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Cofactor Infections and HIV Epidemics in Developing Countries: Implications for Treatment

By

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Abstract

This article shows that the burden of certain tropical disease infections, after controlling for other factors, is positively correlated with HIV prevalence. Using cross-national data and multivariate linear regression analysis, we investigate the determinants of HIV prevalence in low- and middle-income countries. We begin with social and economic variables used in other cross-national studies and then incorporate data on parasitic and infectious diseases endemic in poor populations, which are found to be strongly and significantly correlated with—and are potent predictors of—HIV prevalence. The paper concludes by arguing that treating tropical diseases may be a cost-effective add-on to HIV prevention and treatment programs, thus slowing the spread of HIV in disease-burdened populations.

Introduction

To devise effective prevention policies and treatment protocols, we need to understand why some people exposed to a pathogen become infected and others do not, why prevalence varies between populations, and why epidemics spread. HIV prevalence in some African countries is up to 100 times the rates in North America and Europe. Those differences are not adequately explained by the paradigm underlying AIDS policy, which implicitly or explicitly attributes most of the differences in HIV rates to differences in sexual behavior, and thus prescribes mostly behavioral interventions (abstinence, fidelity, or condoms) for HIV prevention.

Vulnerability and contagiousness: key factors in disease dynamics

Between otherwise healthy adults in developed countries, HIV has very low rates of heterosexual transmission (World Bank, 1997). In the developing world, however, the majority of the population is not "otherwise healthy." Poor nutrition and the burden of other infectious and parasitic diseases suppress immune response in HIV-negative sexual partners and infants and increase viral load and viral shedding in HIV-infected partners and mothers (Semba et al, 1994; Landers, 1996; John et al., 1997; Fawzi and Hunter, 1998; Friis and Michaelsen, 1998; Woodward, 1998; Montresor et al., 2001; Nacher, 2002; PPC, 2002; Wolday et al., 2002; Borkow and Bentwich, 2006). Moreover, mounting evidence demonstrates the specific mechanisms whereby biological cofactors increase vulnerability to HIV infection and increase contagiousness of infected persons, and thus increase the probability of transmission. Sexually transmitted infections (STIs), both ulcerative and non-ulcerative, increase the likelihood of HIV transmission and are therefore considered HIV cofactors (Fleming and Wasserheit, 1999;

Grosskurth et al., 1995; Boutlon and Gray-Owen, 2002; Corbett et al., 2002). They produce inflammation and, in some cases, lesions in the genital tract that facilitate passage of HIV.

Certain parasites, common in tropical regions, also produce inflammation and lesions in the genital tract. Lymphatic filariasis has been shown to suppress immune response in HIV-negative persons and increase viral load in HIV-infected persons, affecting individual transmission and population dynamics (Gopinath et al., 2000). Moreover, lymphatic filariasis (LF) affects the lymphatic immune system and also can result in infection of and damage to the genital organs. Urinary schistosomiasis (*S. hematobium*), which afflicts over 200 million people in sub-Saharan Africa (and almost nowhere else), acts as a co-factor of HIV transmission much in the same way as do STIs. Worms and ova of *S. hematobium* infect the reproductive tract of both men and women. They create lesions—open portals for HIV—and inflammation of the genital area (Attili et al., 1983; Feldmeier et al., 1995; Marble and Key, 1995; Leutscher et al., 1998). A recent trial in Zimbabwe found that genital lesions of schistosomiasis increased HIV risk in women three-fold (Kjetland et al., 2006). The WHO Ad Hoc Strategic and Advisory Group on Neglected Tropical Diseases recently identified the interaction of endemic parasitic and infectious diseases with HIV as a priority for research.

Malaria, which is widespread in tropical areas, especially in sub-Saharan Africa, interacts with HIV, increasing viral load up to ten-fold. Viral load remains elevated as much as ten-fold in HIV-infected persons for six weeks after malarial episodes (Hoffman et al., 1999; Kublin et al., 2005; Abu-Raddad et al., 2006). That not only increases individual contagiousness of HIV-infected persons, it also affects the dynamics of the epidemic at a population level (Bloland et al., 1995; Xiao et al., 1998; Hoffman et al., 1999; Whitworth et al., 2000; Corbett et al., 2002; Abu-Raddad et al., 2006; for additional discussion and sources, see Stillwaggon, 2006). Individuals in malaria-endemic areas have a higher probability of sexual contact with persons who have high viral load due to coinfection with malaria, and who are therefore more contagious. The importance of newly infected persons as HIV transmitters because of their elevated viral loads is receiving warranted attention (Quinn et al., 2000; Pilcher et al., 2004; Cohen et al., 2005; Brenner et al., 2007). Other causes of elevated viral load, including malaria, also merit inclusion in models of HIV dynamics.

While all infectious and parasitic diseases have a probable impact on resistance to infection due to immune dysregulation, those diseases that have a substantial impact on viral load (malaria) and those that affect the genital organs (STIs, LF, and schistosomiasis) merit special attention as potential cofactors of HIV transmission, both sexually and vertically.

Methods

This paper presents cross-national multivariate regressions that include disease cofactors in a model of HIV epidemics in developing countries. This research extends the work of several authors who have used cross-national data to analyze factors thought to drive the epidemic (Over, 1998; Stillwaggon, 2000, 2002; Bonnel, 2000; Tsafack, 2006; Tsafack and Bassolé, 2006; Deuchert and Brody, 2007). Each of those studies addressed a different issue: risky sexual behaviors, gender discrimination, inequality, economic growth, iatrogenesis, and (by one of the authors of the current work) nutrition as a disease cofactor. All of the papers begin with the same or similar control variables and then add variables relevant to the specific issue addressed in the

study. Three control variables are used in all of those studies: income inequality, per capita income (level or growth rate), and urbanization (level or growth rate). Most of the studies also include proportion of the population that is Muslim, age of the epidemic, literacy or school enrollment rates, and region.

The present research uses this same approach, first regressing the log of HIV prevalence on a group of control variables found to be statistically important by the current and previous research—which we call the basic model—and then adding to the analysis measures of cofactor infections and an indicator of risky sexual behavior. The null hypothesis is that the burden of cofactor infections has no influence on national HIV prevalence.

Results

The Basic Model: Using data for 80 developing and transition countries,[1] multivariate linear regressions were used to predict the log of adult HIV prevalence in 2006.[2] Regressors in the basic model include the Gini coefficient (the most widely used measure of inequality), log of per capita income on a purchasing power parity basis, percent of adults who are literate,[3] percent of the population living in urban areas, age of the epidemic in years, percent of the population who are Muslim, percent who report using contraceptives, and a binary variable taking the value of 1 if the country is in southern Africa (South Africa, Lesotho, Swaziland, Botswana, Namibia, Zimbabwe, and Mozambique).

The results for the basic model are presented in Table 1. Together, these variables are associated with 73 percent of the variance in the log of HIV prevalence. The Gini coefficient, the age of the epidemic, and location in southern Africa,[4] as expected, have positive coefficients, and percent Muslim, contraceptive use, and per capita income have negative coefficients. All are statistically significant at the 99 percent level. Adult literacy and urbanization are not significant predictors of HIV prevalence in the regression

Adding Cofactor Infections: To the basic model we add diseases suspected of increasing the risk of HIV infection due to increased viral load or genital inflammation and/or lesions. They are schistosomiasis, lymphatic filariasis, gonorrhea, chlamydia (measured by disability-adjusted life years or DALYs) and malaria (measured by prevalence).[5] When added one at a time, each of the five cofactor infection variables is statistically significant at the 99.9 percent level.[6] These statistics, however, do not indicate the true importance of each disease because none of the five regressions accounts for the other four cofactor infections. On the other hand, if all of the five cofactor infection variables are put into a regression at the same time, only two remain statistically significant at the 95 percent level. Those are the classic indicators of multicollinearity.

To present a picture of the statistical importance of the cofactor infections taken together rather than individually, two steps are taken. First, similar diseases are grouped into summary variables. We sum DALYs for gonorrhea and chlamydia to form a new variable, called sexually transmitted infections (STIs). Similarly, the sum of DALYs for schistosomiasis and lymphatic filariasis constitutes the variable, worms. This helps but does not eliminate the problem of multicollinearity. For example, the simple correlation between the two composite variables (worms and STIs) is 0.889. Thus, we also address multicollinearity among the five cofactor infections by measuring their joint statistical significance using the F-test.

Table 2 presents the regression with the basic model plus all of the diseases entered together (some grouped). Adding the cofactors in this way raises the R-squared statistic from .73 to .81. The worm composite variable and malaria prevalence are significant at the 99 percent and the 96 percent confidence levels, respectively, despite their high collinearity. All of the diseases taken together are very highly significant (at the 99.99 percent level) with an F statistic of 13.61. Thus we can decisively reject the hypothesis that these cofactors, whether considered individually or jointly, are unrelated to HIV prevalence.

Taken at face value, the coefficients produced by this regression suggest that the cofactor infections have an important impact on HIV prevalence. There are a number of reasons why the regression coefficients might be upwardly biased[7], but it is nonetheless instructive to illustrate the importance of the disease cofactors in concrete terms. According to the regression, all else being equal, the difference in HIV prevalence between a country without any schistosomiasis or lymphatic filariasis and one that has the average burden of the two diseases (194 DALYs per 100,000 people in our sample), is about 40 percent (for example, 6.1 percent prevalence instead of 10 percent.) The same calculation for the STIs variable produces a predicted difference of about 48 percent in HIV prevalence.

Adding a measure of risky sexual behavior: In many developing countries, sexual activity is the likely mode of most HIV transmission. Consequently, as important as coinfections are, it is appropriate to include some measure of risky sexual behavior in the model to avoid specification error (missing variable bias). There are direct measures of risky sexual behavior for only a limited number of countries. Information on median age of first sexual activity for females is the most widely available measure of risky sexual behavior, and even that is available for only 45 of the developing countries in our data set. Those 45 countries include only half of sub-Saharan African countries and fewer than a third of other developing countries, leaving both groups (but especially non-African countries) woefully underrepresented.[8]

Table 3 presents statistics from three regressions using the reduced data set of 45 countries for which data have been collected on median age at first sex for females. The regression on the log of HIV prevalence using the variables in the basic model is shown in the first column of Table 3. The second column shows the results after adding median age at first sex for females to the basic model, which raises the R-squared from .77 to .84. Age at first sex for females is significant at the 99 percent confidence level and has the expected sign (younger sexual initiation is associated with higher HIV prevalence). The third column shows the results after adding the cofactor infections, which raises the R-squared even further to .89. The smaller sample size and high collinearity among the cofactor infection variables do not allow us to detect statistically significant effects for the cofactor infections individually, but as a group, they are significantly correlated with HIV prevalence at the 99 percent confidence level with an F statistic of 4.44.

Further Research: A fully specified model would include other factors that are also important in the spread of HIV and that are not adequately addressed in this analysis. Gender inequality and gendered roles have an important impact on many aspects of health, including nutrition, access to medical care, household tasks that expose women and children to different environmental risks from those faced by men, differential access to schooling, and constraints on women's and girls'

choices of safe behaviors. Unfortunately, data to represent satisfactorily the differential risks of women and girls are not readily available.

Another very important factor in the HIV epidemics in the developing world is the risk of infection from unsafe medical, quasi-medical, and cosmetic procedures. Incorporating data on medical transmission into the model in this paper would likely further improve its predictive power in analyzing the determinants of HIV spread (Drucker et al., 2001; Potterat et al., 2002; Gisselquist et al., 2003; Brewer et al. 2003; Brody, 2004; Deuchert and Brody 2006, 2007).

It is important to emphasize that a cross-national statistical analysis of the sort presented here is only suggestive. In particular, statistical associations are just that; they do not demonstrate causality. Medical researchers have greater confidence in the results of clinical trials because they suggest causality at the individual, rather than population, level. (Clinical trials, however, are rarely designed to test for the complex interactions of multiple factors. They specifically abstract from endemic conditions that may play an important role in explaining the differential risks between populations.) So far, only a few clinical studies (cited above) have attempted to demonstrate the effect of cofactor infections on HIV incidence. The present analysis helps to build the case for more clinical trials that address coinfections of HIV and endemic parasitic and infectious diseases.

Discussion

AIDS prevention policy fails to recognize the risky environment in which sexual and vertical transmission of HIV occur in developing countries. Endemic parasitic and infectious diseases are not just background noise. They increase the likelihood of HIV infection and alter the dynamics of epidemic spread. The standard prevention policies—ABC, now augmented by male circumcision and sometimes by STI treatment—are not enough to stem the epidemic in risky environments, as is clear from the meager results of AIDS policy so far. Experimentation with deworming and other interventions for endemic diseases is a pragmatic and ethically sound strategy. Such interventions have substantial beneficial outcomes on their own, in better health, better school performance, and higher productivity. And they allow for structured learning about disease interactions at very low cost, and using medicines that are safe and effective. Moreover, the improvement in overall wellbeing in itself promotes healthier behaviors in healthier people.

AIDS policy is paralyzed by its crisis mode. Policy makers need to step out and try something in addition to the behavioral interventions (“ABC”). That means some HIV prevention funds should be spent on deworming, sanitation, and safe water, and antiretroviral treatment protocols should include deworming and nutrition, just as they already include treatment for tuberculosis. Of the numerous economic, biological, and social determinants of HIV epidemics, treating cofactors infections may be the most policy-sensitive and least expensive interventions and have the most immediate return on investment.

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Tables

Table 1. **HIV Prevalence and the Basic Model**
Number of observations = 80
Dependent Variable = log of HIV prevalence
R-squared = 0.73

Regressor	*Regression Coefficient*	t *statistic*	*Probability*
Gini coefficient	0.0409	3.09	0.003
log per capita income	-0.6363	-2.68	0.009
adult literacy percent	0.0072	0.90	0.370
urban percent	0.0020	0.22	0.824
age of the epidemic	0.1114	2.98	0.004
Muslim percent	-0.0105	-3.44	0.001
contraceptive use percent	-0.0273	-3.86	0.000
southern Africa	2.3357	6.40	0.000
constant	1.7669	1.15	0.253

Table 2. **HIV Prevalence with the Basic Model and All Cofactor Infections**
Number of observations = 80
Dependent Variable = log of HIV prevalence
R-squared = 0.81

Regressor	*Regression Coefficient*	t *statistic*	*probability*
Gini coefficient	0.0405	3.36	0.001
log per capita income	-0.1408	-0.59	0.560
adult literacy percent	0.0196	3.50	0.001
urban percent	0.0008	0.11	0.912
age of the epidemic	0.0487	1.29	0.201
Muslim percent	-0.0114	-4.55	0.000
contraceptive use percent	-0.0116	-1.58	0.119
southern Africa	1.4660	4.13	0.000
STIs	0.0041	1.61	0.113
Worms	0.0025	2.60	0.012
malaria prevalence	0.00001	2.12	0.038
constant	-3.7904	-2.07	0.042

Table 3. **HIV Prevalence with the Basic Model, Median Age at First Sex for Females, and Cofactor Infections in the Reduced Sample**
Dependent Variable = log of HIV prevalence
The *t* statistic is in parentheses and the probability is in brackets.

Regressors	*Basic Model Only*	*Basic Model and age at first sex, female*	*Basic Model and age at first sex, female, and all cofactor infections*
Gini coefficient	0.0390	0.0092	0.0134
	(2.31) [0.027]	(0.53) [0.597]	(0.85) [0.402]
log of per capita income	-0.5151	-0.0929	0.2333
	(-1.75) [0.088]	(-0.35) [0.732]	(0.68) [0.499]
adult literacy percent	0.0187	0.0307	0.0338
	(1.82) [0.077]	(2.88) [0.007]	(3.92) [0.000]
urban percent	-0.0186	-0.0321	-0.0253
	(-1.67) [0.103]	(-2.60) [0.013]	(-2.51) [0.017]
age of epidemic	0.1475	0.1316	0.0696
	(2.77) [0.009]	(3.37) [0.002]	(1.60) [0.119]
Muslim percent	-0.0105	-0.0118	-0.0139
	(-2.49) [0.018]	(-2.61) [0.013]	(-3.82) [0.001]
contraceptive use pct.	-0.0325	-0.0278	-0.0106
	(-2.95) [0.006]	(-3.02) [0.005]	(-1.03) [0.312]
southern Africa	2.1279	1.4684	0.7596
	(5.18) [0.000]	(4.07) [0.000]	(2.44) [0.020]
age at first sex, female		-0.4096	-0.3429
		(-3.61) [0.001]	(-2.92) [0.006]
STIs			0.0043
			(1.23) [0.226]
worms			0.0019
			(1.42) [0.166]
malaria prevalence			0.00001
			(1.32) [0.198]
constant	-0.0325	6.4016	1.0108
	(-2.95) [0.006]	(2.37) [0.023]	(0.30) [0.767]
Observations	45	45	45
R-squared	0.77	0.84	0.89

[1] The data were drawn from UNAIDS, 2006 and 2007 (Adult HIV prevalence in 2006); World Development Indicators (Gini coefficient, per capita GDP-PPP, urbanization); UNDP, 2005 (adult literacy rate, contraceptive use, malaria prevalence); US Department of State, 2004 (percent Muslim); USAID (median age at first sex, female); World Bank, 1997, 318–324 (age of the epidemic); and WHO, 2004 (disability-adjusted life years per 100,000 population, or DALYs, for each condition). Countries with per capita income in 2003 of less than U$S12,000 on a purchasing power parity basis were included in the analysis. Rather than imputing missing values, countries with missing data were dropped from the analysis, leaving a data set of 80 countries. The present study follows established practice by using the log form of HIV prevalence and per capita income, which reduces the influence of outliers and generally leads to more robust and efficient estimates when analyzing highly skewed variables such as these.

[2] It would have been preferable to use HIV incidence to describe how the epidemic is unfolding. Prevalence includes historical information and is confounded by greater survival in countries with effective antiretroviral delivery programs. But incidence data are generally not available.

[3] All measures of literacy and school enrollment in our sample are highly correlated and perform similarly as regressors. In our sample, the adult literacy rate and the female-to-male literacy ratio are virtually identical in a statistical sense (with a simple correlation of 0.93). Using the latter variable, however, gives the misleading impression that the variable measures gender discrimination; hence the present study uses the more straightforward variable, the adult literacy rate.

[4] In a forthcoming article, the authors demonstrate that much of the elevated prevalence of HIV in southern Africa can be explained by the higher prevalence of endemic diseases in that region

[5] Because the vast majority of deaths from malaria are in infants, the DALYs associated with malaria are extremely high. That measure, however, does not reflect the burden of malaria among sexually active adults, unlike the DALYs from other diseases. We have therefore chosen to use malaria prevalence.

[6] To check against the possibility of spurious correlation (that diseases in general or tropical diseases specifically are correlated with HIV prevalence rather than the ones for which there is evidence of an association), we added about 30 other diseases one at a time to the basic model. The only ones significantly (at the 95 percent or better level) and positively correlated with HIV prevalence were opportunistic infections (such as tuberculosis), which could not be included in the regressions due to endogeneity, and trachoma. (Other than immune dysregulation, we are not aware of any reason why trachoma might lead to HIV infection, but its statistical association of HIV suggests that further research may be fruitful.)

[7] Two important reasons why these coefficients might overstate the importance of cofactor infections are endogeneity (reverse causality) and specification errors (especially missing variables positively correlated with the cofactor disease variables).

[8] The sexual behavior surveys reflect a bias in data collection common in AIDS policy documents. The assumption that the AIDS epidemics in sub-Saharan Africa result from something distinctive about African sexuality influences the decision to expend greater efforts to collect data on sexual behavior in African countries than in other parts of the world.