 1.57) | 1.81 (1.33, 2.48) |
| **Weighted mean** | | | | **1.2 (1.1, 1.4)** | **1.4 (1.2, 1.7)** | **2.0 (1.4, 2.8)** |

bDNA, branched DNA signal-amplification assay (Chiron, Emeryville, CA, U.S.A.); RT-PCR, reverse transcriptase – polymerase chain reaction (Amplicor HIV monitor test, Roche Diagnostic Systems, Inc., Branchburg, NJ, U.S.A.).

[a] History of heterosexual couple contacts based on self-report.

[b] Viruses sequenced to exclude non-transmitting couples from analysis.

[c] Cross-sectional study that did not measure incident infections nor exclude individuals with other HIV infection risk factors for transmission.

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**Table 2**

Relative risk of progression to an AIDS-defining event or AIDS related death per 0.3, 0.5, and 1.0 $\log_{10}$ increment of plasma HIV RNA concentration.

| Reference | No. of Events | $CD4^+$ cells/μl[a] | Primary Outcome | Viral assay | Risk ratio per $\log_{10}$ Δ HIV RNA | | |
|---|---|---|---|---|---|---|---|
| | | | | | 0.3 | 0.5 | 1.0 |
| Welles et al. [35] | 187 | 139 | AIDS, Death | bDNA | 1.36 (1.12, 1.66) | 1.67 (1.20, 2.32) | 2.79 (1.44, 5.38) |
| Coombs et al. [36] | 97 | 85 | AIDS, Death | bDNA | 1.26 (1.03, 1.54) | 1.47 (1.05, 2.05) | 2.26 (1.10, 5.13) |
| Sterling et al. [37] | 202 | 659 | AIDS, Death | RT-PCR | 1.14 (0.98, 1.32) | 1.24 (0.97, 1.59) | 1.55 (0.95, 2.52) |
| Phillips et al. [38] | 219 | NP | AIDS | Combination[b] | 1.24 (1.17, 1.31) | 1.42 (1.30, 1.57) | 2.03 (1.68, 2.46) |
| Lavreys et al. [39] | 40 | 498 | Death | Gen-Probe | 1.28 (1.10, 1.47) | 1.51 (1.17, 1.89) | 2.28 (1.36, 3.59) |
| **Weighted mean** | | | | | **1.25 (1.08, 1.44)** | **1.44 (1.14, 1.84)** | **2.13 (1.33, 3.62)** |

bDNA, branched DNA signal-amplification assay (Chiron, Emeryville, CA, USA.); RT-PCR, reverse transcriptase – polymerase chain reaction (Amplicor HIV monitor test, Roche Diagnostic Systems, Inc., Branchburg, NJ, USA.); NASBA, nucleic acid sequence based amplification technique (Organon Teknika, Boxtel, Holland); Gen-Probe (Gen-Probe HIV-1 viral load assay; Gen-Probe, Inc., San Diego, CA, USA); NP, not provided.

[a] Values reflect median $CD4^+$ T lymphocyte count/μl among infected persons at baseline.

[b] 55% of viral loads was measured by RT-PCR, 17.9% by an unknown method, 14.6% by NASBA, 7.8% by bDNA, and 4.8% by another method.