The Economics of HIV Testing in Africa

by

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ABSTRACT

This thesis examines the problem of resource allocation in Africa to combat the HIV/AIDS epidemic. It focuses on the use of one specific technology, the anti-HIV antibody test. After describing the characteristics of the epidemic, the special problems that accompany the allocation of health resources in Africa are explored. A short description of the biological and technical aspects of HIV testing is followed by three case studies which examine different uses of the technology.

(1) A model of the use of HIV testing to screen blood donors is demonstrated in several hypothetical situations to evaluate under which circumstances HIV screening is cost-effective and which is the most cost-effective of a number of testing systems.

(2) Use of the HIV test is considered from a cost-effectiveness perspective for the purpose of helping to confirm the diagnosis of HIV-related disease. Possible benefits of testing (including more rapid initiation of appropriate treatment, avoidance of the cost and iatrogenic complications of inappropriate treatment, and more efficient rationing of health care resources) are compared to possible costs (including monetary costs, emotional costs, and costs associated with false test results). A detailed protocol is presented of a prospective study to evaluate the appropriate use of the HIV test in the inpatient hospital setting.

(3) Serologic surveys, including procurement of samples and testing for HIV, comprise the bulk of any program to monitor and characterize the epidemiology of the HIV/AIDS epidemic. The descriptive data thus gathered can then be used to more effectively target interventions to prevent further HIV spread and alleviate the impact of HIV/AIDS. Two models are presented which can be used to optimize the cost-efficiency of serologic surveys by improving the selection of sample size and testing method.

The conclusions draw upon the findings of the three case studies. They place the fight against AIDS in its social and economic context in Africa; outline the general rules that govern the use of HIV testing technology; and underscore the need for cost-effectiveness assessments to improve the efficiency of resource allocation by national AIDS programs.

Thesis Supervisor: Dr. Jeffrey Harris

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I

THE EPIDEMIOLOGY OF HIV/AIDS IN AFRICA

The World Health Organization (WHO) Global Program on AIDS (GPA) has estimated that more than 11 million persons have been infected with the human immunodeficiency virus (HIV) in sub-Saharan Africa from the start of the epidemic in the last 1970's through mid 1995. The cumulative number of cases of HIV infection that have progressed to AIDS is estimated at over 3 million. Such estimates are very imprecise because of incomplete disease identification and reporting, especially in developing countries. As of 1995, less than 0.5 million of the over 3 million estimated cases of AIDS in Africa were officially reported by countries to WHO.[1]

The total population of sub-Saharan Africa, excluding South Africa, is approximately 489 million,[2] the estimated numbers of people living with HIV infection is approximately 9 million,[3] thus the average HIV seroprevalence is in the neighborhood of 1.8%.

However, this number is misleading because it conceals an enormous range of variation. First, the age distribution of the population is pyramidal, with approximately 48% of the population under 15 years of age.[4] The HIV prevalence in the population over 15 years of age is approximately 10 times what it is in the population under 15.[5] Second, the variation between countries is even greater. The diagram below graphically represents national average HIV seroprevalence estimates which range from less than 1 per 1000 to more than 1 in ten -- a difference of more than two orders of magnitude.

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1 World Health Organization, Global Programme on AIDS *The Current Global Situation of the HIV/AIDS Pandemic* 3 July 1995.

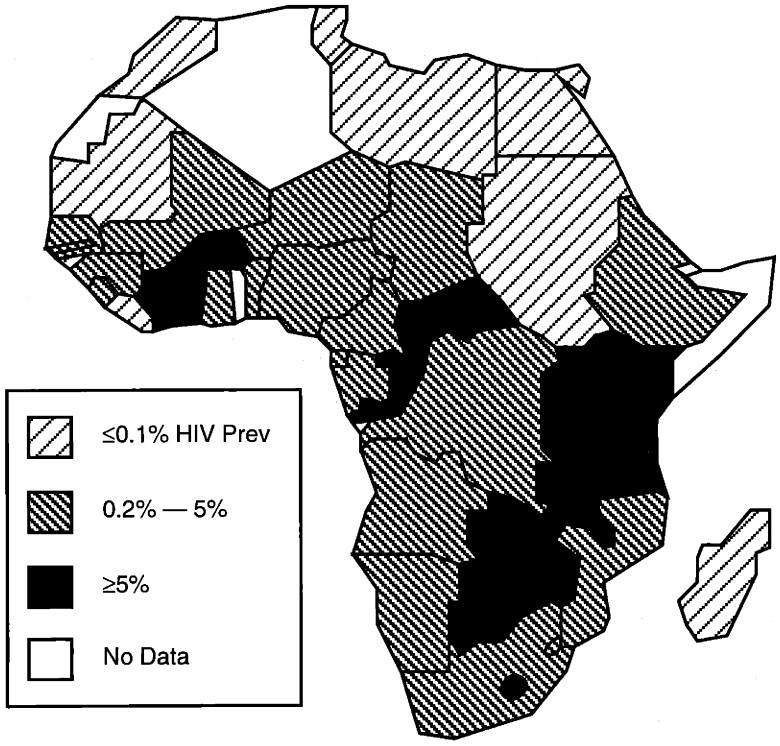
2 Table 1. Basic indicators, World Development Report 1993, World Bank.

3 World Health Organization, Global Programme on AIDS *The Current Global Situation of the HIV/AIDS Pandemic* 3 July 1995.

4 Table 26. Population growth and projections, World Development Report 1993, World Bank.

5 WHO Global Programme on AIDS, Surveillance, Epidemiology & Forecasting, Personal communication

African HIV-1 Seroprevalence for Low-Risk Urban Populations: Circa 1993[6]



Third, HIV prevalence is very heterogeneously distributed among social groups. The highest rates are typically found among urban women who self identify as prostitutes, hospitalized patients, people who attend sexually transmitted disease (STD) clinics, clients of prostitutes, truck drivers, and military personnel. For example, estimates from the Côte d'Ivoire, Kenya and Rwanda suggest that HIV prevalence among some populations of urban commercial sex workers approaches 90%.[7,8,9]

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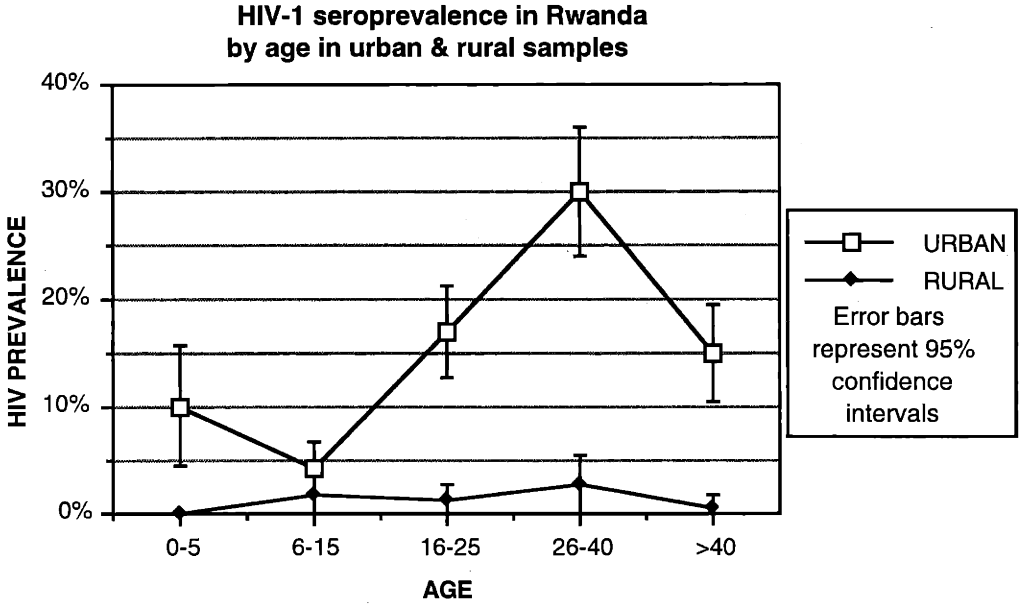
6 U.S. Bureau of the Census, Center for International Research, HIV/AIDS Surveillance Database, December 1993

7 U.S. Bureau of the Census, Center for International Research, HIV/AIDS Surveillance Database, June 1995

8 Simonsen JN; Plummer FA; Ngugi EN; Black C; Kreiss JK; Gakinya MN; Waiyaki P; D'Costa LJ; Ndinya-Achola JO; Piot P; et al HIV infection among lower socioeconomic strata prostitutes in Nairobi. *AIDS*. 1990 Feb.; 4(2): 139-44.

9 Diallo M; Ghys P; Traore-Ettiegne V et al. Immunosuppression and AIDS in female prostitutes in Abidjan. in *Abstract Volume, Nineth International Conference on AIDS*.. Berlin, June 1993 PO-C14-2900

Fourth, in most countries, major urban areas have much higher prevalence rates than rural areas. As an example, the graph below presents data from the national seroprevalence survey in Rwanda.[10]



Exceptions to the urban > rural pattern occur, most notably in the Kagera region of Tanzania and the Rakai district of Uganda.[11,12,13] However, even within these high prevalence "rural" areas, the highest prevalence rates are found in the largest towns and along trade routes (e.g. in Bukoba, the capital of the Kagera province, the prevalence among adults between ages 20 and 40 approaches 50%.). Variation between rural areas in a single country can be similar to that found across countries, as the diagram below of reported seroprevalence rates from Tanzania reveals. Thus, estimates of average national HIV seroprevalence can be misleading and certainly mask a reality that is far more complex.

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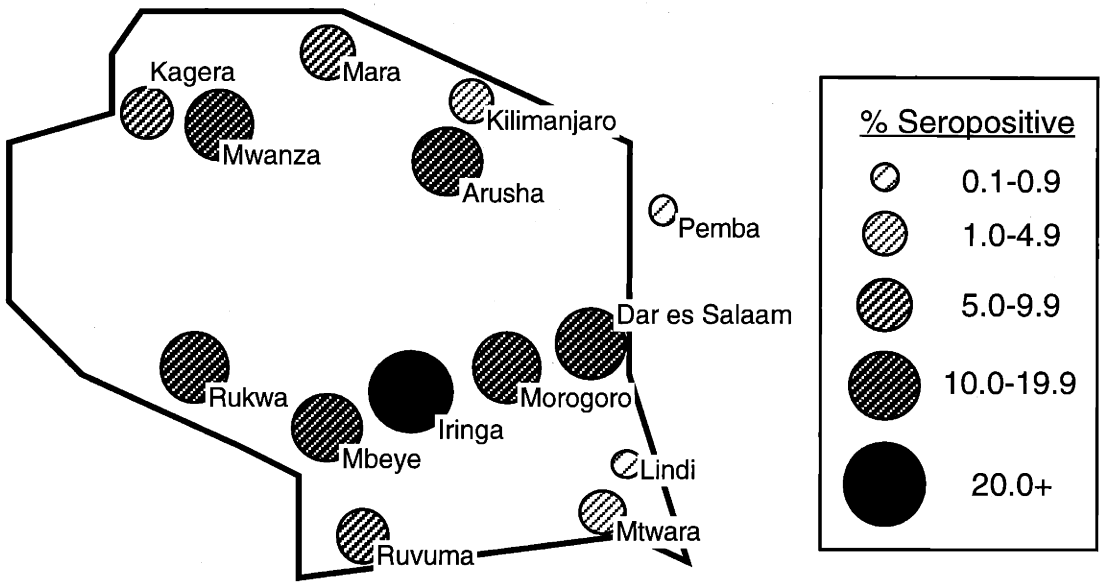
10 Nationwide community-based serological survey of HIV-1 and other human retrovirus infections in a central African country. Rwandan HIV Seroprevalence Study Group. *Lancet.* 1989 Apr. 29; 1(8644): 941-3.

11 Wawer MJ; Serwadda D; Musgrave S; Sewankambo N; Musagara M; Konde-Lule J; "Geographic and community distribution of HIV1 infection in rural Rakai District, Uganda." in *Abstract Volume, Sixth International Conference on AIDS.* San Francisco, June 1990. 232.

12 Serwadda D; Musgrave S; Wawer MJ; Musagara M; Konde-Lule J; Sewankambo N; "HIV1 risk factors in a randomly selected population in rural Rakai district, Uganda." in *Abstract Volume, Sixth International Conference on AIDS. San* Francisco, June 1990. 2: 114.

13 Killewo J; Nyamuryekunge K; Sandstrom A et al; "The Epidemiology of HIV-1 Infection in the Kagera Region of Tanzania [abstract]." in *Abstract Volume, Third International Conference on AIDS and Associated Cancers in Africa* . 1988. 23.

Seroprevalence of HIV-1 for Low-Risk Populations in Tanzania[14]



In Europe and North America, AIDS was first reported in men, reflecting the initial spread of the HIV epidemic in the male homosexual population.[15] Subsequent spread through the blood supply, in the community of intravenous (IV) drug users, from bisexual men to women, and via heterosexual transmission has reduced the male to female ratio somewhat from its initial peak, but it remains very high, over 5:1.[16] In contrast, in most of Africa, the male to female ratio is close to one.[17]

In Africa, as everywhere, there are three primary modes of transmission of HIV: (1) via sexual contact, (2) via infected blood, and (3) from a mother to her fetus in utero, during delivery, or through breast milk.[18]

Sexual contact is the most important mechanism of HIV transmission in Africa and is responsible for over 80% of cases. Unlike Europe and North America, the

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14 U.S. Bureau of the Census, Center for International Research, HIV/AIDS Surveillance Database, June 1994

15 Gotlieb MS et al: *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men. *N Engl J Med* 305:1426, 1981.

16 Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report, Summary of findings.* 1994;6(no. 2)

17 World Health Organization, Global Programme on AIDS. *The HIV/AIDS Pandemic: 1994 Overview*, WHO/GPA/TCO/SEF/94.4

18 N'galy B; Ryder RW; Epidemiology of HIV infections in Africa. *J Acquir Immune Defic Syndr.* 1988; 1(6):551-8.

overwhelming majority of sexual transmission has been and continues to be via heterosexual intercourse. Although homosexual contact is certainly not unknown, its contribution to HIV transmission is not significant.[19]

The predominance of heterosexual, as opposed to homosexual, transmission has been used to explain the sex ratio of HIV infection (male to female) near unity. However, the biology of heterosexual transmission might be expected to lead to a sex ratio that is actually less than one. Heterosexual intercourse exposes more of a woman's mucous membrane to the man's potentially infectious secretions than it does the man's mucous membrane to the woman's potentially infectious secretions. This, coupled with the finding that infected men have higher viral concentrations in their semen than do women in their vaginal secretions,[20] supports the hypothesis that an infected man is more likely to infect an uninfected female partner than the converse. Several studies have confirmed the existence of a difference in the probability of transmission; one large European study suggested that female to male transmission is 1.9 times more effective than female to male.[21] If male to female transmission is more effective, then in Africa where the overwhelming majority of infected adults are infected via heterosexual contact, a higher HIV prevalence would be expected among women -- assuming the male population is randomly mixing with the female population. Seroprevalence studies have not borne out this prediction.

While in most parts of Africa, the sex ratio of HIV infection is near unity. Abidjan, the capital of the Côte d'Ivoire is an exception. There, the male to female ratio was reported to be approximately 5 in 1989, although the ratio appears to be diminishing over time.[22,23] The most likely explanation for why the predicted female preponderance is <u>not</u> seen lies in the difference in the distribution of sexual activity in the male and female population. In any population with equal numbers of men and women, the average number of new heterosexual partners per year and the average number of heterosexual acts per year is the same for men and for women (every time a man has a new partner, so does a woman, and vice versa). However, the distribution of sexual activity may differ greatly by

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19 *HIV/AIDS Surveillance Report, op cit*

20 Borzy MS; Connell RS; Kiessling AA. Detection of human immunodeficiency virus in cell-free seminal fluid. *J Acquir Immune Defic Syndr.* 1988; 1(5): 419-24.

21 European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. *BMJ.* 1992;304:809-13

22 De-Cock KM; Porter A; Odehouri K; et al. Rapid emergence of AIDS in Abidjan, Ivory Coast. *Lancet.* 1989 Aug 19;2(8660):408-11.

23 U.S. Bureau of the Census, Center for International Research, HIV/AIDS Surveillance Database, June 1994.

sex. It is likely that in some places, a large percentage of men have multiple sexual partners, while comparatively few women have multiple partners; the difference being made up by a small number of women who have very many partners. In such a situation, this small group of women with many partners would have an especially high incidence of infection. If a large portion of the male population comes into contact with this small group of women, one would expect a higher average seroprevalence among men. As the epidemic progresses, these infected men are likely to infect their wives or steady partners, increasing the average female seroprevalence and thereby decreasing the male:female ratio of HIV infection. This oversimplification of the actual epidemiology in any actual city suggests an explanation for the seemingly illogical pattern of infection. Cities in which there are more men than women, such as Abidjan, which has a large populations of male migrant workers, might be expected to have an especially high male to female infection ratio, especially in the early years of the epidemic.[24,25] Unfortunately, as those migrant workers return to their home countries and communities they carry the virus with them.

The second route of HIV transmission is via contaminated blood. Although there are many possible ways in which blood or a blood product from one individual is introduced through the skin of another individual, only a few are common enough to contribute in an important way to the epidemic. In industrialized countries universal screening of all blood for transfusion and voluntary deferral of all donors who have a history of high risk behaviors has virtually eliminated the transmission of HIV via blood *transfusion* . Unfortunately, contaminated blood continues to be a major, and in some places the major, source of spread because of the sharing of injection equipment by injecting drug users.

In Africa intravenous drug use is uncommon. Some HIV transmission results from use of improperly sterilized medical equipment (approximately 1.5%), but the majority of HIV transmitted via blood is transmitted by blood transfusions (approximately 6%).[26] Universal screening of blood for transfusion is not a reality in most of Africa. The high cost of HIV tests, shortage of trained technicians, and difficulty obtaining a consistent

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24 *Demographic Yearbook* United Nations, 1988. 164.

25 Larson, A; "The Social Context of HIV Transmission in Africa: A Review of the Historical and Cultural Bases of East and Central African Sexual Relations." *Review of Infectious Diseases*. Sept.-Oct.. 1989; 11(5): 716-31.

26 Chin J ; Sato PA; Mann JM Projections of HIV infections and AIDS cases to the year 2000. *Bull World Health Organ.* 1990; 68(1): 1-11.

supply of materials, all contribute to the low rate of utilization of HIV tests, especially in rural areas, in even the most heavily affected countries.

The United States is accustomed to thinking of blood transfusion as a procedure which is rarely necessary outside of a hospital and which is primarily used for trauma and major surgery. Given the scarcity of emergency medical resources in Africa, one might expect that transfusion is relatively rare in Africa. Unfortunately, the opposite is true. Blood transfusion is very "low technology" treatment. In some places it is easier to transfuse blood than infuse saline because blood has the advantages of being already mixed and sterile. High prevalence of malaria in many countries combined with poor average nutritional status and a high average parasite load combine to make anemia one of the most common health problems, especially in children. Similarly, woman in many African countries are likely to have large numbers of closely spaced children which, especially if their nutrition is also poor, increases the incidence of anemia.

The third and final mode of transmission is from an infected woman to her fetus, either in utero, during birth or via breast feeding. This mode represents approximately 10% of all HIV transmission.[27] "Overall, approximately one-third of children born to HIV-infected mothers will acquire HIV-1 infection from their mothers[28] Most mother to child transmission occurs during pregnancy and delivery, although recent data suggests that up to 15% of babies breast-fed by HIV infected mothers may become infected through breast-feeding..."[29] The percent of all infants who are infected is much higher in Africa than in Europe or North America, for the same overall HIV prevalence, because women are a much larger proportion of the pool of infected adults.

This short overview has highlighted the heterogeneity of HIV epidemiology across the African continent as well as stressed the constants (worldwide, HIV is only transmitted three ways). However, absent is discussion of the mystery that accompanies the heterogeneity. Kigali is the capital of Rwanda, the most heavily Roman Catholic country in Africa. Kinshasa, the capital of neighboring Zaïre, is known not for its piety, but rather for its active night life. AIDS was recognized in both capitals at approximately the same time,

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27 Mertens TE; Low-Beer D. Analysis of public health surveillance of HIV and AIDS: Where is the epidemic going? *WHO Bulletin.* in press

28 Dunn DT; Newell ML; Ades AE; Peckham CS. Risk of human immunodeficiency virus 1 transmission through breastfeeding. *Lancet* 1992, 340:585-588.

29 Mertens TE; Belsey E; Stoneburner RL et al. Global estimates and epidemiology of HIV-1 infections and AIDS: further heterogeniety in spread and impact. *AIDS.* 1995; 9(suppl A):S259-S272.

yet Kigali now has a prevalence among young adults of approximately 30%, while Kinshasa appears to be stabilizing at less than 10%.[30,31] Hypotheses about sexual mixing patterns, as alluded to above with respect to Abidjan, have been advanced to help explain such dramatically different epidemic paths. However, the full explanation of why the epidemic is behaving so differently across countries is perhaps this decade's foremost epidemiological enigma.

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30 U.S. Bureau of the Census, Center for International Research, HIV/AIDS Surveillance Database, June 1994.

31 Kamenga M; Ryder R; N'Galy B; Behets F; Ngoy T; Liambi A et al; "An HIV serosurvey in the general population of Kinshasa appears feasible." in *Abstract Volume, V International Conference on AIDS. Montreal, June 1989*. 973.

II

HIV/AIDS IN AFRICA: A ROLE FOR ECONOMIC RESEARCH[1]

Introduction

Although resources for preventing AIDS and for reducing its social and economic impact are scarce everywhere, in Africa the scarcity is more acute and the competition for funds more intense than in industrialized countries. Resources wasted in Africa are associated with a greater human cost because the cost of disease prevention is lower. To illustrate, evaluations of disease prevention programs in the U.S. may speak of spending $50,000 or $100,000 to gain one year of healthy life;[2] similar benefit has been suggested in African countries for $10, $100, or $1000.[3] Early in the HIV epidemic, international relief organizations provided priority funding for AIDS prevention in Africa. To maintain that priority in the face of other pressing health problems on the continent, programs will need to demonstrate that AIDS prevention activities are more cost-effective than competing uses for those funds.

The reader is referred to a recent article, "The impact of AIDS on socioeconomic development" by Nabarro and McConnell[4,5] that reviews at length the literature describing the impact of AIDS and HIV infection on the economies of developing countries. Other

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1 A version of this chapter has been previously published as:
Bertozzi SM; Combatting HIV in Africa: a role for economic research. *AIDS.* 1991; 5(suppl 1):S45-S54

2 Goddeeris JH; Bronken TP; Benefit-cost analysis of screening. A comparison of tests for gonorrhea. *Med-Care.* 1985 Nov; 23(11): 1242-55.

3 Jamison DT; Mosley HW: Disease control priorities in developing countries: an overview. in *Disease Control Priorities in Developing Countries*, edited by Jamison DT ; Mosely HW. Washington, DC: World Bank 1993, pp 3-34.

4 Nabarro D; McConnell C: The impact of AIDS on socioeconomic development. *AIDS* 1989, 3(suppl 1):S265-S272.

5 Scitovsky AS; Over M: AIDS: Costs of Care in the Developed and Developing World. *AIDS* 1988, 2(suppl 1):S71-S81.

work has specifically examined the cost of the epidemic to the health care system,[6-12] to industry,[13-15] to food production,[16,17] and to national economies.[18]

The focus of this chapter is different. Rather than ask, "what is the cost of HIV infection ?" this discussion will address the question, "how should societal resources be allocated to fight the epidemic and its effects?" Without answering the question, it seeks to outline the underlying economic issues. Its goal is to encourage AIDS policy makers to place greater emphasis on comparing the cost-effectiveness of proposed interventions and to encourage the data collection that can make such comparisons possible. For simplicity, 'a case of HIV infection' will refer to the average spectrum of clinical disease associated with one infection. No attempt is made to distinguish HIV I from HIV II.

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6 Davachi F; Baudoux P; Ndoko K; N'Galy B; Mann J: The economic impact of AIDS on families of children with AIDS in Kinshasa, Zaire. in *The Global Impact of AIDS: Proceedings of the First International Conference on the Global Impact of AIDS* edited by Fleming AF, Carballo M, FitzSimons DW, Bailey MR, Mann J. New York: Alan R. Liss, 1988, pp 167-70.

7 Mposo N; Engele B; Bertozzi S; Hassig S; Ryder R: Prospective quantification of the economic and morbid impact of perinatal HIV infection in a cohort of 245 Zaïrean infants born to HIV(+) mothers. in *Abstract Volume, V International Conference on AIDS*. Montreal: June 1989, p 1033.

8 Bertozzi S; Mposo N; Green S; Mandiyangu M; Walker D; Ryder R: Increased hospital revenue associated with admitting HIV positive patients to a rural Zaïrean hospital. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2:283.

9 Faye-Ndao M, oral presentation, *Fifth International Conference on AIDS in Africa* Kinshasa: October 1990.

10 Tapia-Conyer R; Martin A; de la Rosa B; Garcia A; Peitrahita C: The economic impact of AIDS in Mexico. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2:43.

11 Tapia-Conyer R; Martin A; Revuelta A; Rodriguez S: The economic impact of AIDS at the household level in Mexico. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2:291.

12 Tapia-Conyer R; et al.: Estimation of AIDS treatment cost through a prospective study. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2:283.

13 Nkowane BM: The impact of human immunodeficiency virus infection and AIDS in a primary industry: mining (a case study of Zambia). in T*he Global Impact of AIDS . op cit.* pp 155-60.

14 Desmond GM: Policy challenges of the socioeconomic impacts of the AIDS pandemic: A co-ordinated response by the United Nations system. in *Abstract Volume, V International Conference on AIDS* Montreal: June 1989, p 1034.

15 Desmond GM: The impact of AIDS on socioeconomic development: A sectoral approach. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 3:302.

16 Abel N; Barnett T; Bell S; Blaikie P; Cross S: The impact of AIDS on food production systems in East and Central Africa over the next ten years: A programmatic paper. in *The Global Impact of AIDS. op cit.*. pp 145-54.

17 "Potential Impact of AIDS on Food Production and Consumption: Tabora Case Study—Tanzania". London: Overseas Development Natural Resources Institute, 1989.

18 Over M; Bulatao R; Jamison D; Lau L: A production function approach to estimating the aggregate macroeconomic impact of AIDS on central African economies. in *Abstract Volume, V International Conference on AIDS* Montreal: June 1989, p 1050.

The discussion is divided into two interrelated resource allocation problems, each of which has a different target audience. The first is how to allocate funds among diseases. Assuming a fixed quantity of resources for health prevention, how much priority should be given to HIV prevention relative to prevention of measles, malaria, or any other important cause of morbidity and mortality in Africa. The decision makers most concerned with this problem are not those primarily concerned with AIDS, but rather international donor organizations or national ministries of health who must allocate limited funds across the spectrum of health problems, including AIDS.

The second problem is how to allocate funds among interventions that reduce HIV transmission. The policy makers most concerned are those, like directors of National AIDS Control Programs (NACPs), who are directly responsible for AIDS prevention. Although it is useful to consider these two allocation problems separately, they are fundamentally interrelated. As funds are re-allocated more efficiently among interventions to prevent HIV transmission, such prevention assumes a higher priority relative to the prevention of other diseases.

'More efficient allocation' implies movement toward a goal of optimal efficiency. The definition of 'optimal efficiency' depends critically upon the values and perspective of the policy maker. For example, it is irrelevant to the government of Italy that the money spent to assure one year of healthy life for a child in Naples would buy a greater amount of healthy life if spent in Nairobi. However, an international relief organization may want to maximize the total healthy life years saved by their programs and thus inter-national differences in cost per healthy life year saved become central to their decision making process. This review makes the simplifying assumption that a policy maker is concerned only with a defined population (e.g., a government minister in Zaïre is only concerned with the population of Zaïre, while the Director General of the World Health Organization is concerned with the worldwide population), and that, within that population, an additional year of health is of equal value to any member of the population. Optimally efficient allocation of preventive and curative heath resources maximizes the total health benefit in the defined population.

A unit of health benefit will be defined for these purposes as a healthy life year (HLY). Although HLYs are assumed to have equal value regardless of who directly benefits, HLYs in the present are assumed to be of greater value than HLYs in the future. The value of discounted healthy life years (DHLYs) has been adjusted for the delay

between the present and the time in the future when the HLY will be gained/lost. Use of DHLYs permits comparison between interventions that save HLYs at different future times.[19]

Benefit of Preventing HIV Infection vs. Other Diseases

Does prevention of HIV infection deserve an especially high priority among disease prevention programs? If the stated goal is to minimize total DHLYs lost, then disease prevention programs may be compared by estimating the average number of lost DHLYs per case of a disease, estimating the cost of preventing an additional case of the disease, and dividing the two estimates to generate a cost per lost DHLY prevented. A 'case' may be defined in whatever way is most convenient for each disease, as long as the DHLY estimate and the prevention estimate both use the same definition. With respect to HIV-related disease, a case will be defined as a new HIV infection.

No mention was made in the preceding paragraph of total disease burden (lost DHLYs per case multiplied by the total number of cases) associated with different diseases. Total burden is relevant when considering complete eradication of a disease, because the prevention of most disease occurs

> ...at the margin, allocating 10% more resources to this prevention effort, perhaps by cutting resources on another effort. As the [Ghana Health Prevention Project[20]] recognized, estimates of total burden are not useful for these marginal decisions.[21]

If a policy maker is given an additional $100 to spend on either measles or HIV, he or she is not concerned with whether there is more total HIV-related disease or more total

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19 Most people would prefer to lose a year of healthy life five years in the future than immediately. For them to be indifferent to the trade-off, the time lost in the future would have to be longer than one year; the further in the future, the longer the time would have to be. Consider how many healthy years, 50 years in the future, most people would trade for an additional healthy year today. The rate at which years become 'less valuable' is the discount rate (similar to a negative interest rate) which is used to discount or devalue future HLYs (DHLYs). The choice of discount rate will influence the outcome of a cost-effectiveness analysis. For example, the higher the rate, the more that HLYs far in the future will be devalued and the smaller the differences between the DHLYs lost by an infant compared to a 20 year old. "Individuals in different circumstances can have legitimately different discount rates. Poor people will usually discount future enjoyments (and inflate present ones) more than the non poor do, due to the real pressure of their circumstances..." [Menzel PT: *Medical Costs, Moral Choices: A Philosophy of Health Care Economics in America* New Haven: Yale University Press, 1983, p 88.]

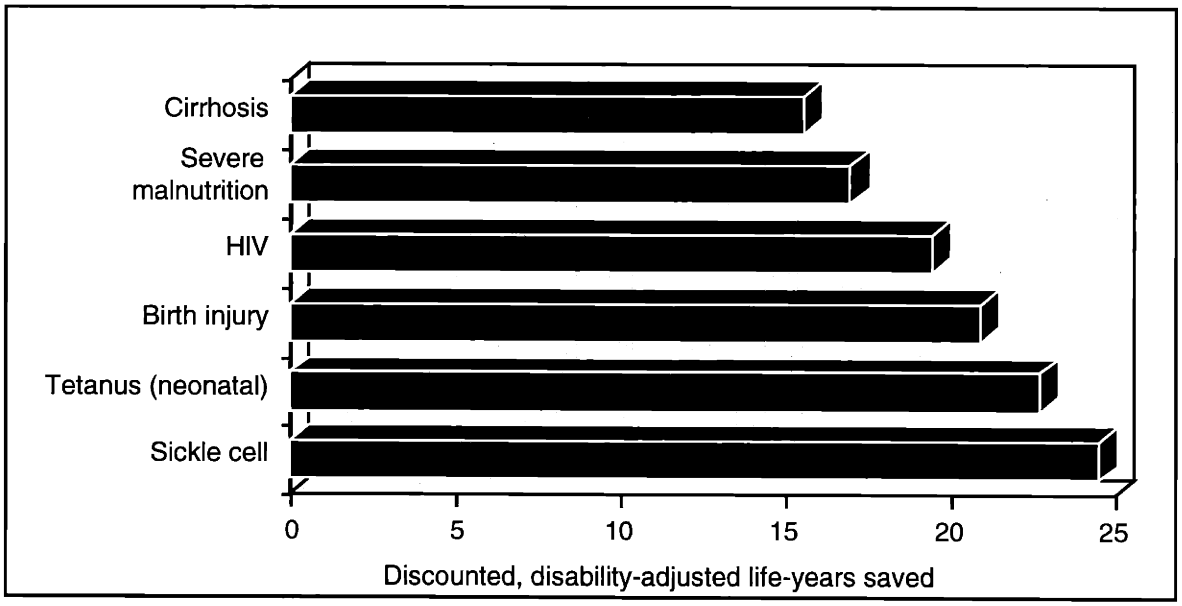
20 Ghana Health Assessment Team, Morrow RM: A quantitative method of assessing the health impact of different diseases in less developed countries. *Int J Epidemiol* 1981, 10:73-80.

21 Over M; Piot P: HIV infection and sexually transmitted diseases. in *Disease Contrrol Priorities in Developing Countries* edited by Jamison DT Mosely HW. Washington, DC: World Bank 1993, pp455-527.

measles, but rather with where would the $100 buy the greatest number of DHLYs. Funding priority should be given to the diseases with the lowest cost per DHLY gained. As more cases of a disease are prevented, the cost of preventing an additional case eventually rises (though it may fall at first) until it becomes more worthwhile to prevent a disease which initially had a higher cost per DHLY. Ideally, when funds are properly allocated, the cost per DHLY should be similar across diseases.

Benefit of Preventing a Case of HIV/AIDS Infection

Over *et al.*[19-23] used data from the Ghana Health Assessment Project to compare the DHLYs lost per case of HIV infection to those lost per case of other important diseases in Africa. The six diseases associated with the greatest number of lost DHLYs were sickle cell anemia, neonatal tetanus, birth injury, HIV infection, severe malnutrition , and cirrhosis. The DHLY lost per HIV infection were calculated under the assumption that 100% of infected persons progress to AIDS and death, with an average time from infection to death of 10 years.



A case of each of the six diseases corresponded to a loss of between 16 and 24 years of discounted healthy life.[24] A high probability of death or permanent disability, a

22 Over M; Bertozzi S; Chin J; N'Galy B; Nyamuryekunge K: The Direct and Indirect Cost of HIV Infection in Developing Countries: The Cases of Zaire and Tanzania. in *The Global Impact of AIDS. op cit.* 123-135

23 Over M; Bertozzi S; Chin J: Guidelines for Rapid Estimation of the Direct and Indirect Cost of HIV Infection in a Developing Country. *Health Policy* 1989, 11:169-86.

24 An important cause of young adult mortality is maternal deaths [Lopez, op cit.]. Unfortunately, this cause was not included in the GHAP and thus was also not included in the Over et al. comparative studies. Because the age of death is similar to AIDS and because maternal mortality has less lag

low average age, and a short latency period are all associated with many lost DHLYs per case. HIV infection is among the highest, following the most lethal diseases of early childhood.[25]

By only considering DHLYs that accrue to the diseased individual, the 'index case', benefit to other individuals is ignored. Even if a DHLY is considered to be of equal value to whomever enjoys it, the secondary effects, or effects on others, that accompany a lost DHLY will vary depending upon the characteristics of the individual directly affected. To simplify the analysis the secondary emotional impact of a lost DHLY will be ignored, but differences in secondary economic effects (hereinafter referred to as 'secondary poverty') cannot be ignored. If a single mother of six children dies, the family as a whole will usually suffer more than it would if one of the children dies. Thus, diseases differ not only by the average DHLYs lost per case, but also in the average secondary poverty caused by a case. Each policy maker must decide how to value avoiding poverty versus avoiding ill health. At a minimum, the ill health (lost DHLYs) caused by the poverty must be considered. Since DHLYs are weighted equally, those lost by children because of their mother's death must be added to the DHLYs the mother loses in calculating the benefit associated with averting her death.

Secondary effects of disease are not limited to emotional and economic effects. Some diseases are contagious and have the secondary effects that include additional cases of the disease. For example, a man's HIV-related death, directly prevented by giving a free condom to a prostitute, or his wife's (secondary) death, indirectly prevented by the same condom, are considered of equal value before discounting for any time difference between the deaths.

Thus, the benefits associated with preventing a case of HIV infection, or of any disease, can be thought of as the sum of:

(a) the DHLYs directly gained by the index case;

(b) the DHLYs gained by others who would have been directly or indirectly infected by the index case and who would otherwise not have been infected (by someone else);

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between prevention of a case and averted mortality than HIV, maternal mortality is likely to have more lost DHLYs per case.

25 Over M; Piot P, *op cit.*

(c) the DHLYs gained by others who would have lost DHLYs because of the secondary poverty caused by the index and subsequent cases;

(d) the difference in secondary poverty that is not reflected by the DHLYs in (c) above (clearly poor health is only one of the negative consequences of poverty).

Benefit of preventing secondary cases of HIV/AIDS

The most important difference between HIV infection and other diseases that have similar DHLYs lost per index case is probably a function of category (b) above.

> A key epidemiological concept in this connection is that of the "reproduction rate." Defined as the number of new (or secondary) cases infected by an average case, the reproduction rate can be used to multiply the number of prevented primary cases in order to obtain a crude measure of the total beneficial impact of the prevention effort. Clearly the inclusion of these extra cases among the benefits of an [sexually transmitted disease] STD prevention program will increase the measured cost-effectiveness of preventive efforts. ...it is clear that the present attention allocated to AIDS prevention is almost entirely due to fear of a high reproduction rate.[19]

Over and Piot use short-run epidemic models to examine the benefits associated with preventing cases of HIV infection and other STDs. They calculate the DHLYs saved per case of HIV prevented, including both those associated with preventing the index case and those associated with preventing subsequent cases. They generate estimates under two different sets of assumptions, first in which a case of HIV infection is prevented in a core group of highly sexually active persons and second in the "non-core" general population. The DHLYs saved by the index case are the same for core and non-core, estimated at 19.5. The "dynamic benefit", or DHLYs saved because of subsequent HIV infections prevented are estimated to be 340 when the index case is in the core group and 35 when the index case is in the non-core group. Even for the non-core group, the dynamic benefit dwarfs the "static benefit" associated with the index case.

Clearly, reproduction rate is not only relevant for HIV, but for all communicable diseases.[26,27,28] So, why have cost-effectiveness assessments of measles immunization

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26 Makinen WM: A social benefit-cost analysis of anti-measles vaccinations in Yaounde, Cameroon. PhD dissertation 1980, U. Microfilms International No. 8007783.

27 Shepard DS; Sanoh L; Coffi E: Cost -effectiveness of the expanded programme in immunization in the Ivory Coast: a preliminary assessment. *Soc Sci Med* 1986, 22:369-77.

28 Shepard DS; Robertson RL; Cameron III CSM; Saturno P; Pollack M; Manceau J; et al.: Cost-effectiveness of routine and campaign vaccination strategies in Ecuador. *Bull World Health Organ* 1989, 67:649-62.

programs in Africa typically ignored the effect of reproduction rate?[29] The difference lies in the last clause of (b) above. In the case of measles in Africa, the probability that secondary cases would otherwise be infected elsewhere is high. HIV and other blood-borne pathogens are more difficult to transmit and thus a lower percentage of secondary and subsequent cases would be infected elsewhere if an index case is prevented (difference in attributable risk).

Rowley, Anderson and Ng use a 100 year epidemic model to examine the economic implications of programs to reduce sexual transmission of HIV.[30] Although the results of such long-run models are limited by the drastic simplifying assumptions that must be made, the principal conclusion they draw is important: "both the timing and the effectiveness of reducing HIV transmission are non-linearly related to their potential demographic and economic effects." The paper argues that benefits increase more than linearly per case of HIV transmission averted as more cases are averted and as they are averted earlier. 'Earlier', in this context, refers to earlier in the epidemic, with the implication that there is greater benefit associated with averting a case in areas where the epidemic is just beginning, relative to areas where the epidemic is more mature (the average reproduction rate falls as the epidemic matures). Unfortunately, the cost of averting a case is higher early in an epidemic and falls as the prevalence of the disease rises. In absence of a model that incorporates both the changing benefit and changing cost of averting a primary case, the soundest policy is probably to give highest priority to areas with the highest incidence of HIV infection. Such a policy naturally discounts very low prevalence areas where the cost of prevention is very high as well as areas where the epidemic is mature and the incidence is declining.

Benefit associated with preventing secondary poverty

Characteristics of the HIV epidemic which distinguish the magnitude of its secondary poverty from those of other diseases include: (1) the age distribution of infection *vis a vis* education, (2) the age distribution *vis a vis* number of dependents, and (3) the correlation of disease incidence rates with socioeconomic status (SES).

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29 Robertson RL; Foster SO; Hull HF; Williams PJ: Cost-effectiveness of immunization in the Gambia. *J Trop Med Hyg* 1985, 88:343-51.

30 Rowley JT; Anderson RM; Ng TW: Reducing the spread of HIV infection in sub-Saharan Africa: some demographic and economic implications. *AIDS* 1990. 4:47-56

Age distribution of infection *vis a vis* education

All of the diseases with very high lost DHLYs per case identified above, except HIV infection and cirrhosis, are diseases of early childhood. Over *et al.* did not attempt to consider the value of the average investment in human capital lost per case of each disease. Most formal education occurs between the ages of 5 and 18. Four of the causes of death listed occur overwhelmingly before age 5, AIDS and cirrhosis deaths overwhelmingly occur after age 18. A death after age 18 wastes not only future production, but also past educational investment, while death before age 5 does not. In human, rather than economic terms, consider a family of four that has only been able to put one of the twin children through secondary school and is relying upon her to support her parents as they become infirm. If one of the twins dies at age 20, the family's emotional suffering may be the same regardless of which twin dies, but the secondary be greater if the educated twin dies. In contrast, if the twins were 5 years old, the secondary poverty would be the same regardless of which twin dies because the educational investment can instead be made in the surviving twin.

Age distribution *vis a vis* number of dependents

The highest HIV seroprevalence rates are found among young adults.[31] These adults are more likely to have minor dependent children than the very old or the very young, age categories which traditionally have had high mortality.[32,33] This age distribution suggests that there may be large disruptive effects on dependents who lose their immediate source of economic, social, and emotional support.[34,35] The negative effect is further compounded in relation to most other causes of young adult death because of the tendency of HIV infection to kill both parents in a household. It would be even more negative if AIDS deaths, more than other deaths, tend to cluster within extended families. Logic suggests that each subsequent death in a household or extended family has a greater

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31 Peltzer K; Hira SK; Wadhawan D; Kamanga J; Fergudon DC; Perine PL: Psychosocial counselling of patients infected with human immunodeficiency virus (HIV) in Lusaka, Zambia. *Trop Doct* 1989, 19:164-168

32 Nkowane BM: The impact of human immunodeficiency virus infection and AIDS in a primary industry: mining (a case study of Zambia). in *The Global Impact of AIDS. op cit. pp 155-60.*

33 United Nations DIESA: Age structure and mortality in developing countries: a data base for cross-sectional and time series research in developing countries in New York, United Nations, 1986.

34 Beer C; Rose A; Tout K: AIDS - the grandmother's burden. in *The Global Impact of AIDS. op cit* . pp 171-4.

35 Lloyd GA: HIV infection, AIDS, and family disruption. in *The Global Impact of AIDS.. op cit* . pp 183-90.

negative impact.[36] A proxy measure of the magnitude of this disruptive effect (in addition to the loss of residence discussed below) is the average number of one and two parent orphans created per AIDS death as compared to other deaths. Recent interest in quantifying orphans[37-41] has demonstrated large numbers of orphans in areas of high AIDS mortality. The primary goal of the studies has been to demonstrate the magnitude of the orphan population for the purpose of mobilizing relief funds. They have not focused on how AIDS deaths differ from other causes of death in their effect upon surviving children.

Correlation of disease incidence rates with socioeconomic status (SES).

Wawer and Serwadda have presented convincing evidence that HIV prevalence is correlated with higher individual socioeconomic status (SES) and with higher community SES in Uganda.[42,43] Confirmatory evidence for this association comes from the Projet SIDA studies of two large firms in Kinshasa,[44] from the national seroprevalence survey in Rwanda,[45] and from a study of patients, blood donors, and personnel of a Zambian hospital.[46] These studies do not directly compare the socioeconomic distribution of HIV infection with that of other diseases. However, most major causes of morbidity and mortality in Africa are either inversely associated with SES (e.g. tetanus, malnutrition,

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36 Bertozzi S; Ankrah M; Ngaiza M: Tanzania: Assistance to survivors of the AIDS epidemic: A review of the policy options. Manuscript, June 16, 1990.

37 Nalwanga-Sebina; Sengendo J; "Orphaned and Disabled Children in Luwero and Kabale Districts and in Ugandan Child Care Institutions: A Comparative Profile to the General Child Population". manuscript. December, 1987.

38 Hunter SS: Project for the enumeration and needs assessment of orphaned children in Uganda: Advisory committee report. manuscript. January 9, 1990.

39 Hunter S: Orphans as a window on the AIDS epidemic in sub-Saharan Africa: initial results and implications of a study in Uganda. *Soc Sci Med* 1990; 31(6):681-690.

40 Preble EA: Projected impact of HIV/AIDS on children in central and east Africa. presented at the Conference on the implications of AIDS for mothers and children. Paris: November, 1989.

41 Mutembei IB: AIDS socio-economic impact on adolescents: The case of AIDS orphans in the Lake Zone, Tanzania. presented at the *Second International Symposium on AIDS Information and Education*. Yaounde, Cameroon, October, 1989.

42 Wawer MJ; Serwadda D; Musgrave S; Sewankambo N; Musagara M; Konde-Lule J: Geographic and community distribution of HIV1 infection in rural Rakai District, Uganda. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, (2):606.

43 Serwadda D; Musgrave S; Wawer MJ; Musagara M; Konde-Lule J; Sewankambo N: HIV1 risk factors in a randomly selected population in rural Rakai district, Uganda. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2:114.

44 Ryder RW; Ndilu M; Hassig SE; et al.: Heterosexual transmission of HIV-1 among employees and their spouses at two large businesses in Zaire. *AIDS* 1990, 4:725-732.

45 Bugingo G; Ntilivamunda A; Nzaramba D; et al: Etude sur la séropositivité liée à l'infection au virus de l'immunodéficience humaine au Rwanda. *Revue Médicale Rwandaise* 1988, 20:37-42.

46 Melbye M; Nselesani EK; Bayley A: Evidence for heterosexual transmission and clinical manifestations of human immunodeficiency virus infection and related conditions in Lusaka, Zambia. *Lancet* 1986, 2:1113-5.

measles, diarrhea, & respiratory illness) or are not significantly associated with SES (e.g. sickle cell anemia).

If persons with higher SES on average contribute work of greater value to their community or to their society than persons of lower SES, then a disease that is positively correlated with SES may cause more secondary poverty than a disease which is not. In this context it is important to remember that secondary economic effects of a death extend beyond the decedent's family. For example, the death of an engineer who has started a small business that makes electric hot plates may cause the loss of many jobs as well as lost benefit to consumers who benefited from less expensive, locally produced hot plates. However, a number of considerations may mitigate the effect of the SES correlation, potentially even reversing it:

- A person's SES is imperfectly correlated with the loss that accrues to his or her household upon death. A variety of measures have been employed to estimate SES; some studies use salary, others use assets, others use level of education, or a combination of the above.[39-41] The production lost following a death is only the production associated with the person. Income from productive assets that were owned by the deceased continues to be generated. Thus, when a wealthy (as opposed to highly productive) individual dies, secondary poverty may actually decrease if his or her assets are redistributed. The measures of SES used in the studies cited also do not consider an individual's consumption pattern. If a man raises twenty chickens a year and eats them all himself, the loss to his family associated with his death is less than if the chickens are eaten by everybody in the household. If women in Africa on average consume a smaller percentage of their production than men, the negative impact of a woman's death will be correspondingly greater than that of a man who produces the same total amount.

- In spite of the previous point, an individual's net economic contribution is likely to be positively correlated with his or her total production and with assets, especially in African cultures in which successful individuals often make large contributions to the support of their extended families.

- In the United States, the average SES of newly infected individuals has dropped over time as a smaller percentage of new infections occur among largely middle class male homosexuals and a larger percentage occur among largely poor

intravenous drug users.[47] In Africa, the association of HIV with higher SES is also likely to diminish and may reverse over time, as the better educated, wealthier members of society understand how and have the means to protect themselves against infection. Such a transformation of disease epidemiology may already have taken place in some areas, especially those where AIDS deaths have been apparent for many years. HIV prevalence rates will be slow to reflect such a change because of the long period of asymptomatic infection. A recent study from the Kagera region of Tanzania, where infection rates are among the highest in the world, suggested that HIV prevalence there is inversely correlated with educational level.[48,49] This may only reflect the heterogeneity of HIV epidemiology across the African continent, or it may reflect an area in which the positive SES correlation has been reversed.

- Although a person with high SES may make a larger net economic contribution, the loss of a person with low SES may cause greater economic disruption, at least at the household level. A household that is barely able to feed and house itself is likely to suffer more from the death of a productive member. This is consistent with the economic concept of declining marginal utility of income which observes that the loss of $100 of income imposes more hardship on a poor household than on a rich one. A proxy measure that might be used to study the disruption associated with different diseases is the percentage of households that relinquish their place of residence after a death .

- The distribution of SES in Africa is very different than in industrialized countries, with a much smaller percentage of the population in the higher SES categories.[50] Even if the incidence rate is higher at the top of the SES scale, most HIV infections occur among lower SES persons.[40] Thus, the SES correlation has less of an effect on the average SES per case than it would in a country where the SES distribution is less biased downward.

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47 Krueger LE; Wood RW; Diehr PH; Maxwell CL: Poverty and seropositivity: the poor are more likely to be infected. *AIDS* 1990, 4:811-814.

48 Sandstrom A; Wall S; Epidemiology of HIV infections. Design options with special reference to developing countries. *Scand J Infect Dis Suppl.* 1990; 69: 173-80.

49 Prevalence of HIV-1 infection in the Kagera region of Tanzia: a population based study. *AIDS.* 1990 Nov; 4(11): 1081-1085.

50 World Bank.World Development Report. New York. Oxford University Press. 1988.

- Finally, allocation of public resources for disease prevention must consider the availability of private funds. For example, if higher SES individuals already have the means to purchase condoms, then subsidizing condoms will do more to increase condom consumption if the subsidy is directed toward lower SES populations.

In summary, there are several reasons to question whether the observed correlation of HIV prevalence with socioeconomic status should increase the funding priority for HIV prevention relative to other diseases. Similarly, among HIV preventive interventions, the expected benefit of targeting higher SES individuals is uncertain, especially when the likely negative political repercussions of such a policy are considered. The existence of the SES correlation may be most strategically conveyed to employers, who may be more likely to develop AIDS prevention programs for their work force if their skilled and managerial employees are at greatest risk.

Benefit of preventing different types of HIV infection

HIV infection has thus far been treated as a single homogeneous entity to permit comparison with other diseases. For the purpose of allocating funds among HIV preventive interventions, a policy maker must consider how the benefit of preventing a case varies, depending upon the characteristics of the person whose HIV infection is being prevented. An obvious way to differentiate types of cases of HIV infection is by the 3 major mechanisms of HIV transmission in Africa: sexual intercourse, blood transfusion, and perinatal. Each of these is associated with a different average age, a different average pre-infection health status, and a different average life expectancy. Therefore, they have different average expected DHLYs lost per index case of HIV infection. More importantly, the three are probably very different with respect to reproduction rate. Infant infected in the perinatal period and patients who are ill enough that they require a blood transfusion probably infect many fewer secondary cases, on average, compared to individuals infected via sexual contact. The three groups would also be expected to differ in the average amount of secondary poverty expected per lost DHLY.

Because reproduction rate has a multiplicative effect on total benefits of averting a case, while secondary poverty and DHLYs gained by the index case are only of additive benefit, further research to define the magnitudes of these parameters is likely to confirm that reproduction rate is the most important of the three in determining the optimal targeting of HIV preventive interventions.

Cost of Preventing a Case of HIV Infection

Evidence of benefit is not sufficient for determining funding priorities. As discussed in the introduction, we must also compare the costs of averting lost DHLYs from HIV to the costs of averting lost DHLYs from other diseases.

There is little published literature comparing the cost-effectiveness of different interventions to reduce the spread of HIV. If AIDS prevention activities were controlled by a functioning market which could be relied upon to allocate resources reasonably efficiently, this dearth of research might be understandable. Instead, the bulk of prevention funds in Africa are spent by government ministries and international organizations. It is regrettable, given the importance of efficiently allocating prevention funds, that these institutions have not placed greater emphasis on cost-effectiveness research.

Moses *et al.* presented an estimate of the cost of averting a primary case of HIV infection by distributing condoms to high-risk groups in their pilot intervention in Nairobi.[51] Their estimate was US$ 6 per case averted, an extraordinarily low figure. Over and Piot, using their HIV epidemic model which assumes a small, highly sexually active core group with a seroprevalence of 20% and a general population prevalence of 1%, generate estimates of the cost of averting a lost DHLY by subsidizing condom distribution. They estimate that averting a lost DHLY costs between US$ 0.88 and $7.95 when directed to the core group (depending on the cost of providing protection) and between $2.51 and $22.61 when directed to the non-core group. To permit comparison with the Moses *et al* estimate, the estimates for the cost per DHLY for the core group may be multiplied by the expected DHLYs saved per case averted. These range from $50 to $450 (as compared to $6 for the Nairobi intervention).

A model developed to estimate the cost of averting an HIV infection by blood screening generated an estimate of $119, for an African setting where the HIV seroprevalence among blood donors is 5% and the cost per HIV test is $2.50. As model parameters were varied across the extremes found on the African continent, the cost-per-case-averted ranged from $28 to $13,000. By far the most important determinant of cost was the seroprevalence rate in the donor population.[52]

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51 Moses S; Ngugi EN; Nagelkerke NJD; Bosire M; Waiyaki P; Plummer FA: Cost-effectiveness of an STD/AIDS control programme for high frequency STD transmitters in Nairobi, Kenya. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2: 291.

52 Bertozzi SM: Economic aspects of HIV testing in Africa. in *Abstract Volume, Fifth International Conference on AIDS in Africa* Kinshasa: October 1990.

Voluntary confidential HIV testing is a cornerstone of AIDS prevention in Europe and the United States and is now beginning to diffuse in Africa (Allen, S: personal communication). The NACP in Rwanda, in collaboration with Projet San Francisco, has reduced the cost of their program by developing a video that can be used for group pre-test counseling. Both the program in Rwanda and studies at Projet SIDA in Kinshasa have demonstrated large changes in condom utilization rates when couples are tested and counseled together, but marginal or no change when pregnant women are screened without their spouses.[53,41] Unfortunately, neither the Kigali nor the Kinshasa projects have estimated the cost of averting an HIV infection. Nevertheless, costs per case averted are likely to be substantial, even when couples are counseled together, because of the high costs of the tests, the need in current programs for individual post-test counseling, and the limited effectiveness of the intervention. If the cost of screening and counseling were $7 per couple, using the reported discordance rates, it would cost between $63 (Kigali) and $245 (Kinshasa) to identify a discordant couple (neither both infected nor both uninfected). These costs alone are higher than the above cost estimates of averting a case of HIV transmission in the respective cities by screening transfusions and are also higher than many of the estimate for condom distribution. When one includes the additional cost of providing condoms and follow-up, and considers that both of the studies report a yearly incidence rate of about 3% in spite of the intervention (suggesting that often a case is postponed, rather than averted) then the cost per case averted will be substantially higher. An additional level of complexity is introduced if a substantial percentage of men are officially or *de facto* polygynous. In this situation a 'legal' wife who participates in counseling may not be her husband's primary sexual partner.

In spite of extremely high HIV seroprevalence in some parts of Africa among urban female prostitutes, voluntary programs offering alternative employment to HIV positive prostitutes have received little attention. Suppose that an HIV positive prostitute has 25 sexual partners per week and that the probability of female to male transmission per act is 1/50 because of the high prevalence of STDs in the prostitute/client population and the large difference in prostitute vs. client average seroprevalence.[54,55] If offering employment to one of these women only averted half of those transmissions, it would still avert 12 cases

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53 Tice J; Allen S; Serufilira A; Van de Perre P; Ziegler J; Hulley S: Impact of HIV testing on condom/spermicide use among HIV discordant couples in Africa. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 3:262.

54 Piot P; Plummer FA; Rey MA; et al.: Retrospective seroepidemiology of AIDS virus infection in Nairobi populations. *J Infect Dis* 1987, 155:1108-12.

55 Johnson AM; Laga M: Heterosexual transmission of HIV. *AIDS* 1988, 2(suppl 1):S49-S56.

per year. Consider Kigali as a hypothetical example. If spending $63 is postulated to increase the probability of averting one case by identifying a discordant couple, then $756 may be postulated for 12 cases. In a country where the per-capita gross national product is approximately $290, $756 might be able to employ a prostitute full-time, even if her work produced nothing. If her work was productive, more could be hired for the same cost.

When calculating the cost and benefit of preventing one case of a disease, great care must be taken in carefully defining 'prevention'. If one newborn per hundred non-vaccinated mothers develops neonatal tetanus, then 100 vaccinations may be expected to prevent one case of neonatal tetanus. If the probability of HIV transmission from an infected man to his uninfected wife is 1% per sex act, then use of 100 condoms for 100 sex acts is not expected to prevent one case of HIV infection, but rather to postpone a case by 100 sex acts. However, if an uninfected couple has 100 lifetime sex acts with infected extramarital partners (between them), then 100 condoms may be expected to prevent a case.

Cost of Preventing a Case of HIV Infection Compared to Other Diseases

Jamison and Mosley, as part of an ongoing project to review disease control priorities, have chosen to use cost per DHLY saved to compare adult diseases.[3] They include benefit associated with reproduction rate when appropriate (e.g. HIV, STDs, and tuberculosis), but they do not adjust for secondary poverty. Over and Piot's estimate of $5 per DHLY saved by screening blood donors is the lowest estimate (Plummer *et al.*'s condom distribution estimate and Bertozzi's estimate for screening blood would both be even lower) on a list that includes passive case finding for tuberculosis ($10), condom distribution for HIV prevention ($8-$50), hepatitis B immunization ($50), insulin management of diabetes mellitus ($150), and management of selected AIDS opportunistic infections ($300). Interventions to reduce childhood mortality are considered separately from those for adults, permitting the reader to weigh lost adult years and lost child years differently. Even without any differential weighting, the cost per DHLY gained for the most cost-effective HIV preventive interventions discussed above are within the range of the most cost-effective child health interventions.

Conclusion

HIV infection has been shown to be associated with substantial costs in many sectors of the economy. This has helped to bring the epidemic to the forefront of discussion about ill health in Africa and has helped convince policy makers outside of the

health sector of the seriousness of the threat the epidemic poses. In the most heavily affected countries in Central Africa, it is apparent to any observer that AIDS will have an important economic effect. Less heavily affected African countries in which the epidemic is less mature have greater opportunity and, because they have seen the specter, may have greater impetus to initiate preventive interventions. The limited evidence available suggests that prevention of HIV infection is among the top health priorities in any African country with a significantly high incidence of infection. Additional research focused on the secondary economic effects of HIV infection is needed to further define the benefit associated with preventing a case, but this should no longer be the primary focus of research on the economic aspects of HIV infection in Africa.

The priority should now shift to the evaluation of the cost-effectiveness of interventions to reduce HIV transmission, interventions to treat HIV-related disease, and interventions to reduce the negative impact on survivors. How much does it cost to prevent a case of HIV transmission by distributing condoms, by screening blood for transfusion, or by providing employment for infected prostitutes? The data on cost-effectiveness available to policy makers who must plan a program of interventions is seriously inadequate. National AIDS control programs (NACPs) across the continent have very limited operational capacity. They necessarily and appropriately rely largely on non-governmental and international organizations for the implementation of preventive programs. These organizations may be unlikely to pursue cost-effectiveness evaluations of their programs because they may perceive that they have more to lose than gain from such evaluations. Thus, a major role for an NACP should be to require cost and effectiveness data from implementing organizations that will enable the NACP to compare different interventions. By promulgating standard definitions and default parameter values (e.g. average number of sexual contacts, seroprevalence, infectivity per sexual contact with and without condom, fertility of HIV infected women, etc.), NACPs will further enhance their ability to compare interventions. If the World Health Organization were to assist in the development of these standards, the ability to compare interventions across national borders would be enhanced.

It is not reasonable to expect all organizations in a country proposing AIDS interventions to generate an estimate of the cost per discounted lost healthy life year. But, NACPs could insist upon an estimate, however imprecise, of the expected cost per index case of HIV infection averted. At its simplest, that is the budgeted cost of the intervention divided by the number of cases (or a range of the number of cases) it expects to avert. If

such estimates were expected, then the parameters needed for making the estimates would become more apparent to managers of interventions and more precise estimates would emerge as the interventions were implemented and evaluated. An NACP could adjust the estimates of cost per primary case averted by discounting the cases by the expected delay between expenditure of funds and aversion of cases. The NACP could also use its knowledge of the differences in HIV reproduction rates in different groups to generate estimates of the cost per discounted (primary & subsequent) case averted. These estimates would improve an NACPs ability to allocate funds across interventions, even if they did not perform the further analyses of estimating the DHLYs lost or estimating secondary poverty.

In spite of the imprecision of 'expected cases averted' for many planned interventions, the exercise of performing the estimation may reveal that an intervention would only be cost effective if one of the imprecise parameters were outside the realm of the possible. For example, in estimating the cost-per-case-averted by pre-pregnancy or prenatal HIV screening, the cost of screening and the underlying HIV prevalence are often known with some precision. Estimates of the percentage of the seropositive women who will modify their behavior and avert a case of HIV infection are likely to be much less precise. But, if the cost estimates suggest that the intervention would not be cost effective even if 90% of those women altered their behavior, then it would be difficult to justify launching such an intervention.

Epidemiological evidence or evidence of technical feasibility is often used to recommend policy without considering cost per unit of benefit. For example, a recent article recommended prenatal screening of women with certain signs and symptoms because these signs were associated with significantly higher HIV prevalence.[56] Certainly, screening a subset of women who have a 10% HIV prevalence is likely to be more cost-effective than screening the larger population of women who have a 5% HIV prevalence. But, unless an estimate is generated for the cost per infection averted, no conclusion can be drawn about whether prenatal screening is cost-effective relative to other interventions—even in a population with a 10% HIV prevalence. Benefit cannot be measured as number of HIV infected women identified; that number must be converted to number of cases averted to permit comparison to other types of interventions.

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56 Hassig SE; Kinkela N; Nsa W; et al.: Prevention of perinatal HIV transmission: are there alternatives to pre-pregnancy serological screening in Kinshasa, Zaire. *AIDS* 1990, 4:913-916.

Similarly, the overriding concerns in the literature comparing HIV testing systems and strategies in Africa are (1) reducing technical complexity and (2) optimizing sensitivity and specificity. Virtually absent is consideration of the appropriate trade-off between test cost and test quality.[57-62] Across the continent, many NACPs adopted the policy of requiring Western Blot (as opposed to a less expensive, potentially less accurate test) confirmation of a positive HIV screening test before informing the person tested. This policy has largely been adopted without considering the cost of averting the communication of a false positive result and without deciding what priority to place on averting a false communication relative to averting an infection.

Chapter III examines the role of HIV testing in combating the epidemic. It considers who benefits from the information obtained -- when testing is used for screening, diagnosis, or treatment of HIV infection.

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57 Mitchell S; Tukei P; Mboup S; Mingle J; Hanson D: Field evaluation of an alternative HIV testing strategy. presented at the USAID Miniconference on AIDS. February, 1990.

58 Spielberg F; Kabeya CM; Quinn TC; et al.: Performance and cost-effectiveness of a dual rapid assay system for screening and confirmation of human immunodeficiency virus type 1 seropositivity. *J Clin Microbiol* 1990, 28:303-6.

59 Constantine NT; Fox E; Abbatte EA; Woody JN: Diagnostic usefulness of five screening assays for HIV in an east African city where prevalence of infection is low. *AIDS* 1989, 3:313-17.

60 Smillie JM; Ala FA: Reducing the cost of anti-HIV screening. *J Virol Methods* 1988, 19:181-4.

61 Fortes P; Menitove J; Ross A; et al.: Evaluation of blood collected on filter paper for detection of antibodies to human immunodeficiency virus type 1. *J Clin Microbiol* June 1989, 27:1380-1.

62 Kline RL; Brothers TA; Brookmeyer R; Zeger S; Quinn TC: Evaluation of human immunodeficiency virus seroprevalence in population surveys using pooled sera. *J Clin Microbiol* July 1989, 27:1449-52.

III

HIV TESTING: AN OVERVIEW OF ITS ROLE IN AFRICA

Introduction

This thesis focuses on HIV testing because the cost of testing is potentially a large portion of the total cost of combating AIDS in many African countries and more importantly because the HIV test plays an integral role in most aspects of the fight against the virus and its effects. Because the HIV test is useful for both prevention and treatment, it is hoped that models developed in subsequent chapters to examine the cost-effectiveness of HIV testing will be useful to policy makers who seek to extend this analysis to other preventive and therapeutic technologies.

This chapter will outline the general uses of HIV tests then briefly describe the biology that underlies HIV testing. It will conclude with a discussion of how to compare the performance of different testing methods. This chapter attempts to provide an overview of HIV testing in developing countries in anticipation of the in-depth discussions that follow of three uses of testing.

USES OF THE HIV TEST

Diagnostic Use: Symptomatic Patient

Diagnosis of HIV-related disease is one of the most obvious uses of HIV tests. The HIV test has joined the armamentarium available to help the clinician determine the cause of a patient's medical problem. In the spectrum of diagnostic tests, it is relatively inexpensive and easy to perform; more akin to a hemoglobin measurement or a gonorrhea culture than a CAT scan or an endoscopy.

As with any diagnostic test, obtaining an HIV test can help confirm or eliminate HIV infection as the cause of a patient's signs and symptoms. The results of the test may result in a change in therapy. If a change in management occurs, the patient may benefit if symptoms are relieved more quickly or disease progression is slowed. This change in management may also benefit whoever must pay for the care, if unnecessary care is

avoided. Other patients may also benefit, for example if more efficient care shortens a hospital stay, liberating a bed.

The manifestations of HIV infection are perhaps as varied as those of any known pathologic entity. In the acute period, immediately following infection, the virus can cause a variety of problems, most commonly a flu-like illness. The more important effects of HIV are related to its ability to cause a chronic infection of different types of cells, most importantly cells that mediate the body's immune response. As a result of infection and destruction of these immune cells, the body is unable to effectively defend itself against certain malignancies and infectious organisms. Organisms which normally are unable to cause human disease but which are pathogenic in HIV infected (immunocompromised) persons are termed opportunistic organisms. Opportunistic infections and certain HIV-related malignancies, especially Kaposi sarcoma, are the most visible aspects of HIV-related disease. However, it is important to remember that almost every organ system can be affected and that HIV-related disease can mimic a wide range of non HIV-related problems.

Clinicians typically approach a patient with a problem by constructing a differential diagnosis, meaning a list of the diagnoses that could explain the patient's problem in decreasing order of likelihood. The HIV test provides evidence about whether a patient is infected with the HIV virus. Such knowledge may help the clinician diagnose the patient's illness, often by altering the relative position of items on the differential diagnosis. Most diagnostic tests are useful because they affect the position or relative probabilities of the items on the differential (diagnosis). For example, if a patient presents with a chronic cough, tuberculosis is on the differential. A tuberculosis culture of the patient's sputum, if positive, will move tuberculosis to the top of the list, far above other possible diagnoses. If the culture is negative, tuberculosis moves far down (but not off) the list.

The HIV test can be used in a similar way. For example, if a young, otherwise healthy adult has a decline in cognitive function, HIV dementia might be suspected, among other causes. A positive HIV test would greatly increase the probability that the cognitive decline was secondary to HIV dementia, although it is also possible that the patient has asymptomatic HIV infection and that the dementia is due to an unrelated cause. With HIV there is an additional complexity because it is both a direct cause of disease (e.g. dementia) and an indirect cause via immune suppression. For example, if a patient presents with cough, mild shortness of breath, and a chest radiograph suggestive of pneumonia, the

immediate cause is probably not HIV, although knowledge that the patient was HIV infected would dramatically alter the list of probably etiologies.

Diagnostic tests reduce uncertainty by increasing the probability that the presumptive diagnosis is the correct diagnoses and thereby increase the probability that treatment specific for this diagnosis will be successful. The question that will be addressed in Chapter V is under what circumstances can the HIV test alter the differential diagnosis in a way that has important consequences for patient care or for cost of treatment.

Diagnostic Use: Screening Asymptomatic Individuals

A very different "diagnostic" use of the HIV test is to screen asymptomatic individuals. This "diagnostic" section will be restricted to effects of testing upon the individual being tested (i.e. early diagnosis of HIV infection); HIV screening for prevention of further HIV transmission will not be discussed here. Benefits of screening to allow for early detection include:

- early treatment designed to prevent, or at least delay, the onset of HIV-related disease;
- for infected individuals, ability to plan their lives differently; for example, some people would choose not to have children, others might avoid lengthy educational programs;
- for uninfected individuals, knowledge that they have not been infected, especially for those with a high index of suspicion, might provide psychological benefit.

Prior to the advent of HIV testing, it was fair to generalize:[1]

> One desired outcome (and presumably in most cases the main reason for screening) is the improvement in treatment quality resulting from the detection and treatment of an individual who truly has the illness. [The value of this improvement] will be large when the illness itself is very undesirable, and importantly, when there is an asymptomatic stage during which the prospects for successful treatment are better than after symptoms appear. If the illness is communicable... there may be additional benefits related to other cases prevented due to the early detection of a case by the screening program...

Whether screening is being conducted for sexually transmitted diseases (STD's), hypertension, cancer, phenylketonuria (PKU), diabetes, or tuberculosis, the usual primary

1 Goddeeris JH; Bronken TP; Benefit-cost analysis of screening. A comparison of tests for gonorrhea. *Med-Care*. 1985 Nov; 23(11): 1242-55.

motivation for testing is to improve the quality of life of the individual being tested through the timely initiation of treatment. In these cases it is a *sine qua non* that the expected net utility for the person being tested is positive.

There are exceptions to this general rule. Drug and alcohol screening, whether for sports, employment, or drivers, serves the primary purpose of protecting others; only as a secondary benefit can it be claimed that the individual tested may be helped by being encouraged to seek help. Few people would perceive a positive expected net utility for their individual test, though many may support such a testing program because the positive expected benefits of testing others may exceed the negative expected benefit of being tested themselves. Several authors have advanced similar arguments to support HIV screening of hospitalized patients for the purpose of protecting health care workers.[2]

Another exception to the general rule that testing is done for the benefit of the individual tested is prenatal testing to identify fetal anomalies with the goal of terminating the pregnancy if such an anomaly is found. This has obvious relevance to prenatal HIV screening.

Screening asymptomatic individuals: What can be learned from Huntington's disease?

In an attempt to isolate "psychic" costs and benefits from those associated with treatment or prevention, consider a non-STD example. Long awaited, recombinant DNA technology has opened the door to screening for defective genes that predispose to disease. One of the most visible of these is the new screening test for Huntington Chorea (HC).

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2 AU: Fournier AM; Zeppa R; Preoperative screening for HIV infection. A balanced view for the practicing surgeon. *Arch Surg.* 1989 Sep; 124(9): 1038-40.

3 Goddeeris et al *op cit.*

4 The use of "willing to pay"(WTP) is used to mean all the resources that the individual is willing and able to pay or to have paid on his or her behalf. This will obviously be influenced by the individual's preferences and by his or her financial resources, access to credit, insurance coverage, etc.

5 Including the full discounted value of future consumption would tend to bias the estimate in the opposite direction, because the individual would usually be willing to reduce future consumption to pay to avoid death. Conversely, he or she may be willing and able to increase earnings, if necessary, to pay to avoid early death.

6 In most market transactions the benefit to the consumer is greater than the price paid because of consumer surplus; the price paid only reflects the value of the last unit consumed, which is usually lower than what the consumer would be willing to pay for the first unit. In this example, demand is virtually inelastic. The average American with HZ would not consume any more acyclovir, even if the price were zero. As a result, the quantity (and therefore cost) consumed reveals little about the individual's WTP.

7 $100 to $200 for a normal treatment course ($63.90 per 100 capsules of 200mg), personal communication, pharmacy, Hospital of the University of Pennsylvania.

HC is a fatal neurologic disorder that has a long latency period, not manifesting itself until about age 40. There is no known cure. The disease is transmitted as an autosomal dominant trait, such that someone that is (or will be) affected has a 50/50 chance of passing the disease on to each of his or her children.[8] In some ways, the HC screening test, though it is a more recent development than the HIV screening test, can offer useful insight into the psychology (or utility) of being tested for HIV from the perspective of the person tested. HC and HIV disease are similar in that there is a long latency period and virtually nothing, at least in developing countries where patients often cannot pay for antiretroviral therapy, that can be done to prevent or postpone disease onset. Furthermore, an affected mother with either disease has a high probability of transmitting the disease to her offspring.

Unlike HIV, HC is not contagious and poses no risk to other persons, sexual partners or otherwise. Because of the extensive similarities and this one essential difference, studying the way that people at risk for HC have responded to the emergence of the HC test provides insight into the factors that influence people at risk for HIV, especially those factors that relate to the fatal, incurable prognosis of a positive HIV test rather than the factors related to the desire to test for HIV to reduce sexual or blood-borne transmission. Some have suggested that any rational person would want to know their HIV status: "only a perverted nature would prompt a man to promote a perpetuation of avoidable ignorance,"[9] from which follows the argument that the reasons people don't want to know their HIV status come either from negative aspects of the testing process itself or from negative consequences, such as discrimination, that might follow from being discovered to be positive. The extension of this argument is that if HIV tests results were completely confidential and if the tests were accurate, painless, and accessible, then people at risk would almost universally want to be tested.

Experience with the HC test gives us reason to question this logic.[10-12,]

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8 Cutler, Robert. "Degenerative and Hereditary Diseases," sub-chapter in "Neurology," chapter in *Scientific American Medicine,* ed. in chief Edward Rubenstein, 6. New York: Scientific American, 1988.

9 Black, Douglas.

10 Bloch M; Hayden MR: Opinion: predictive testing for Huntington disease in childhood: challenges and implications. *Am J Hum Genet.* 1990 Jan; 46(1): 1-4.

11 Craufurd D; Dodge A; Kerzin-Storrar L; Harris R: Uptake of presymptomatic predictive testing for Huntington's disease. *Lancet.* 1989 Sep 9; 2(8663): 603-5.

12 Morris MJ; Tyler A; Lazarou L; Meredith L; Harper PS: Problems in genetic prediction for Huntington's disease [published erratum appears in Lancet 1989 Sep 23;2(8665):756] *Lancet.* 1989 Sep 9; 2(8663): 601-3.

There are a number of factors that complicate the comparison between these two screening tests.[13-21] HIV infection is uniquely stigmatizing because of its moral and sexual implications. However, the stigma associated with a diagnosis of the progressive dementia of Huntington Chorea may also be devastating. Another important difference is the way that potentially affected persons perceive their likelihood of being affected. It would be fair to assume that HC offspring who have participated in studies have been counseled and understand that each of them has a 50% chance of being affected. In the case of HIV infection, an individual will have much less complete information. Even if individuals knew the seroprevalence in their peer group, an individual's probability of being infected is influenced by his or her own past behavior. Thus, an individual's perception of his or her probability of being infected would depend upon how he or she believes that behavior has influenced the risk.

Suppose a man is faced with a decision, such as whether to marry. Suppose that if he knew he was HIV positive (or HC positive), he would not want to marry, but that otherwise he would. The more certain he is that he either is or that he is not affected (the further from 50% he perceives the probability to be), the less he expects to gain by having himself tested. If he thinks that there is a 5% chance he is infected and marries, he does so believing that an HIV test would only have altered his decision 1 in 20 times. If, however, he thinks he has a 50% chance of being infected, there is a 1 in 2 chance that an HIV test would alter his decision.

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13 Fahy M; Robbins C; Bloch M; Turnell RW; Hayden MR: Different options for prenatal testing for Huntington's disease using DNA probes. *J Med Genet.* 1989 Jun; 26(6): 353-7.

14 Bloch M; Fahy M; Fox S; Hayden MR: Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. *Am J Med Genet.* 1989 Feb; 32(2): 217-24.

15 Evers-Kiebooms G; Swerts A; Cassiman JJ; Van den Berghe H: The motivation of at-risk individuals and their partners in deciding for or against predictive testing for Huntington's disease. *Clin Genet.* 1989 Jan; 35(1): 29-40.

16 Evers-Kiebooms G; Decision making in Huntington's disease and cystic fibrosis. *Birth Defects.* 1987; 23(2): 115-49.

17 Shaw MW; Testing for the Huntington gene: a right to know, a right not to know, or a duty to know. *Am J Med Genet.* 1987 Feb; 26(2): 243-6.

18 Markel DS; Young AB; Penney JB; At-risk persons' attitudes toward presymptomatic and prenatal testing of Huntington disease in Michigan. *Am J Med Genet.* 1987 Feb; 26(2): 295-305.

19 Meissen GJ; Berchek RL; Intended use of predictive testing by those at risk for Huntington disease. *Am J Med Genet.* 1987 Feb; 26(2): 283-93.

20 Mastromauro C; Myers RH; Berkman B; Attitudes toward presymptomatic testing in Huntington disease. *Am J Med Genet.* 1987 Feb; 26(2): 271-82.

21 Kolata G; Genetic screening raises questions for employers and insurers [news] *Science.* 1986 Apr 18; 232(4748): 317-9.

Even if statistics suggest that HC offspring have a 50% chance of being affected, they certainly don't uniformly perceive a 50% probability.[22] Ask almost any pregnant woman about the sex of the child she is carrying (before it has been determined) and she is likely to have an opinion. Likewise, HC offspring will probably believe that luck, God, or any of a host of other factors pushes their individual probability away from 50% in one direction or the other. Thus, an indication of perceived benefit from testing for a population is the mean difference-from-50% of individuals' pre-test probabilities. Even without objective evidence, it is almost certainly true that the mean difference for the population at risk for HC is smaller than for the population at risk for HIV infection -- if for no other reason than statistical HIV risks are distributed from 0% to 100%, while statistical HC risk is always 50%. Therefore, all else being equal, persons at risk for HC should be **more** interested in being tested than persons at risk for HIV infection.

Suppose a person at risk for HC was surreptitiously tested and found to be negative. The psychic value of a negative test result could be conceptualized as the benefit that would accrue to the individual upon being told of the negative result while not having known that they had been tested. While value would in theory be reflected in willingness-to-pay (WTP), in this hypothetical scenario the individual could not be "willing to pay" for something that they didn't know existed. If the individual knew that the test had been done, then it would no longer represent the value of a negative result, but rather the value of knowing the result of the test which would incorporate the costs, benefits, and probabilities associated with true and false positive and negative test results. The cost of a true positive result could be conceptualized similarly, as the cost associated with being informed that the test result is positive. However, one might argue that this unfairly inflates the size of the cost because the vast majority of people at risk for HC will develop the disease and therefore eventually find out that they are affected. In this case the only effect of the test is to inform them earlier of something that they would learn later anyway. All else being equal, normal time preference suggests that people prefer to reap benefits as soon as possible and to delay costs as long as possible. Thus, while it may seem far fetched, one could imagine a discount rate for information. The economic person would be willing to pay a premium to receive good news earlier and likewise pay a premium to have bad news delayed. This is an economic conceptualization of what ethicists have termed the "right not to know".[23]

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22 Markel DS, Young AB, Penney JB, *op cit*

23 Shaw MW *op cit* .

Thus, perhaps the better way to conceptualize the value of an HC test result is as the difference between the value of learning the test result in the present and the discounted value of learning the test result in the future. This theoretical structure is easily adapted to incorporate false positive and false negative results, as these also compare the psychic cost or benefit of the learning the (false) result now, with the weighted, discounted cost or benefit of learning the (true) result in the future. It has been suggested that bad news (such as a positive test result) is not an economic "good", but an economic "bad". Some people, thinking back to the quote above: "only a perverted nature... ", would argue that truthful information, whether good news or bad, is always an economic good and therefore has a positive discount rate associated with it. Such a view may consider "psychic costs" as insignificant relative to the value of being able to act upon the information if it is available sooner. For example, a person at risk for HC might wish to know early, even if the result is positive, so that they can modify plans for career, marriage, child rearing, or whatever.

Influence of religious or supernatural beliefs

Belief in magical or supernatural causes of disease are prevalent worldwide and do not necessarily conflict with biological explanations of the same disease process. For example, consider how many physicians in the U.S. would pray if they became sick, in the hope that God would help make them well. In developing countries, belief structures more frequently credit certain individuals with the power to cause disease in others. Phenomena which may be explained by the science of probability seem to be most amenable to incorporation into a mystical belief structure, be that sorcery or a monotheistic religion. These beliefs are likely to influence an individual's willingness to be tested. HIV infection is especially well suited such explanations because both its transmission and its progression to AIDS are highly variable probabalistic events that run counter to peoples' prior experience with disease:

- HIV is contagious, but the probability of it being transmitted with any particular sexual act is low. Thus, when someone is infected, some of that person's sexual partners will become infected, others not. (It is very difficult to explain to someone why they slept with someone once and became infected, while somebody else slept with the same person 100 times and did not became infected.)
- someone can catch a fatal disease and die of it without the transmitter even being sick. (Even more difficult, is explaining to a man whose wife has been diagnosed with AIDS that the virus did not necessarily pass from her to him, just because she was the first to develop symptoms.)

- even when somebody is infected, there is great uncertainty about when he or she will become symptomatic. For one person it could be 2 years, for another, 20 years.

When both disease transmission and disease progression are probabilistic events, each with a low probability (probability of transmission per contact or probability of developing AIDS per year), it is easy to believe that the probability of each can be influenced by magic (or "luck"). It is conceivable that someone could believe that the process of being tested could influence the probability of being HIV positive or the probability of becoming symptomatic. It could also be that someone believes that their infection status is truly undetermined (in a state of flux depending upon the prevailing supernatural forces) but that once the test is done the infection state becomes fixed. In that way, the test could actually lock somebody into the state of being infected. While these postulated relationships between HIV testing and beliefs about the magical basis of disease are only hypotheses, there is no question that in many parts of Africa and other developing countries the belief that some people with strong magic are able to induce disease in others is widely held.[24-26] Although people in industrialized countries are less likely to believe in the magical powers of individuals, analogous beliefs that are very prevalent maintain that God increases the probability of disease for sinners; decreases its probability for the faithful; and is influenced in his actions by prayer. Whatever the local belief structure, it is important that the influence of culturally dependent views of disease on the acceptability of HIV testing be studied prior to launching large scale programs, especially when considering the design of counseling components.

Testing to distinguish HIV+ and HIV- individuals

The use of the HIV test to distinguish HIV+ from HIV- individuals for the purpose of restricting the access of one or the other group to opportunities, services, or whatever, poses greater ethical dilemmas than using the test for diagnosis or prevention. Proponents of testing in a particular setting are likely to point to the advantage of being able to discriminate *between* the two groups, while opponents of the testing are more likely to point out that the test is discriminating *against* one or the other group. Familiar settings in which the HIV test is used to distinguish the two groups include:

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24 Fabrega H; Nutini H; Witchcraft-explained childhood tragedies in Tlaxcala, and their medical sequelae. *Soc Sci Med.* 1993 Mar; 36(6): 793-805.

25 Zeitlyn S; Rowshan R; Mahalanabis D; Faruque A; The ethnophysiology of digestion and diarrhoea in a Bangladeshi hospital population. *J Diarrhoeal Dis Res.* 1993 Dec; 11(4): 243-8.

26 Reynolds P; Zezuru turn of the screw. On children's exposure to evil. *Cult Med Psychiatry.* 1990 Sept; 14(3): 313-37.

- mandatory screening to restrict access to health or life insurance;[27,28]
- mandatory pre-employment screening to exclude HIV positive persons as done by the U.S. Foreign Service, the U.S. military and large numbers of private employers worldwide;[29,30]
- mandatory screening to determine eligibility for scholarships, educational fellowships, training programs or other long-term investment in human capital;
- mandatory screening of international visitors and immigrants, such as required by the United States;
- mandatory screening for the purpose of quarantining infected individuals, such as has been practiced in Cuba[31,32] and in some prisons;[33,34]
- screening to determine eligibility for medical services, such as infertility surgery;
- screening as a prerequisite for a professional license, such as has been suggested for health care personnel and prostitutes;
- screening as a prerequisite for marriage;[35,36]
- screening as a prerequisite for access to services reserved for HIV positive persons, such as government employment programs.

These issues will not be discussed further.

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27 Hiam P; Insurers, consumers, and testing: the AIDS experience. *Law Med Health Care.* 1987-88 Winter; 15(4): 212-22.

28 Hollowell EE; Eldridge JE; AIDS and the insurance industry. The debate within the debate. *J Leg Med.* 1989 Mar; 10(1): 77-87.

29 Brundage JF; Burke DS; Gardner LI; McNeil JG; Goldenbaum M; Visintine R; Redfield RR; Peterson M; Miller RN; Tracking the spread of the HIV infection epidemic among young adults in the United States: results of the first four years of screening among civilian applicants for U.S. military service. *J Acquir Immune Defic Syndr.* 1990; 3(12): 1168-80.

30 Gostin LO; Curran WJ; Clark ME; The case against compulsory casefinding in controlling AIDS--testing, screening and reporting. *Am J Law Med.* 1987; 12(1): 7-53.

31 Bayer R; Healton C; Controlling AIDS in Cuba. The logic of quarantine. *N Engl J Med.* 1989 Apr 13; 320(15): 1022-4.

32 Molinert HT; Galban Garcia E; Rodriguez Cruz R; Prevalence of infection with human immunodeficiency virus in Cuba. *Bull Pan Am Health Organ.* 1989; 23(1-2): 62-7.

33 Harding TW; AIDS in prison . *Lancet..* 1987 Nov 28; 2(8570): 1260-3.

34 Andrus JK; Fleming DW; Knox C; McAlister RO; Skeels MR; Conrad RE; Horan JM; Foster LR; HIV testing in prisoners: is mandatory testing mandatory? *Am J Public Health.* 1989 Jul; 79(7): 840-2.

35 Turnock BJ; Kelly CJ; Mandatory premarital testing for human immunodeficiency virus. The Illinois experience. *JAMA.* 1989 Jun 16; 261(23): 3415-8.

36 Petersen LR; White CR; Premarital screening for antibodies to human immunodeficiency virus type 1 in the United States. The Premarital Screening Study Group. *Am J Public Health.* 1990 Sep; 80(9): 1087-90.

Preventive use: Transfusion

Use of the HIV test to prevent transmission of HIV via blood transfusion is perhaps its best known and least controversial use. The ELISA (Enzyme Linked ImmunoSorbent Assay) HIV test was developed largely in response to the need for a very sensitive test that could virtually eliminate the probability of transfusing an infected unit of blood. It has been so successful in developed countries, where virtually all blood products are screened, that there has been a tendency to assume that a policy of public sector funding of universal ELISA screening of transfusions is appropriate worldwide.[37] Chapter IV will argue that such a policy should be questioned in resource poor settings with a low incidence of HIV infection and will address the question of when and by what means HIV screening of transfusions is appropriate.

Preventive use: Maternal-Fetal

A far more controversial use for the HIV test is to reduce the incidence of maternal-fetal HIV transmission. Such a use is most commonly discussed in the context of screening women prenatally for infection with HIV. The implication is that some of the women who are infected will choose to terminate their pregnancy, thereby reducing maternal-fetal transmission. Other infected pregnant women will choose to continue their current pregnancy but will avoid becoming pregnant again, thereby also reducing transmission.

The cultural context in which these decisions are made is perhaps even more important than for sexual transmission. This has been highlighted in the United States as more HIV infected pregnant women are identified. Most of these women acquired their infection by sharing IV injection equipment or via sexual contact with someone who shared equipment. Sharing IV injection equipment is associated with the lowest socioeconomic stratum in the U.S.[38,39] Thus, when middle class health providers attempted to project their values about how they would react if pregnant and HIV-infected onto the population of HIV infected pregnant woman, they were surprised to find their expectations not

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37 Singh YN, Malaviya AN, Tripathy SP, et al: Human immunodeficiency virus infection in the blood donors of Delhi, India. *J Acquir Immune Defic Syndr.* 1990; 3(2):152-154.

38 Schrager L; Friedland G; Freiner C; Kahl P; Demographic characteristics, drug use, and sexual behavior of i.v. drug user with AIDS in Bronx, New york. *Public Health Rep.* 1991 Jan-Feb; 106(1): 78-84.

39 Shayne VT; Kaplan BJ; Double victims: poor women with AIDS. *Women Health.* 1991; 17(1): 21-37.

fulfilled.[40] A 40% chance of having an infected baby for one woman, may be a 60% chance of having a healthy baby for another woman.

Preventive use: Sexual transmission

In most contexts, the primary goal of screening is to influence the behavior of those being screened in the hope that infected individuals will modify their behavior to reduce the chance that they will transmit the virus and that seronegative individuals will modify their behavior to reduce the possibility that they will become infected.

In the United States, voluntary, confidential testing is a cornerstone of public health policies to reduce sexual transmission of HIV. This policy is predicated on the assumptions that individuals will altruistically change their behavior to protect the health of their sexual partners and that couples will decide to be tested in their mutual self-interest. However true these assumptions are in the USA,[41,42] it is dangerous to attempt to extrapolate their experience to Africa where circumstances are completely different .[43-45] To cite a few examples, American values place great importance on an individual's right to privacy and our legal system provides redress for individuals harmed by an illegal breach of confidentiality; both are much less true in most African countries. Legally and culturally, the role of men and woman in Africa is more disparate in Africa, which usually means that it is more difficult for a woman to ask a man to use a condom, more difficult for woman to refuse sex, and more difficult for a woman to ask a man to be tested for HIV.

In most African cultures it is much less common and less acceptable, compared to the U.S., for a couple to decide that they do not want children.[46] Since conception and safe sex are mutually contradictory, a strong desire to bear children may take priority over a

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40 Sunderland A; Ninkoff HL; Handle J, et al: The impact of human immunodeficiency virus serostatus on reproductive decisions of women. *Obstet and Gynecol.* 1992 Jun; 79(6): 1027-31.

41 Patterns of sexual behavior change among homosexual/bisexual men- selected U.S. sites, 1987-1990. *MMWR.* 1991 Nov 22; 40(46): 792-794.

42 Detels R; English P; Visscher BR; et al; Seroconversion, sexual activity, and condom use among 2915 HIV seronegative men followed for up to 2 years. *J Acquir Immune Defic Syndr.* 1989; 77-83.

43 Ryder RW; Batter VL; Nsuami M; et al.; Fertility rates in 238 HIV-1 seropositive women in Zaire followed for 3 years post-partum. *AIDS.* 1991 Dec; 5(12): 1521-7.

44 Allen S; Serufilira A; Bogaerts J; et al; Confidential testing and condom promotion in Africa. Impact on HIV and gonorrhea rates. *JAMA.* 1992 Dec. 16; 268(23): 3338-3343.

45 Allen S; Tice J; Van de perre P; et al; Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. *BMJ.* 1992 Jun 20; 304(6842): 1605-9.

46 Cochrane S; Sai F; Excess Fertility. in *Disease Control Priorities in Developing Countries* edited by Jamison DT Mosely HW. Washington, DC: World Bank 1993, pp 333-362.

desire to avoid infection.[47] The importance attached to a disease that has a long, asymptomatic latency period cannot be assumed to be the same. Less average exposure to Western medicine, makes it less likely that the a biologic explanation for a disease will be accepted, especially when the biologic explanation is as implausible as it is for HIV, with its long infective, asymptomatic latency period.

As alluded to above, belief in the powers of magic and witchcraft are widespread, at all socioeconomic levels, in many African cultures.

It will be difficult to predict the acceptance of or the response to voluntary, confidential testing (VCT) in Africa by extrapolating from U.S. and European experience. Interestingly, in high prevalence African communities, the most important role of VCT may be to convince HIV negative individuals that they have not been infected in spite of their past exposure and that it is in their self interest to practice safe sex.

Preventive use: Monitoring the epidemiology of the epidemic

Finally, HIV testing has a critical role to play in monitoring the progress of the epidemic. Such epidemiologic monitoring provides data that is vital in planning strategies both for preventing further spread of HIV and for alleviating the impact of the epidemic.

The percentage of the population affected by a disease is described by the incidence and prevalence of the disease. The incidence refers to the numbers of new cases, e.g. new infections, over a period of time, usually one year. It is expressed as the number of new cases over the size of the total population in which they occurred. Note that the total population includes both infected and non-infected persons. If the desired probability is that of a non-infected person becoming infected, it is calculated as the number of new cases over the total population at-risk (i.e. not-infected). This probability is often referred to as the seroconversion rate and is also usually calculated over a period of one year.

The prevalence of a disease is the percentage of the population that has the disease either at a point in time (point prevalence) or at any time during a year (annual prevalence). The relationship between incidence and prevalence depends upon the average duration of illness. If the duration of illness is very short, such as the common cold, the incidence and

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47 Sembaje ISL: Socio-cultural supports for high fertility in Buganda. in Ruzika LT, ed: *The Economic and Social Supports for High Fertility: Proceedings of the Conference held in Canberra 16-18 November 1976, Changing African Family Companion Series;* vol 2, 1977.

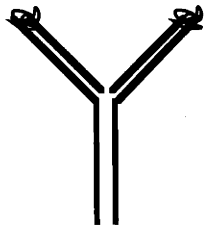
48 United Nations DIESA: Age structure and mortality in developing countries: a data base for cross-sectional and time series research in developing countries. New York, United Nations, 1986.

the annual prevalence are similar. If the average duration of illness is very long, as with HIV infection, then the incidence, at least once the epidemic has reached a steady state, will be much smaller than either the point or the annual prevalence. If the average duration is about one year, as with AIDS in Africa, then the annual incidence and the point prevalence will be similar.

Biology of HIV testing

Bacterial infections are typically diagnosed by taking a sample from a patient (e.g. blood, sputum, urine, wound drainage), culturing it, and identifying the bacteria that grow. It is possible to culture viruses, but it is difficult technically because they grow in cultures of cells, a technique only possible in sophisticated laboratories. Even in such laboratories, viral culture is not very sensitive and misses a large number of samples that can be shown to be infected by subsequent attempts at culturing or by other means. Molecular biologists have also developed a number of sophisticated tests (e.g.. polymerase chain reaction (PCR)) to detect HIV infection that are not appropriate for use in developing countries and will not be discussed further.[49]

Most laboratory diagnosis of viral infections makes use of the fact that the body's immune system makes antibodies to viruses as part of its attempt to eliminate the infection. Antibodies are proteins whose molecular structure is shaped like the letter "Y". At the two ends of the Y are two identical binding sites than enable an antibody to become attached to an infecting organism.



Variability in the amino acid sequences at the two ends of the Y permits virtually unlimited variation in the molecular configuration (and therefore of the binding properties) of those ends. When the body encounters a "foreign" entity, like a virus, it is able to select among the millions of different circulating antibody configurations those that bind to the virus and to "amplify" them, greatly increase the number of circulating antibodies that bind to that particular virus. A foreign entity that stimulates amplification of antibodies is called

49 Jackson JB; Detection and quantitation of human immunodeficiency virus type 1 using molecular DNA/RNA technology. *Arch Pathol Lab Med.* 1993 May; 117(5): 473-7.

an antigen. Normally, when large numbers of these antigen specific antibodies are produced, they bind to the antigen thus enabling the immune system to eliminate the infection.

Definition of HIV Testing

Detection of these amplified antibodies, which bind specifically to a particular virus, is what makes possible the indirect diagnosis of viral infection . Specific antibodies are relatively easy to detect precisely, because they attach themselves to a particular "antigen". Their "Y" shape also facilitates detection because they can attach themselves to two antigens, potentially linking them. The available tests include ELISA (Enzyme Linked ImmunoSorbent Assay), Western Blot, immunofluorescence, and various rapid tests. An in depth evaluation and description of each of these tests will not be provided here.

Antibodies permit *indirect* detection of infection. This is a potential source of difficulty. Most infections agents, viral or bacterial, provoke an amplification of antibodies which, in combination with other immune responses, successfully eliminates the infections organism. After the agent is no longer present to "stimulate" the immune system, the number of antibodies declines slowly, though the new steady state is usually higher than the pre-infection state. This provides "immunity," or the ability to more quickly defend against the infectious agent in the future. Clinicians use the rise and fall in antibody numbers, or "titer", to follow infection and recovery from infection. An elevated antibody titer implies that an individual has been infected with the agent sometime in the past, but is not necessarily currently infected. A falling titer suggests a recent infection that has been successfully eliminated and a rising titer suggests that the body is actively fighting an infection. Unfortunately, antibody titers are not very useful in following the progress of HIV infection.

HIV is different because the immune defense is unable to eliminate the virus. HIV attacks the immune system itself. All available evidence suggests that HIV is almost never eliminated after infection occurs.[50] Thus, while elevated HIV titers theoretically only suggests HIV infection at sometime in the past, practically, because HIV is not eliminated, it means that there is a current infection. A more important problem results from the delay that occurs between infection and antibody amplification. An infected individual may be infectious (capable of infecting others) before having a detectable anti-HIV antibody titer.

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50 Shaw G; Wong-Staal F; Gallo R; Etiology of AIDS: Virology, molecular biology, and evolution of human immunodeficiency viruses. in *AIDS Etiology, Diagnosis, treatment, and prevention.* edited by Devita VT; Hellman S; Rosenberg S; second ed. J.B. Lippincott , Philadelphia 1988; pp11-31 .

This period of "invisible" infection, known as the "window period" is variable, but thought to average approximately 6 weeks.[51-54] Thus, while an elevated HIV antibody titer almost invariably suggests active infection, absence of an elevated antibody titer does not necessarily suggest absence of infection if exposure has been recent. An additional difficulty arises because HIV attacks the very cells that produce antibodies. It is theoretically possible, and supported by disputed evidence,[55] that some infected persons with advanced disease will lose their elevated titers. For practical purposes, unless stated otherwise, "HIV positive" is assumed to be equivalent to "infected with HIV" and to "elevated HIV antibody titer".

Measurement of HIV Test Performance

Analyses of the cost-effectiveness of HIV testing, and of testing generally, must incorporate measures of performance that represent how "good" a particular assay is at detecting the condition it is testing for. For those readers unfamiliar with the relevant terminology, a short description follows. A discussion of how epidemiologic methods must be modified for economic analysis is also included.

Assume that a sample (usually of blood, although HIV tests can be performed on other samples, most notably saliva) is either infected or not-infected; and that the result of a test is either positive, negative, or indeterminate. Temporarily ignoring indeterminate results, the possible combinations are:

- True positive (TP): when an infected sample is tested and the test result is positive
- True negative (TN): when a non-infected sample is tested and the test result is negative
- False positive (FP): when a non-infected sample is tested and the test result is positive
- False negative (FN): when an infected sample is tested and the test result is negative

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51 Belsey EM; Maskill WJ; Emmanuel JC; Tamashiro H; Heymann DL; Evaluation of antigen testing using a model of the 'window' period for HIV-infected blood. 1994 July; submitted for publication.

52 Tindall B; Cooper DA; Primary HIV infection: host responses and intervention strategies. *AIDS.* 1991; 5:1-14.

53 Gains H; Albert J; Von Sydow; et al; HIV antigenaemia and virus isolation from plasma during primary HIV infection [letter]. *Lancet.* 1987; 1:1317-8.

54 Daar ES; Moudgil T; Meyer RD; Ho DD; Transient high levels of viremia in atients with primary human immunodeficiency virus type 1 infection. *N Engl J Med.* 1991; 324:961-4.

55 Nelson AM; Hassig S; Kayembe M; et al; HIV-1 seropositivity and mortality at University Hospital, Kinshasa, Zaire, 1987. *AIDS.* 1991 May; 5(5): 583-586.

It is intuitively clear that if two methods are compared, the one with fewer "false" results is "better". "Better" is measured using two probabilities that permit comparisons between tests:[56]

- Sensitivity is defined as the probability that an infected sample will have a positive test result.
- Specificity is defined as or the probability that a non infected sample will have a negative test result .

Sensitivity and specificity are useful to a laboratory director who is comparing different methods, but are not very useful to a clinician. He or she would like to know the probability that a patient is infected, if they have a positive HIV test result. This probability is not only a function of the method's sensitivity and specificity, but also of the HIV prevalence in the patient population .

Consider an example: if a population in rural Japan with no infected individuals is tested, then all positive test results will be false positive results. Conversely, if the patients in an AIDS ward of a Ugandan hospital are tested, all of whom are infected, then all positive test results will be true positives. The percentage of all positive results that are true positives will increase as the percentage of the samples that are infected increases. Similarly, the percentage of all negative results that are true negatives falls as the HIV prevalence in the population rises.

Test results can only be divided into TP, TN, FP, and FN if the test result and the "true" infection status of each sample is know. Knowing the "true" status implies that the method is being compared to a gold standard which has no inherent error. A truly "error-free" test to verify infection with HIV does not exist. The gold standard that has most commonly been used is a combination of ELISA and Western Blot. It is not known what the sensitivity and specificity are of the combination, however, the rate of indeterminate results is high enough to show that this gold standard is far from error free. With this *caveat* in mind, two clinically useful probabilities are:

- Positive predictive value (PPV): the probability that a sample is infected, given that the test is positive. This is equivalent to the expected percentage of all positive tests that will be true positives.

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56 In the equations that follow, assume that an HIV test method has been used to test a population. TP, TN, FP, and FN refer to the number of each result obtained.

- Negative predictive value (NPV): the probability that a sample is not infected, given that the test is negative. This is equivalent to the expected percentage of all negative test results that will be true negatives.

Consider example: when screening populations with a low percentage of infected individuals, even a very "good" test can lead to surprisingly many false positives. If one person per thousand is infected and the test has a 99% sensitivity and a 99% specificity then for each true positive test result, approximately ten false positive results are expected.

It is important to note that sensitivity and specificity are independent of prevalence, and thus are characteristics only of the method. PPV and NPV are critically dependent upon prevalence.

Although sensitivity, specificity, PPV, and NPV are useful in deciding whether to employ a test, they do not consider the cost of the test, the discomfort and other harm to the patient that accompanies performing the test, and of the probability that the test will yield no information because of an indeterminate result.

The above definition of sensitivity would not differentiate between two methods, one yielding 10% indeterminate results and the other 1%, yet this difference is essential when comparing the cost effectiveness of the methods. An indeterminate result assumes greater importance in Africa where cost and technological requirements limit the availability of confirmatory tests.

Most diagnostic methods, including those to detect HIV antibodies, yield a continuous (rather than discrete or dichotomous) result. A threshold level is established which divides the range of output into a negative and a positive domain. Alternately, two thresholds are established, dividing the range of test result into positive, negative, and indeterminate domains. In the U.S., an initial diagnostic HIV test (ELISA) is treated as if there were only two possible results, negative and indeterminate, because a "positive" result is never reported to a patient unless a second, confirmatory test (usually Western Blot) is performed.

In Africa, a confirmatory test may be unjustifiably expensive or unavailable, in which case the optimal approach may be to establish three ranges, so that a single method may yield both positive and negative results. In a setting where one method is used both for screening low prevalence populations (where the PPV is low) and high prevalence

populations (where the PPV is high), the optimal approach may be to use different threshold values for the different populations.

Chapter IV considers the economics of HIV screening blood for transfusion in developing countries and presents two models for estimating the costs associated with averting an HIV infection through donor/blood screening so that screening may be compared to other interventions for AIDS prevention in resource poor settings.

IV

HIV Testing to Reduce Transfusion-related Transmission

Introduction

Unlike Western industrialized countries, which universally screen all blood for transfusion for the presence of anti-HIV antibodies, the vast majority of African countries are struggling with the questions of 1) where should screening be implemented? 2) where should other programs be implemented to reduce transfusion associated HIV transmission? and 3) where it is decided to implement screening, what is the appropriate level of program performance, assuming that improved performance can be purchased at higher cost? This chapter develops a simple model that can be used to help answer these questions. The model can be estimated with a pocket calculator and uses data that should be available with little effort anywhere widespread HIV testing in blood transfusions is being considered. After the model is developed, several examples of possible uses are given. Finally, a more complex model is developed and compared to the simple model in an attempt to confirm the robustness of the assumptions that underlie the simple model.

In industrialized countries the decision to test blood for transfusion is inexorably linked to a program that counsels the HIV positive donors detected. The economic reality on most of the African continent has led many centers to begin screening blood for transfusion even if resources are not available to confirm and counsel seropositive donors. It is therefore useful to evaluate a screening program separately from a program to confirm and counsel seropositive donors. Donors who **test** positive on a transfusion center screening test are at very high risk of **being** HIV positive. If it is decided to begin a program of screening people with the goal of changing their behavior, it may make sense to begin with the population of blood donors who have screened positive. However, that decision is distinct from the decision about whether it is worthwhile to screen blood for transfusion.

The goal of screening blood prior to transfusion is to prevent new HIV infections, so cost is evaluated with respect to that goal; expected cost will be expressed per HIV infection averted. The two most important determinants of that cost will be (1) the cost of the HIV test and (2) the seroprevalence in the donor population.

Model Development

A troublesome aspect of discussions of the costs and benefits associated with preventing HIV/AIDS is that there is no general consensus on what is the appropriate unit of benefit. Options include an HIV infection averted, a case of AIDS averted, and a death averted. The first offers the advantage of being the direct consequence of the prevention activity -- whether screening a unit of blood or wearing a condom -- and thus the easiest to measure.

At its simplest, estimation of the cost of preventing an HIV infection via blood screening would estimate the cost of detecting an infected unit of blood and equate that to the cost of preventing an HIV infection. However there are several important corrections which must be made:

- Even if it is assumed that HIV positive blood is 100% infectious and that 100% of patients infected with HIV would progress to die of AIDS (average delay of 10 years), detecting an HIV positive blood donor is still not equivalent to preventing a heterosexual transmission of HIV. Patients who receive transfusions are sick—many of them will never live long enough to suffer any consequences of their HIV positive transfusion.[1] If the cost of screening blood for HIV is to be compared to the cost of other interventions to prevent HIV transmission, then it must be corrected for the higher mortality of the blood recipients. In addition, detection of an infected unit of blood before it is transfused into a patient already infected with HIV cannot be considered an HIV infection averted.

- Some places that transfuse blood derive several blood products, on average, from each donated unit of blood. The most common example is the separation of whole blood into plasma and packed red blood cells. Large urban blood banks may routinely fractionate blood, while small transfusion centers usually transfuse whole blood. If an infected unit is fractionated, then all of the patients transfused with the different components derived from the unit may be exposed to the virus. Conversely, detecting and eliminating an

1 In Mama Yemo Hospital in Kinshasa, Zaire, HIV negative patients on the internal medicine service had approximately a 30% chance of not leaving the hospital alive [Hassig SE; Perriens J; Baende E; *et al.* An analysis of the economic impact of HIV infection among patients at Mama Yemo Hospital, Kinshasa, Zaire. *AIDS.* 1990 Sept; 4(9);883-7]

infected unit would avert as many exposures as the number of people who would have received infected components.

- The additional cost of implementing a blood screening program includes not only the costs of screening, but also the costs of discarding and replacing any units that test positive (whether truly infected or not).

Variable definitions:

CHIV ..... Cost per "standard" HIV infection averted
CDETECT ..... Cost per infected unit detected
SURV ..... Percentage of recipients of HIV infected blood products expected to survive till they develop AIDS[2]
BLOOD ..... Average number of blood products derived and transfused from a single donated unit
CSCREEN ..... Expected cost of HIV screening necessary to identify an infected unit
CREPLACE ..... Expected cost of replacing all units that test (true and false) positive per infected unit identified
SN ..... HIV test sensitivity
SP ..... HIV test specificity
PREV ..... HIV seroprevalence among donors
TP ..... Probability that an HIV test will have a true positive test result
FP ..... Probability that an HIV test will have a false positive test result
TEST ..... Average cost of screening one unit
REPL ..... Average cost of replacing one unit[3]

$$TP = PREV * SN$$

$$FP = (1-PREV)(1-SP)$$

$$CSCREEN = TEST\left[\left(\frac{1}{TP}\right)+1+\left(\frac{1}{TP}\right)FP\right] \qquad \text{eq } 1^{4}$$

2 Not including recipients who are already HIV infected at the time of transfusion.

3 The cost of replacing a unit that tests positive will vary from setting to setting, but it will include the cost of recruiting a replacement donor, the cost of any tests that are done before the HIV test, such as blood typing or hemoglobin, and the cost of any HIV pre-test counseling that is done. In blood banks that test the unit after collection (most), the cost will include the cost of collecting a unit (including blood bag, tubing, needle and labor).

4 The cost of HIV screening necessary to identify an infected unit [CSCREEN] is approximately equal to :

- The cost per individual HIV test (TEST) multiplied by the total number of HIV tests that need to be done.

$$\text{CREPLACE} = \text{REPL}\left[1 + \left(\frac{1}{\text{TP}}\right)\text{FP}\right] \qquad \text{eq } 2^{5}$$

$$\text{CDETECT} = \text{CSCREEN} + \text{CREPLACE} \qquad \text{eq 3}$$

$$\text{CHIV} = \text{CDETECT}\left(\frac{1}{\text{SURV}}\right)\left(\frac{1}{\text{BLOOD}}\right) \qquad \text{eq 4}$$

To correct for the higher mortality of blood recipients, CHIV is divided by the percentage of recipients expected to survive till they develop AIDS (SURV).[6] CHIV is further divided by the average number of blood products that are derived from a unit of blood (BLOOD).

- 1/TP represents the average number of tests that will be done until one positive donor is identified. If TP is the probability that a donor will be HIV infected and be detected by the screening test (a true positive result), then the inverse of TP is the average number of donors that must be screened to find one true positive. PREV is the percentage of the donor population that is HIV positive; PREV x SN is the percentage of the population that is HIV positive that will be detected by the screening test, or TP, the probability that a unit will have a true positive test result.
- The "1" represents the test needed to test the donor who replaces the positive donor.
- The last part of the second term (1/TP)FP, is the average number of tests that will be done to replace the HIV negative donors who falsely tested positive on the screening test. FP is the probability that a donor will have a false positive test result. It is the product of the probability that a donor will be HIV negative (1-PREV) and the probability that an HIV negative donor will falsely test positive (1-SP). As explained above, the inverse of TP represents the average number of tests that are done to identify one true positive. When that is multiplied by FP, the result is the expected number of those tests that will have a false positive result.

For example, if twenty percent, or one fifth, of the donor population is HIV positive then five (or the inverse of one fifth) donors will have to be tested, on average, to find the first positive donor. Another test will have to be done to replace the positive donor. Additional tests will have to be done to replace any of the four negative donors that falsely test positive.

5 The cost of replacing one donor (REPL) is multiplied by the total number of positive tests, as in eq 1 above.

6 The precise definition of "probability that a patient will survive long enough to suffer consequences of transfusion acquired HIV infection" is purposely left somewhat vague so that the user of the model can define it in a way that is locally relevant. The variable, SURV, corrects for the fact that preventing infection of an average transfusion recipient is not equivalent to preventing infection of an average sexually active adult. Because transfusion recipients are ill, they are less likely to live long enough to develop AIDS. They are less likely to become pregnant and transmit the virus perinatally and they are less active sexually and thus less likely to transmit the virus sexually. They are also more likely to already be infected with HIV and in those patients HIV infection cannot be averted. The locally appropriate value for SURV will depend in part on the survival characteristics of transfusion recipients and in part on the end point that is used to evaluate other AIDS prevention programs. If evaluation of a condom distribution program is evaluated per primary HIV infection prevented, then SURV should reflect the probability that a recipient of an HIV positive transfusion will develop AIDS; if it is evaluated per primary and secondary HIV infection averted, or per any other end point, then SURV can be modified accordingly.

The model was estimated using the parameter values below (Table IV.1). These were chosen not to describe any particular place, but because they reasonably could describe a setting in Africa. It deserves emphasis that all of the inputs to the model should be obtainable without great difficulty anywhere widespread HIV screening is being seriously considered. One way to estimate the percentage of patients who survive long enough to suffer sequelae of HIV infection would be to conduct a retrospective review of the charts of transfusion recipients to see what percentage die prior to leaving the facility or are discharged with a lethal diagnosis (including HIV infection!).[7]

Table IV.1: Baseline Values for Input Parameters

	Sensitivity	Specificity	Preva–lence	% Survive	Cost per test	Cost replace donor	# Blood products per unit
Variable name	SN	SP	PREV	SURV	TEST	REPL	BLOOD
Baseline value	95%	95%	5%	50%	$2.50	$1.00	1

CHIV = $119

When these values are used to calculate the cost per "standard" HIV infection averted, the cost is $119, which suggests that a testing program, under these conditions, is an inexpensive way to avert a death — in comparison to the cost of averting a death in most African countries using other disease prevention programs, such as measles vaccination. It is less clear whether $119 is an inexpensive way to avert an HIV infection — in comparison to other programs to reduce HIV transmission, such as AIDS education, distributing condoms, or offering alternative employment to HIV positive prostitutes.

Sensitivity Analysis

One hundred and nineteen dollars does not necessarily represent the cost of averting an HIV infection anywhere in Africa, it is just the value obtained by estimating the model using the above "reasonable" baseline values. To better understand how the

7 In many African hospitals the HIV prevalence in the patient population is very high, much higher than the percentage of patients with HIV related diagnoses. Since these patients can no longer be protected against HIV infection, it is essential to consider the HIV prevalence, not just the diagnosis of AIDS, when estimating the percentage of transfusion recipients who would suffer consequences of an HIV infected transfusion.

cost would change in different environments, let us examine how sensitive this $119 result is to changes in the initial parameters specified . For each parameter, a range of values was chosen that should encompass the vast majority of situations in Africa and have estimated the model to see how much the cost-per-infection-averted changes as each individual parameter is varied across that range of values, holding all other parameters constant (Table IV.2).

Table IV.2: Ranges of Variation of Input Parameters for Sensitivity Analysis

	Sensi-tivity	Speci-ficity	Preva-lence	% Survive	Cost per test	Cost replace donor	# Blood products per unit
Variable name	SN	SP	PREV	SURV	TEST	REPL	BLOOD
Baseline value	95%	95%	5%	50%	$2.50	$1.00	1
Range of variation	100% to 80%	100% to 80%	35% to 0.04%	80% to 30%	$1.00 to $15.00	$0.25 to $10.00	5 to 1

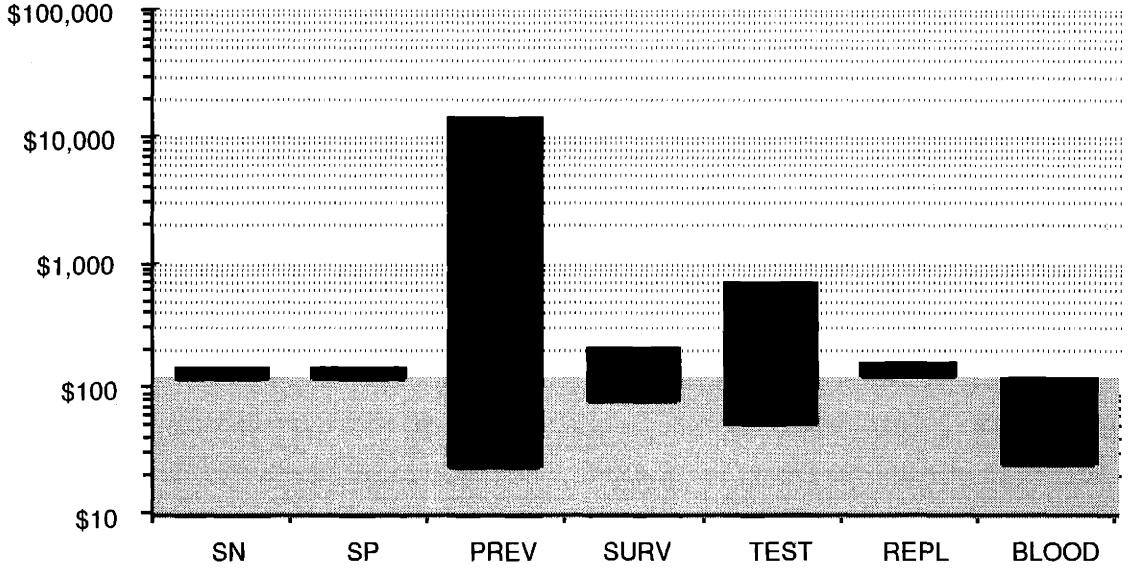

Figure IV.1: Cost per HIV Infection Averted by Screening Blood for Transfusion, Sensitivity Analysis

The gray area in Figure IV.1 corresponds to the $119 baseline cost obtained above. The bars represent the changes in cost-per-infection-averted that correspond to the range of variation of each individual parameter. Note that the y-axis has a log scale.

Varying sensitivity (SN) and specificity (SP) from 100% down to 80% has little effect on cost-per-infection-averted. The cost varies enormously, as expected, over the seroprevalence (PREV) range. At a seroprevalence of 35%, the cost of averting an

infection is estimated to be $28, while, when the rate falls to four per ten thousand, the cost is almost $13,000 per infection averted. The lower limit of 4 per 10,000 was chosen only because an article by Singh and colleagues[8] in New Delhi reported that rate and drew the conclusion that "stringent screening of donated units of blood has become mandatory in India." Since $13,000 will save many lives in India, as in most of Africa, if used for other health preventive programs, these results would not support their conclusion.

The percent of patients who would survive to suffer HIV sequelae (SURV) has an important impact, but not as great as the cost per test (TEST), which has an almost linear relationship with cost-per-infection-averted. The cost of replacing donors does not have an important effect. Finally, the average number of blood products per unit (BLOOD) is also linearly related to cost, but the range of expected variation of the input parameter is less than for the cost per test, which explains why the variation in cost per infection averted is smaller.

Examples of Applications

Why is it useful to calculate a cost-per HIV infection averted? Using this model, as was done in the preceding hypothetical example, can be helpful in deciding whether a transfusion screening program is a useful investment of AIDS prevention funds if a similar calculation has also been done for a competing AIDS prevention program. To expand the example, suppose that:

- condoms cost 15¢ for each condom purchased, distributed and used
- the probability of transmission per act of sexual intercourse between an infected to an uninfected partner is 1 in 100 without a condom and 1 in 1000 with a condom
- the HIV seroprevalence in the population is 5%
- the probability that one and only one person is infected in any pair of sexual partners is 9.5%[9]

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8 Singh YN; Malaviya AN; Tripathy SP; Chaudhuri K; Khare SD; Nanu A; Bhasin R "Human immunodeficiency virus infection in the blood donors of Delhi, India." *J Acquir Immune Defic Syndr.* 1990; 3(2): 152-4

9 9.5% would be expected with a seroprevalence of 5% if pairing was random, which it is not. A high risk person is more likely than a low risk person to choose a high risk sexual partner and vice

If 10,500 condoms were provided and used then 1000 potentially infectious couplings would be protected and 9 primary HIV infections would be averted. At 15¢ per condom, that is approximately $175 per HIV infection averted. If these two hypothetical AIDS prevention activities (condoms and screening) were competing for funds, the analysis suggests that it would be preferable to fund the transfusion screening program because it would be able to prevent more infections for the same investment.[10]

Now, suppose that in this hypothetical community it is possible to change the method of recruiting blood donors, by creating blood donor clubs in local high schools where the HIV seroprevalence is 1%, rather than 5%.[11] Recruiting high school donors is more expensive than recruiting donors from the general population, suppose that it costs $1.50 more per donor. Thus, altering donor recruitment alone (using the baseline values above) would avert four HIV positive transfusions per 100 donors recruited which corresponds to two HIV infections averted (recall the higher mortality of transfusion recipients), or a cost of $75 per HIV transmission averted. The policy decision now faced by an AIDS program manager is more complex. If the donor recruitment program

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versa. This would tend to bias the percentage down; so would the tendency for seroprevalence between discordant partners to become concordant over time (as the uninfected partner becomes infected). However, preferential use of condoms for high-risk encounters would increase the average seroprevalence of protected sexual acts. Not knowing which effect is likely to dominate, 9.5% was used for the purpose of this hypothetical example.

10 The condom distribution example in the text is only developed to illustrate the use of the blood screening model. It greatly oversimplifies the issues that must be considered when evaluating the costs and benefits associated with condom distribution. Perhaps the most important issues that are ignored are the effects of condom utilization on fertility and on the prevalence of other sexually transmitted diseases.

11 A model high school recruitment program has been operating very successfully for several years in Goma, Zaïre. The model program is much more sophisticated than the simple change in recruitment proposed in the text example. Blood donor clubs, with both social and public service functions, have been formed at local high schools. Potential members go to the blood bank where they are screened for, and counseled about HIV infection, regardless of whether they are positive or negative. They are entered into a computerized data bank of blood donors and then participate in regular blood drives to maintain an adequate blood supply at the hospital blood bank. In addition to screening donors at initial recruitment, all donated units are also screened for HIV infection. While this program has been unquestionably successful in 1) educating high school students about HIV infection, 2) creating a local tradition of volunteer blood donation, 3) providing the blood bank with a low risk donor population, and 4) ensuring a non-infected blood supply, it has not been subjected to an economic analysis to examine whether the program is economically rational in that environment. The model program benefits from generous support from the Italian government which permits it to offer an optimal service. It is unlikely that such optimal service, with targeted recruitment, donor screening, and blood screening, could be economically justified outside of a research center in Zaïre, where most transfusion centers employ none of these measures to decrease transfusion associated HIV transmission. The most valuable lesson to be learned from this model program is that high schools and their students are potentially willing volunteer participants in a program to reduce blood donor seroprevalence.

is implemented alone, it would cost less per HIV infection averted than a transfusion screening program, but it would not avert as many infections. Suppose that there are sufficient funds to implement either or both of the programs to reduce transfusion-related risk, but that the funds used would be taken from the condom distribution program described above. Should the program manager change donor recruitment, screen the blood donors, or both?

First, let us evaluate the option of using both. Conceptually, suppose that high school donor recruitment is operating and one is considering adding blood screening.[12] The HIV testing model developed above can be used to find the additional cost per infection averted by adding blood screening to the donor recruitment program. The calculation is identical to the one done previously, with the modifications that the donor seroprevalence is now 1% rather than the 5% in the baseline example and the cost of recruiting replacement donors is increased by $1.50. The new cost per infection averted is now approximately $588 for each additional infection averted. If it only costs $175 to avert an infection by condom distribution, then it is not cost effective to implement both high school donor recruitment and blood screening.

Though it was determined that implementing both programs is not desirable, it is not clear which of the programs to choose; answering the question: Blood testing costs more but it also averts more infections, is it worth the extra cost? The relevant cost here is the cost per additional infection averted by substituting HIV screening for donor recruitment. The HIV testing model can be used again, with an additional modification. One percent seroprevalence is again used instead of 5% seroprevalence, as in the previous paragraph, so that the only infected donors considered are those who would not have been averted by donor recruitment. Now, the cost of what the donor recruitment program would cost if it were the only program must also be subtracted. The cost associated with substitution is of interest, which considers the difference between the cost of the two programs. In the previous paragraph the entire cost of the testing program was considered because it was being added to the donor recruitment program.

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12 When evaluating a joint program consisting of A and B, one should consider the marginal unit cost of B given A and the marginal unit cost of A given B. If either marginal unit cost is higher than that for a competing program then the joint program is contraindicated. In practice, it is often obvious by inspection whether A|B or B|A is likely to have the higher marginal cost, in which case the other formulation can be ignored. In this example, we have already calculated the unit cost for the two components standing alone and can predict that the marginal unit cost of adding testing to recruitment is likely to be higher than the marginal unit cost of adding recruitment to testing.

The cost associated with the donor recruitment program (if it were the only program) per additional infection averted by the testing program is equal to the cost of recruiting one student ($1.50) multiplied by the number of donors screened by the testing program before an additional HIV infected unit is detected. Replacement donors are not considered because there would not be any recruitment of replacement donors if only the donor recruitment program were operating. The modified (modifications are bold) equation below replaces Equation 1 above.

$$\begin{matrix}\text{ADDITIONAL} \\ \text{COST OF HIV} \\ \text{TESTS REQUIRED}\end{matrix} = \text{TEST} - \left(\begin{matrix}\text{COST PER} \\ \text{STUDENT} \\ \text{RECRUITED}\end{matrix}\right)\left(\frac{1}{TP}\right) \qquad \text{eq 5}$$

When the modified model is estimated, the marginal cost-per-infection-averted associated with substituting HIV testing for donor recruitment is approximately $273. The policy implication in our hypothetical example is: while it would be worthwhile to take money away from condom distribution for HIV screening of blood transfusions if HIV screening were the only program available, it would not be worthwhile if a high school donor recruitment program were available.

The examples above consider situations in which the HIV testing model is being used to decide whether an HIV testing program should be started. Let us consider a different situation, that of an HIV testing program which must choose a screening test, or which is considering changing the test it uses.

Baseline parameters will be used for one test and assume that the other test has both sensitivity and specificity improved from 95% to 98%, and the cost per test increased to $5. With the baseline test it costs $119 to avert an infection; by switching to the new test, additional infections will be averted because of the improved sensitivity, but the cost per additional infection averted is about $3,200.

This $3,200 is not what the cost-per-infection-averted would be if one used test 2. It reflects a comparison between the two tests; how much it would cost per additional infection averted by using test 2 that would have been missed by test 1, using the same logic applied above when choosing HIV testing or donor recruitment. At a seroprevalence of 5%, test 2 can find a positive donor that test 1 would have missed, on average, every 648 tests. The $3,200 cost is a function of the difference in the cost of the two tests summed across the 648 tests that need to be done before an additional infected donor is detected.

To calculate this additional cost-per-infection-averted, three substitutions must be made in the basic model: 1) for TP, substitute the change in the probability that a donor will have a true positive test result (ΔTP), 2) for FP, substitute the change in the probability of a false positive result (ΔFP), and 3) for TEST, substitute the change in the cost of one test (ΔTEST).

$$\Delta TP = TP_2 - TP_1 = PREV\,(SN_2 - SN_1)$$
$$\Delta FP = FP_2 - FP_1 = (1\text{-}PREV)\,(SP_1 - SP_2)$$
$$\Delta TEST = TEST_2 - TEST_1 \qquad \text{eq 6}$$

It is inappropriate to draw general policy conclusions from any of the hypothetical examples presented here; rather, policy makers should estimate the model using parameters that reflect their local situation. In spite of this reluctance, the immediately preceding example demonstrated a general result of the model which contradicts widely held beliefs about the design of testing programs. Those beliefs place a strong emphasis on selecting the test which demonstrates superior sensitivity and specificity. A test with a sensitivity and specificity of 98% is considered to be a great improvement over a test with sensitivity and specificity of 95% in spite of the fact that the improvement is only 3%. This improvement is often not considered in the context of the associated cost differential. Such emphasis is more understandable in a country such as the United States, where screening programs that cost $100,000 per death averted are considered reasonable and where the cost of missing a positive donor may be much higher because of a tort system that may hold liable any institution which uses a test that is anything less than the best available; it is not understandable on most of the African continent, where the opportunity cost associated with buying the "best" test may be extremely high.

It is difficult to respond to the emotional charge: "If American lives are worth protecting with the best screening test, why should anything less be used to protect African lives? Are all human lives not of equal value?" without appearing calculating and unconcerned with fundamental ethical principals. On the contrary, such a charge is destructive to the very principals of social justice it seeks to advance. It is the economic equivalent of a mixed metaphor. Between the richest and the poorest countries, the per capita gross national product (GNP) varies more than 100 fold. This difference is directly reflected in the resources that individuals in those countries can expend to protect themselves from illness and death. Though enormous, this range underestimates the true variation, because in both the richest and the poorest country, the resources at the

disposition of any individual also vary by at least 100 fold, if not by 10,000. Whatever the moral/ethical imperative to more equitably distribute mankind's resources, it is not relevant to the choice of HIV testing strategy in any particular setting. If the goal of such a testing program is to avert avoidable deaths, then it is by that yardstick that its success must be measured, regardless of whether or not it uses the same methods as are used in another country. If the U.S.A. can afford to spend $100,000 to avert a death, its optimal testing strategy is likely to be very different from that in a country that can afford to spend only $1000.

The preceding example, comparing two tests with different sensitivities and specificities, demonstrates that one must carefully evaluate the value of a marginal increase in test quality. The improvement in quality is unlikely to be worth the increase in cost unless the order of magnitude increase in cost is similar to the order of magnitude increase in quality. In this example, a 3% increase in "quality" (as measured by the average improvement in sensitivity and specificity) was accompanied by a 100% increase in cost. Such a large mismatch is unlikely to represent a worthwhile improvement in settings where the cost of averting a death by other means (other than marginally increasing HIV test quality) is as low as it is in most African countries.

A final example to consider is the case of an HIV testing program that is considering changing from a test that only detects HIV I to one which also detects HIV II. Suppose that the baseline conditions apply for the HIV I test, the HIV II seroprevalence is 0.5%, the HIV I/II dual test has the same sensitivity and specificity (95%) for both viruses, and that the dual test costs $4.00 per test. As in the previous examples, the model is used in a way that considers the additional HIV positive donors detected and the additional cost associated with detecting one of those donors.

In this example the test characteristics (SN & SP) have not changed with respect to HIV I, so one must only consider the additional cost/benefit associated with HIV II detection. Had the characteristics changed for both HIV I and HIV II, the analysis would need to combine elements of this example and elements of the previous example in which HIV I detection characteristics changed.

To determine the additional cost-per-infection-averted, using the basic model and the parameters that apply for HIV II: the HIV II prevalence (PREV = 0.5%), the cost

associated with adding HIV II capability to the test[13] (TEST=$1.50), and the sensitivity and specificity for HIV II (SN=SP=95%). Using these parameters, the cost of adding HIV II capability is $689 per additional infection averted. In the hypothetical community described, it would not be justifiable to purchase the dual test.

Development of a Second Model to Validate the Simple Model

When the basic model described above was presented at the Fifth Annual Conference on AIDS in Africa, Kinshasa, October, 1990, it was unexpectedly well received. Presumably this was because the inputs should be available in most African countries; it is simple to compute; easily estimated with a pocket calculator; and there is an increasing realization both among policy makers and laboratory directors that proper design of a screening program must consider local conditions: economic, epidemiological, and laboratory performance. However, the model implicitly makes several simplifying assumptions which may or may not be justified.

- The model ignores the possibility that a replacement donor for a donor who tests positive (true or false) may also test positive, necessitating a second replacement donor. Although this is certainly not important at low seroprevalence levels, might it become important at higher levels?

- The second assumption is that the probability of a patient becoming infected from a particular unit is independent of the total number of transfusions the patient receives. As the average number of transfusions per patient increases, it becomes more costly to avert a infection of HIV transmission because some patients would receive more than one infected transfusion.[14]

To address these issues, a more complex model is described below and then compared to the basic model already discussed. Consider the collection of one unit of blood. A donor will be recruited and tested. There are four theoretical outcomes of that test: true positive, false positive, true negative, and false negative. Either positive outcome (true or false) will cause the donor to be rejected and the process repeated, and

13 Analytically, it makes no difference whether this is the cost difference between a test that detects one virus and a test that detects both viruses, or the cost of adding a second independent test for HIV II to the testing protocol— the approach to calculating the marginal cost is the same.

14 A third concern, that will not be addressed, is that there is likely to be a relationship between the number of transfusions received and the probability that a patient will survive to suffer consequences of HIV infection (SURV); other factors equal, a patient who receives more transfusions is more likely to be critically ill.

if the result is positive again, the process will be repeated again, etc. Whenever a test has a negative outcome, the donor is accepted and the process stops. By summing the probabilities associated with these various outcomes, it is possible to determine the expected number of tests required to accept one donor that tests negative (true or false).

- The probability that the first test will be done is 1
- The probability that a second test will be done is the probability that a first test will be done multiplied by the probability that the first test has a positive result, or 1 x (TP + FP)
- The probability that a third test will be done is the probability that a second test will be done multiplied by the probability that the second test has a positive result, or 1 x (TP + FP) x (TP + FP), etc.

Let[15] TP = SN * PREV
FP = (1-SP)(1-PREV)
TN = SP (1-PREV)
FN = (1-SN)PREV

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15 Variable definitions:

CHIV	Cost per "standard" HIV infection averted
CACPT	Cost of accepting one donor who tests negative
SURV	Percentage of recipients of HIV infected blood products expected to survive till they develop AIDS[15]
BLOOD	Average number of blood products derived and transfused from a single donated unit
CSCREEN	Expected cost of HIV screening necessary to identify an infected unit
TEST	Average cost of screening one unit
REPL	Average cost of replacing one unit
n	number of units transfused minus 1
T	average number of units transfused per patient
SN	HIV test sensitivity
SP	HIV test specificity
PREV	HIV seroprevalence among donors
TP	Probability that an HIV test will have a true positive test result
FP	P(false positive)
TN	P(true negative)
FN	P(false negative)

$$\text{No. of TESTS} = \sum_{i=0}^{\infty}(TP+FP)^i = \frac{1}{1-(TP+FP)} \qquad \text{eq 7}$$

When the expected number of tests is multiplied by the cost per test, the result expresses the cost of tests to identify one donor that tests negative.

$$CSCREEN = \frac{TEST}{1-(TP+FP)} \qquad \text{eq 8}$$

To that must be added the cost of recruiting replacement donors, which is simply the cost of recruiting one replacement donor multiplied by the expected number of tests minus one.

$$REPL\left(\frac{1}{1-(TP+FP)}\right)-1 \qquad \text{eq 9}$$

Thus, similar to Equation 3 of the simple model, the expected cost of accepting one donor who tests negative is the sum of the expected cost of the tests and the expected cost of recruiting replacement donors.

COST OF ACCEPTING ONE DONOR THAT TESTS NEGATIVE = CACPT

$$CACPT = TEST\left(\frac{1}{1-(TP+FP)}\right)+REPL\left(\left(\frac{1}{1-(TP+FP)}\right)-1\right) \qquad \text{eq 10}$$

$$CACPT = \left(\frac{TEST+REPL}{1-(TP+FP)}\right)-REPL \qquad \text{eq 11}$$

The above is an expression for the cost associated with accepting a donor that tests negative (CACPT). One must now determine an expression for the cost associated with averting an HIV infection (CHIV). To relate the two, CACPT is adjusted for circumstances that modify the probability that accepting a donor that tests negative will result in the aversion of an HIV infection. The circumstances that will be explicitly addressed are:

a) If multiple blood products are made from a donated unit then multiple infections from one unit may result. Detecting and eliminating a true positive donor may avert multiple infections, decreasing the cost per infection averted (as in the basic model).

b) As in the basic model, a "standard" HIV infection can only be averted if the transfusion recipient survives long enough to suffer any consequences of the infected transfusion.

c) The final acceptance of a donor that tests negative can only result in an infection or infections averted if the donor who would have been accepted in the absence of testing would have been HIV infected, and if the replacement unit is a true negative (and thus not infected).

d) If any of the transfusions received by a patient are from a donor that had a false negative test result, then no infection is averted, regardless of how many true positive donors are eliminated. Furthermore, if the patient would not have otherwise received an infected transfusion, then not only is an infection not averted, one is created.

e) If a patient would receive multiple transfusions and more than one of them would have a true positive test result, then the benefit associated with eliminating one true positive donor must be reduced proportionately.

Each of these, (a) through (e), will be addressed separately. A general comment is needed concerning the distribution of the number of transfusions received by patients. This distribution is discrete[16] and it has a small mean, so that it is poorly approximated by the normal distribution. Because number-of-transfusions has a non-linear relationship with CHIV, the distribution cannot be summarized by its mean. A modified Poisson distribution[17] was chosen because data on the actual distribution of number of transfusions per patient in Africa is lacking.[18] The Poisson distribution assumes

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16 The number of transfusions received by a patient is always an integer; any part of a transfusion is assumed to be as infectious as if they had received the entire transfusion.

17 The Poisson probability function is: $P(X = n) = \frac{m^n e^{-m}}{n!}$, where "m" is the mean of the Poisson variable. [Ingram D; Bloch RF *Mathematical Methods in Medicine: Part I: Statistical and Analytical Techniques.* (1984) John Wiley and Sons, Chichester, United Kingdom]

18 A cost-benefit analysis of screening of blood for transfusion has recently been performed [Foster S; Buvé A. Benefits of HIV screening of blood transfusions in Zambia. *Lancet.* 1995; 346: 225-7] using data from Zambia —and is the only published cost-benefit of cost-effectiveness analysis know to this author to use data from Africa. The data on number of transfusions per patient was reported only as a mean (app. 1.5) and the cost-benefit model used by the authors implicitly assumed that the number of transfusions was normally distributed around the mean. While a number of different distributions could be used in developing this model, subsequent analysis will show that the analysis is not sensitive to the shape of the distribution (in fact, the entire correction

independence of events (here, number of transfusions). This assumption is clearly not valid when considering the population of all patients: P(patient receives 2nd transfusion given that patient has already received first) > P(patient receives first transfusion). The probability of receiving a second transfusion, given that one has already been received, is certainly greater than the probability of receiving an initial transfusion, in a patient who has received none. Thus the Poisson distribution will be assumed to approximate the distribution of number of transfusions per patient only among the population of patients who receive at least one transfusion.

Consider the Poisson distribution of the number of transfusions minus one, or the distribution restricted to those patients who have received at least one transfusion. Thus, P(Ø) is the probability that a patient receives zero transfusions in addition to the first, or exactly one transfusion. As would be the case with any distribution chosen, this transformed Poisson is still likely to be a biased representation of the true distribution, but neither available data nor intuition about clinical behavior suggest what direction the bias is likely to be. Furthermore, subsequent analysis will show that cost estimates are robust to reasonable changes in the shape of the distribution.

a) The correction for multiple blood products from each unit is identical to that in the simple model; CACPT is divided by BLOOD, the average number of recipients of blood products derived from each unit of donated blood. (BLOOD ≥ 1, so this will decrease CHIV, relative to CACPT)

b) The correction for reduced survival of transfusion recipients is also identical to that in the simple model; CACPT is divided by SURV, the percentage of transfusion recipients expected to survive to suffer consequences of their infection. (1 $\geq$ SURV, so this will increase CHIV, relative to CACPT)

c) The probability that the index (initial) donor is infected and would be eliminated (true positive) is TP. The probability that the replacement unit is a true negative is $\frac{TN}{FN+TN}$. Thus, CACPT is divided by

$$TP \frac{TN}{FN+TN} = P(dec) \qquad \text{eq 12}$$

(1 $\geq$ TP, so this will increase CHIV, relative to CACPT)

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for multiple transfusions per recipient can be dropped without significant effect—over reasonable ranges of donor seroprevalence and number of transfusions per recipient).

d) The probability that a blood product is administered to a patient who receives no false negative units[19] is the sum of: the probability that it is transfused with no other units multiplied by one, the probability that it is transfused with one other unit multiplied by the probability that unit is not false negative, the probability that it is transfused with two other units multiplied by the probability that neither is false negative.

Let: n = number of units transfused minus 1
T = average total number of units transfused per patient

$$P(\text{Pt. receives } n+1 \mid \text{receives} \geq 1) = P(n, T-1) = \frac{(T-1)^n e^{-(T-1)}}{n!} \qquad \text{eq 13}$$

P(unit transfused with n other units) =

$$P(T_n) = \frac{(n+1)\,P(n,T-1)}{\sum_{n=0}^{\infty}(n+1)\,P(n,T-1)} = \frac{(n+1)\,P(n,T-1)}{T} \quad (\text{see note}^{20}) \qquad \text{eq 14}$$

$$P(\text{no units test false negative} \mid \text{all units test negative}) = \left(1-\frac{FN}{TN+FN}\right)^n = \left(\frac{TN}{TN+FN}\right)^n = \theta \qquad \text{eq 15}$$

Thus:
P(unit is transfused to Pt. who receives no other false negative units) = P(Øfn)

$$P(Øfn) = \sum_{n=0}^{\infty} P(T_n)\,q = \frac{1}{T}\sum_{n=0}^{\infty}(n+1)\,P(n,T-1)\,q \qquad \text{eq 16}$$

$$P(Øfn) = \frac{1}{T}(\theta(T-1)+1)\,e^{-(T-1)(1-\theta)} \qquad \text{eq 17}$$

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19 In (b) we have already accounted for the possibility that the first donor or his/her replacement might be false negative. Here, we are concerned with the possibility that any of the other transfusions are false negative.

20 Since the summation of Poisson probabilities is 1, $\sum_{n=0}^{\infty} P(n,T-1) = 1$ and

$\sum_{n=0}^{\infty} nP(n,T-1) = T-1$ so that $\sum_{n=0}^{\infty}(n+1)\,P(n,T-1) = T$

The probability that the index unit would have been uninfected, but that because of testing it was replaced in error with an infected unit (possibly creating, rather than averting, an infection) must be subtracted from the probability of averting an infection. The situation would only arise if the first donor has a false positive test result and the unit eventually transfused has a false negative test result.[21]

$$P(\text{initial false positive and current false negative} \mid \text{current negative}) = P(\text{inc})$$

$$P(\text{inc}) = FP\left(\frac{FN}{TN+FN}\right) \qquad \text{eq 18}$$

e) Given that the current unit is not a false negative (from (c)), and that the unit it replaces would have been a true positive (from (b)), one must correct for the possibility that it is being transfused to a patient who is also receiving other units which, in the absence of testing, would have tested true positive. If the unit would have been transfused with one other true positive, then averting transfusion of the index unit accomplishes half of what would have been accomplished if the unit was transfused with no other true positive units. Likewise, if the patient would have received a total of three, one third of the prevention of infection is accomplished by preventing transfusion of each of the three infected units. Thus, CACPT must be multiplied by the total expected number of true positive transfusions that are co-transfused with the index unit (including the index unit), which is the sum of:

> the probability that the index unit would have been transfused without other true positive units multiplied by one, the probability that the index unit would have been transfused with one other unit multiplied by 2...

The probability that the index unit would have been transfused with y other true positive units is the sum of:

> the probability that it was transfused with y other units (from(c)) multiplied by the probability that all y were true positive, the probability that it

21 To maintain complete symmetry between the "infections created" and the "infections averted" it would be necessary to correct for the possibility that multiple infected units could be transfused to a patient who would otherwise have received none. Since the incidence of creating an infection is much smaller than the incidence of averting one, I will ignore the possibility that they occur multiply in the same patient.

was transfused with y+1 other units multiplied by the probability that y of y+1 were true positive...

$$P(\text{unit transfused with y other units}) = P(T_n)$$

$$P(\text{y of n units would have been true positive}^{22} \mid \text{none false negative}) = \binom{n}{y}\left(\frac{TP}{1-FN}\right)^{y}\left(1-\frac{TP}{1-FN}\right)^{n-y} = B(y;n,\lambda) \text{ if } \lambda = \left(\frac{TP}{1-FN}\right) \quad \text{eq 19}$$

$$P(\text{unit transfused with y other true positive units}) = \sum_{n=y}^{\infty} P(T_n)\ B(y; n, \lambda) \quad \text{eq 20}$$

$$E(\text{number of co-true positive units}) = E(tp)$$

$$E(tp) = \sum_{y=0}^{\infty}\left[(y+1)\sum_{n=y}^{\infty}P(T_n)\,B(y; n, l)\right] \quad \text{eq 21}$$

$$E(tp) = \sum_{y=0}^{\infty}\left[(y+1)\sum_{n=y}^{\infty}\frac{(n+1)P(n,T-1)}{T}\,B(y; n, l)\right] \quad \text{eq 22}$$

$$E(tp) = \frac{1}{T}\sum_{y=0}^{\infty}\left[(y+1)\sum_{n=y}^{\infty}(n+1)P(n,T-1)\,B(y; n, l)\right] \quad \text{eq 23}$$

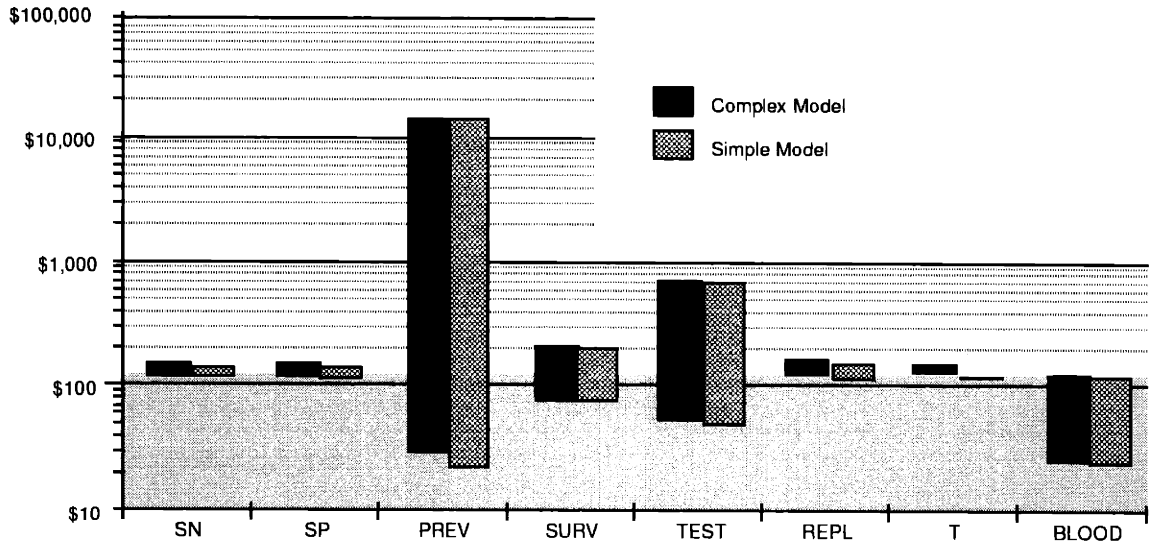
$$\text{Thus, CHIV} = \text{CACPT}\ \frac{E(tp)}{BLOOD \times SURV \times P(\varnothing fn) \times [P(dec) - P(inc)]} \quad \text{eq 24}$$

Figure IV.2 below compares the simple model with the complex model by repeating the sensitivity analysis that was done above for the simple model, Figure IV.1. The black bars represent the range of variation in cost-per-infection-averted for the complex model, the gray bars for the simple model. The data that were used to construct Figure IV.2 are presented in the first two blocks of data (PREV = 5%) in Table IV.3. The results of the two models are remarkably similar, considering the great difference in computational simplicity, which strongly supports the claim that the simplifying assumptions inherent in the first model are acceptable over the ranges of variation in the input parameters likely to be encountered in Africa.

22 Beyer WH *CRC Handbook of Mathematical Sciences, 6th Edition.* (1987) CRC, Boca Raton, Florida 722

To further explore the differences between the two models, the sensitivity analysis is repeated in Table IV.3 using an HIV prevalence among donors (PREV) of 25%. Each block of data in the table begins with three rows which contain, for each of the input parameters, the low (A), baseline, and high (B) cost-per-infection-averted corresponding to the range (A-B) of the input parameter seen at the top of each column. In the second and fourth block of data, there is a fourth row labeled $\Delta 5$ or $\Delta 25$. These rows contain the average difference between the values A and B obtained using the complex model and those obtained using the simple model. These numbers are all small, especially if considered as a percentage of the cost-per-infection-averted. The most significant difference between the two models is associated with variation in average number of transfusions per patient. This might be expected, as this variable is not included in the simple mode. Thus, the simple model should be used with caution anywhere the average number of transfusions per patient transfused is especially high.

Figure IV.2 Cost per HIV Transmission Averted by Screening Blood for Transfusion, Comparative Sensitivity Analysis



By including the sensitivity analysis at 25% HIV seroprevalence, it is possible to see whether the differences between the models become more or less pronounced as seroprevalence climbs. The last row of Table IV.3, labeled $\frac{\Delta 25}{(\Delta 25+\Delta 5)\div 2}$, is the ratio of the difference between the models at PREV = 25% to the average of the difference between the models at 5% and at 25%. A positive number suggests that the difference between the models increases with increasing seroprevalence, a negative number suggests that the difference decreases with increasing seroprevalence. The difference increases with respect to all of the parameters with the exception of specificity (SP),

suggesting that the simple model should also be used with some caution at a high seroprevalence. In spite of the tendency for bias to increase, even at a seroprevalence of 25%, the absolute difference between the models is sufficiently small that it will rarely be decisive.

Table IV.3 Comparative Sensitivity Analysis of Simple & Complex Models

	Sensitivity	Specificity	Prevalence	% Survive	Cost per test	Cost replace donor	Trnsfsns per patient	# Blood products per unit
Variable name	SN	SP	PREV	SURV	TEST	REPL	T	BLOOD
Baseline value	95%	95%	5%, 25%	50%	$2.50	$1.00	2	1
Range A to B	100% to 80%	100% to 80%	35% to 0.04%	80% to 30%	$1.00 to $15.00	$0.25 to $10	1 to 5	5 to 1

	SIMPLE MODEL, HIV PREVALENCE = 5%							
1	A	$114	$112	$23	$75	$50	$116	$119	$24
	BASELINE	$119	$119	$119	$119	$119	$119	$119	$119
	B	$140	$140	$14,086	$199	$696	$155	$119	$119

	COMPLEX MODEL, HIV PREVALENCE = 5%							
2	A	$115	$113	$29	$76	$51	$118	$122	$24
	BASELINE	$122	$122	$122	$122	$122	$122	$122	$122
	B	$147	$154	$14,175	$203	$708	$162	$152	$122
	Δ5	$4	$8	$48	$3	$7	$5	$18	$2

	SIMPLE MODEL, HIV PREVALENCE = 25%							
3	A	$28	$28	as above	$18	$13	$27	$29	$6
	BASELINE	$29	$29		$29	$29	$29	$29	$29
	B	$33	$32		$49	$163	$50	$29	$29

	COMPLEX MODEL, HIV PREVALENCE = 25%							
4	A	$31	$31	as above	$21	$15	$31	$33	$7
	BASELINE	$33	$33		$33	$33	$33	$33	$33
	B	$42	$42		$56	$184	$63	$78	$33
	Δ25	$6	$7		$5	$12	$9	$27	$3
	$\frac{\Delta 25}{(\Delta 25+\Delta 5)\div 2}$	20%	-7%		33%	28%	31%	19%	25%

Conclusion

This chapter has demonstrated the robustness of a simple model that can be used to calculate the estimated cost of preventing HIV transmission via blood transfusion. Critics of the application of cost effectiveness (CE) methodologies to this technology have argued that it is unethical to apply the same CE standard to blood screening as to "traditional" public health interventions such as childhood vaccination because infection via blood transfusion is iatrogenic and thus its prevention has a greater moral imperative.

Even if one accepts the argument that prevention of iatrogenic illness is more important, it is not possible to argue that the CE of screening blood for HIV should not be compared to the CE of prevention of other iatrogenic illnesses (such as screening blood for hepatitis B). However, any claims for preferential investment in the prevention of certain diseases or for certain types of patients merit critical review, especially when there are possible conflicts of interest for policy makers. In the case of prevention of transfusion-related transmission, such investment is likely to preferentially benefit the higher socio-economic segments of the population, as those are the segments that have access to health services. Health sector policy makers would be expected to be especially interested in preventing any illness that might "taint" the reputation of the sector. Another concern is that an expressed preference for prevention of iatrogenic illness is but a more palatable expression of a preference for protecting "innocent" people infected via blood transfusion over "guilty" people infected via sex or injecting drug use.

An additional factor that must be considered when allocating public funds among competing HIV prevention interventions is the degree to which the intervention is a public good. The envelope of resources invested in HIV prevention is likely to be maximized by concentrating public investment in interventions for which individuals are unwilling or unable to pay. A recent study conducted in China suggested that the average individual's willingness-to-pay to ensure that he or she received blood that had been tested for HIV substantially exceeded the local cost of testing.[23]

The chapter that follows evaluates the costs and benefits of HIV testing in a clinical setting for the purpose of diagnosing HIV infection in symptomatic patients.

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23 Yu J; Yuan J; Xu Y; *et al.* The economic analysis for selective HIV/AIDS prevention strategies in People's Republic of China. manuscript, August 1994

V

HIV TESTING: ITS ROLE IN THE DIAGNOSIS OF HIV-RELATED DISEASE

Introduction

It is difficult for a physician to enter into discussions of *cost-effective* diagnosis and treatment of HIV positive persons, especially in developing countries, because the medical instinct to act as an advocate for the individual patient comes quickly into conflict with the need to limit outlays for medical treatment of insufficient benefit. This chapter will explore the appropriate role in Africa of HIV testing of *patients*. It will identify the information which is necessary, though presently unavailable, to make informed policy decisions about when HIV tests should, and should not, be used to help establish a diagnosis of HIV infection. However, until such data become available, one must use what data there are to make educated guesses about when to use diagnostic HIV tests in Africa.

The chapter will not address the subject of testing asymptomatic persons with the goal of limiting HIV transmission by encouraging behavioral change. Rather, it will focus on the clinical setting in which a patient is seeking treatment from a medical professional. What are the characteristics of the patient or of the setting which suggest that an HIV test could be cost effectively employed to help diagnose the patient's disease? The chapter begins with a table of potential costs and benefits of diagnostic HIV testing (Table V.1). The columns of the table represent, in an idealized structure, the four different parties who potentially purchase HIV tests and who must therefore decide when it is in their interest to do so. The chapter will examine the cells and structure of the table, thus it may be useful for the reader to separate the table from the text for easy reference.

The four different potential purchasers of HIV tests are: (1) **P**atients; 2) **H**ospitals; 3) third-party-payers (such as employers, **I**nsurers, or patients' extended families, but not governments); and (4) **G**overnments.[1]

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1 Individual health providers, including physicians, are certainly also important decision makers, but their perspective will not be considered separately because they are less often in a position of purchasing an HIV test. They will be assumed to either act in their role as patient agent/advocate or as an agent for their employer, assumed to be the hospital.

	BENEFIT if + COST if -	Purchasers of HIV Tests			
		Patient	Hospital	Insurer	Govt.
1	↓ duration/↑ effectiveness of Tx	+	+	+	+
2	Prolonged productive life	+	+	+	+
3	Prolonged non-productive life	+/?	?	-/?	-/?
4	Earlier prophylaxis for opportunistic infections	+	+/?	+/?	+/?
5	↓ time till diagnosis	?	+	+	+
6	↓ cost of diagnosis	+/?	+	+	+
7	↓ cost of Tx	+/?	+	+	+
8	↓ HIV transmission	+	+	+	+
9	↓ HIV occupational risk	+	+	+	+
10	Cost of HIV test	-	-	-	-
11	Cost of false (+) and false (-) tests	-	-	-	-
12	↑ cost of Tx	-	-	-	-
13	Social/economic discrimination	-	-	?	?
14	Medical discrimination	-	+	+	+
15	↑ HIV transmission	-	-	-	-
16	Foreshortened productive life	-	-	-	-
17	Foreshortened non-productive life	-/?	?	+/?	+/?

Table V.1, Costs & Benefits of Diagnostic HIV Testing

Economists, in attempting to model the behavior of individuals, use "utility" to represent the combination of everything that an individual wants more of—whether wealth, health, happiness, longevity, or whatever. A "benefit" of an intervention is an effect that increases utility and a "cost" is a negative benefit, or an effect that decreases utility. When analyzing medical interventions, it is often convenient to simplify the concept of utility and assume that the individual makes choices not to maximize utility, but just to maximize health. Previous chapters have discussed the use of discounted healthy life years (DHLY) as one way to quantify changes in health. Unfortunately, individual choices about HIV testing are not limited to its expected effect on health. Although the benefits of testing may be adequately captured by observing change in health (caused by changes in medical management initiated because of the test result), the costs of testing can potentially include

devastating social and economic discrimination. While such discrimination may also have negative health effects, those health effects greatly underestimate the total costs; and therefore the ratio of costs to benefits.

Thus, when considering costs and benefits at the individual patient level, one must consider them in relation to a definition of utility broader than health alone. All four of the potential purchasers of HIV tests have constrained resources. However, the hospital, third-party-payer, and government all have an additional constraint: they must have the approval of the patient to perform the test. Therefore, even though it may be cost effective for the government to offer patients HIV testing at government expense, the testing will only occur without coercion if the patients are convinced the benefits outweigh the costs, even if the test is offered free of charge.

An idealized hospital, for purposes of this discussion, is an institution that seeks only to maximize improvement in health *in the population it serves* through delivery of - curative medical services. If DHLYs are used as the units of health, then a hospital seeks to maximize DHLYs regardless of which individual patient benefits. Since resources are constrained, patients will be denied access to services if the expected benefit in DHLYs is low and the cost of the services high.

An idealized third-party-payer has contracted with the covered population to provide certain services. The payer would like to minimize the cost of providing those services. Since health insurance companies are relatively rare in Africa, most payers will be employers or extended families of the patients'. Both of these are also interested in maximizing the patients productive years.

The government can be idealized as analogous to a national hospital. Given a national government budget for health, the government is interested in using those funds to maximize total health benefit across the national population. The major difference between the government and the hospital is that the hospital is largely limited to curative services, while the government must choose between curative and preventive options.

Patients' Perspective

A patient's interest in any diagnostic test is primarily driven by: will the test permit more rapid initiation of beneficial treatment, more rapid cessation of harmful or ineffective treatment, and thus a health outcome that is both better and arrived at more quickly. Therefore, under what circumstances does performing an HIV test lead to such an improvement in therapy? There will only be improvement following a test if two

conditions are met: 1) treatment for a patient's condition is different depending upon whether or not the patient is HIV infected, and 2) in absence of the test, the care givers would *not* have made the *correct* assumption about the patient's HIV status.[2]

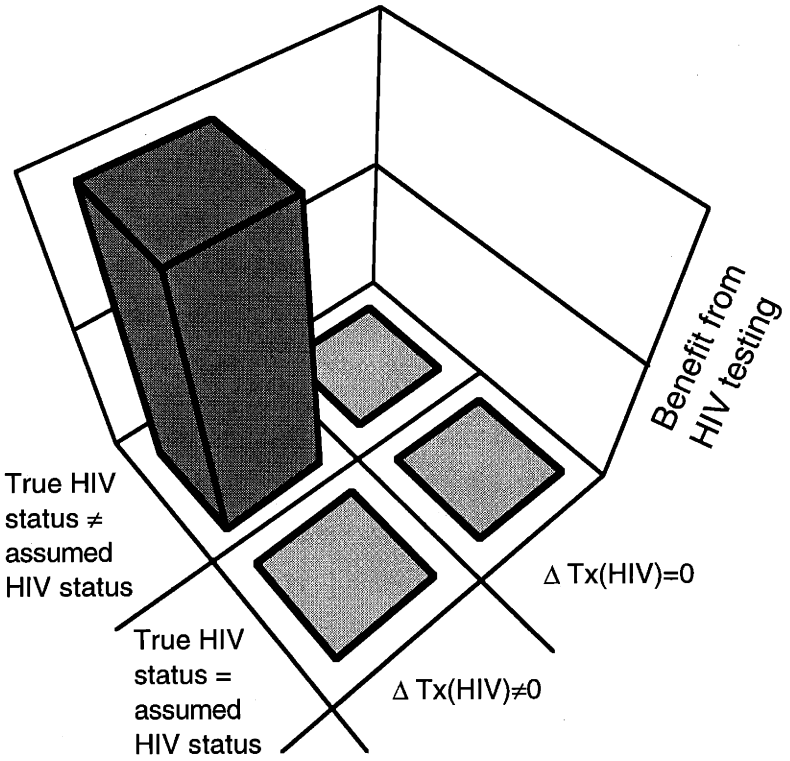

Figure V.1

As figure V.1 shows, of the four possible states, only one corresponds to a situation in which testing *may* positively influence outcome. Furthermore, it is not sufficient that treatment be different for HIV positive vs. negative (Δ Tx(HIV)≠0), there must also be a different outcome that accompanies the change in treatment.

Whether or not HIV testing will influence treatment depends upon the clinical presentation of the patient and upon what treatment options are locally available. It is in these two areas, and especially the later, that the differences between sub-Saharan Africa and industrialized countries become apparent. The following quote is from a Ugandan manual of diagnostic and treatment strategies for AIDS. It reveals one perspective from a developing country about the indications for testing. Especially noteworthy is the rejection of the need to confirm HIV infection in a patient with "obvious AIDS":

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2 To argue that a caregiver faces only two treatment paths "Tx assuming HIV +" and "Tx assuming

Who should have a HIV blood test? Table 5.7 gives a reasonable way to look at the indications for doing the test. The only absolute indication for the test is in screening blood donors...

Table 5.7
Who should have an HIV Blood test?

ALWAYS
People wishing to donate blood for transfusion.

FREQUENTLY
People who... want to make an informed decision regarding future pregnancy, marriage or other personal and family matters.
Patients who agree with the health worker's advice that the test would make a difference in diagnosis and treatment of their disease or future care.

RARELY
Patients who have not given informed consent to have the test.
Patients with obvious AIDS...

In actual practice, at the time of the writing of this book [1989], the HIV test is usually ordered because the doctor wants to know the results. There are some clinical situations in which this is justified (i.e. chronic disease in which the Clinical Criteria are not met; difficult neurologic syndromes...), but in most cases the test results do not influence therapy very much...[3]

The following discussion about various clinical presentations of HIV infection in Africa, referring also to Tables V.2, V.3, is not intended to be exhaustive, but rather is intended to provide the reader with examples of when HIV testing is likely to result in alterations in therapy. Table V.2 summarizes the clinical discussion, focusing on whether HIV status makes a difference in the usual treatment of a patient . Table V.3 is taken from the Ugandan treatment manual and illustrates the drugs that the Ugandan program feels are of greatest priority.

The *treatment* of HIV-related disease *in Africa* has received remarkably little attention in the medical literature. As an example, three important books[4] on the clinical

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HIV -", excludes a third possibility "Tx with HIV uncertain" which may be different .

3 Katabira E; Goodgame R; eds. *AIDS care: diagnostic and treatment strategies for health workers.* Entebbe: AIDS Control Program, Ministry of Health, Republic of Uganda, 1989.

4 Levy JA; ed.: *AIDS: Pathogenesis and Treatment.* 1989, New York: Marcel Dekker.

Leoung G; Mills J; eds.: *Opportunistic Infections in Patients with the Acquired Immunodeficiency Syndrome.* 1989, New York: Marcel Dekker.

Giraldo G; Beth-Giraldo E; Clumeck N; Gharbi Md-R; Kyalwazi SK; de Thé G; eds.: *AIDS and Associated Cancers in Africa.* 1987, Basel: Karger.

	Clinical Presentation	Difference in Treatment HIV(+) vs. HIV(-)
	Skin/mucosal lesions	
i	Herpes Zoster	no difference in treatment; acyclovir not available
ii	Oral/Esophageal Candidiasis	no difference; ketoconazole & gentian violet often available; fluconazole & amphotericin B not available
iii	Rash	no difference; e.g. calamine lotion
iv	Kaposi's Sarcoma	chemotherapy of HIV(+) not successful, chemotherapy may not even be available for HIV(-) patients; presentation predicts HIV status without HIV test
v	Chronic diarrhea	
vi	Stool microscopy diagnostic	no difference; indicated antibiotic, e.g. T/S, metronidazole
vii	Stool microscopy non-diagnostic	? different empirical antibiotic ? if HIV(+) abandon diagnostic search/empirical treatment more quickly
viii	Cough/Shortness of Breath	
ix	Sputum microscopy diagnostic	no difference; indicated antibiotic(s), TB possible exception
x	Sputum microscopy non-diagnostic	different empirical antibiotic, e.g. HIV(+)=T/S, HIV(-)=PCN
xi	Fever	
xii	Blood smear for malaria(+)	no difference; standard anti-malarial Rx
xiii	Blood smear for malaria (-)	? different empirical antibiotic, e.g. for TB; ? skin test for TB; ? if HIV(+) abandon diagnostic search more quickly
xiv	Central Nervous System (CNS)	
xv	CSF microscopy diagnostic	no difference; indicated antibiotic(s)
xvi	CSF microscopy non-diagnostic	? empirical treatment for toxoplasmosis, syphilis, or tuberculosis
	PREVENTION	
xvii	Anti-HIV	no difference; zidovudine (AZT), ddI, & ddC not available
xviii	Mantoux (+) (tuberculosis)	? prophylaxis for HIV(+) but not HIV(-)[5]
xix	Anti-p. carinii (PCP)	low incidence in Africa, inability to use CD4 counts to identify patients at risk, & high cost of chronic therapy (T/S, dapsone, or pentamidine)—all argue against anti-PCP prophylaxis
xx	Pyrimethamine weekly as anti-malaria, toxoplasmosis, & isosporiasis	suggested because of high rate of toxoplasmosis in Uganda and possibility of more lethal malaria; ? cost-effective[6]

Table V.2, Difference in Treatment, HIV(+) vs. HIV(-), by Clinical Presentation

aspects of AIDS contain extensive material on the natural history and clinical manifestations of AIDS in Africa (and how they differ from the USA and Europe), but make little or no mention of how treatment is or should be different. Groups in Uganda and Zaïre have

5 Katabira E, *op cit.*

6 *ibid.*

formulated treatment algorithms for HIV-related disease, as quoted above,[7,8] but these have not been widely circulated.

i A common presenting illness in HIV infected patients is herpes zoster (also known as shingles; it is caused by a reactivation of the Varicella-zoster virus which causes chicken pox), a painful skin eruption which in a young, previously healthy African adult greatly increases the suspicion of HIV infection.[9] The "standard of care," regardless of HIV status, is treatment with the anti viral drug acyclovir orally or intravenously depending upon severity.[10]Although HIV positive patients are more likely to have severe disease, the results of an HIV test would probably not alter therapy, which should be modulated in response to clinical severity. Acyclovir (Zovirax) is still under patent protection to the Burrows Wellcome company and is priced so that it is unavailable in Africa except to the wealthiest segment of the population.

Priority Drugs for the Palliation of AIDS Patients		
DRUG	INDICATION	ALTERNATIVES
ketoconazole	candida infections tinea	nystatin, gentian violet topical antifungals, griseofulvin
cotrimoxazole [T/S]	isospora diarrhea, shigellosis skin sepsis, salmonella infections bacterial pneumonia	tetracycline, ampicillin erythromycin, ampicillin [sic] chloramphenicol, many antibiotics
metronidazole	giardia diarrhea, amebic colitis	
chlorpromazine	nausea and vomiting, itching sleeplessness, psychosis	phenergan, metochlorpropamide chlorpheniramine, phenergan diazepam
chloroquine	malaria	fansidar
aspirin/paracetamol	pain, fever	
codeine	severe pain, diarrhea	other narcotics, loperamide, lomotil
multivitamines ± iron	anemia, deficiencies	
calamine lotion	many skin problems	
petroleum jelly	dry skin	
hydrocortisone cream	atopic skin disease	
NOTE: Drugs for tuberculosis are an essential part of AIDS care		

Table V.3 (Table 1.1 from the Ugandan AIDS Care Strategies)[11]

ii Oral/esophageal candidiasis (yeast infection, also known as thrush) is another very common ("has been reported as occurring in about 75% of both [AIDS-related complex]

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7 Katabira E; *op cit*

8 Gernier, M; personal communication.

9 Colebunders R; Mann JM; Francis H; Bila K; Izaley L; Ilwaya M; Kakonde N; Quinn TC; Curran JW; Piot P: Herpes zoster in African patients: a clinical predictor of human immunodeficiency virus infection. *J Infect Dis.* 1988 Feb; 157(2): pp314-8.

10 Erlich KS: Herpes simplex and varicella-zoster virus infections in acquired immunodeficiency syndrome. in *Opportunistic Infections...* 173-194.

11 *ibid.*

ARC and AIDS patients"[12,13]), rarely lethal, yet very uncomfortable early HIV-related disease. Like herpes zoster, it is usually diagnosed by clinical exam. The standard of care is again independent of HIV status and related to disease severity. Topical (swish & swallow) application of nystatin is recommended in milder infections, and systemic ketoconazole or fluconazole when symptoms are more severe.[14] Fluconazole, at US$7 per tablet,[15] is priced so as to be largely irrelevant in Africa. Fortunately for African patients, who may not even have access to nystatin and ketoconazole, gentian violet is an inexpensive alternative which has been reported to be equally effective for oral candidiasis.[16-18]

iii A maculopapular, pruritic rash (a rash of discolored, itchy bumps) is also a very common presenting complaint in Africa (less so elsewhere). Treatment is symptomatic and unrelated to HIV status.[19]

These three sub-diseases are debilitating because they are painful or uncomfortable, but they are generally not life threatening. Their seriousness is more a function of what they portend. In an area with a significant amount of HIV infection, any of the three would greatly increase a clinician's suspicion of HIV infection. They are so commonly associated with HIV infection that in communities with high HIV prevalence, individuals may want to conceal the symptoms for fear of being labeled HIV infected. For treatment of the symptoms, knowledge of the patient's HIV status may not be useful, especially because many of the specific drugs are often unavailable. However, all three also are associated with serious systemic diseases other than HIV infection. In these cases, the benefits of testing are likely to be found in the avoidance of additional diagnostic steps that are taken to rule out the possibility of other *treatable* disease. For example, the first two diseases may

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12 Greenspan D; Greenspan JS: Oral manifestations of human immunodeficiency virus infection. in *Opportunistic Infections...* 143-152.

13 Pindborg JJ; et al.: Suggestion for a classification of oral candidiasis in patients with AIDS, ARC, and serum antibodies for LAV/HTLV-III. *J Dent Res* 1986, 65:765.

14 Colebunders R; Quinn TC; Retroviruses and the human immunodeficiency syndrome. in Warren KS; Mahmoud AAF; eds *Tropical and Geographical Medicine* 1990 McGraw-Hill, New York, 733.

15 Fluconazole representative, personal communication.

16 Gernier M, personal communication.

17 McEvoy GK; ed.: *AHFS Drug Information 90.* 1990, Bethesda, MD: American Society of Hospital Pharmacists, 2002-2003.

18 Nyst MJ; Perriens JH; Kimputu L; Lumbila M; Nelson AM; Piot P. Gentian violet, ketoconazole and nystatin in oropharyngeal and esophageal candidiasis in Zairian AIDS patients. *Ann Soc Belg Med Trop* 1992 Mar, 72(1) 45-52.

19 Cockerell CJ; Friedman-Kien AE: Cutaneous infections in patients with human immunodeficiency infection. in *Opportunistic Infections...* 135-142

occur with many diseases that interfere with immune function, including infections and neoplasms (cancers). The third is commonly seen with toxic exposures or allergic reactions to drugs.

iv Kaposi's sarcoma (KS) is a neoplasm which was very rare in North America prior to the emergence of the HIV virus. When KS is diagnosed now in industrialized countries it is overwhelmingly HIV-related, or epidemic, KS. In Africa, an endemic form[20,21] of KS has been known since the 1960's. Unlike the epidemic disease, which is aggressively lethal, endemic KS usually

> runs an indolent course, with many patients surviving 10 years or more.... Chemotherapeutic agents such as actinomycin D, which were found to be effective when first studied in endemic KS patients, have been found to be less effective and more toxic in African patients with epidemic KS. Many reports have documented a higher rate of complications following radiation therapy (i.e., oral mucositis) in HIV-positive KS patients, and a significant number of HIV-positive KS patients successfully treated with radiation therapy will relapse in the treated area....
>
> HIV serology is expensive and not widely available in developing countries. We have shown that our clinical case definition for epidemic KS has a sensitivity of 91%, a specificity of 95%, and a positive predictive value for HIV seropositivity of 98.5%. The predictive value of the clinical case definition for HIV seropositivity was 100% in women and males [sic] under the age of 60 years. The definition is straightforward and most patients can be classified in the basis of simple physical examination.[22]

The work of Lesbordes et al. in the Central African Republic confirm the findings of Desmond-Hellman et al. reported above. Patients with biopsy-proven KS who meet the clinical criteria for *epidemic* KS provide perhaps the most convincing example of a group of patients in which it is almost certainly not cost effective to perform HIV tests. As reported above, the positive predictive value for HIV seropositivity was estimated at 98.5%—as good or better than a screening HIV test in most African settings.

Patients identified clinically in Africa as having epidemic KS probably do warrant further treatment both because of the ineffectiveness of currently available treatment and because of the high costs associated with either chemo- or radio-therapy. A more difficult

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20 Desmond-Hellmann SD; Mbidde EK; Kizito A; Hellmann NS; Ziegler JL. The value of a clinical definition for epidemic KS in predicting HIV seropositivity in Africa. *J Acquir Immune Defic Syndr.* 1991; 4(7) 647-51.

21 Lesbordes JD; Martin P; Ravisse P; Georges-Courbet MC; Georges AJ. Clinical and histopathological aspects of Kaposi's sarcoma in Africa: relationship with HIV serology. *Annales de l'Institute Pasteur. Virology,* 1988 Apr-Jun, 139(2): 197-203.

22 Desmond-Hellmann *et al, op cit.*

question arises in the case of a patient with KS who does not meet the clinical criteria for epidemic KS. Should this subset of patients be tested for HIV? The answer will depend upon the relative prevalence of endemic and epidemic KS in an area, upon whether treatment is available for endemic KS, and upon the cost of that treatment. If no treatment is available, then distinguishing the two is of little benefit.

v Diarrhea, especially chronic diarrhea associated with profound weight loss, is a common presenting complaint and a common persistent problem associated with HIV infection in Africa.[23]

> Progressive weight loss is often the first sign of HIV-1 infection. Weight loss, asthenia, anorexia, and intermittent fever or diarrhea are the most frequent symptoms. A diarrheal wasting syndrome occurs particularly often among AIDS patients in Africa.[24] Stools are generally liquid or semi-liquid, and blood and mucus are rarely present. Diarrhea can be caused by various bacterial and viral agents, protozoa, and helminths, but in 30 to 50 percent of the cases no specific cause is identified.[25,26]

However, diarrhea is a very non-specific symptom. There are an estimated 28 billion episodes of diarrhea each year in the developing world[27] of which a small minority are HIV-related. The specificity of the symptom increases in adults and when the diarrhea is chronic and associated with weight loss. Even so, the differential diagnosis for chronic diarrhea is very long. A positive HIV test clearly changes the order of diagnoses on the differential, but how much does it result in change of therapy, especially when used in conjunction with other diagnostic tests?

vi A positive HIV test increases the probability that the diarrhea has an infectious etiology. However, especially in Africa, an infectious etiology is most likely,[28-30] even in

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23 Colebunders R; Quinn T; *op cit.*

24 Serwadda D; Mugerwa RD; Sewankambo NK; et al: Slim disease: A new disease in Uganda and its association with HTLV-III infection. *Lancet* 1985 ii:849-852.

25 Colebunders R; Francis H; Mann JM; et al: Persistent diarrhea, strongly associated with HIV-1 infection in Kinshasa, Zaïre. *Am J Gastroenterol* 1987 82(9):859-64.

26 Sewankambo N; Mugerwa RD; Goodgame R; et al: Enteropathic AIDS in Uganda: An endoscopic, histological and microbiologic study. *AIDS* 1987 1:9-13.

27 Walsh JA: Estimating the burden of illness in the tropics. in Warren KS; Mahmoud AAF; eds *Tropical and Geographical Medicine* 1990 McGraw-Hill, New York.

28 Guerrant RL; Hughes JM; Lima NL; Crane J: Diarrhea in developed and developing countries: magnitude, special settings, and etiologies. *Rev Infect Dis.* 1990 Jan-Feb; 12 Suppl 1(): S41-50.

29 Simango C; Dindiwe J: The aetiology of diarrhoea in a farming community in Zimbabwe . *Trans R Soc Trop Med Hyg.* 1987; 81(4): 552-3.

30 Eko FO; Utsalo SJ: Comparative study of the prevalence and clinical profiles of diarrheas due to Aeromonas and other enteric pathogens.*J Hyg Epidemiol Microbiol Immunol.* 1990; 34(2): pp183-9.

the HIV negative patient, so that initial therapy may be unchanged. Before treating presumably infectious diarrhea, it is desirable to identify the responsible organism so that specific antibiotic therapy can be instituted. Although, by international standards, the diagnostic armamentarium available in most African hospitals is very limited, a microscope is available in most community clinics. A trained microscopist can identify several of the infectious causes of diarrhea by examining stained and unstained stool smears. These organisms include, in the HIV negative patient, *Giardia lamblia, Entamoeba histolytica, Mycobacterium tuberculosis, Strongyloides,* and *Schistosomes. Cryptosporidia* and *Isospora belli* are diagnosable by modified acid fast stain. They may cause self limiting diarrhea in immune competent patients, but are the most frequently found causes of persistent diarrhea in HIV positive patients.[31,32] Other, non-tubercular mycobacteria can cause diarrhea in HIV positive persons and are indistinguishable microscopically from *M. tuberculosis.* Examination of the stool can also reveal the presence of blood, fat, and leukocytes (white blood cells) which may help to differentiate invasive from non-invasive diarrheas and identify those associated with malabsorption. Identification of specific bacterial and viral (as opposed to parasitic) diarrheal etiologies in industrialized countries usually requires more sophisticated diagnostic techniques such as culture, serologic tests, biopsy, or immunologic staining; techniques which are much less commonly available in African hospitals.

An HIV test would not supplant microscopic stool examination because it does not identify the agent directly responsible for the diarrhea, nor does it eliminate all treatable causes of diarrhea. If an organism is identified by microscopy then the indicated therapy, if any, will likely be independent of the patient's HIV status.

vii If microscopy is non-diagnostic and other diagnostic modalities are unavailable, initial therapy will be empirical. A positive HIV test, as mentioned, greatly raises the probability of cryptosporidiosis and isosporiasis, as well as a host of other viral, bacterial, and malignant possibilities. "There is currently no known effective therapy for

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31 Colebunders R; Quinn T; *op cit.*

32 Colebunders R; Francis H; Mann J; *et al, op cit.*

cryptosporidiosis."[33-36] Isosporiasis is well treated with trimethoprim/sulfamethoxazole (T/S, Bactrim, Septra; US$ 0.05/tablet, 0.10/day[37]), however T/S is also effective against a number of infections common in HIV negative persons including *Salmonella, Shigella,* and *E. coli,* and might be an appropriate first choice in this population as well. In the event initial treatment fails, additional antibiotic clinical trials are possible in both HIV positive and HIV negative populations. Without studies demonstrating that clinicians change their therapy of diarrhea in response to an HIV test, it is difficult to predict whether it has an effect either on patient well-being or on the cost of treatment.

The most likely effect of a positive HIV test, if trials of available antibiotics fail, is to reassure the patient and physician that the diarrhea is probably HIV-related and virtually eliminate from the list of suspected problems a myriad of other diseases which can cause chronic diarrhea, including intestinal tumors, Crohn's disease, ulcerative colitis, irritable bowel syndrome, carcinoid and other secreting tumors, diverticulitis, intestinal ischemia, hyperthyroidism, diabetes, amyloidosis, and enteroenteric fistulas.[38]

Thus, a positive HIV test might enable physician and patient to accept that if a trial of T/S (and perhaps also metronidazole and erythromycin) fails, that further treatment should be limited to ensuring adequate hydration and perhaps constipating medications—at home. The patient would benefit from reduced hospital stay and avoidance of the discomfort and expense of continuing to search for a diagnosis.

viii Another common presenting problem is cough/shortness of breath (SoB), not only in the HIV positive patient, but in the HIV negative population as well.[39]

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33 Soave R; Weikel CS; *Cryptosporidium* and other protozoa including *Isospora, Sarcocystis, Balantidium coli,* and *Blastocystis.* in Mandell GL; Douglas RG; Bennett JE; eds *Principles and Practice of Infectious Diseases.* 1990 Churchill Livingston, New York.

34 Since this was written, both paromomycin sulfate and octreotide (somatostatin) have been used with some success in treating cryptosporidial diarrhea in the U.S.A. (references below).

35 Clezy K; Gold J; Blaze J; Jones P: Paromomycin for the treatment of cryptosporidial diarrhoea in AIDS patients. *AIDS*, 1991 Sep, 5(9):1146-1147.

36 Kreinik G; Burstein O; Landor M; Bernstein L; Weiss LM; Wittner M: Successful management of intractable cryptosporidial diarrhea with intravenous octreotide, a somatostatin analogue. *AIDS*, 1991 Jun, 5(6):765-7.

37 Kimberly Bergstrom, UCSF/Mt. Zion, personal communication.

38 Goldfinger SE; Constipation and Diarrhea. In *Harrison's Principals of Internal Medicine* edited by Wilson JD; Braunwald E; Isselbacher K; Petersdorf RG; Martin JB; Fauci AS; Root RK. New York, McGraw Hill Inc. 1991, pp 256-9.

39 Colebunders R; Quinn T; *op cit.*

HIV positive patients are at risk of developing opportunistic pneumonias from organisms such as *Pneumocystis,* cytomegalovirus (CMV), and fungi. However, they are also at high risk of developing active tuberculosis (TB), pneumococcal pneumonia, or other pneumonias common in the HIV negative population. Bacterial culture, viral culture, viral serologies, bronchoscopy, and other techniques for identification of specific pulmonary pathogens are unlikely to be available in most African settings. The differential diagnosis is likely to be based upon the clinical presentation, sputum gram stain, sputum acid-fast stain, and possibly a chest radiograph.

ix If sputum examination reveals an organism that is likely to be responsible for the patient's symptoms, the patient's HIV status will probably not significantly alter therapy. The only common exception may be therapy for TB. Recent studies have suggested that TB is more virulent in the HIV infected host and has a higher relapse rate following treatment. Ongoing studies will help define whether the optimal treatment regimen for TB is different for HIV positive and HIV negative patients.[40,41]

x Depending upon the patient's presentation, HIV status *might* significantly alter preferred treatment for presumed pneumonia where sputum examination and/or x-rays are unavailable or non-diagnostic. Without extensively discussing the differential diagnosis of pneumonia in the HIV positive and negative African patient, T/S is unlikely to be first line empirical therapy for a community acquired pneumonia in the HIV negative patient. If suspicion of tuberculosis is low because of negative sputum samples, a trial of penicillin or ampicillin is likely to be first, because of the prevalence of pneumococcal pneumonia, penicillin/ampicillin's reasonably broad spectrum of activity against other etiologic agents, and its low cost. Erythromycin and tetracycline would certainly be considered for atypical presentations. None of those are likely to be effective against *Pneumocystis carinii,* which, though much less common in African AIDS patients than among patients in the USA or Europe, still represents an important source of morbidity and mortality in some

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40 Houston S; Pozniak A; Ray CS: Therapeutic review: tuberculosis. *Cent Afr J Med* 1991 Aug;37(8):250-9.

41 Perriens JH; Colebunders RL; Karahunga C; Willame JC; Jeugmans J; Kaboto M; Mukadi Y; Pauwels P; Ryder RW; Prignot J: Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with "standard" chemotherapy in Kinshasa, Zaire. *Am Rev Respir Dis* 1991 Oct;144(4):750-5.

areas.[42,43] If *P. carinii* is suspected, then T/S will be much more likely to be the drug of choice.

Perhaps the most important difference, in Africa, between treatment of HIV-positive vs. HIV-negative pulmonary disease regards empirical treatment of tuberculosis. Tuberculosis often presents atypically in the HIV positive patient without the x-ray findings characteristic of usual adult reactivation tuberculosis. It is thus much more difficult to diagnose even where x-ray facilities are available. An acid-fast stain of the sputum is very helpful if the result is positive because the test has a high specificity for TB in Africa where the incidence of other pulmonary mycobacterial infections in AIDS patients is much lower than in the U.S. Negative sputum stains certainly do not rule out TB, though they suggest that the patient is less likely to infect others. In Uganda, the AIDS Control Program has suggested that empirical therapy for TB is appropriate, especially in rural areas without access to diagnostic tests, though one must wonder whether the recommendation would change if anti-TB drugs were not available at reduced or no cost through a special, parallel national program. Because of the high cost of chronic (in HIV patients, probably lifelong) treatment of TB, and the fact that TB infection often precedes other signs of HIV infection, the following clinical setting is one in which HIV testing may be especially cost-effective:

- chronic pulmonary symptoms,
- non-diagnostic or unavailable x-ray and acid-fast sputum stain,
- absence of other signs and symptoms strongly suggestive of HIV infection.

However, such testing would only be cost effective if the presence or absence of HIV infection would determine whether or not the patient is treated empirically for TB.

xi-xiii Like cough/SoB and diarrhea, fever is also a common presenting complaint in both the HIV-infected and -non-infected African adult population. Although studies to date have failed to show a strong correlation between malaria and HIV infection, malaria is likely to be at least as common in the HIV-infected as -non-infected population.[44-46] Thus

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42 Kapita B; Colebunders R; Lusakumunu K; Henry MC. [Oportunistic parasitic diseases in Africa. Clinical aspects and diagnosis]. *Ann Parisitol Hum Comp,* 1990 65 Suppl 1:45-7.

43 Carme B; Mboussa J; Andzin M; Mbouni E; Mpele P; Datry A: Pneumocystis carinii is rare in AIDS in Central Africa. *Trans R Soc Trop Med Hyg* 1991 Jan-Feb;85(1):80.

44 Greenberg AE; Nsa W; Ryder RW; Medi M; Nzeza M; Kitadi N; Baangi M; Malanda N; Davachi F; Hassig SE. Plasmodium Falciparum malaria and perinatally acquired human immunodeficiency virus

patients in endemic areas presenting with fever and without localizing signs must be evaluated for malaria regardless of HIV status. The cited studies do not support the hypothesis that treatment strategy for malaria should be modified by HIV status. There are even less data available on the usefulness of the HIV test in guiding the diagnosis and treatment of patients who present with fever of undetermined etiology. Extrapulmonary tuberculosis, a common cause of such fever even in the HIV-negative patient, is much more common in the HIV-positive patient. Unfortunately, HIV positive patients with active tuberculosis are also more likely to have falsely negative TB skin tests, making TB more difficult to diagnose. As discussed above, when considering the possibility of pulmonary TB, HIV testing might be cost-effective if it lead to different empirical therapy. If, for example, patients would receive TB therapy regardless of HIV status, then testing is more difficult to justify.

xiv If a patient presents with symptoms suggestive of central nervous system (CNS) disease in the United States, the first diagnostic procedure performed is likely to be a computer processed brain scan using equipment that costs hundreds of thousands or millions of US dollars per scanner. For obvious reasons, such scanners are accessible to only a tiny fraction of the population in Africa. The lumbar puncture (LP), with subsequent microscopic examination of the cerebrospinal fluid (CSF), is widely available.

xv-xvi Table V.4 lists some common causes of HIV-related CNS disease and their treatment. Only two of the causes, TB meningitis and toxoplasmosis, are potentially treatable in Africa. A recent large study from Spain suggests that one in ten HIV-positive patients with tuberculosis had meningeal infection, a much larger number than in HIV -negative patients.[47] Of patients with TB meningitis, 65% had clinical or radiographic evidence of TB elsewhere in the body. If proportions are similar in Africa, where the incidence of tuberculosis is much higher, then one would expect a high prevalence of TB meningitis. Cerebral toxoplasmosis is also difficult to diagnose definitively in Africa, though preliminary studies suggest that it, too, may be more prevalent among African AIDS patients than in industrialized countries. A study from the Congo in which anti-

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type 1 infection in Kinshasa, Zaire. A prospective, longitudinal cohort study of 587 children.. *N Engl J Med* 1991 Jul 11;325(2):105-9.

45 Colebunders R; Bahwe Y; Nekwei W; Ryder R; Perriens J; Nsimba K; Turner A; Francis H; Lebughe I; Van der Stuyft P. Incidence of malaria and efficacy of oral quinine in patients recently infected with human immunodeficiency virus in Kinshasa, Zaire. *J Infect* 1990 Sep;21(2):167-73

46 Katabira E, *op cit.*

47 Berenguer J; Moreno S; Laguna F; et al: Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N Engl J Med* 1992 Mar 5;326(10):668-72.

toxoplasma antibody titers were measured in blood and CSF estimated that 20% of the AIDS patients (as defined by the Bangui criteria, outlined below, and a positive HIV test) had CNS toxoplasmosis[48]. HIV-infected patients are certainly also susceptible to all of the CNS diseases that affect non-infected patients. HIV testing is likely to be of help only when it leads to a change in therapy. Figure V.2 illustrates a possible diagnostic algorithm for a patient who presents with CNS symptoms. HIV testing is only part of that algorithm when it would be used to decide whether or not to treat empirically for TB or toxoplasmosis.

Also listed in the table and included in the figure are cerebral malaria and neurosyphilis. These infections may be more severe in the HIV-infected host, though they both certainly also occur in HIV-uninfected patients. Treatment is not different depending on the patient's HIV status.

	HIV-related CNS Pathology[49,50]	**Treatment**
	HIV dementia	no treatment available
	Toxoplasmosis[51]	no difference in treatment; pyrimethamine & sulfadiazine which is feasible in Africa
	Cryptococcal meningitis	intravenous amphotericin is not practical in most of Africa; oral fluconazole is prohibitively expensive
	CNS lymphoma	no effective treatment in AIDS patients
	M. tuberculosis meningitis	no significant difference in treatment HIV+ vs. HIV-
	Progressive multifocal leukoencephalopathy	no treatment available
	Viral encephalitis	no treatment available
	?HIV-related CNS Pathology	
	cerebral malaria	no difference in treatment
	neurosyphilis	no difference in treatment

Table V.4 HIV-related CNS pathology and treatment in Africa

48 Carme B; M'Pele P; Mbitsi A, et al: Parasitoses et mycoses opportunistes au cours du SIDA. Leurs frequences a Brazzaville [Opportunistic parasitic diseases and mycoses in AIDS. Their frequencies in Brazzaville (Congo)]. *Bull Soc Pathol Exot Filiales* 1988;81(3):311-6.

49 Perriens JH; Mussa M; Luabeya MK; Kayembe K; Kapita B; Brown C; Piot P; Janssen R: Neurological complications of HIV-1-seropositive internal medicine inpatients in Kinshasa, Zaire. *J Acquir Immune Defic Syndr* 1992;5(4):333-40.

50 Luft BJ; Castro KG: An overview of the problem of toxoplasmosis and pneumocystosis in AIDS in the USA: implication for future therapeutic trials. *Eur J Clin Microbiol Infect Dis* 1991 Mar;10(3):178-81.

51 Carme B; M'Pele P; Mbitsi A; et al*: op cit.*

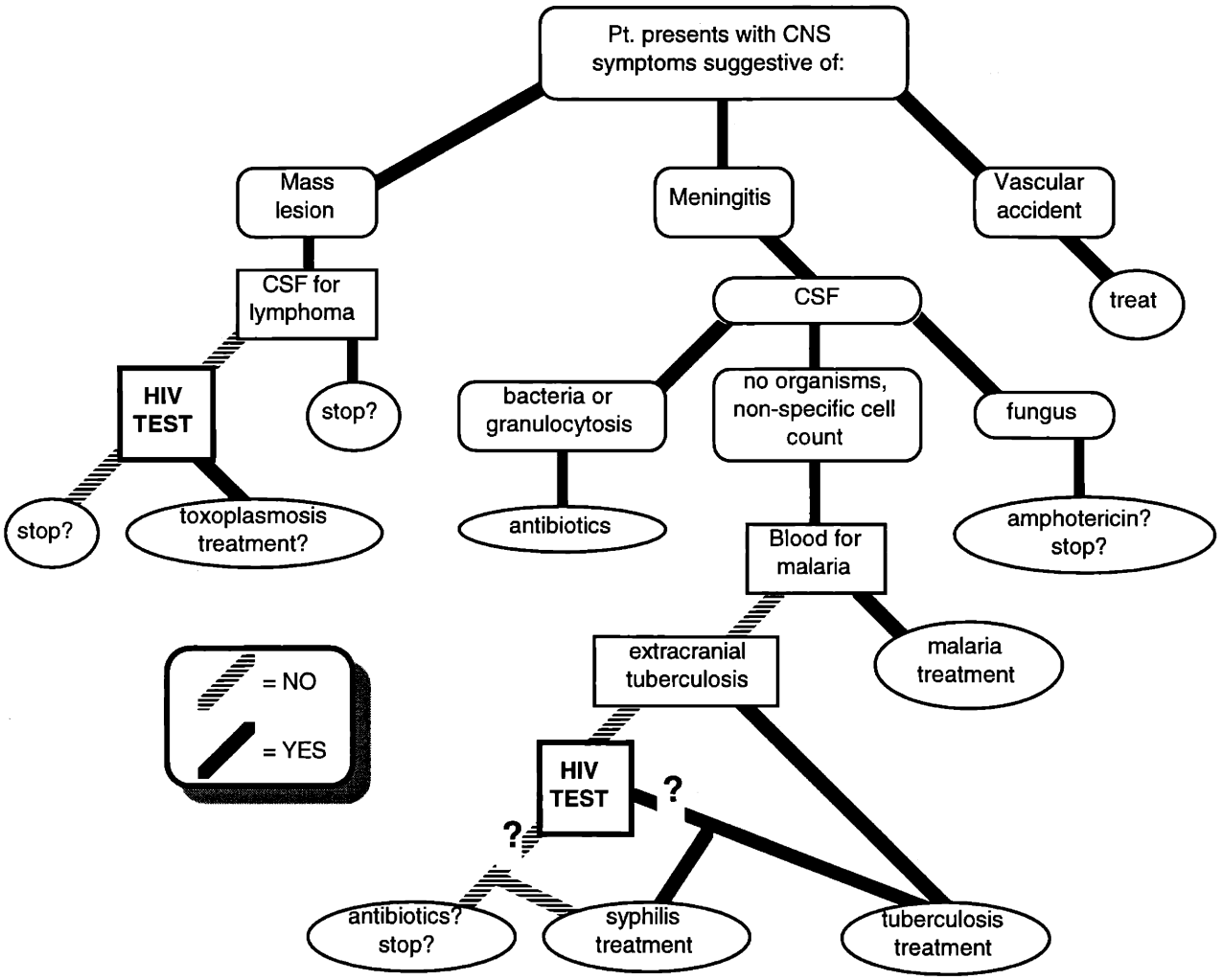

Figure V.2, A simplified diagnostic algorithm for neurologic disease illustrating use of the HIV test

xvii The discussion above has focused on how HIV testing might lead to changes in therapy for HIV-related opportunistic infections and cancers. Advocates of testing in industrialized countries have become more vocal recently with the development of antiretroviral drugs to treat HIV infection itself (as opposed to treating its associated opportunistic illnesses), and with the development of more sophisticated means of tracking immune competence to be able to appropriately begin prophylactic therapy against common opportunistic infections. Except for the very highest socioeconomic groups in African (for whom the cost of an HIV test is inconsequential), anti-HIV treatment is far out of reach. As new and better therapies become available in wealthy countries, the monopoly power of companies such Burroughs-Wellcome, manufacturer of AZT, will fall and the price of earlier, less effective antiretroviral drugs may drop, bringing them within the reach of African populations.

xviii-xix The question of whether to begin prophylactic therapy against opportunistic infections is more complex. In the U.S., usual medical practice for HIV-infected patients includes:

- screen for exposure to TB with a skin test and treat prophylactically all who test positive;[52]
- regularly (e.g. every 3 to 6 months) follow the CD4 lymphocyte count (a white blood cell destroyed by the AIDS virus) and begin prophylaxis against PCP when it falls below 200;[53]
- some practitioners are suggesting prophylaxis against toxoplasmosis for those with serologic evidence of previous exposure, and against *Mycobacterium avium* and CMV when the CD4 count is less than 50, though these practices remain experimental.[54]

xviii In Africa, a positive TB skin test in an HIV-negative, otherwise asymptomatic person is <u>not</u> usually treated with anti-TB therapy. The reasons include the high percentage of the population exposed to TB in childhood ("about half of the population aged 20-40 have been infected"),[55] the use of the BCG vaccine against TB which can cause the skin test to be falsely positive,[56] the cost of treatment, and the inability to monitor individuals for signs of drug toxicity. Several studies, including one recently published on Malawi, Mozambique, and Tanzania, confirm that treatment of persons with TB in their sputum (smear positive) is very cost effective. This cost effectiveness was even demonstrated for HIV-infected patients because most of the benefits associated with treatment result from avoidance of secondary cases, not from the years of life saved in the index case.[57] There are very few data from Africa on cost and effectiveness of treating patients who have a

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52 Daniel TM; *Tuberculosis*: In *Harrison's Principals of Internal Medicine* edited by Wilson JD; Braunwald E; Isselbacher K; Petersdorf RG; Martin JB; Fauci AS; Root RK. New York, McGraw Hill Inc. 1991, pp 637-45.

53 Fauci AS; Lane HC; The acquired immunodeficiency syndrome (AIDS) in *Harrison's Principals of Internal Medicine* edited by Wilson JD; Braunwald E; Isselbacher K; Petersdorf RG; Martin JB; Fauci AS; Root RK. New York, McGraw Hill Inc. 1991, pp 1402-1410.

54 *ibid.*

55 Harries AD. Tuberculosis and human immunodeficiency virus infection in developing countries [see comments]. *Lancet* 1990 Feb 17;335(8686):387-90

56 Tuberculin reactions in apparently healthy HIV-seropositive and HIV-seronegative women--Uganda. *MMWR Morb Mortal Wkly Rep* 1990 ;39(37):638-9, 645-6.

57 Murray CJ, DeJonghe E, Chum HJ, et al: Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet* 1991 Nov 23;338(8778):1305-8.

positive skin test but no evidence of active TB, especially in the HIV positive population. Styblo and the MMWR, for example, argue against prophylactic treatment for all persons with a positive skin tests in developing countries because of the high cost/benefit ratio. However, the higher rates of TB reactivation in HIV-positive patients may increase the expected benefit.[58-61] Because of the enormous magnitude of combined TB/HIV infection in Africa, research on the cost-effectiveness of prophylaxis is urgently needed.

xix Any prophylaxis that relies on serial CD4 lymphocyte counts is clearly impractical in Africa. In the case of PCP in particular, the incidence is so much lower in Africa[62] that even if it were possible to determine CD4 counts, the benefit in reduced PCP might not even offset the cost of drug toxicity, not to mention the cost of the drugs themselves.

xx The apparently high incidence of toxoplasmosis in Africa has lead some to suggest that prophylactic pyrimethamine should be used. This drug has the theoretical advantage of providing protection against malaria and isosporiasis in addition to toxoplasmosis. As with TB prophylaxis, studies are also needed to evaluate this proposed treatment. Not only does the question of whether or not to begin prophylaxis need to be addressed, but also the question of when to start. Should one start as soon as HIV infection is confirmed? should only patients with symptomatic HIV-related disease take prophylaxis? or should it be reserved for those who meet the AIDS case definition?[63]

Returning now to figure V.1 above, the intervening discussion has focused on the clinical circumstances in which the result of an HIV test might be expected to change therapy. Figure V.1 illustrates that for HIV testing to positively influence outcome, another condition must be met, that in the absence of an HIV test, the treating clinician would have made the wrong assumption about the patient's HIV status. If the clinician would have guessed correctly and treated accordingly, then a "confirmatory" HIV test would not alter

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58 Styblo K. Preventive chemotherapy for tuberculosis control in developing countries. The case against preventive chemotherapy [comment]. *Bull Int Union Tuberc Lung Dis* 1990-91;66 Suppl:27-8.

59 Africa's tuberculosis burden and chemoprophylaxis [editorial]. *Lancet* 1990 May 26;335(8700):1249-50.

60 Tuberculosis in developing countries. *MMWR Morb Mortal Wkly Rep* 1990 Aug 24;39(33):561, 567-9.

61 Braun MM, Badi N, Ryder RW, et al. A retrospective cohort study of the risk of tuberculosis among women of childbearing age with HIV infection in Zaire. *Am Rev Respir Dis* 1991 Mar;143(3):501-4.

62 Colebunders R; Quinn TC; *op cit.*

63 World Health Organization: Acquired immunodeficiency syndrome (AIDS). WHO/CDC case definition for AIDS. *wkly epidemion rec* 1986. 61:69-76.

therapy. An obvious implication of this line of reasoning is that the greatest benefit will be associated with those clinical situations in which the clinician is most unsure about the patient's HIV-status and therefore the most likely to guess incorrectly.

AIDS in industrialized countries is diagnosed by confirming the presence of HIV infection and any of a number of opportunistic illnesses.

> For surveillance purposes in developing countries and to enable clinicians to diagnose AIDS in the absence of sophisticated diagnostic facilities, a clinical case definition of AIDS was proposed by the World Health Organization (WHO) [Table below].[64] Field evaluation in central Africa showed that this definition was highly specific (94 percent) but relatively insensitive (62 percent) for HIV-1 infection.[65]

World Health Organization (WHO) clinical case definition of AIDS in adults when diagnostic resources are limited

AIDS in an adult is defined by the existence of at least two of the major signs associated with at least one of the minor signs, in the absence of known causes of immunosuppression, such as cancer or severe malnutrition, or other recognized etiologies.

1. Major signs
   a. Weight loss >10% of body weight
   b. Chronic diarrhea >1 month
   c. Prolonged fever >1 month
2. Minor signs
   a. Persistent cough for >1 month
   b. Generalized pruritic dermatitis
   c. Recurrent herpes zoster
   d. Oropharyngeal candidiasis
   e. Chronic progressive and disseminated herpes simplex infection
   f. Generalized lymphadenopathy

Generalized Kaposi's sarcoma and cryptococcal meningitis are sufficient by themselves for the diagnosis of AIDS

Such definitions are of unquestionable value in monitoring the epidemiology of the epidemic for which a standard definition must exist about what constitutes a "case" of AIDS. Several papers have been published about the sensitivity and specificity of AIDS

64 World Health Organization: Acquired immunodeficiency syndrome (AIDS). WHO/CDC case definition for AIDS. *wkly epidemion rec* 1986. 61:69-76.

65 Colebunders RL; Mann JM; Francis H, et al: Evaluation of a clinical case definition of AIDS in Africa. *Lancet* i:492-494, 1987.

case definitions.[66,67] This body of research has helped to clarify the usefulness of various clinical signs in predicting whether a patient is infected with HIV.

The quote also illustrates the uncertainty that accompanies clinical diagnoses. The relatively low specificity quoted above is expected; AIDS is the end of the spectrum of HIV-related disease and thus an AIDS case definition should not detect people with early HIV-related disease. The relatively high specificity can be misleading. In a community in which 5% of patients are HIV infected, then meeting the AIDS case definition suggests that a patient has a 45% chance of being HIV infected. In contrast, if 50% of patients in a community are HIV-infected, then 94% of those meeting the definition will be HIV-infected. In the former case an HIV test is likely to provide greater benefit to a patient.

Included in the list of costs and benefits of HIV testing in Table V.1 are "↓ time till diagnosis" and "↓ cost of diagnosis." The inclusion of these as benefits distinct from effects of testing on treatment suggests that there is inherent benefit associated with "making a diagnosis." This is certainly the tradition of allopathic physicians, probably dating from a time when few treatments were available and application of the scientific method to arrive at a diagnosis was the primary task of a physician. In this tradition, establishing a diagnosis is beneficial because it provides a service to the patient, independent of whether treatment is available or of whether establishing the diagnosis influences choice of treatment.

Certainly there are potential non-health-related benefits that may be associated with establishing a diagnosis. People may want to know about a lethal diagnosis so that they can make more appropriate personal and business decisions. Some would choose not to have additional children, others to move to a shorter-term investment strategy. Others may want to know that they are <u>not</u> HIV-infected so that they can proceed with wedding plans, education plans, or plans to start a business. However, the discussion in Chapter III about testing for Huntington's Chorea suggests that knowing a diagnosis is not necessarily perceived as a benefit by patients, even in industrialized countries, when the diagnosis will not affect treatment. Certainly it is unfair to extrapolate across cultures and assume that patients in Africa necessarily derive benefit from the establishment of a diagnosis.

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66 Colebunders RL; Mann JM; Francis H, *op cit.*

67 Colebunders R; Quinn TC; *op cit.*

In the U.S.A., the medical community has historically paid little attention to the potential harm associated with collecting diagnostic information.[68] Even the cost of acquiring the information (cost of test), is often ignored because commonly neither the clinician nor the patient is directly affected by the cost of care. To the materials and labor cost of performing a test, must be added the cost of the harm that will result if the test result is inaccurate, inaccurately interpreted, or used in an inappropriate way. HIV testing has brought the issue of harm from testing to the forefront of public and scientific debate. The most visible harm has resulted from failures to keep test results confidential and the devastating discrimination which has ensued. Even when positive results have not been disclosed outside of the medical team, they have resulted in patients being inappropriately refused treatment.[69,70] False positive or false negative results may not only result in inappropriate, potentially harmful treatment, they are also likely to increase the cost of care.

The U.S.A. has seen decades of increasing empowerment of the patient in medical settings. The patients right-to-know about his or her care and the need to obtain a patient's consent before instituting treatment are paramount in this trend. The HIV test has turned attention to the patients right *not* to know and thus the need to obtain consent before obtaining information. Some people, especially if they are asymptomatic, would prefer not know if they are infected with a lethal, incurable organism. These people will be harmed if they are informed against their will.

It is essential to understand that patient's rights in the context of their medical care are perceived very differently in other countries. The United States has changed greatly in this regard, largely as a result of the consumer's rights movement, most visible in the 1970's. It would be naive to assume that other countries shared our views in the 1950's or that they have undergone similar transformation.

Establishing a diagnosis, because of the patient's poor long-term prospects, may result in denial of care that would be of short-term benefit, thus decreasing his or her quality of life. Some patients would prefer to be informed of a lethal diagnosis as late as possible and may view *early* diagnosis as inherently decreasing their quality of life.

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68 Feldman W: How serious are the adverse effects of screening ? *J Gen Intern Med.* 1990 Sep-Oct; 5(5 Suppl): ppS50-3.

69 Currey CJ; Johnson M; Ogden B: Willingness of health-professions students to treat patients with AIDS. *Acad Med.* 1990 Jul; 65(7): pp472-4.

70 Yeh SM; Yuan HS; Ko YC: Factors related to the willingness of nurses to care for AIDS patients in Taiwan. *Kao Hsiung I Hsueh Ko Hsueh Tsa Chih.* 1990 Aug; 6(8): pp422-7.

Another consideration in examining costs and benefits from the patients' perspective is that not all patients subscribe to the same Oslerian biologic view of disease. Just as in our society many believe in supernatural healing powers, many in Africa believe in magical powers that can cause and remove illness. Suppose it were possible to magically take away an infection until it was shown to be there by a test; or that testing itself is bad luck so that people who are tested are more likely to be infected.

Hospitals' Perspective

Assume that a "hospital" is a private, not-for-profit hospital and that its primary goal, given its financial constraints, is to maximize the benefit to its patient population from the curative medical services it provides. Thus the hospital is interested not only in how to improve the health of each individual patient, but also in how to best ration its services so that the services generate the maximum possible benefit. In this context, an HIV test may serve two, potentially conflicting, purposes:

- to provide information to treating clinicians that may alter and improve medical therapy;
- to provide information to the hospital that helps to predict the likelihood that a patient will respond to therapy and the number of years the patient is likely to live to enjoy the benefits of the therapy.

The first purpose is indistinguishable from the patient's interest in HIV testing. It is the addition of the second purpose that distinguishes the interests of the patient from those of the hospital. For example, suppose that the tuberculosis ward at a hospital is full. The hospital may want to give preference to tuberculosis patients who are HIV negative because the likelihood that they will be cured is greater and because even if both are cured, HIV-negative tuberculosis patients have a greater life expectancy. In this situation, a patient who is at higher than average risk for HIV infection may have a negative expected benefit from HIV testing. Table V.1 refers to this "cost of testing" as "Medical discrimination". The existence of dual purposes of testing complicates the study of the impact of testing. For example, in a hospital based study it may be difficult to distinguish effects of more appropriate treatment from effects of limiting access to services. If the average length of stay of HIV positive patients falls with the introduction of HIV testing, is it because they have been treated more successfully—or because they were treated less?

Some members of the U.S. medical community, most visibly Dr. L. Day in San Francisco,[71-74] have argued that hospitals have another purpose in testing patients: so that health care workers can take appropriate measures to protect themselves from HIV infection. This view is has *not* been endorsed by the Centers for Disease Control, which instead recommends that universal precautions be observed with all patients to protect health care workers form all blood borne diseases.[75,76] Universal precautions are clearly not practical for Africa where even the most basic infection control measures, such as gloves for midwives, are often lacking. Even in North America, the cost-effectiveness of universal precautions has been questioned, with one Canadian study suggesting that (in Hamilton, Ontario) universal precautions cost more than $500,000 per year of life saved.[77] A potential benefit of testing hospitalized patients in Africa is that scarce protective equipment, such as gloves, could be preferentially used with HIV positive patients thus decreasing transmission to health care workers.

In spite of this theoretical benefit, evidence from a seroprevalence study in a large hospital in Kinshasa, Zaïre[78] suggests that hospital workers with frequent patient contact are not at higher risk of infection than staff members who are not directly involved in patient care—thus the magnitude of any benefit to health care workers is likely to be small. Studies of HIV incidence in health care workers at *very* high risk of exposure, such as rural midwives in high prevalence areas, would be ethically questionable because such studies would require drawing blood repeatedly from these workers *without* providing them with the means to protect themselves against infection. Consideration of this possible benefit of HIV testing patients could be incorporated into a hospital-based study of HIV testing, but the data collected would be limited to observing behavioral changes; it would be

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71 Day LJ: AIDS: an occupational hazard for orthopaedic surgeons? A conversation with Lorraine J. Day. [interview] *Orthop Rev.* 1989 Apr; 18(4): 493-7.

72 Day L: The informed professional: another view of HIV testing: an interview with Dr. Lorraine Day. *Del Med J.* 1988 Aug; 60(8): 35-7.

73 Day L: Perils of orthopedic surgery [letter] *Can Med Assoc J.* 1988 Dec 1; 139(11): 1035-6.

74 Howard RJ: Human immunodeficiency virus testing and the risk to the surgeon of acquiring HIV. *Surg Gynecol Obstet.* 1990 Jul; 171(1): 22-6.

75 Leads from the MMWR. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings.*JAMA.* 1988 Jul 22-29; 260(4): 462-5.

76 Hagen MD; Meyer KB; Pauker SG: Routine preoperative screening for HIV. Does the risk to the surgeon outweigh the risk to the patient? *JAMA.* 1988 Mar 4; 259(9): 1357-9.

77 Stock SR; Gafni A; Bloch RF: Universal precautions to prevent HIV transmission to health care workers: an economic analysis. *Can Med Assoc J.* 1990 May 1; 142(9): 937-46.

78 Mann JM; Francis H; Quinn TC; *et al* HIV seroprevalence among hospital workers in Kinshasa, Zaire. Lack of association with occupational exposure. *JAMA.* 1986 Dec 12; 256(22): 3099-102.

very difficult to conduct a study large enough and long enough to measure differential HIV incidence rates among hospital personnel.

Third-party-payers' (Insurers') Perspective

A third-party-payer, in this formulation, is any entity that supports the cost of a patient's medical care other than the patient's nuclear family, the hospital and the government. The two most common examples in many African countries are the patient's extended family and his or her employer. As with the patients' perspective, the insurers are interested in improving the effectiveness of medical therapy for its covered population. There is no conflict of interest between patient and insurer as regards medical care that will enable a speedy return to healthy, productive life.

Referring back to Table V.1, rows 2 and 3 of the table contain "Prolonged productive life" and "Prolonged non-productive life." The reader may wonder why these merit separate rows (are they not subsumed under "↓ duration/↑ effectiveness of Tx?") as more effective therapy will prolong both productive and non-productive life. While a patient may be interested in health care that prolongs non-productive life, an insurer is much less likely to value that same care. From the perspective of an employer, if an employee is temporarily disabled, then it is in the company's and in the patient's interest for that employee to be able to return to work as soon as possible. However, if an employee has retired or has been permanently disabled then medical care to prolong life will only increase company costs without company benefit. In the former case medical care can be expected to shorten the period of disability, while in the latter case it will prolong it. Even extended families, despite their desire to assist their members, are forced to place lower priority on medical care that is not expected to return the recipient to productive life.

In this context, diagnostic testing may have a dual purpose, much as it did for the hospital. It provides potential benefit by permitting modifications in therapy, and it provides information to the insurer about the likelihood that the patient will be able to return to productive life. To the extent that such information limits a patient's access to health care, it will encourage patients to resist testing.

While the patient and the hospital may be primarily interested in curative services, insurers are very interested in prevention of disease in its 'covered' population, at least to the extent that prevention will result in net cost saving by reducing expenditures for curative services. Thus if an insurer is also responsible for the health care of patient's dependents, it is likely to also be interested in limiting secondary HIV transmission. Whether testing

patients and informing them of their HIV status results in a subsequent decrease in HIV transmission is a question that remains to be answered.

Anecdotally, some medical providers express reluctance to test and inform patients because they fear the information will have a paradoxical effect on HIV transmission.[79] They believe that notification of a positive test result may lead to breakup of the family with a subsequent increase in number of sexual partners. Others believe that some patients will respond pathologically to being informed of their HIV status, positive or negative, by increasing their unsafe sexual activity—positives because their anger makes them want to "take others with them" and negatives because their feelings of invulnerability have increased. The most commonly expressed reservation is that telling a patient they are infected will hasten their clinical deterioration because they will become depressed, stop eating, and may become suicidal. The arguments about patient's pathological responses to learning of their HIV infection may represent cultural differences between American and African patients. Or, they may represent rationalizations by health providers who are accustomed to a more paternalistic medical system and naturally resist transferring information, and thus decision making power, to patients.[80]

One set of results which lends credence to those who argue that informing patients is unlikely to be beneficial is the results of the studies in Kinshasa, Zaire of women tested for HIV prior to giving birth. Those women, despite extensive counseling about HIV infection and safe-sex, did not have a measurable drop in their fertility rate as compared to the uninfected women in the study.[81]

One usually thinks of reducing the incidence of HIV infection in an insured population by reducing transmission, for example by educating patients who are found to be HIV-infected about how to avoid infecting their sexual partners. However, incidence can also be reduced by limiting immigration of infected persons into (or evicting infected

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79 The observations about the reluctance of physicians to inform patients are based solely upon my personal interviews with physicians in rural and urban hospitals in Tanzania and Zaïre. Over the years during which this research was conducted, I noted declining resistance as programs to counsel HIV infected persons were established. However, the existence of markedly different attitudes between the United States and these two countries concerning the acceptability of withholding information from patients is unmistakable.

80 Chela CM; Campbell ID; Siankanga Z: The Salvation Army Chikankata Hospital, Mazabuka, Zambia. In *abstract International Conference on AIDS.* 1989 Jun 4-9: 5 P369 (abstract no. W.B.P. 265).

81 Ryder RW; Batter VL; Nsuami M; Badi N; Mundele L; Matela B; Utshudi M; Heyward WL: Fertility rates in 238 HIV-1-seropositive women in Zaire followed for 3 years post-partum. *AIDS,* 1991 Dec, 5(12):1521-7.

persons from) the population. In the case of an extended family, the family could encourage the testing of fiancés or encourage divorce from an infected spouse. A company may similarly want to perform HIV tests on prospective employees either with the goal of not hiring HIV positive persons or with the goal of not providing them with health care benefits.

Testing performed with the goal of excluding HIV positive persons is clearly outside of "diagnostic testing" as defined above. However, the potential for using testing for exclusionary purposes is likely to influence patients' perception of the costs (including potential harm) and benefits of HIV testing offered to them in a diagnostic setting.

Governments' Perspective

Society is presumed to be interested in maximizing health benefits across the population. Chapter II discussed maximizing total discounted healthy life years (DHLYs) gained, (corrected for the amount of secondary poverty caused by a lost DHLY) and did not differentiate between DHLYs gained by prevention and those gained by treatment. Often the distinction between the two is blurred, as in Over and Piot's discussion of the benefits associated with treating and preventing (non-HIV) sexually transmitted diseases (STDs)[82]. Because cure of an STD shortens the period of infection, STD treatment gains DHLYs both because the index case is not ill as long and because secondary cases are prevented. (Because STDs seem to increase the likelihood of HIV transmission, treatment of STDs may also have secondary benefits associated with reduction of HIV transmission.) In asymptomatic STD carriers, treatment may be of benefit only because of secondary prevention. HIV is paradoxical in this regard. Treatment is not curative and thus at best prolongs the period of infectivity. This translates into DHLYs gained by the index case and the possibility of DHLYs lost because of secondary cases that would otherwise not have occurred. Of course, preventive activities that accompany treatment (counseling, condom distribution, etc.) may result in reduced probability of secondary infections.

Jamison and Mosley, in summarizing the cost per DHLY gained by different preventive and therapeutic interventions, reveal a large differential between the two. The difference in cost per DHLY gained by the 10 most cost-effective hospital interventions is more than an order of magnitude greater than that for the 10 most cost-effective preventive

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82 Over M, Piot P: HIV infection and sexually transmitted diseases. in *Disease Contrrol Priorities in Developing Countries* edited by Jamison DT Mosely HW. Washington, DC: World Bank 1993, pp455-527.

interventions.[83] It would not be difficult to conclude that efficiency dictates the removal of all public (governmental and non-governmental) subsidies from most African hospitals, especially in the poorest countries, so that the funds may be re-directed to more cost-effective preventive interventions. Such a suggestion is at best not realistic, and even if it were, it paternalistically disregards the preferences of the people concerned, who would strongly object to such a restructuring of funding priorities.[84]

Finding such a great difference between the predicted equilibrium in the health care market (in which each intervention is funded to the point that the cost per unit of benefit, in this case DHLY gained, is equal) and reality suggests that the model does not accurately represent the market and/or that there are serious imperfections in the market that prevent it from approaching the theoretical equilibrium.

Although it may be logically consistent and more conducive to concise modeling, it is inconsistent with observed behavior to assume that society values a DHLY saved by prevention as highly as one saved by curing. "Society's" actions may not necessarily reflect its collective self interest, but rather the cumulative self interest if its members. Individuals typically value personal curative care more highly than personal preventive care if the expected change in DHLYs is similar.[85,86]

Another explanation of the difference between the collective preference for preventive versus therapeutic care is that the hypotheses made in previous chapters about time preference do not reflect reality in Africa. The assumption that a DHLY is of equal benefit, regardless who gains it, may be a reasonable basis for social policy. However, it may not reflect the cumulative preferences expressed by the individuals in society, each of whom place greater priority on the DHLYs they gain themselves than on DHLYs gained by others. Since an individual will die at some indeterminate point in the future, the longer the delay between an intervention and expected benefit from that intervention, the less likely that the individual will be alive to reap the benefit. Thus, two important factors increase the individual's preference for early benefits: his or her expectation of time until death and the degree of uncertainty (variance) of that estimate. In other words, a person who expected to

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83 Jamison DT; Mosley WH: Disease control priorities in developing countries: health policy responses to epidemiological change. *Am J Public Health*, 1991 Jan, 81(1):15-22.

84 Stebbins KR: Curative medicine, preventive medicine and health status: the influence of politics on health status in a rural Mexican village. *Soc Sci Med.* 1986; 23(2): 139-48.

85 Yoder RA: Are people willing and able to pay for health services? *Soc Sci Med.* 1989; 29(1): 35-42.

86 Weinstein MC: The costs of prevention. *J Gen Intern Med.* 1990 Sep-Oct; 5(5 Suppl): S89-92.

die in 5 years has greater time preference than a person who expects to die in 10. Between two people who expect to die in 10 years, if one knows that death will occur in exactly 10 years, he or she has less time preference than the person who has a 5% chance of dying in each of the next 20 years. For both reasons, the time preference of individuals in poorer countries (with both lower age-specific life expectancies and higher variance of those expectancies) would be expected to be higher than in wealthier countries.

The effect of time preference is theoretically accounted for by discounting the difference in time between the time of the intervention and the time of the expected benefit. Perhaps to avoid appearing to have a cynical disregard for the value of human life, economists are unwilling to assign discount rates to lost years of life that exceed those for capital. If time preference is to be used to explain the observed difference in preference for preventive and therapeutic care, then the discount rate used must be greatly increased.[88]

How does this discussion of preventative vs. curative care relate to governments' choices about purchasing or not purchasing diagnostic HIV tests? If the argument against curative services is convincing, then diagnostic testing would probably be rejected, along with other curative services, in favor of more cost-effective preventive strategies. Practically, governments are not rejecting curative services. Thus, one must question how a government's perspective on the decision to purchase a diagnostic HIV test is different from that of the other payers discussed above.

Governments' interest certainly incorporates patients' interest, in that a government wants better, faster treatment for people's illnesses. It also incorporates the hospitals' interest in using resources allocated for curative services as efficiently as possible, so as to maximize the health benefit to the population. Governments share the concern of insurers in prevention and in decreasing HIV incidence (some, like that of the U.S., even use the test to limit immigration), especially if the prevention is expected to reduce expenditures for curative services. The governments interest in potential effects of diagnostic HIV testing

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88 One way to explain a higher time preference for HLY than capital is to incorporate the probability of being alive to benefit from the future HLYs expected from the preventive action. Consider the perspective of a man in an urban area where the HIV prevalence is 10%. Assuming homogeneous mixing, a probability of transmission per sexual contact (between an infected and a non-infected) of 1%, and 100 sexual contacts per year; if the man adopts no behavioral change he would expect to become infected in 11.1 years and would expect to become symptomatic 14 years after that (25.1 years later). Depending on the discount rate one uses, this corresponds to:

Rate	2.5%	5%	7.5%	10%
Value	54%	29%	15%	8%

on HIV transmission is even greater than that of the third-party-payer because the government is not only interested in transmission within an insured population. It is also interested in transmission to health-care workers, casual sex partners, and extended families, for example.

Conclusion

To which patients and in what settings should diagnostic HIV testing be offered? This chapter has attempted to provide a framework for answering this question. It examines the question from the perspective of four different purchasers of the test and discusses the ways in which their interests are concordant and discordant. Without answering the question, it seeks to help the reader make an educated guess about when and for whom testing is likely to be cost-effective. In appendix V.1 two models are presented with corresponding outlines of research protocols which could be used to study, from the perspective of one or many hospitals, when it would be cost-effective for the hospital(s) to offer diagnostic HIV testing.

When examining HIV testing from the patients' perspective the arguments suggest that HIV testing will rarely have an important influence on medical treatment. This suggests that it would rarely be cost-effective for patients with a specific medical problem to purchase an HIV test just to help their physicians/care-givers decide what to do. However, these narrow clinical indications for testing are likely to be overshadowed by other considerations. For example, the result of an HIV test may not affect management of the current disease episode, but the potential clinical benefits of testing extend to future disease episodes, especially if the test is positive. These potential future benefits are much more difficult to examine, as a study would have to be long-term and community based.

For some patients learning about a diagnosis early—even if it never results in a change of therapy— is a benefit of testing, for other patients it is a cost. Policy makers, schooled in the belief that more-perfect information is always desirable, must actively avoid imposing their belief structure on people who may not share it. In calculating costs, remember that the monetary cost of a test, while high, may be small in comparison to the cost associated with social, economic, and medical discrimination that could accompany a positive test result. Thus, an individual's decision to refuse testing, though it may superficially appear irrational and uninformed, may be an appropriate utility maximizing strategy for that person.

The complex issues surrounding an individual patient's decision to purchase, or not to purchase an HIV test, while interesting, are likely to be less relevant for policy makers than the issues surrounding institutional purchase of tests. In most countries, availability of HIV testing to individuals will probably be determined more by the marketplace rather than by policy makers.

Policy makers are more likely to be involved in helping hospitals, insurers, and governments decide whether or not to offer HIV testing. If, as suggested above, clinical benefit is not likely to be a major determinate of the costs and benefits associated with testing, then for any of the institutional purchasers to determine that testing is cost-effective, the non-clinical benefits must be significant. These "non-clinical benefits" hearken back to the first line of this chapter : "the medical instinct to act as an advocate for the individual patient comes quickly into conflict with the need to limit outlays for medical treatment of insufficient benefit."

Anybody who has worked with persons with HIV infection (PW-HIV) in any country has witnessed the double burden they bear of disease and outcast. To use the words "justifiable discrimination" in this context appears profoundly insensitive if not outright cruel. To suggest that it might be justifiable in some contexts to limit the access to services of HIV-positive persons only appears to validate the efforts of others who seek to expel HIV-infected persons from normal society on the grounds that they are either dangerous or morally unfit. In wealthy countries the apparently obvious answer is to ignore the comparatively minor costs of providing sometimes inefficient care to HIV positive persons and lend ones voice unambiguously to the chorus calling for an end to discrimination against persons infected with HIV. If only the same costs in Africa could be called "comparatively minor."

In a setting where health care resources are <u>severely</u> constrained and health facilities frequently operate at capacity, there must exist some ways of rationing resources. The choice of rationing method is one that must be made by the population involved. Some may choose to ration by ability to pay, others by first-come-first-served, others by some sort of lottery; but a large number will choose a system that relies on the medical tradition of triage in which greatest priority is given to those who are most critically ill <u>and</u> who are most likely to benefit from available treatment. If triage is done inefficiently, then more people die (or lose DHLYs) than otherwise would. Thus if a society chooses to use a form of triage to ration, then it should welcome efforts to make that system as efficient as possible. HIV testing can be used to improve triage because in some circumstances a

patient's HIV status can radically change his/her life expectancy with and without treatment—and thus the likelihood of benefit from treatment.

When discussing rationing of medical services by medical triage, some very important distinctions must be made between types of medical services provided. Medical services are commonly subdivided into preventative and curative services, with triage being used to distribute curative services. However, in the following discussion about triage and "justifiable discrimination," it is essential that "curative services" be further subdivided into treatment and palliation.

One can convincingly make the economic argument that treatment of bacterial pneumonia in an otherwise healthy 35 year old man is likely to be of greater social benefit than treatment of the same pneumonia in a patient with AIDS. However, no such argument can be made about whether to provide two similar patients with pain medication for an outbreak of herpes zoster (shingles). In the former case, the patients are distinguished by the amount of time treatment is likely to prolong their life. In the latter, palliation will not affect disease outcome or longevity, but only patient comfort. Thus, both are equally entitled to palliation. Unfortunately, it is often not so easy to distinguish treatment from palliation. For example, "treatment" will often shorten the course of a disease episode and improve patient comfort, serving the dual role of treating and palliating the disease.

The understandable concern by advocates for the rights of PW-HIV is that use of HIV tests for "justifiable discrimination" in a medical setting, will facilitate in a slippery-slope fashion, use of the HIV test to discriminate in other settings. Economic arguments, similar to those supporting the use of the test in medical triage, can be used to justify discrimination in other settings. The medical triage argument, to its advantage, is supported by convincing claims of altruistic intent. How does this compare to arguments in favor of testing by insurers and governments?

Consider the example of an insurer, in this case, an extended family. Suppose a woman who experiences problems during a pregnancy undergoes an HIV test which reveals her to be HIV-infected. Suppose that her husband's extended family (her health insurer) expels her from the family because of the presumption that she was the first in the family to have symptoms of HIV-infection and therefore is to blame for having brought the infection into the family. In such a case most would argue that a diagnostic HIV test resulted in "unjustifiable" discrimination, discrimination which should be resisted by communities and governments. Similar arguments could be applied to a company that

responds to a positive HIV test by firing the tested worker, not because he or she was no longer able to perform the job, but because HIV-infected workers do not fit with the company's healthy wholesome corporate image. Most observers would, as with the first example, consider such an action "unjustifiable discrimination."

Suppose that the same extended family included a young woman who approached her family elders for permission to marry a suitor and was granted permission, provided her suitor was tested for HIV and found to be negative. Or, suppose that the company decided to send one of its junior managers overseas for advanced management training and included in the selection criteria the requirement that the trainee be HIV-negative. In both of these situations the insurer could argue that they were making a long-term investment in human capital and could not afford to invest in someone with a short life expectancy. They would use a similar argument to justify why they would choose to send a 30 year-old trainee rather than a 65 year-old trainee. Whether or not the reader is convinced by the merit of these "justifiable discrimination" arguments, they illustrate why PW-HIV activists would be concerned about extension of the triage argument to use of the HIV test to improve the economic efficiency of decisions in other areas.

In closing, it is appropriate to return to the perspective of the physician and the first ethical principle of medicine, *Primum non nocere* (above all, do no harm). Few are accustomed to the idea that harm may result from efforts to better characterize a patient's illness. While it is true that HIV testing has the potential to improve treatment of patients and the potential to improve the rationing of medical services, these potential benefits must be weighed against not only the monetary costs associated with testing, but also the harm to a patient that might result from it.

Chapter VI considers the less controversial role of HIV testing for monitoring the epidemiology of the epidemic, and develops models for maximizing the cost-effectiveness of seroprevalence surveys.

APPENDIX V.I

MODEL DEVELOPMENT

Two different models are presented which could be used to help policy makers decide when to use HIV tests for diagnostic purposes. The choice between them would depend upon the priorities of policy makers and upon the completeness of hospital accounting data. Both approaches employ regression models with patient characteristics comprising most of the independent variables. The first approach assumes that the study is limited to one hospital with good accounting data that permit estimation of the cost (not price) of a patient's hospital stay. Performing such a study would require a relatively sophisticated data collection phase but would generate data that could be used to examine the influence of HIV testing and of HIV status on the different services that make up the cost of a hospital stay (such as laboratory tests and medications). The disadvantage of this approach is that it would be difficult and expensive to extend the study beyond one hospital, thus limiting the study's ability to be generalized.

The second model uses length of stay (LoS) as a proxy for cost of hospitalization, and assumes that several hospitals will be studied. The independent variables include hospital specific parameters, such as HIV prevalence rate and medication availability, that would be expected to influence inter-hospital variation.

With either of the models, in addition to estimating cost (or LoS), the model could instead be used with clinical outcome as the dependent variable to test the hypothesis that HIV testing influences the patient's quality of life. The easiest outcome variable to collect would be in-hospital mortality. If greater follow-up is possible, one month mortality would also reflect differences in quality and would be unaffected by bias introduced by early discharge of patients following testing.

The structure of the models derives from the following hypotheses: Given the high HIV seroprevalence rates in parts of Africa, hospitals in those areas are likely to have a very high percentage of HIV positive patients, only some of whom will be diagnosed as having HIV-related disease. As an example, in a recent survey of Hôpital Mama Yemo, the large, public hospital in Kinshasa, Zaïre,[89] 50% of the patients in the internal medicine

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89 Hassig SE; Perriens J; Baende E; Kahotwa M; Bishagara K; Kinkela N; Kapita B: An analysis of the economic impact of HIV infection among patients at Mama Yemo Hospital, Kinshasa, Zaire. *AIDS*. 1990 Sep; 4(9): pp883-7.

wards were HIV positive, even though only 6-8% of the adult population was HIV positive.[90] Therefore, in an African hospital located in an area with a significant HIV seroprevalence, a substantial proportion of the pathology will be due to unsuspected HIV-related disease. Testing of patients on admission will alter therapy for some subsets of patients in a way that improves patient quality of life, reduces the cost of care or both in a way that such testing, at least for those sub-groups, is cost-effective. The models will differentiate patients by presenting complaint, by the ward they are admitted to, and by clinical suspicion of HIV infection (using the clinical criteria that comprise the WHO clinical AIDS definition). Thus, the models are designed to help understand which patients (in which facilities) are cost-effective candidates for HIV testing.

The form of the one hospital cost model is (ß's not numbered for conciseness):

$$C = ß + (T+1)(ßA + ßM_1 + ßM_2 + ßM_3 + ßM_4 + ßR + ßG + ßH + ßN + ßF + ßP + ßM + ßS + ßB + ßI + ßE) + ßV + ßT + ßD$$

Variable definitions

C = **C**ost of patient's hospital stay

Admitting complaint (dummy)

- F = **F**ever
- G = **G**astrointestinal
- H = **H**eart (cardiac)
- N = **N**eurologic
- R = **R**espiratory

Hospital ward (dummy)

- B = **B**aby (pediatrics)
- I = **I**nfectious disease (isolation)
- M = internal **M**edicine
- S = **S**urgery

Patient characteristics (dummy)

- A = 15 ≤ **A**ge ≤ 50
- P = **P**athologic diagnosis
- E = **E**mployed (or dependent)
- M_1 = **1** Major AIDS criterion
- M_2 = **2** Major AIDS criteria
- M_3 = **3** Major AIDS criteria or Kaposi's sarcoma or cryptococcal meningitis
- M_4 = 1 or more **M**inor signs
- T = HIV **T**est performed on admission
- V = **V**irus (patient HIV+)
- D = **D**ied in hospital

The model structure reflects its primary goal: to identify, in a particular hospital setting, those patients for whom HIV testing on admission is likely to influence the cost of care. Thus, there are two types of independent variables: 1) variables unknown on admission that are likely to have an influence on cost, such as whether the patient died in the hospital and whether the patient is HIV positive; and 2) variables known on admission.

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90 Kamenga M; Ryder R; N'Galy B; Behets F; Ngoy T; Liambi A et al; "An HIV serosurvey in the general population of Kinshasa appears feasible." in *Abstract Volume, V International Conference on AIDS*. Montreal, June 1989. 973.

The latter group are present in the model both individually and multiplied by a dummy variable that equals one if the patient is HIV tested on admission. Thus, when the model is estimated, the coefficients of the complex variables will help policy makers decide which patient characteristics should be used to identify patients who should be HIV tested on admission.

Cost per patient, the dependent variable, may be calculated by abstracting a patient's medical record and combining those data with hospital accounting data to generate a total cost per patient. Because the cost of medications is such a high percentage of the cost of medical care in Africa and because one hypothesizes that HIV testing will influence the choice and cost of medications, it is most important to retain medication costs as a separately itemized cost item.

The cost accounting scheme that follows attempts to balance the desire for detailed patient level information with the need to be realistic about the detail available from accounting departments of most African hospitals.

$$\textbf{Cost/Patient}_i = C_{Di} + C_{Hi} + C_{Li} + C_{Mi} + C_{Ri} + C_{Si} + C_{Ti} - P_{Ei} - P_{Pi}$$

C_{Di} = (Cost per hospital **D**ay) * Days_i =

$$\frac{\text{Total hospital costs exclusive total } C_D,\ C_L,\ C_M,\ C_R,\ C_S \ \&\ C_X}{\text{Total bed days}} * \text{Days}_i$$

C_{Hi} = (Cost per **H**IV test) * V_i

C_{Li} = (Cost of non-HIV **L**aboratory test) * $\text{Tests}_i = \frac{\text{Total non-HIV lab cost}}{\text{Total tests}} * \text{Tests}_i$

C_{Mi} = Cost of **M**edications$_i = \sum_{j=1}^{n}$ (Cost of Drug$_j$) * (Quantity$_i$ of Drug$_j$)

C_{Ri} = Cost of **R**adiological tests$_i = \frac{\text{Total radiology cost}}{\text{Total number radiological tests}} *$ Quantity$_i$ tests

C_{Si} = Cost of **S**urgery$_i = \frac{\text{Total surgical cost}}{\text{Total number of surgical procedures}} *$ Quantity$_i$ procedures

C_{Ti} = Cost of special **T**reatment (calculation will depend upon what is available at the hospital being studied, e.g. intensive care, deluxe rooms, private nurses, etc.)

P_{Ei} = Amount **P**aid by **E**mployer or 3rd party payer

P_{Pi} = Amount **P**aid by **P**atient and family

The cost per laboratory test is simplified to the average cost per laboratory test except for the HIV test, which is itemized separately. Similarly, the cost of radiological

and surgical procedures are averaged for all procedures. If greater precision is required, surgical procedures could be indexed by time in the operating room and radiological tests could be indexed by the amount of radiographic film used. "C_{Ti}" is included because some hospitals have expensive extras available which should not be lumped into the cost per day category. Such extras might include private duty nursing, intensive care, or hotel-like first class accommodations.

The final two terms in the cost equation, P_{Ei} and P_{Pi}, reflect that the cost equation above is formulated from the hospital's perspective. If the patient's perspective is considered, then the cost equation simplifies to $C= P_{Pi}$ and if the third-party payer's perspective is considered, then $C= P_{Ei}$. If society's perspective is considered, then one may only want to consider total cost, without considering the patient's ability (directly or via third-party) to pay for services. In that case, the cost equation would not include P_{Ei} and P_{Pi}, but otherwise remain the same as the above equation.

To calculate the average cost per laboratory, radiological, or surgical procedure, the total expenditure for each department must be calculated. Included in these expenditures are labor, cost of capital equipment (using an appropriate depreciation schedule), cost of supplies (such as reagents or film), and a percentage of total maintenance and upkeep (probably apportioned on the basis of percent of total capital equipment and percent of total square footage used by the department). Any gifts of labor, capital, or supplies; whether they originate from the government or the private sector, should be valued by their local market value. Thus, in the case of a hospital managed and subsidized by an international non-governmental organization (NGO), gifts of supplies will probably be valued higher than their cost to the non-governmental organization. Gifts of expatriate labor will often be valued below their cost to donor organizations; even if the expatriates are working without compensation because the costs of transporting and supporting expatriates often exceeds the cost of hiring replacement local labor.

Performing a single hospital study would not only help determine which patient characteristics are associated with benefit from HIV testing, but would help to characterize in what ways HIV-related disease is different from other diseases in its use of health care resources. If the study had resources to collect additional variables on severity of illness at discharge, the study could also evaluate whether HIV testing decreases the probability that a patient will be admitted or is correlated with patients being discharged "quicker and sicker".

Multi-Hospital Model

Preliminary studies suggest that the impact of HIV infection and the benefits of HIV testing varies greatly from hospital to hospital. In some places, the average LoS and the cost of care is dramatically different between HIV positive and negative patients; in other hospitals no difference is discernible.[91],[92] Only by performing a multi-hospital study will it be possible to better understand why hospitals seem to have such different experiences with HIV and in which of them HIV testing is indicated. The "multi-hospital model" is only a simplified version of the previous model; one that requires a much less complex data set, permitting collection of data from multiple sites without necessitating detailed cost accounting data from participating hospitals or abstracting of patient records. The model's disadvantage is that it does not permit resolution of the effect of HIV testing on the different components (medications, laboratory, etc.) that comprise total cost.

The independent variables may retain the variables in the above model, all of which are patient specific. To those must be added a number of hospital specific variables.

Hospital characteristics					
U	=	urban (dummy)	Q	=	government operated (dummy)
J	=	HIV prevalence (%)	K	=	for profit (dummy)
L	=	size (beds)	W	=	occupancy rate (%)
			ϕ	=	fees as % of revenue

Thus, the right hand side of the model becomes:

$$ß + (T+1)(ßA + ßM_1 + ßM_2 + ßM_3 + ßM_4 + ßR + ßG + ßH + ßN + ßF + ßP + ßM + ßS + ßB + ßI + ßE) + ßV + ßT + ßD + \mathbf{(T+1)(ßU + ßJ + ßL + ßQ + ßK + ßW + ß\phi)}$$

However, a study of multiple hospitals may not be able to collect such extensive data on the characteristics of individual patients. Thus, a simplified version of the model uses only those data available from the patients admission sheet:

$$ß + (T+1)(ßA + ßM + ßS + ßB + ßI + ßE) + ßV + ßT + ßD + \mathbf{(T+1)(ßU + ßJ + ßL + ßQ + ßK + ßW + ß\phi)}$$

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91 Bertozzi S; Mposo N; Green S; Mandiyangu M; Walker D; Ryder R: Increased hospital revenue associated with admitting HIV positive patients to a rural Zaïrean hospital. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2:283.

92 Hassig *et al, op cit.*

The single hospital model used cost as the dependent variable. The multiple hospital model uses variables that can be collected at the end of the patient's hospital stay. Which variable is used when estimating the model will depend upon which perspective interests the policy maker. LoS may be thought of as a proxy for cost; it can be converted to estimated cost by multiplying it by the institution's total cost per bed-day.[93]

From the hospitals' perspective, the financial impact of HIV infection or testing may be studied by using as the dependent variable in the model, C', an estimate of the net financial effect of a patients stay. This estimate is the difference between the amount paid by the patient/employer and the cost of the hospital stay (estimated solely on the basis of length of stay):

$$C' = \left(P_P + P_E\right) - \left(\frac{\text{Hospital Budget}}{\text{Total Bed-days}} \times \text{LoS}\right)$$

Employers and patients' families are not concerned with cost per day or hospital cost recovery, but only with their total cost. Thus, the dependent variables when the model is estimated from the patient or the third-party perspectives are P_P and P_E, respectively, as in the single-hospital model.

DRAFT PROTOCOL[94]

Introduction

Collecting a data set that could be used to estimate either of the two models described above must be done with acute sensitivity to a number of ethical concerns. A major concern is that the models contain both a variable (T) representing whether or not a patient's HIV status is determined on admission and a variable (V) representing the patient's HIV status. The methodologically obvious way to generate such data would be to test everybody upon admission and only reveal the results of the test to the providers of a subset of the patients. However, this implies withholding data about a patient from the patient's provider—something that might be ethically justifiable if reasonable doubt existed about whether the data was likely to help or harm the patient. Ultimately, such decisions must be made by the appropriate ethical review committee. However, in most settings test

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93 Changes in LoS, without performing the conversion to cost, in hospitals that operate at capacity may provide insight into the effect of HIV testing on the opportunity cost associated with unnecessary hospitalization of HIV infected patients.

94 An earlier version of this protocol was developed in French with Mposo Ntumbanzondo in Zaïre.

results will probably be viewed as likely to be beneficial to the patient and therefore data that cannot ethically be withheld.

The following protocol attempts to circumvent this ethical problem by both performing rapid HIV tests on some patients at the time of admission and by also drawing blood from all patients for later testing at a central reference laboratory. Such an approach has several advantages in addition to addressing the ethical dilemma. It permits analysis of the reliability and suitability of rapid HIV tests as diagnostic rather than screening tests;[95] it permits samples from multiple sites to be tested under identical circumstances at one central laboratory; and it facilitates laboratory quality control.

Data collected for the above models could also serve other, complementary purposes:

- The data could be used to evaluate the use of rapid HIV tests for diagnosis rather than screening. Most trials of rapid tests, including the Mulanga study, have focused primarily on the comparative performance of tests when used to screen blood donors. Performance may be very different when used on a symptomatic population.[96] The methodology described below will permit comparison of a rapid test with more traditional methods (ELISA, Western Blot) in a symptomatic population and could easily be expanded to perform a comparative evaluation of several different rapid tests.
- The data could be analyzed to better understand the nature of the financial impact of HIV infection on hospitals, regardless of whether HIV testing is available.
    - How does a hospital's occupancy rate affect the impact of the HIV epidemic upon its finances? If a hospital was previously operating at capacity, HIV will have a limited ability to increase total hospital *expenditures* because an increase in HIV positive patients can only occur with a decrease in HIV negative patients. However, HIV may cause a decrease in hospital *revenue*. Conversely, a hospital with excess capacity may experience a substantial

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95 Spielberg F; Kabeye CM; Ryder RW; Kifuani NK; Harris J; Bender TR; Heyward WL; Quinn TC: Field testing and comparative evaluation of rapid, visually read screening assays for antibody to human immunodeficiency virus [see comments]. *Lancet*, 1989 Mar 18, 1(8638):580-4.

96 Behets F; Bishagira K; Disasi A; Likin S; Ryder RW; Brown C; Quin TC: Diagnosis of HIV infection with instrument-free assays as an alternative ti the ELISA and western blot testing strategies: an evaluation in Central Africa. *J Acquir Immune Defic Syndrr*, 1992, 5(9):878-82.

increase in expenditures when faced with increasing demand for services, but it may also realize a more than compensatory increase in revenue.

- Does the source of a hospital's operating funds help determine its vulnerability to financial hardship from an increase in HIV positive patients. In Zaïre, it is not uncommon for a hospital to derive 80% of its operating expenses from patient fees, while in another country, 80% may come from the government—reflecting large country to country variability in health care financing methods. Hospitals that depend upon self-financing will be more sensitive to changes in the ability-to-pay of their patient population; those who operate on fixed government or non-governmental organization (NGO) budgets will be more sensitive to changes in demand.

- HIV positive patients have a very high in-hospital mortality. How important is this differential in explaining a financial impact associated with HIV infection. In the aforementioned study at Mama Yemo, the mortality among HIV positive patients was 50% in the internal medicine wards, as compared to 30% for HIV negative patients.[97] Hospitals with more diverse, less economically disadvantaged, patient populations will have lower mortality in both groups, but a substantial mortality differential between the two groups is likely to remain.[98] The financial effect on Mama Yemo of this mortality differential was not studied, but hospitals that depend upon patient revenue and do not insist upon payment in advance are likely to have greater difficulty collecting from (families of) patients who die.

- How do differences in socioeconomic status between HIV-positive and HIV-negative patients influence hospital finances? HIV is likely to cause chronic illness (on average approximately one year [99]), gradually depleting

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97 Hassig et al, *op cit.*

98 Bertozzi S; Mposo N; Green S; et al *op cit.*

99 Extensive research has been done estimating survival time of patients in industrialized countries from time of diagnosis with AIDS. The estimates vary, but one year is not an unreasonable approximation. Very little research has examined survival time in Africa, but available evidence suggests that it is significantly shorter. If one is talking about "duration of illness" rather than duration of AIDS, then one year may not be unreasonable, in absence of better data, as an estimate for Africa. The explanation for why seroprevalence data is widely available for Africa but survival data is not, probably lies in the paucity of medical records and the difficulty tracing the families of patients who die.

the household's resources. Medical expenses become a larger portion of household consumption and revenue falls because the ill individual and those individuals providing nursing care are less able to work. HIV is also likely to infect more than one member of a household (or extended family), further depleting their resources.[100] As a result, hospitalized patients who are HIV positive may be less able than HIV negative patients to pay for their care. The proposed protocol does not collect data that is directly correlated with patient wealth, however, it does collect data on what patients and families pay for services.

Other factors may result in patients with HIV-related disease being better able to reimburse hospitals for their care. As discussed previously, HIV seroprevalence in many localities appears to be positively correlated with socioeconomic status. To the extent this is true, the average HIV positive patient will be in a better financial position (at least prior to onset of illness) than HIV negative patients, especially since many other diseases are inversely correlated with SES. However, the distribution of income in the population is heavily skewed toward the bottom, with a relatively small middle class. Thus, even if the seroprevalence is higher in the higher socioeconomic groups, their small total size will mean that most HIV

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Friedland GH; Saltzman B; Vileno J; Freeman K; Schrager LK; Klein RS: Survival differences in patients with AIDS. *J Acquir Immune Defic Syndr.* 1991; 4(2): 144-53.

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positive patients will be poor. The greater proportion of infected wealthy would only make a significant difference to the hospital if the hospital is able to charge them much more for hospital services, something attempted in both Tanzania and Zaïre through the creation of small "VIP" wards at hospitals with improved services. A small study performed at a rural hospital in Kimpese, Zaïre highlighted another factor that may also improve cost recovery from HIV positive patients relative to other patients.[101] HIV positive patients are, on average, more likely to be young adults than other patients and more likely to work for a large company.

Kimpese is on a major trade route and many of the young adult patients are employed or are married to an employee. Large employers are required by Zaïrian law to provide health insurance for their employees. Hospitals such as the one in Kimpese use this legal structure to their advantage, establishing one fee schedule for "indigent" patients (anybody who must pay out-of-pocket for services) and another fee schedule for insured patients. The firms pay 3 to 10 times as much for services received by their employees compared to what non-insured patients pay. Both regression models include employment status among the independent variables in an attempt to capture the variation in net hospital cost associated with this variation in fee schedules. If choice of fee schedule is not directly related to employment status, the models may need to be modified to include dummy variables that specify which fee schedule is used for a particular patient.

An important limitation of these models and of this data collection methodology that will need to be addressed by any study performed is that cost data is only collected for *one* hospitalization, while the costs and benefits associated with establishing a patient's HIV status may accrue over multiple hospitalizations. Thus, while the benefits of testing an HIV positive patient with diarrhea might not outweigh the costs, the balance might shift if one were also to consider the benefits of knowing the patient's HIV status when he later presents with meningitis.[102]

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101 Bertozzi et al, *op cit.*

102 In 1989, we presented an approach to measuring the direct cost (the medical treatment cost) of HIV infection which modeled HIV infection as a collection of other illnesses. [Over M, Bertozzi S, Chin J: Guidelines for rapid estimation of the direct and indirect costs of HIV infection in a developing country. *Health Policy* 1989, **11**:169-189] A modification of this approach could be used with the

Choice of hospital

The first task is to choose (an) appropriate hospital(s). The hospital should have a reasonably high HIV seroprevalence among its patients to reduce the time and cost associated with identifying and following a study cohort. The hospital should serve the general public and not cater solely to a particular patient population, such as the employees of a company. The hospital should have a reasonably well developed system for maintaining medical records, including records of payment, so that the study need only reinforce the existing system rather than be required to develop a new system. Hospitals that have an extensive "informal" payment network, in which nurses, technicians, administrators, and physicians expect payment before serving a patient will be more difficult to study because of the difficulty of quantifying such a network and because the staff of such a hospital may be more resistant to participating in a study.

Identification of Cohort

The study would seek to follow a cohort of patients from the time they are hospitalized until their discharge. Patients would be recruited at admission and asked to donate a blood sample for HIV testing. One half of those who are bled, randomly chosen, would be tested immediately with a rapid diagnostic test and their physician would be informed of the test result. All blood samples would be sent to a central testing facility for ELISA testing and confirmation by Western Blot. Upon receipt of the test results, the

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models presented to estimate the sum of the expected benefits and costs of HIV testing across different disease episodes. The direct cost model presented has the following structure: HIV disease is a collection of n illnesses, each of which occurs in an HIV infected person at least *once* with probability P_i. Given that illness i occurs in a particular patient, then the expected number of different episodes of that illness is E_i and each episode costs, on average, C_i. Thus, the average total cost per case of HIV infection is :

$$\sum_{i=1}^{n}(PiEi)Ci$$

For the purpose of this simplistic model, each of the sub-diseases was assumed to be independent. They are not independent.[Suppose that three sub-diseases had equal P's and E's, that sub-diseases 1 and 2 were almost uniformly fatal, while the third was rarely so. The probability of sub-disease 2 given a history of sub-disease 3 (two diseases that are almost always fatal occurring in the same patient) is almost certainly lower than the probability of sub-disease 2 given sub-disease 1.] Although it may be useful to ignore the statistical and biological interactions between the sub-diseases when making first approximation cost estimates, it will be more difficult to ignore them when considering the cost-effectiveness of diagnostic HIV testing.

Although the decision to test is made in the context of a patient presenting with a specific complaint, if the patient is infected with HIV, the benefits from having performed the test will potentially accrue for all subsequent episodes of illness, whether of the same or different sub-diseases.

responsible physician would again be informed of the test result, although it is likely that many and probably most of the patients would already have been discharged prior to receipt of the test results from the central facility.[103]

Four principal groups would be identified in this way:

(a) HIV positive, identified on admission

(b) HIV negative, identified on admission

(c) HIV positive, identified at central laboratory

(d) HIV negative, identified at central laboratory

In any hospital in which the HIV seroprevalence is less than 50%, admission screening will identify more HIV negative patients than HIV positive patients. In that situation it will probably be more efficient to follow a larger HIV negative cohort than HIV positive cohort, although that will depend upon the relative cost of HIV testing versus the cost of collecting data about a patient's stay. In any event, it will only be possible on admission to reduce the size of the HIV negative cohort that has been screened with the rapid test ('b', above); the size of the other HIV negative cohort can only be reduced after the results return from the central laboratory.

Data collected on admission

Certain data will be collected for all patients entered into the study, regardless of whether the one- or multi-hospital model is used. These are data which should be available, even retrospectively, for all patients being admitted to any hospital:

- age & sex;
- whether the patient is an employee or a dependent of an employee (i.e., whether the patient has employer provided health insurance);
- ward (or service) to which the patient is admitted.

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103 It may be difficult, practically and ethically, to assure compliance with the proposed recruitement method in some sites. If rapid HIV tests are performed on some patients, then conflict is likely to arise if a provider believes a patient who was not tested would benefit from testing—especially if the patient is able to pay for testing. This is not likely to be a problem in settings where HIV testing is already available in the community. However, where it is not, the study will be introducing testing capability to the community—and patients and providers are likely to demand access to that capability.

If the one-hospital model is used, and if possible also with the multi-hospital model, additional data would be collected on admission that would require completion of an intake questionnaire. These data could not reliably be collected retrospectively since documentation in the patient's chart (or even availability of the chart) is likely to be incomplete:

- admitting diagnosis, categorized into: fever, gastrointestinal, cardiac, neurologic, respiratory, and other;
- whether the patient, on admission, has a pathologically confirmed diagnosis. These data are collected in an attempt to distinguish patients who are admitted for diagnosis and treatment from those who are admitted with a "confirmed diagnosis" for treatment. For example, a patient admitted with cough, shortness of breath, and fever would be distinguished from a similar patient who had microscopic confirmation of mycobacteria in his or her sputum. Similarly, a patient admitted for spiking fevers with headache would be distinguished from a similar patient with laboratory confirmation of malarial parasites.
- Which major and minor signs of the WHO clinical case definition of AIDS (see above) are present in the patient on admission.

Data collected during hospitalization

For the single hospital model, each patient in the study must be followed throughout his or her hospitalization and data collected on the types and quantities of goods and services the patient consumes. As mentioned above, it will be most important to collect careful data on the medications consumed by the patient—whether provided by the hospital pharmacy or purchased by the patient's family in the community—as drug costs in Africa are likely to be both the largest portion of total costs and the portion of costs most likely to be affected by HIV testing. Local costs will need to be assigned to the medications used. In previous studies a survey of drug prices in local pharmacies was used to estimate drug costs which helped to eliminate bias introduced by NGO donations of drugs to hospitals.

Given the limited accounting information available in a typical African hospital, it will not be feasible to assign costs to each individual laboratory or diagnostic service. However, the total number of laboratory tests and total number of radiographs performed would be readily available for each patient. The average cost per laboratory test and per radiograph would then be estimated from hospital accounting records. The only exception

to use of average cost of services would be the HIV test itself. For that test, it is essential to estimate the capital, labor, and materials costs associated with performing the test. This estimation is necessary regardless of whether one or many hospitals are studied.

It will be most difficult to estimate costs for specialized services whose cost, unlike the pharmacy, laboratory, and radiology, are largely independent of cost of materials. These services include use of operating rooms, delivery rooms, specialized nursing, deluxe accommodations, etc. Data should be collected for each patient on any major procedures performed and on whether the patient had regular or deluxe accommodations. The ability to include these data in the calculation of cost of hospital stay will depend upon the detail available in the hospital accounting data.

Data collected at end of hospital stay

At the end of the hospital stay the patients length of stay, whether the patient is discharged alive, total hospital charges, and complete payment information are collected. Payment information must include both amount and source of payment to permit differentiating costs that are borne by the patient's family from those borne by employers or the government. The length of stay is the most fundamental quantity used to calculate the cost of the patient's hospitalization. If no data are available on the cost of specific services (such as is likely to be the case in a multi-hospital study), then cost of hospitalization simplifies to:

$$\text{cost of hospitalization} = \text{length of stay} * \underbrace{\frac{\text{year budget}}{\text{bed days/year}}}_{=\ \text{cost per bed day}}$$

If specific services are itemized separately, then the budgets for those departments are not included in "year budget" when calculating the cost per bed day (see model descriptions above).

Model Simulation

In an attempt to better understand the potential usefulness of the proposed models, a simulation of a simplified version of the proposed models was conducted. Several variables were omitted, and one composite variable, WHO, was created. WHO is a dummy variable indicating whether the patient met the WHO clinical AIDS definition. In practice, it could be derived from the variables M_1-M_4.

The simplified model is:

$$\text{Length of Stay (LoS)} =$$

$$ß + (ßH + ßG + ßA + ßWHO) + ßT + ßV + ßD + T(ßH + ßG + ßA + ßWHO)$$

A patient population was simulated by generating a matrix of patients presenting with different characteristics (variables H, G, & A) and estimating for each patient type its HIV prevalence and what percentage of the total patient population it comprises. Using those percentages, a population of 100 "potential" patients was generated. One half of each patient type receives an HIV test on admission (variable T). A modified Monte-Carlo technique was used to generate values for the other variables. No attempt was made to ensure that variables were normally distributed.

RAND = 0 < random number ≤ 1

V = 1 if RAND ≤ HIV Prevalence
WHO = 1 if RAND ≤ V * 0.62
(62% is the estimated percentage of HIV positive patients who will meet the WHO criteria for AIDS)

D = 1 if RAND ≤ MAX OF(15%,WHO*65%,V*40%)

If	Mean LoS equals:
D=1	7
D=0, and:	
T=V=1 and G=1	9
T=V=1 and H=G=0	11
T=V=1 and H=1	13
Otherwise,	14

The length of stay for any particular patient was randomly chosen using the Poisson distribution corresponding to the mean LoS for that patient's characteristics (from the table above). The population of 100 "potential patients" was sampled six times to generate a data set with n=600. This data set was used to estimate the simplified model below; the results of the estimation follow directly (ESTIMATION 1). The estimated model predictably revealed that the variables which were not used in determining mean length of stay had coefficients that did not reach statistical significance. For example, WHO was used in estimating probability of death, which in turn, influenced LoS. However, the effect of WHO on LoS would be fully captured by D, and thus the coefficient of WHO was not significant. The variable T*H did have a small effect upon a patient's mean LoS, but the effect was not large enough to reach significance in the test population of 600 patients.

ESTIMATION 1
LoS=ß + (ßH + ßG + ßA + ßWHO) + ßT + ßV + ßD + T(ßH + ßG + ßA + ßWHO)

Count:	R:	R-squared:	Adj. R-squared:	RMS Residual:
600	0.69	0.47	0.46	3.27

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	5565.06	505.91	47.36
RESIDUAL	588	6281.02	10.68	p = .0001
TOTAL	599	11846.07		

Beta Coefficient Table

Variable:	Coefficient:	Std. Err.:	Std. Coeff.:	t-Value:	Probability:
INTERCEPT	13.88				
GI	-0.52	0.42	-0.05	1.25	0.2125
Heart	0.39	0.65	0.03	0.59	0.5527
Age=15-50	0.79	0.42	0.09	1.88	0.0608
WHO AIDS	-0.56	1.96	1.65	1.29	0.1964
Tested	-0.58	0.46	-0.07	1.24	0.2138
HIV?	-1.01	0.31	-0.11	3.26	0.0012
Died	-5.54	0.3	-0.61	18.33	0.0001
T•Heart	0.45	0.92	0.02	0.49	0.6251
T•GI	-0.19	0.59	-0.02	0.32	0.752
T•Age	-0.47	0.56	-0.05	0.84	0.4033
T•WHO	-0.17	0.59	-0.01	0.29	0.7702

Confidence Intervals and Partial F Table

Variable:	95% Lower:	95% Upper:	90% Lower:	90% Upper:	Partial F:
INTERCEPT					
GI	-1.34	0.3	-1.21	0.17	1.56
Heart	-0.89	1.67	-0.69	1.46	0.35
Age=15-50	-0.04	1.61	0.1	1.48	3.53
WHO AIDS	-4.42	3.3	-3.8	2.68	1.67
Tested	-1.49	0.33	-1.34	0.19	1.55
HIV?	-1.62	-0.4	-1.52	-0.5	10.65
Died	-6.14	-4.95	-6.04	-5.04	335.86
T•Heart	-1.36	2.26	-1.07	1.97	0.24
T•GI	-1.34	0.97	-1.16	0.78	0.1
T•Age	-1.56	0.63	-1.38	0.45	0.7
T•WHO	-1.33	0.99	-1.14	0.8	0.09

When the model was estimated on a population of 6,000 patients (an unrealistically high sample size) T*H did reach significance.

The simplified model was further modified (ESTIMATION 2) to eliminate variables that did not have significant coefficients. Note that because of co-linearity between G and T*G, when G was eliminated from the model, T*G became significant. Policy makers are most interested in which of the *multiplicative* variables are significant because those identify the types of patients for whom HIV testing reduces length of stay. Thus, a model that retains T*G is more useful than one that retains G. Knowing that the simulated patient population was designed with no independent relationship between G and LoS makes it easy to choose between G and T*G in refining the model. In an actual study, the process of refining the model would be more difficult.

ESTIMATION 2

LoS=ß + ßT + ßV + ßD + T(ßG)

Count:	R:	R-squared:	Adj. R-squared:	RMS Residual:
600	0.68	0.46	0.46	3.28

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	5437.21	1359.3	126.2
RESIDUAL	595	6408.87	10.77	p = .0001
TOTAL	599	11846.07		

Beta Coefficient Table

Variable:	Coeff.:	Std. Err.:	Std. Coeff.:	t-Value:	Probability:
INTERCEPT	13.98				
Tested	-0.6	0.3	-0.07	2.01	0.0452
HIV?	-0.96	0.28	-0.11	3.46	0.0006
Died	-5.69	0.28	-0.63	20.15	0.0001
T•G I	-0.86	1.96	1.65	2.12	0.0344

Confidence Intervals and Partial F Table

Variable:	95% Lower:	95% Upper:	90% Lower:	90% Upper:	Partial F:
INTERCEPT					
Tested	-1.18	-0.01	-1.09	-0.11	4.03
HIV?	-1.51	-0.42	-1.42	-0.5	11.95
Died	-6.25	-5.14	-6.16	-5.23	406.16
T•G I	-4.72	2.99	-4.1	2.37	4.5

The modified model was then estimated using a new data set of the same size, n=600. The results appear in ESTIMATION 3. Note that the variable T is no longer significant.

ESTIMATION 3

LoS=ß + ßT + ßV + ßD + T(ßG) - Redone with new data set

Count:	R:	R-squared:	Adj. R-squared:	RMS Residual:
600	0.67	0.44	0.44	3.56

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	6007.86	1501.96	118.29
RESIDUAL	595	7554.94	12.7	p = .0001
TOTAL	599	13562.79		

Beta Coefficient Table

Variable:	Coefficient:	Std. Err.:	Std. Coeff.:	t-Value:	Probability:
INTERCEPT	14.14				
Tested	-0.25	0.32	-0.03	0.78	0.4386
HIV?	-1.21	0.31	-0.13	3.91	0.0001
Died	-5.84	0.31	-0.6	18.66	0.0001
T•G I	-1.25	1.96	1.65	2.81	0.0051

Confidence Intervals and Partial F Table

Variable:	95% Lower:	95% Upper:	90% Lower:	90% Upper:	Partial F:
INTERCEPT					
Tested	-0.89	0.38	-0.78	0.28	0.6
HIV?	-1.81	-0.6	-1.71	-0.7	15.3
Died	-6.45	-5.22	-6.35	-5.32	348.02
T•G I	-5.1	2.61	-4.48	1.99	7.9

One final regression (ESTIMATION 4) was run to estimate a model that reflected the "true" structure of the simulated patient population. This served as a test of the modeling methodology. The theoretical variable coefficients should fall within the confidence interval of the estimated variable coefficients. As can be seen, the 95% confidence interval for T*V* $\overline{D}$ *G does not include 5, the theoretical coefficient. To further validate the technique, the model was run again on a different, larger (n=3000) population with the result that the coefficient for T*V* $\overline{D}$ *G was 4.85—well within even the 90% confidence interval.

ESTIMATION 4

LoS=ß + ßD + (T * V * (not D)) * (ßG + ßH + ß(not H * not G))

Count:	R:	R-squared:	Adj. R-squared:	RMS Residual:
600	.72	.52	.51	3.1

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	6115.96	1528.99	158.77
RESIDUAL	595	5730.11	9.63	p = .0001
TOTAL	599	11846.07		

Beta Coefficient Table

Variable:	Coefficient:	Std. Err.:	Std. Coeff.:	t-Value:	Probability:
INTERCEPT	13.88				
Died	-6.71	.27	-.74	24.77	.0001
T*V*$\overline{D}$*G	-3.11	.77	-.15	4.07	.0001
T*V*$\overline{D}$*H	1.74	2.25	.02	.77	.4393
T*V*$\overline{D}$*$\overline{HG}$	-2.62	1.96	1.65	5.11	.0001

Confidence Intervals and Partial F Table

Variable:	95% Lower:	95% Upper:	**Predicted coefficient**	**Theoretical coefficient**	Partial F:
INTERCEPT			**13.88**	**14**	
Died	-7.24	-6.18	**-6.71**	**-7**	613.78
T*V*$\overline{D}$*G	-4.62	-1.61	**-3.11**	**-5**	16.55
T*V*$\overline{D}$*H	-2.67	6.15	**1.74**	**-1**	.6
T*V*$\overline{D}$*$\overline{HG}$	-6.48	1.24	**-2.62**	**-3**	26.16

Table AV.1 is a listing of the dichotomous dependent variables used in the models above. For each variable is listed its sum over the 600 simulated patients used in the first, second and fourth model estimations above. The low numbers associated with some variables, especially T*V*$\overline{D}$*H, helps to explain why such large samples are needed to achieve statistical significance.

TABLE AV.1

Variable	Sum (n=600)
GI	192
Heart	60
Age=15-50	300
WHO AIDS	206
Tested	300
HIV?	321
Died	243
T•Heart	30
T•GI	96
T•Age	150
T•WHO	102
T*V*$\overline{D}$*G	27
T*V*$\overline{D}$*H	2
T*V*$\overline{D}$*$\overline{HG}$	71

Conclusion

This chapter begins by discussing the role of the HIV test in the diagnosis and treatment of patients by focusing on the uncertain costs and benefits of such testing. It proposes several perspectives and two models as well as a draft protocol that could be used to evaluate these costs and benefits in one or several African hospitals.

In an attempt to illustrate the potential use and usefulness of the models proposed, a simulated patient population was created. This population, which could be repeatedly sampled, was used to refine and then estimate a simplified version of the models proposed above. Although this was an artificial exercise, it was meant to be instructive and illustrative of the models' practicality.

VI

HIV Testing as a Tool for Monitoring the HIV/AIDS Epidemic

Introduction

In the preceding two chapters, examples were presented on using the HIV test to prevent HIV transmission and to improve treatment. This chapter examines its use in charting the epidemiology of the epidemic and will show how such epidemiological monitoring provides data essential for planning treatment and prevention. Then, it will explore cost-effectiveness considerations in collecting epidemiological data. Finally, two models will be presented that can help guide cost-effective design of seroprevalence surveys.

Importance of serologic screening

In Chapter IV, reduction of transfusion-related HIV transmission, the most important input parameter in the models presented was the HIV *prevalence* in the donor population. Similarly, in Chapter V, evaluation of when it is cost-effective to use the HIV test to confirm or exclude an HIV-related diagnosis depends critically on the prior probability *(or prevalence)* of HIV infection. In Chapter II, reproduction rate (expected number of secondary HIV infections) was essential in determining the relative priority of different interventions and target groups. Reproduction rate is calculated using disease *incidence* and *prevalence*. Evaluation of the effectiveness of interventions designed to reduce HIV transmission is to see if there has been a change in the *incidence* of infection. Finally, the social and economic effects of HIV-related disease and death are related to the number of deaths in the community. Thus, social welfare efforts to assist survivors will also need information about HIV *prevalence* and AIDS *incidence* to appropriately target their interventions.

Almost any planning efforts to thwart the HIV virus are dependent upon estimates of its extent and rate of spread. Obtaining such estimates is a costly process which often competes directly for funds with the interventions themselves. The same questions that are asked about the costs and benefits of interventions need to be posed about the efforts to obtain estimates of HIV prevalence and incidence. What is the value of the information obtained? In particular, what is the value of the marginal change in the

information which is the result of making the estimation method a little better or a little worse?

HIV is unlike most of the major causes of morbidity and mortality in Africa because of its long latency period. (Smoking, the most important cause of preventable mortality in the United States, has an even longer latency period, especially if *addiction* to tobacco is considered the morbid event, rather that the mid-point of tobacco exposure).[1] Some of the parasitic diseases in Africa also have long latency periods, but most of the infectious diseases are acute illnesses with latency between infection and onset of symptoms measured in days rather than years.[2] As a result of the long, asymptomatic latency, and the fact the epidemiology is changing rapidly relative to the length of the latency period, the incidence and prevalence of HIV *infection* are imperfectly correlated with the incidence and prevalence of HIV-related *disease* and death. The success of efforts to control neonatal tetanus or measles can be detected within months of the intervention by measuring changes in the incidence of disease. With HIV, incidence of disease may be useful for planing treatment and survivor assistance, but is a poor measure of the prevalence of HIV infection and an even worse measure of the incidence of HIV infection. Thus, if knowing the incidence and prevalence of infection is important, the information must be obtained through serologic testing rather than via reporting of disease.

Circumstances in Africa

The reasons for performing epidemiological screening are not dissimilar in Africa and in industrialized countries, but the circumstances under which the screening is carried out are very different. As has been stressed several times herein, the costs of technologic inputs traded on the international market, such as HIV test kits, do not differ very much between countries. Developing countries may choose to purchase less expensive versions, but the cost of an ELISA test used in Africa and one used in the United States will probably differ by much less than the cost of labor employed to perform the test. Because the ratio of the cost of materials to the cost of labor is higher in Africa, optimal strategies for conducting serologic surveys typically will use proportionately fewer materials and more labor than surveys in the United States.

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1 *Smoking and Health, a National Status Report: a Report to Congress.* US Office of Smoking & Health, 1990.

2 Warren KS; Mahmoud AAF; *Tropical and Geographic Medicine.* McGraw-Hill, 1990 1112.

Serologic surveys must not only test samples, but obtain samples. Here again, labor costs are dominant in industrialized countries, while in Africa they are comparatively less important. Transportation is expensive in Africa. Infrastructure (roads, trains, etc.) is limited and vehicles are expensive to operate relative to labor costs. As an example, consider that hiring a driver when renting an Avis automobile in Kinshasa, Zaïre adds approximately 5% to the cost of the rental. Inaccessible or unreliable electricity, especially in rural areas, complicates collection of blood samples that must be refrigerated. Inadequate census data complicates the generation of sampling frames. As a result of such complicating factors, optimal sample collection methodologies are likely to be quite different in African environments. Surveys will typically use cluster sampling methods that minimize the need for transportation. Sample collection techniques that do not require refrigeration are likely to be favored. The best developed of these is collection of blood onto a piece of filter paper which may then be dried and transported at room temperature.[3]

Other circumstances in Africa facilitate conducting surveys. Representative, population based surveys have been virtually impossible to conduct in Europe and North America, while several have been carried out in Africa, both in the general population[4,5,6,7] and among employees of large businesses.[8] Possible explanations for the increased acceptability of such surveys include:

- less protection of an individuals right to privacy;

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3 Fortes P; Menitove J; Ross A; Steece R; Cabrian K; Ferrera C; Perkins PA; Sturge J; Lealos R; Krieger MS . Evaluation of blood collected on filter paper for detection of antibodies to human immunodeficiency virus type 1. *J Clin Microbiol.* 1989 Jun; 27(6): 1380-1.

4 Nationwide community-based serological survey of HIV-1 and other human retrovirus infections in a central African country. Rwandan HIV Seroprevalence Study Group. *Lancet.* 1989 Apr 29; 1(8644): 941-3.

5 Wawer, Maria J; Serwadda, D; Musgrave, S; Sewankambo, N; Musagara, M; Konde-Lule, J; "Geographic and community distribution of HIV1 infection in rural Rakai District, Uganda." in *Abstract Volume, Sixth International Conference on AIDS.* San Francisco, June 1990. 232.

6 Killewo, J; Nyamuryekunge, K; Sandstrom, A et al; "The Epidemiology of HIV-1 Infection in the Kagera Region of Tanzania [abstract]." in *Abstract Volume, Third International Conference on AIDS and Associated Cancers in Africa* . 9/16/88. 23.

7 Kamenga M; Ryder R; N'Galy B; Behets F; Ngoy T; Liambi A et al; "An HIV serosurvey in the general population of Kinshasa appears feasible." in *Abstract Volume, V International Conference on AIDS.* Montreal, June 1989. 973.

8 Ryder RW; Ndilu M; Hassig SE; et al ; Heterosexual transmission of HIV-1 among employees and their spouses at two large businesses in Zaire . *AIDS.* 1990 Aug; 4(8): 725-32.

- greater degree of control by local leaders and a more authoritative government structure;
- less of a duty to inform, such that surveys may be performed to screen for "health problems" rather than explicitly screening for AIDS;
- less suspicion that information collected by the ministry of health might be used in a discriminatory way against the people being tested;
- belief that cooperation with a survey might bring improved health benefits (a clinic, etc.), especially because local officials may raise such hopes to encourage cooperation; and
- less aggressive and more constrained media, such that there is less public debate about the pros and cons of a survey and less discussion of it's "true" (i.e. HIV-related) purpose.

Costs and benefits of serologic information

Data on the prevalence of HIV infection in a population is collected to permit more cost-effective targeting of interventions. However, collecting the prevalence data is costly, and policy makers must consider whether the savings from improved targeting are greater than the cost of obtaining the serologic data. The concepts of marginal cost and marginal benefit are essential in this context.

A proposed serologic survey may be thought of as a continuum. The smaller and less representative the sample is, the less expensive the survey will be and the less precise the results will be. However, these relationships are not linear. As a survey becomes larger and more representative, precision increases, but each incremental increase in size and cost results in a smaller increase in precision. In other words, the cost of each additional (marginal) unit of precision is usually greater than the previous one.

Similarly, the benefit associated with each marginal unit of precision is less than the last. Since poorer countries are able to purchase less benefit, the optimal serosurvey design in poorer countries will tend to obtain estimates that are less precise. Purchasing more precision than is needed has a higher opportunity cost in Africa (more benefit could otherwise have been purchased with those funds) than in the U.S., so it is especially important to seriously consider what data decision makers need.

Although theoretically there is a continuum of representativeness and size in serologic surveys, practically, policy makers conceptualize prevalence surveys as being of two types: population based representative samples and convenience samples of sentinel populations. In the former, the survey population is described geographically, such as a city, region, or entire country. A random or pseudo-random sample of that population is then generated. Most surveys that have been done use a cluster sample methodology which involve a hierarchy of random choices, for example first randomly choosing sub-regions, then randomly choosing villages, and finally randomly choosing homes from within those clusters.[9,10,11] Such techniques minimize the amount of census data that must be gathered about the population being surveyed prior to being able generate a sample. The sample size necessary depends upon the size of the confidence interval desired and upon the number of sub-groups one wishes to be able to differentiate. If national level surveys are being performed for the purpose of generating rational averages, the sample size may be relatively small. However, if description of prevalence within age, socioeconomic, occupational, educational or other sub-groups is desired, the sample size must be correspondingly larger.

Surveys that use convenience samples of sentinel populations are logistically much easier to conduct and thus are much less expensive. The most commonly sampled populations are those which naturally contact the health system (including blood donors, pregnant women, and persons who visit sexually transmitted disease clinics), those which are of special epidemiological interest (such as prostitutes), and those which are especially accessible (such as employees, students, and members of the military).[12]

National epidemiological monitoring programs may logically include both representative and convenience samples, providing the large cost differential between the two is balanced against the additional data obtained. For example, consider the problem of how to allocate funds across regions in a country. The national program is probably

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9 Nationwide community-based serological survey of HIV-1 and other human retrovirus infections in a central African country. Rwandan HIV Seroprevalence Study Group. *Lancet.* 1989 Apr 29; 1(8644): 941-3.

10 Wawer MJ; Serwadda D; Musgrave S; Sewankambo N; Musagara M; Konde-Lule J; "Geographic and community distribution of HIV1 infection in rural Rakai District, Uganda." in *Abstract Volume, Sixth International Conference on AIDS.* San Francisco, June 1990. 232.

11 Killewo J; Nyamuryekunge K; Sandstrom A et al; "The Epidemiology of HIV-1 Infection in the Kagera Region of Tanzania." in *Abstract Volume, Third International Conference on AIDS and Associated Cancers in Africa* . 9/16/88. 23.

12 Way P, US Bureau of the Census, Data base on HIV prevalence rates.

most interested in relative incidence rates, but will initially need to rely on relative prevalence rates, assuming those to be correlated with incidence rates. Small differences in prevalence rates across regions are unlikely to be significant statistically and unimportant for allocating across regions. However, a national AIDS control program would like to know if a region has a rapidly increasing prevalence. Even a 2% increase in prevalence would be difficult to detect if successive surveys had a confidence interval of ±1%. But, a 2% increase in prevalence in the general population is likely to be preceded/accompanied by a much larger (and therefore easier to detect) change in prevalence among the female prostitutes.

Since the rate of change of HIV prevalence is likely to be greatest in the prostitute population, monitoring HIV prevalence in prostitutes is likely to be the most sensitive way to detect an increase in disease incidence in the general population. However, because of the biases inherent in data from such an unstable, marginal segment of the population, the specificity of using prostitutes as a sentinel population may be poor. For example, a rise in HIV prevalence among prostitutes in a rural area may simply reflect new discriminatory policies against these women causing them to return home from an urban center to which they had migrated.

Blood donors are an obvious source of prevalence data because such data are often generated with minimal effort in places already screening blood for transfusion. Blood donors in industrialized countries provide imperfect information about HIV prevalence even within the sub-population of employed adults because persons with known risk factors are asked to exclude themselves. In Africa, regional cultural variations in attitudes about blood donation and institution (hospitals, health centers, etc.) specific policies about blood collection make extrapolation from donor prevalence to population prevalence even more difficult. For persons accustomed to the United States, where blood banks that store blood are ubiquitous and almost universally conform to the norms established by the American Association of Blood Banks and the American Red Cross, the heterogeneity that exists within any one African country may not be obvious. Of all the sites that transfuse blood, a small percentage are able to *bank* blood, to maintain a constant supply of different blood types. Rather, most are transfusion centers that do not have the capacity to store blood and therefore must link transfusion directly to collection. Frequently families of patients are responsible for assuring that the necessary blood is donated, either by donating themselves and enlisting their friends, or by paying donors. Neither families of patients nor paid donors are likely to be representative of the

general population. More importantly, transfusion centers are responding in various ways to the HIV epidemic, ranging from organized efforts to reduce the HIV prevalence in the donor population to nothing at all.

A third obvious and commonly used convenient population for monitoring HIV prevalence is pregnant women. Although these women would appear very representative of all reproductive aged women, important biases exist here as well. For pregnant women to be screened, they must usually come into contact with the health care system (most commonly for delivery). Since many African women deliver at home, perinatal screening preferentially samples urban women and women of higher socio-economic status (SES). Only sexually active women are represented in the sample; those who use contraception are underrepresented; and women who are infertile are also under represented. Since sexually transmitted diseases are an important cause of female sterility, these infertile women may be a group at especially high risk of being HIV infected.

Although the presence of biases with any of the available convenience samples would seem to argue against their use and in favor of representative surveys, the presence of bias does not necessarily indicate a lack of usefulness. For the purposes of planning, absolute accuracy is often less important than relative accuracy, meaning that whether town A has an actual prevalence of 8 or of 10% and town B a prevalence of 3 or 4% is less important than that the prevalence in town A is much higher than in town B. Thus, it may be more important to know whether biases are changing over time, rather than their exact magnitude. The biases affecting populations such as students, military personnel, employees, and pregnant women are likely to be fairly constant over time. In contrast, the population of women who self-identify as prostitutes is likely to be much more variable. Thus, surveys of prostitutes are probably not a good way to predict population prevalence. However, they may be the best way of predicting which areas are at greatest risk of having a rapid rise in population prevalence.

One possible strategy might be to do small, geographically dispersed representative surveys to establish baseline average valves for different geographic areas and then to follow such a survey with regular monitoring of selected sub-populations. If large inter-regional differences are detected in the ratio of the prevalence in a particular sub-population to the prevalence in the representative sample, further representative study of that region or sub-region may be indicated to clarify the local epidemiological pattern.

Data requirements depend critically upon the allocation decision for which the data are needed. A general rule is that allocating funds to alleviate the effects of the epidemic requires information about the *absolute* differences in prevalence rates between sub-populations, while allocation of preventive funds requires information about the *relative* difference in prevalence rates (ratio of prevalence rates).

To illustrate the difference, consider villages with different HIV prevalences. As the prevalence approaches zero, the total impact from lost earnings due to HIV infection also approaches zero. However, the cost of averting one infection by screening blood donors or by distributing condoms approaches infinity as the prevalence approaches zero. In a different example, consider the perspective of the benefits manager of a company with two plants. In the first plant the HIV prevalence rose last year from 0.01% to 1%, while in the other plant it rose from 1% to 2%. The expected future health benefits that will be consumed by the newly infected employees is approximately the same at the two plants; at each plant approximately 1% of the workers were newly infected last year. However, the need for HIV prevention at the two plants is very different because the first plant witnessed a 100 fold increase in prevalence while the second only a 2 fold increase.

How does this influence design of a seroprevalence survey? For the decision maker interested in absolute differences, the confidence interval required is relatively independent of the seroprevalence. Whether the estimate is 20% ±1% or 4% ±1%, the level of precision is accurate enough to permit prioritizing interventions to alleviate impact. However, if the decision maker is interested in relative differences, then the size of the confidence interval required must vary in proportion to the prevalence rate. For example, 10% ±1% is similar to 1% ±0.1%.

In the latter case, the cost of conducting the survey increases dramatically with lower prevalence rates because much larger sample sizes are needed to achieve comparable precision. In this situation, decision makers must decide before conducting the survey, not so much what precision is needed, but what is the lowest seroprevalence threshold that will be decisive. For example, if HIV screening of blood donors is not cost effective below a seroprevalence of 1%, then it is not necessary for a survey to distinguish between a prevalence of 0.1% and 0.8%.

The degree of precision needed by decision makers is likely to increase as resources available to fight AIDS increase. For example, in the U.S., the seroprevalence threshold at which screening for HIV II becomes cost-effective, compared to other

screening programs, is very low, assume that it is 1 in 10,000. In this situation, survey information would need to distinguish a 1 in 10,000 prevalence from a 1 in 100,000 prevalence. If in an African country the threshold was 1%, the size and cost of the survey are correspondingly lower.

Once the desired confidence interval has been determined, the survey type (convenience vs.. representational) selected, and the study population identified, then the technical aspect of the survey must be determined. Use of dried blood or filter paper was mentioned above as a technique that holds lots of promise for cost-effective sample collection in Africa.[13] Using saliva instead of blood is another recently developed technique that is promising.[14] Not only is collection of saliva easier and less invasive, but it is likely to be much more easily accepted by the population being tested. This is especially true in areas where loss of blood has negative cultural implications.

The ELISA test seems to be clearly superior to other techniques for screening large numbers of samples because many samples are processed simultaneously.[15]

Many different ELISA kits are available on the market. Comparing the performance of the kits for survey purposes is easier than for other uses because samples will usually be tested in a central laboratory where conditions will be most similar to those in industrialized countries. Thus, the published specifications are more likely to reflect the performance that will be observed in actual use than for kits that will be used in rural hospitals.

Finally, several studies have demonstrated the feasibility of pooling serum samples prior to performing an HIV test.[16,17,18,19] The result of a test of a pool of sera is

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13 Fortes P, et al. *op cit.*

14 Behets FM; Edidi B; Quinn TC; Atikala L; Bishagara K; Nzila N; Laga M; Piot P; Ryder RW; Brown CC. Detection of salivary HIV-1-specific IgG antibodies in high-risk populations in Zaire . *J Acquir Immune Defic Syndr.* 1991; 4(2): 183-7.

15 Spielberg F; Kabeya CM; Ryder RW; Kifuani NK; Harris J; Bender TR; Heyward WL; Quinn TC. Field testing and comparative evaluation of rapid, visually read screening assays for antibody to human immunodeficiency virus. *Lancet.* 1989 Mar 18; 1(8638): 580-4.

16 Kline RL, Brothers TA, Brookmeyer R, Zeger S, Quinn TC. "Evaluation of human immunodeficiency virus (HIV) seroprevalence in population surveys using pooled sera". *Journal of Clinical Microbiology*, 1989; 27:1449-1452.

17 Patrascu IV; Evaluation of efficacy of pooled sera in a human immunodeficiency virus antibody prevalence in population surveys. *Rev Roum Virol.* 1990 Jan-Mar; 41(1): 45-51.

either negative, suggesting that all of the samples are negative, or positive, suggesting that *at least one* of the samples is infected. Using pools of up to 15 samples have been shown to have no effect or only a minimal effect on test sensitivity and specificity.

Development of Cost-Effectiveness Models to Evaluate the Use of Pooling Samples Prior to Testing

There are two fundamentally different ways to use the pooling technique. The first pools the sera, tests the pools, and then returns to each of the positive pools to test the individual samples. The end result is determination of the serology of each individual sample and is indistinguishable, in terms of data produced, from a survey that tests each sample individually. This technique will subsequently be referred to as **INDIV**. Since the serology of each sample is ultimately determined, it makes almost no difference whether the pools are randomly composed from the samples. **INDIV** is most useful for serologic surveys that collect information about the individuals sampled because in subsequent analysis individual characteristics may be correlated with serologic status.

The second technique (hereafter **PREV**) is used to generate a prevalence estimate for the population sampled, but does not provide information about the serology of each individual. The precision theoretically associated with this technique depends upon the pools being randomly composed from the population of samples. Much of the following discussion of the use of the two pooling techniques has recently been published in *AIDS*.[20] No effort will be made to specifically attribute quoted passages. Since the work was published, several authors have reported successful reduction of cost in field settings with implementation of pooled testing.[21-24] Others have explored a variety algorithms

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18 Cahoon-Young B; Chandler A; Livermore T; Gaudino J; Benjamin R; Sensitivity and specificity of pooled versus individual sera in a human immunodeficiency virus antibody prevalence study. *J Clin Microbiol.* 1989 Aug; 27(8): 1893-5.

19 Behets F; Bertozzi S; Kasali M; et al. *op cit.*

20 *ibid.*

21 Monzon OT; Paladin FJE; Dimaandal E; *et al* Relevance of anitbidy content and test format in HIV testing of pooled sera. *AIDS* 1992, 6:43-48

22 Perriens JH; Magazani K; Kapila N; *et al* Use of a rapid test and an ELISA for HIV antibody screening of pooled serum samples in Lubumbashi, Zaire. *J Virol Methods,* 1993 41:213-222

23 Ko YC; Lan SJ; Chiang TA; *et al* Successful use of pooled sera to estimate HIV antibody seroprevalence and eliminate all positive cases. *Pac J Public Health.* 1992/1993 6(3):146-9

for further testing of positive pools (other than testing each individual sample), e.g. repeatedly halving the pool size.[25] Such different algorithms will not be considered here for two reasons. (i) This analysis focuses on testing in Africa where the level of laboratory sophistication, especially with regard to quality assurance/monitoring and supervision is likely to be low. Thus, the error rate is likely to be high, magnifying the potential harm of introducing complexity into the testing procedure. (ii) As the subsequent analysis will show, the benefit associated with pooling falls with increasing seroprevalence. The seroprevalence among samples in a pool that tests positive is high, thus the potential benefit of introducing subsequent pooling steps would be minimal, even if it were feasible.

Wein and Zenios, in soon to be published work,[26] raise several interesting points. They point out that ELISA, the most commonly used testing method, does not have a dichotomous test result, but rather a continuous optical density (OD) measurement. The OD reading is correlated with the antibody concentration in the serum being tested and thus affected by the dilution of serum that occurs with pooling. This correlation with OD could be exploited in optimizing pooling by varying the OD cutoff (to distinguish positive from negative tests) as a function of the number of samples in the pool and the characteristics of the test. Since OD also varies with the number of positive samples in a pool, the authors propose for estimation of seroprevalence to not dichotomize the test result, but rather take advantage of the more complete information contained in the OD. They develop a method for estimating the prevalence which also optimizes pool size under a budget constraint. Unfortunately, in an African context, the level of complexity introduced by these approaches is not feasible, especially as any OD-dependent method would have to be calibrated for a particular test and laboratory. However, a lesson emerges from the work which is important in any setting. A conservative OD cutoff should be used with pooled sera to counteract the dilution effect, especially when screening blood for transfusion. In addition, the analysis reinforces the point that there is likely to be a trade-off between price and quality (as measured by fewer false negative

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24 Babu PG; Saraswathi NK; Vaidyanathan H; John TJ. Reduction of the cost of testing for antibody to human immunodeficiency virus, without losing sensitivity, by pooling sera. *Indian J Med Res.* 1993 97:1-3

25 Gwa LH; Hsieh CC; Ko YC; Lan SJ. Beyond simple pooling for HIV testing. *J Immunology.* 1992 13(4): 545-57

26 Summarized in Zenios SA. Health care applications of optimal control theory: Thesis proposal. Manuscript August, 1995.

and false positive test results)—and thus the more restricted the resources, the lower the "quality" of the optimal test or testing algorithm is likely to be.

Two micro computer models (**INDIV** & **PREV**) are constructed below and their behavior examined in various circumstances to show how they could be used to select optimal sample size and pool size as a function of local conditions and precision needed. All precision values will be expressed as the 95% confidence interval for the seroprevalence estimate.

The models use several different cost parameters. Since they focus primarily upon the testing aspects of a survey, rather than upon sample collection, an important simplifying assumption is made. The marginal and average cost of collecting a sample is assumed to be equal. Thus, the only cost parameter relating to sample collection is the 'cost of collecting a sample'. If the models are used without modification in a setting where the decision makers have estimates for both marginal and average cost of collecting a sample, the marginal cost estimate should be used. Changes in sample size as a result of changes in pool size will generally be small in relation to the total sample size and thus more accurately represented by marginal cost. If the cost equations are to be used to generate total cost estimates, rather than to optimize the survey design, then the average cost estimate should be used. The cost of collecting a sample (SAMP) incorporates all related costs, including labor, transportation, counseling, blood drawing equipment, blood tube, and generation of the sampling frame.

Five cost inputs for the laboratory portion of the survey are individually specified: (1) materials cost of composing a pool (VIAL), (2) fixed labor cost of composing a pool, which is independent of the size of the pool (LA_PF), (3) variable cost of composing a pool, which is multiplied by the number of samples per pool (LA_PV), (4) materials cost of performing an HIV test (MAT), and (5) labor cost of performing an HIV test (LA_T). All labor costs are expressed as an average hourly wage for a laboratory technician multiplied by the hours of time required.

Prevalence Estimation without Identification of Seropositive Individuals (PREV)

Using **PREV**, the HIV prevalence in the population is estimated as follows:

P = prevalence S = number of positive pools

A = number of sera per pool N = total number of pools

The probability an individual sample is positive is P and the probability that it is negative is (1-P). Thus, the probability that a pool will be negative is equal to the probability that every sample is negatives or $(1-P)^A$ which is equal to the expected proportion of the pools that will be negative. Setting that equal to the observed proportion of negative pools:

$$(1-P)^A = \left(1-\frac{S}{N}\right) \qquad \text{eq 1}$$

solving for P, the estimated seroprevalence, gives:

$$P = 1 - \left(1 - \frac{S}{N}\right)^{\frac{1}{A}} \qquad \text{eq 2}$$

An estimate of the variance of the estimator (eq 2) of P that is appropriate for large N is:[27]

$$V = \frac{\frac{S}{N}\left(1 - \frac{S}{N}\right)^{\frac{2}{A} - 1}}{A^2 N} \qquad \text{eq 3}$$

The 95 % confidence interval for P equals $P \pm 1.96\sqrt{V}$

The variance equation (eq 3) is derived making the assumption that the population in which the prevalence is being estimated is sampled with replacement, meaning than an individual is randomly selected, bled, and then returned to the pool of persons eligible to be selected. Of course, no survey is actually conducted with replacement, but as long as the size of the population is ten times or more the size of the sample, sampling without replacement reasonably approximates sampling with replacement.

Almost any representative survey of a geographically defined population will sample far less than 10% of the population, so it is reasonable to assume sampling with replacement. When sampling convenience populations, the assumption will be valid less often. When the prevalence is estimated using the **PREV** pooling technique, there are two sources of variation in the prevalence estimate. The first source arises from how the sample is chooses from the population and the second from how the pools are comprised from the sample. As the size of the sample approaches the size of the population, the

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27 Kline et al. *op cit.*

number of different ways that the sample can be chosen from the population approaches one, and that source of variation disappears. For example, studies of the seroprevalence among the employees of one factory in Kinshasa sampled the entire work force. In that case the sample was virtually 100% of the population and there is no variance associated with how the sample was chosen from the population. In absence of a general form for the variance equation, when the sample is greater than 10% of the population, the variance may be estimated by Monte Carlo simulation, as was done for the Kinshasa study in which the 8000 samples represented the majority of workers and their spouses at a large factory.

Estimation of the model for **PREV** requires an *a priori* estimate of the HIV prevalence in the population, specification of the width of the confidence interval desired and the labor and materials cost parameters described above.

The model utilizes the following cost function for a seroprevalence survey and performs a constrained minimization of that function holding the variance (and therefore the confidence interval) constant. Variable definitions appear below.[28]

$$\text{Cost of a Seroprevalence Survey} = C = \begin{bmatrix} (\text{Cost of obtaining one sample} \times \text{Pool Size}) \\ \text{Cost of composing a pool} \\ \text{Cost of testing the pool} \\ \text{Cost of retesting the pool if positive} \end{bmatrix} \frac{\text{Sample Size}}{\text{Pool Size}} \qquad \text{eq 4}$$

$$C(A,Z) = \left[(SAMP*A) + (LA\_PF + LA\_PV*A + VIAL) + \gamma + \gamma(1 - \beta^{A})\right]\frac{Z}{A}$$

28

Variable Name	Definition
A	Number of samples/pool
LA_PF	Fixed labor cost of composing pool
LA_PV	Variable labor cost of composing pool
LA_T	Labor cost for testing a pool
MAT	Materials cost for testing a pool
N	Total number of pools
P	HIV prevalence rate
S	Number of positive pools
SAMP	Cost of obtaining one sample
VIAL	Materials cost to compose pool

Variable	Definition
Z	Sample size
α	(VIAL + LA_PF)
β	(1 - P)
γ	(MAT + LA_T)
θ	(SAMP + LA_PV)
f(A)	$(\alpha + 2\gamma - \gamma\beta A)$
f'(A)	$(-\gamma\beta A \ln\beta)$
g(A)	$(\beta 2\text{-}A - \beta 2)$
g'(A)	$(-\beta 2\text{-}A \ln\beta)$

$$C(A,Z) = \left[\theta A + \alpha + \gamma (2 - \beta^A)\right] * \frac{Z}{A} \qquad \text{eq 5}$$

If the desired confidence interval is the 95% confidence interval of the estimate and is specified as $\pm K$, then $K = 1.96\sqrt{v}$ and $v = \left(\frac{K}{1.96}\right)^2$ The variance equation (eq 3)

$$V = \frac{\frac{S}{N}\left(1 - \frac{S}{N}\right)^{\frac{2}{A}} - 1}{A^2 N} \qquad \text{eq 3}$$

is expressed in terms of observed proportions of positive pools and must be expressed in terms of expected proportions of positive pools, thus if sample size equals the number of pools multiplied by the samples per pool, $Z = AN$, and the observed proportion of positive pools is equal to the expected proportion of positive pools

$$\left(\frac{S}{N}\right) = 1 - (1 - P)^A = 1 - \beta^A \qquad \text{eq 6}$$

$$V = \frac{\beta^2 - \beta^{2-A}}{AZ} \qquad \text{eq 7}^{29}$$

and

$$Z = \frac{\beta^2 - \beta^{2-A}}{AV} \qquad \text{eq 8}$$

substituting for Z in $C(A,Z)$, eq 5 , above,[30]

$$C(A) = \left[\theta + \frac{f}{A}\right] * \frac{g}{AV} \qquad \text{eq 11}$$

Minimize $C(A)$ using Newton's method to find the zero's of the first derivative of the cost function.[31]

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29 $$V = \frac{(1 - \beta^A)\,(1 - 1 - \beta^A)^{\frac{2}{A}-1}}{AZ} = \frac{(1 - \beta^A)\,(-\beta^{2-A})}{AZ} = \frac{\beta^2 - \beta^{2-A}}{AZ} \qquad \text{eq 7}$$

30 $$C(A) = \left[\theta A + \alpha + \gamma(2 - \beta A)\right] * \frac{\beta 2 - \beta 2\text{-}A}{A2V} \qquad \text{eq 9}$$

$$C(A) = \left[\theta + \frac{\alpha + 2\gamma - \gamma\beta A}{A}\right] * \frac{\beta 2 - \beta 2\text{-}A}{AV} \qquad \text{eq 10}$$

$$A_{new} = A - \frac{C'}{C''} \qquad \text{eq 12}$$

$$C' = \frac{(Af' - f)g + (Ag' - g)(\theta A+f)}{A^3V} = \frac{hg + i(\theta A+f)}{A^3V}$$

eq 15[32]

$$C'' = \left[\frac{A\ln\beta[f'g - g'(\theta A+f)] + (Af' - f)(Ag' - g)\frac{2}{A}}{A^3V} \right] \qquad \text{eq 23}^{33}$$

$$A_{new} = A - \frac{C'}{C''} \qquad \text{eq 12}$$

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31 Thomas GB., *Calculus and Analytic Geometry.* 1968 Addison-Wesley, Reading, Massachusetts, 324-328

32
$$C' = \left(\frac{f'}{A} - \frac{f}{A^2}\right)\left(\frac{g}{AV}\right) + \left(\frac{g'}{AV} - \frac{g}{A^2V}\right)\left(\theta + \frac{f}{A}\right) \qquad \text{eq 13}$$

$$C' = \left[\frac{(Af'-f)g}{A3V}\right] + \left[\frac{(Ag'-g)(\theta A+f)}{A3V}\right] \qquad \begin{matrix} h = (Af' - f) \\ i = (Ag' - g) \end{matrix} \qquad \text{eq 14}$$

33
$$C'' = \left[\frac{h'g + hg' + i'(\theta A+f) + i(\theta A+f)'}{A3V}\right] - \left[\frac{hg + i(\theta A+f)}{A4}\right] \qquad \text{eq 16}$$

$$C'' = \left[\frac{h'g + h(g' - \frac{g}{A}) + i'(\theta A+f) + i\left[(\theta A+f)' - \theta - \frac{f}{A}\right]}{A3V}\right] \qquad \text{eq 17}$$

$$C'' = \left[\frac{h'g + h(g' - \frac{g}{A}) + i'(\theta A+f) + i\left[f' - \frac{f}{A}\right]}{A3V}\right] \qquad \text{eq 18}$$

$$C'' = \left[\frac{h'g + hi\frac{1}{A} + i'(\theta A+f) + hi\frac{1}{A}}{A3V}\right] \qquad \text{eq 19}$$

$$C'' = \left[\frac{h'g + i'(\theta A+f) + hi\frac{2}{A}}{A3V}\right] \qquad \text{eq 20}$$

$$C'' = \left[\frac{A\ln\beta f'g - A\ln\beta g'(\theta A+f) + hi\frac{2}{A}}{A3V}\right] \qquad \text{eq 21}$$

$$C'' = \left[\frac{A\ln\beta[f'g - g'(\theta A+f)] + hi\frac{2}{A}}{A3V}\right] \qquad \text{eq 22}$$

The final form of the minimization equation is below. Optimal pool size, A, is obtained by iteratively replacing A on the right side of the equation with A_{new} until A_{new} ceases to vary.

$$A_{new} = A - \frac{(Af' - f)g + (Ag' - g)(\theta A+f)}{A\ln\beta\left[f'g - g'(\theta A+f)\right]f + (Af' - f)(Ag' - g)\frac{2}{A}} \qquad \text{eq 24}$$

This final form equation does not contain either the sample size or the variance, revealing that choice of optimal pool size is independent of both.

The total cost using pooling is then compared to the total cost without pooling because the cost equation (eq 4) does not recognize that when the pool size is one, there are no costs associated with making the pools. Finally, the sample size necessary to achieve the desired confidence interval can be calculated from the variance equation (eq 8) above.

In the Kinshasa study, 8000 samples were available at no cost from a previous survey. If the 8000 sera are assumed to be a random sample from a much larger population, then, when the 800 pools of 10 sera are tested, the same precision is obtained as would result from individually testing 7,141 samples, representing a 78% cost savings. It would be even more efficient to test a sample of 8,550 using pools of 15 for an 82% cost savings. Figure 6.1, curve A shows how these results vary with HIV seroprevalence rate.

If parameters are specified which are more realistic for an industrialized country, with an hourly wage rate of US$ 20 and a cost of obtaining a sample of US$15, pooling is no longer cost efficient if the seroprevalence is as high as it was in the Kinshasa population (2.44%). It only becomes cost efficient if the seroprevalence is lower than 1.5%. (Figure 6.1, Curve B)

The model presented above does not consider the contribution of imperfect ELISA test performance to the variance of the seroprevalence estimate obtained by a survey. When the true seroprevalence is high and the decision makers precision requirements are modest, then it may be appropriate to ignore the false positive and false negative test results. However, when the true prevalence is low compared to the false positive rate, then the test results will not reflect the actual HIV prevalence. For example, a test method which has a 99% specificity would be expected to have 1%

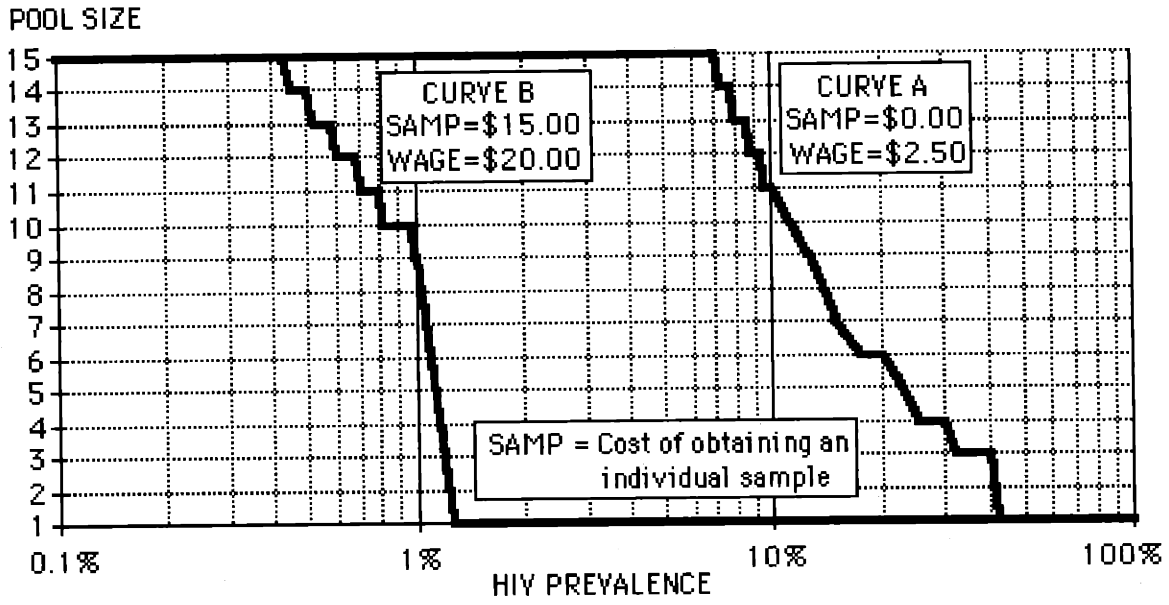

Figure 6.1: Optimal pool size for seroprevalence survey without identification of individual seropositives

positive test results when there are 0% anti-HIV antibody positive samples. It would be impossible using only such a test to obtain seroprevalence estimates below approximately 1% that were significantly different from zero.

The magnitude (and the variance) of the false positive rate may be reduced by using a confirmatory test to re-test positive samples. This improves the performance of the test method, permitting it to be used to estimate lower seroprevalences. The above **PREV** model assumes that a confirmatory test is performed using the same ELISA, or at least one that has the same materials and labor cost. Thus, the variances associated with the sensitivity of one ELISA and the specificity of two ELISAs should be added to the variances already incorporated in the model. Test performance may be further improved by performing a Western Blot confirmatory test. As discussed above, the decision to perform any confirmatory test and the choice of confirmatory test must be guided by the precision requirements of the decision maker. If condom distribution campaigns are to be instituted anywhere the prevalence is greater than 3%, then confirmatory tests may not be necessary. However, if blood donors will be screened anywhere the seroprevalence is >0.5%, then confirmatory tests may be needed to distinguish 0.5% from 0.1%.

Estimates of Seroprevalence with Identification of Individual Prevalence (INDIV)

Serologic surveys that collect descriptive information from each individual sampled may use **INDIV** to permit correlation of individual descriptive characteristics with individual serology. It is also theoretically possible to use **INDIV** in most testing situations where individual testing is performed, including screening blood donors, patients, or for voluntary confidential testing (VCT). However, as discussed below, in many cases it will not be practical and/or not be cost-effective.

Since each individual sample serology is identified, the variance of the seroprevalence estimate is independent of the pool size. (For **PREV**, the variance of the prevalence estimate is not independent of pool size, although it was shown that the choice of optimal pool size is independent of desired variance.) With **INDIV**, rather than minimizing the cost of the survey with a variance constraint, it is sufficient to minimize the cost per sample to determine optimal pool size. Sample size may be directly determined from the desired variance.

As with **PREV**, it is assumed that each positive test result is confirmed with a second ELISA. In the case of **INDIV**, this results in positive pool tests requiring confirmation as well as positive individual tests. Thus, the cost per sample, C(A) is:

$$\text{Cost Per Sample} = \frac{1}{A}\Big[\text{Cost of composing pool} + \text{Cost of testing pool} + \text{Cost of re-testing pool if positive}\Big] + \Big[\text{Cost of testing individual if pool was positive} + \text{Cost of re-test if indiv was positive}\Big] \quad \text{eq 25}$$

$$C(A) = \frac{1}{A}\Big[(LA\_PF + LA\_PV * A + VIAL) + \gamma + \gamma(1-\beta^A)\Big] + \Big[\gamma(1-\beta^A) + \gamma(1-\beta)\Big] \quad \text{eq 26}$$

$$C(A) = LA\_PV + \gamma(2-\beta) + \frac{1}{A}\Big[f\Big] - \gamma\beta^A \quad \text{eq 29}^{34}$$

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34 $$C(A) = \frac{1}{A}\Big[\alpha + LA\_PV*A + \gamma(2-\beta A)\Big] + \gamma(2-\beta A-\beta) \quad \text{eq 27}$$

$$C(A) = LA\_PV + \frac{1}{A}\Big[\alpha + 2\gamma - \gamma\beta A\Big] + \gamma(2-\beta A-\beta) \quad \text{eq 28}$$

$$C' = \frac{1}{A^2}\left[-f + Af'\left[A+1\right]\right] \qquad \text{eq } 33^{35}$$

$$C'' = \frac{f\frac{2}{A} + f'\left[\ln\beta A(A+1) - 2\right]}{A^2} \qquad \text{eq } 39^{36}.$$

As with **PREV**, Newton's method is used to obtain optimal pool size by iterating the final form equation.

$$A_{new} = A - \frac{C'}{C''} \qquad \text{eq } 12$$

$$A_{new} = A - \frac{-f + f'A(A+1)}{f\frac{2}{A} + f'\left[\ln\beta A(A+1) - 2\right]} \qquad \text{eq } 40$$

When the 8000 samples in the Kinshasa study were tested in pools of 10 sera (**INDIV**) there were cost savings of 56% compared to individual testing. Figure 6.2, middle curve, shows how cost savings changes vary little (< 5%) between a pool size of

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35 $C' = -\frac{1}{A2}\left[f\right] + \frac{1}{A}\left[f'\right] - \gamma\beta A\ln\beta$ eq 30

$C' = \frac{1}{A2}\left[-f\right] + f'\left[1+\frac{1}{A}\right]$ eq 31

$C' = \frac{1}{A2}\left[-f + A2f'\left[1+\frac{1}{A}\right]\right]$ eq 32

36 $C'' = \frac{1}{A3}\left[2f\right] + \frac{1}{A2}\left[-f'\right] + f''\left[1+\frac{1}{A}\right] + f'\left[-\frac{1}{A2}\right]$ eq 34

$C'' = \frac{1}{A3}\left[2f\right] + \frac{1}{A2}\left[-2f'\right] + f''\left[1+\frac{1}{A}\right]$ eq 35

$C'' = \frac{\frac{1}{A}\left[2f\right] + \left[-2f'\right] + f''A2\left[1+\frac{1}{A}\right]}{A2}$ eq 36

$C'' = \frac{\frac{1}{A}2f - 2f' + f''A\left[A+1\right]}{A2}$ eq 37

$C'' = \frac{\frac{1}{A}2f - 2f' + f'\ln\beta A\left[A+1\right]}{A2}$ eq 38

5 and 15. As can be seen from the other two curves, cost savings is more sensitive to pool size (above a pool size of 4 or 5) at higher and at lower seroprevalence rates.

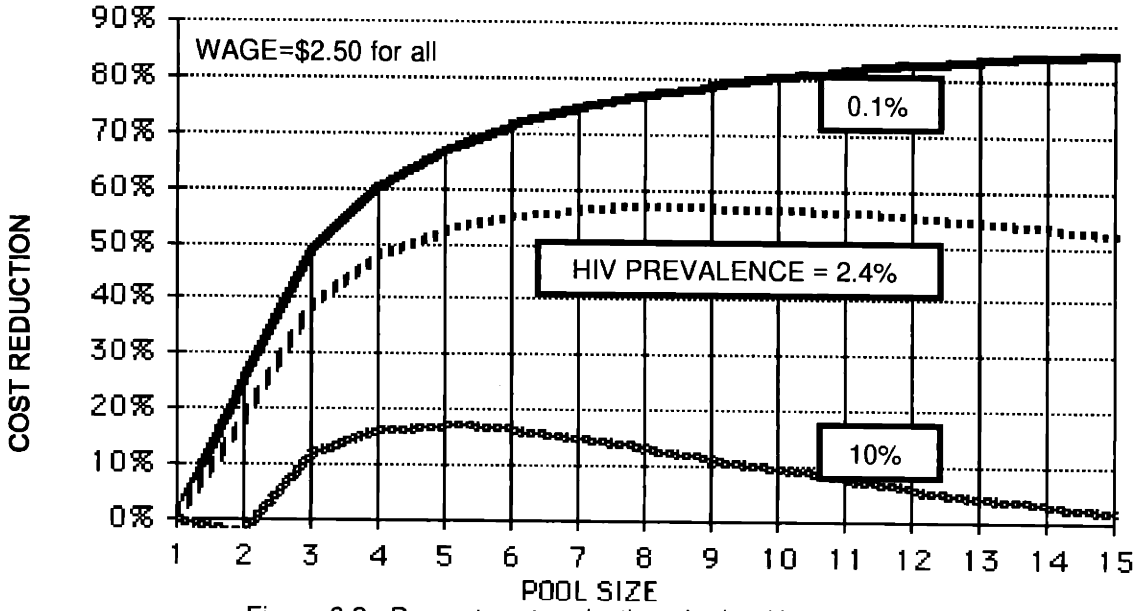

Figure 6.2 Percent cost reduction obtained by using pools with identification of individual positives

As discussed above with **PREV**, the **INDIV** model does not incorporate variance introduced by false positive and false negative test results. These effects will also be important for **INDIV**, especially the effect of false positives at low true prevalences. Consider as an example the survey in the Kinshasa study. If the Western Blot is used as the reference standard, then the use of the one-ELISA-if-negative/two-if-positive method generated estimated sensitivity and specificity of 100% among the samples that did not have an indeterminate Western Blot result. If the samples with indeterminate results are assumed to be HIV negative, then the percentage of indeterminate samples must be factored into the confidence interval of the sensitivity.

Discussion

In the Kinshasa field study, HIV-1 seroprevalence was determined by testing pools of 10 sera using the Vironostika ELISA. Testing 800 pools resulted in an estimated seroprevalence of 2.42% ± 0.12% compared to the prevalence of 2.44% established by testing 8000 individual sera (ignoring variance associated with sensitivity and specificity).

Pooling can result in considerable cost savings. When pooling is used for identification of individual seropositives, cost savings depend most importantly on the

true seroprevalence (the higher the seroprevalence, the lower the savings) as well as on the balance between the cost of labor and the cost of materials. The cost-efficiency of pooling without individual identification is further dependent on the cost of increasing the sample size to maintain comparable precision. The models developed can be conveniently used to determine when it is cost-efficient to pool samples and to identify optimal pool and sample sizes.

Practical applications of pooling with individual identification (**INDIV**) include prevalence surveys that correlate serologic status with individual epidemiological and demographic variables. Under appropriate conditions pooling is the most cost-efficient way to survey such populations .

Another setting in which pooling **INDIV** may be the best alternative is public health screening programs such as voluntary test centers and prenatal screening.

In a previous study, Emmanuel et al., pooled sera to efficiently carry out ELISA testing for HIV antibody detection in a blood bank in Zimbabwe.[37] While perhaps useful in some countries, ELISA testing, which requires 2 to 3 hours, is not practical in Zaïre nor in much of Africa. Stored blood is not available and therefore blood is transfused almost immediately after collection. In high volume transfusion centers, rapid HIV antibody assays could be used for screening of pooled sera, though this technique remains to be evaluated.

When testing is performed for diagnostic purposes, pooling is unlikely to be cost-efficient because of the high seroprevalence among individuals with clinical evidence of HIV infection.

Testing pooled sera **PREV** for anonymous seroprevalence surveys can represent a valuable alternative to expensive individual screening. An important caveat is that the accuracy of the prevalence estimate depends upon the pools being constituted randomly from the samples. If the pooling is not random then the estimate is likely to be low.

Surveys can be used to estimate both HIV *prevalence* and *incidence* . The former is less difficult. If blood samples are taken from a population, the percent of the samples

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37 Emmanuel JC; Bassett MT; Smith HJ; Jacobs JA; Pooling of sera for Human Immunodeficieny virus (HIV) testing: An economical method for use in developing countries. *J Clin Path* 1988, 41:582-585.

that test HIV positive is an estimate of the point prevalence in the population . Incidence is the number of new infections per unit time. Theoretically, it can be estimated by returning to individuals previously sampled, drawing their blood again, and determining what percentage of the seronegative individuals seroconverted, or became seropositive. The technique is limited by one's ability to locate the individuals in the original sample, a constraint which may be especially important in Africa where migration may be common and tracing techniques (such as forwarding addresses, new telephone numbers, driver's license, etc.) comparatively unavailable. Furthermore, it is very difficult ethically and practically to do such an incidence study on a 'control' group. If an intervention identifies a control cohort which will be re-bled to determine HIV incidence, is it ethical not to teach them about HIV prevention and not to provide them with the means to protect themselves?

An alternative technique is to take a new sample of the same population, calculate a new prevalence, correct the new prevalence for the mortality during the intervening period, and calculate the incidence. Since the average time from infection to death is very long (in excess of eight years), yearly incidence will usually be very small relative to point prevalence unless the epidemic growth rate is extremely high. Calculating incidence from the difference between two prevalences is limited by the accuracy of *each* of the prevalence estimates and the accuracy of the estimated mortality of HIV infected persons. Thus, if prevalence estimates are to be used to estimate incidence rates, they will usually need to be much more precise (and much more expensive) than if a survey is only being done to describe prevalence rates.

VII

CONCLUSION

My goal has been to take a reader who is neither economist nor physician, but interested in the work of both, on a tour of the health economics landscape in Africa. I have chosen to focus on AIDS because it commands our attention; no other current health problem has its potential to wreak economic havoc, at least in the most affected countries. Furthermore, the rapidity with which its epidemiology is changing not only lends greater urgency to prevention efforts, but provides unequaled opportunities for study of the economics of illness.

In an environment of extreme scarcity, as found on so much of the African continent, the rules of economic analysis may still apply but the optimal use of resources will be very different from that in wealthier countries. Thus, the purchase of supplies for a rapid HIV test, which might represent one half of one hour's wages for an American, might represent more than a week's work for a rural Zaïrian. Clearly, decisions about when to test in will be made differently—and should be made differently—in Zaïre than in the USA.

I hope the reader leaves these pages with greater appreciation of the difference in the value of a dollar between industrialized countries and Africa. As an indication, consider that the per-capita gross national product (GNP) in Zaïre in 1988 was approximately $150 and in the United States, approximately $19,000.[1] Regardless of how much those figures are corrected to account for the black market economy, or for the difference in buying power between the countries, there remains an enormous difference in the resources available to ensure the well-being of people in the two countries. If there are people who do not have access to primary education, basic health care, or housing in the United States, it is because the GNP is unevenly distributed and society chooses to spend its collective resources on other priorities. In Zaïre, even if the GNP were uniformly distributed across the population, education and basic health care would not be uniformly available. In reality, wealth is extremely *unevenly* distributed in

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1 World Development Report. 1989, World Bank by Oxford University Press. pp 164-165; figures are not available for Zaire in the 1993 report.

Zaïre. To help illustrate the constraints faced by health policy makers in Zaïre, consider public funding for health care. In the U.S.A., though we think of most health care financing as private, the government still spent approximately $500 per capita per year on health care. The government of Zaïre was able to spend about $1.

Throughout this document, there have been frequent references to 'Africa,' as though it were a homogeneous entity. As a geographic region comprising more than 50 countries and a much larger number of ethnic groups, it obviously is *extremely* heterogeneous. By restricting the discussion to the countries south of the Sahara and north of South Africa the degree of variation is only marginally reduced. The generalizations that follow are meant only to illustrate the vast differences between western industrialized countries and those in Africa. Most of sub-Saharan Africa shares a colonial past, low levels of industrialization, low levels of post-primary education, low average health status, and low standard of living. While some parts of the world have witnessed dramatic increases in standard of living over the past 20-30 years, most of sub-Saharan Africa has seen little economic growth and rapid population growth, such that per capita gross national product has stagnated, or in many countries, actually declined.

In the U.S.A., health policy makers resist acknowledging that not everybody receives the same quality medical care, preferring to pretend that one standard of care exists for everybody. For emergency treatment of life-threatening problems, it is reasonably true that care is available to everybody. Licensing, accreditation, and government approval of pharmaceuticals and medical devices all assume one standard of medical care, as does the court system in determining medical liability. The Food and Drug Administration decides whether a drug is "safe and effective." It does not decide whether it is effective *enough* to be covered by the government health insurance program for the poor. As a result, the government health dollar provides some segments of the population (e.g., those over age 65) with first class care. For many workers it provides tax subsidies for health insurance. For those unfortunate segments that are not included, it may provide nothing. The U.S. government places much higher priority on saving healthy life years over the age of 65, the age at which most people become eligible for Medicare benefits. We in the U.S.A. are able to maintain the fiction of one standard of care in part because differences in <u>access</u> to non-life-threatening care are less visible than explicit differences in <u>standards</u> of care would be.

In Africa, it is impossible to pretend that only one standard of care exists. Standards of care that vary by institution, by location, and by the patient's means are

glaringly apparent. A large portion of the population has no access to biologically based medical care (45% in many African countries according to a recent World Bank estimate).[2] People die even in large teaching hospitals because of shortages of antibiotics and scores of children die each year from diseases easily and inexpensively prevented by vaccination.[3] In this setting, government policies that considers "safe and effective" but ignore cost becomes glaringly inadequate. Unfortunately, even under such extreme circumstances, allocation decisions often are made passively rather than actively. As an example, I visited a hospital in Tanzania that received standard monthly drug shipments through the national UNICEF-sponsored essential drug distribution program. Unfortunately, the supplies of most of the drugs were exhausted well before the end of each month. While I was there, a child with meningococcal meningitis, who was allergic to penicillin, died because the month's supply of chloramphenicol was already exhausted, having been used for other patients, some of whom did not have life threatening infections or could have been treated with a different drug. This example illustrates how it is often easier to use a drug whenever it is medically indicated—until it runs out, than to establish priorities for administration of a drug and set a threshold level so that it will usually be available for the highest priority uses. Setting a threshold forces explicit differentiation between people based on level of need, while the "easy" option avoids making an explicit choice but implicitly assigns higher priority to children who develop meningitis near the beginning of the month.

Regarding AIDS, the same general argument applies. People needlessly become infected with HIV because funds for AIDS prevention are spent without setting explicit priorities. At the national level, just as in the chloramphenicol example, it is often easier to make allocation decisions passively. It is more difficult to ask, actively, "Where will distribution of condoms prevent the greatest number of new HIV infections?" — especially if the answer is "among men who buy sexual services," because that would involve explicitly acknowledging that some men do.

Economic analysis in this context is powerful because it provides data to decision makers that allow them to make explicit decisions based on reasonable estimates of cost and effectiveness. When dealing with AIDS, the natural resistance to setting explicit

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2 World Bank; Better Health in Africa. 1993 Dec; Report No. 12577-AFR; p2.

3 Walsh JA: Estimating the burden of illness in the tropics. in Warren KS; Mahmoud AAF; eds *Tropical and Geographical Medicine* . 1990 McGraw-Hill, New York.

priorities may become significantly stronger because of political barriers. Unfortunately for HIV prevention efforts, AIDS is inexorably linked to sex and death—and thereby interwoven with multiple layers of cultural and religious taboos.

> The reluctance of politicians to launch health education campaigns that talk openly about sex, condom use, and reduction of promiscuity is universal. In this context... reluctance on the part of governmental or religious leaders may seriously hinder education of the public.[4]

The effect of these political and cultural barriers is to make cost effective allocation of resources for AIDS prevention even more difficult than for other, less culturally and politically sensitive diseases. A likely consequence is overemphasis on prevention of non-sexually related HIV transmission, for example, via transfusions or contaminated skin piercing instruments—thus avoiding the "sex" issue.

Although the "reluctance of politicians" may be universal, some aspects of African political structures and of the epidemiology of HIV in Africa make policy implementation easier than it is in the U.S.A. The political power structure in the U.S. is remarkably untouched, personally, by AIDS. Most cases continue to occur among homosexuals and intravenous drug users, marginalized segments of society. The opposite appears to be true in Africa where members of the power structure, on average, are probably more likely to be affected. This was emotionally demonstrated by President Kenneth Kounda of Zambia when he spoke of the pain of losing his son to AIDS in his plenary speech to the Vth International AIDS Conference in Montreal.

In the U.S.A., the system for funding medical care and the constraints imposed by the tort system also pose greater obstacles than they do in much of Africa. Harlem hospital, which not uncommonly spends $200,000 on care for an infant with AIDS,[5] is unable to reallocate those funds to the community in a way that might save more discounted healthy life years (DHLYs), for example by creating pediatric hospices or funding prevention programs. Once the child enters the hospital, then withholding care from an indigent infant is "unethical" and could easily lead to malpractice charges if, under the same circumstances, care would not be withheld from an infant with insurance.

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4 N'Galy B; Bertozzi S; Ryder R; Obstacles to the optimal management of HIV infection/ AIDS in Africa. *J Acquir Immune Defic Syndr.* 1990; 3(4) 430-7.

5 Hegarty JD; Abrams EJ; Hutchinson VE; Nicholas SW; Suarez MS; Heagarty MC; The medical care cost of human immunodeficiency virus-infected children in Harlem. *JAMA* 1988 Oct. 7; 260(13): 1901-5.

The "ethical standard" used in the USA ignores the children who would not become infected if the funds were used differently. In Africa, a regional or district health officer may have greater discretion in allocating regional or district resources than does, for example, the commissioner of health in New York City.

This dissertation has focused on one particular technology, HIV testing. It was chosen not because it is necessarily the most important technology, but because it is especially amenable to study and because it is a component of almost every type of intervention to thwart the HIV virus, from reducing HIV transmission via transfusion, to reducing sexual transmission, reducing perinatal transmission, improving treatment of patients, and assisting bereaved survivors.

Reducing HIV Transmission via Transfusion

The cost of performing an HIV test is not substantially different in Africa than in industrialized countries, yet African countries are able to spend much less to prevent the loss of one healthy life year (HLY). As a result, the epidemiological circumstances under which HIV testing is cost-effective are not the same in the two settings; nor are optimal test strategies the same. We must first question the notion that testing is always indicated when there is a risk of HIV transmittal via transfusion and also question the notion that the "best" test available (i.e., the most sensitive/most specific) is necessarily the optimal choice.

For example, when the seroprevalence in the blood donor population is sufficiently low, testing is not cost-effective. The threshold level that determines "sufficiently low" will vary from country to country. The wealthier a country is, the more it is able to spend on preventing a lost HLY, and thus the lower the seroprevalence will be at which testing is cost-effective.

Other approaches to reduce transfusion related transmission, such as recruiting donors from low-risk populations, rely less on imported technology and more on labor. Their cost varies more in proportion to the wealth of the country because of the relationship between local wages and a country's wealth. The rule that emerges from this observation is that poorer countries, for the same seroprevalence, should place greater emphasis on labor intensive approaches (as opposed to imported, technologic approaches) to reduce transmission.

Similar lessons emerge concerning optimal choice of testing method. Improved performance of a method is normally correlated with increased cost (a method that improves performance at lower cost is always preferable). Thus, the optimal test method in poorer countries (that are able to spend less to prevent lost HLY) will usually perform less well than the optimal method in a wealthy country.

Health planners make a major conceptual error when they compare the number of infected units of blood that are missed by different methods. Using this approach, a test with a sensitivity of 99% is "five times as good" as a test with a 95% sensitivity, and thus worth five times as much.[6] This formulation of the problem assumes that the appropriate policy goal is to minimize the failure rate of one particular method, rather than maximizing the total number of new HIV infections averted. Suppose a country with a donor seroprevalence of 5% had the means to buy 100,000 of the 95% sensitive tests. Those tests would detect 4750 infected donors. If, instead, the country bought the better test for five times the price, it would only be able to buy 20,000 tests and thus identify 990 infected donors. Instead of being 500% better, the 99% sensitive test is only 4.2% better and therefore worth only 4.2% more in any country where total cost limits the total number of tests that can be bought.

Notification of donors

Standard operating practice in many, probably most, African transfusion screening sites is to reject the blood from a donor who has a positive HIV test without informing the donor of the reason for the rejection. The logic applied is that "standard medical practice" dictates that an individual can only be informed of a positive result if the result has been confirmed by a Western Blot test or by two additional ELISA tests. Since many transfusion sites cannot afford to perform these confirmatory tests, they do not inform the donor. Unfortunately, WHO encourages such policies with its reluctance to acknowledge that guidelines of standard medical practice must be modified to reflect resource constraints. It may be just as important in Rwanda as in Switzerland to avoid falsely informing an individual that they are HIV infected, but just as Rwanda cannot

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6 In the U.S., this approach may be an appropriate response to the biases that exist in the value system. The benefit that accrues to a blood bank director from preventing an HIV infection is much smaller that the harm he or she will suffer if an infection occurs that could have been prevented by choosing an improved, more expensive test. The attorneys for the infected individual will not be interested in how many additional infections were averted with the money that would have been spent to insure that their client would not become infected.

afford to spend as much as Switzerland to avoid a new HIV infection, so can it not afford to spend as much to avoid falsely informing someone that they are infected. A policy that automatically accepts a single confirmatory standard has not weighed the benefits associated with truthfully informing infected and non-infected individuals of their infection status against the harm that is done by falsely informing others of their status. Whether nationally, locally, or at each institution, these benefits and harms must be weighed so that appropriate policy can be formulated.

Evaluation of programs to notify blood donors, just as with evaluation of blood screening programs, need to consider both costs and benefits. The benefits of such a program include the relief to individuals who discover they are not infected and, most importantly, the reduction of HIV transmission that results from behavioral change. The costs of such a program include the cost of any additional testing and the harm associated with truthfully and falsely informing people that they are infected. A policy maker may wish to place greater weight on avoiding harm than on generating benefit, but very similar models to those used for HIV screening of donors could be used to evaluate the costs and benefits of using confirmatory tests and counseling in the notification of HIV infected donors.

HIV Testing and the Diagnosis of HIV-related Disease

A country with a low per capita GNP will have comparatively low labor costs in the health sector and thus the cost of pharmaceuticals, which must largely be purchased on the international market, will represent a greater proportion of total health costs.[7] Efforts to reduce the cost of HIV-related medical care in the U.S.A. logically focus on reducing the costs of hospitalization and physician services because these labor dependent services consume a large majority of total health care costs.[8] The most visible efforts have been the development of home-care and hospice alternatives to hospitalization in San Francisco.[9,10,11] The lower the per capita GNP, the more that cost

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7 Over M; Bertozzi S; Chin J; et al: The direct and indirect cost of HIV infection in developing countries: The cases of Zaire and Tanzania. In *Abstract volume, IV International Conference on AIDS . 1988 .*

8 Social Security Bulletin. Annual statistical supplement. 1991

9 Volberding PA: Caring for the patient with AIDS. An integrated approach. *Infect Dis Clin North Am.* 1988 Jun; 2(2): 543-50.

10 Arno PS: The nonprofit sector's response to the AIDS epidemic: community-based services in San Francisco. *Am J Public Health.* 1986 Nov; 76(11): 1325-30.

reduction efforts should shift toward reducing costs of drugs and other imported technologies. This would naturally increase the relative importance of developing treatment protocols in comparison to other cost reduction efforts. As these protocols are developed they will be forced to specify under what circumstances should diagnostic HIV testing be performed.

Two principal reasons for using HIV testing in a health care setting are reviewed: 1) to help establish a diagnosis so that treatment can be altered to better address the patient's disease and 2) to detect HIV infection because certain services may only be available to HIV negative (or only to HIV positive) persons.

1) Improved treatment

The extent to which testing will benefit the patient depends upon the probability that the patient is infected and upon how much the result of an HIV test would change therapy. Expected benefit is low if the pre-test probability of infection is far from 50%, in either direction, and if the expected change in therapy is small. Since the spectrum of HIV-related disease is vast, the expected benefit depends critically upon the patient's risk history and presenting complaints (which influence both the pre-test probability of infection and the degree to which therapy is contingent on the test result). The impact of HIV testing on the cost of care depends upon the cost difference between the average cost of therapy that would be chosen with and without testing.

The experimental protocol presented in Chapter V suggests that a prospective study be done to quantify the change in treatment that accompanies the receipt of HIV test results. The study would describe the institutional and patient characteristics that predict clinical and financial benefit from HIV testing. The total cost differential associated with testing could be estimated, as well as the more detailed cost implications for the patient, the hospital, and any third-party payers. How the monetary costs/savings and clinical benefits are distributed will help clarify who has what interests in testing. If the hospital expects cost savings, it may be interested in offering testing at its own expense. If there are clinical benefits for the patient or cost savings for the payers, then the hospital will be more likely to attempt to recover the cost of testing.

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11 Beresford L: Alternative, outpatient settings of care for people with AIDS. *QRB*. 1989 Jan; 15(1): 9-16.

Hospitals need not await the results of such a prospective study to begin policy formulation. A rapid assessment could be made by grouping patients into several categories by presenting complaint (pulmonary, gastrointestinal, neurologic, etc.) and then seeking advice from the medical staff about how much an HIV test would be expected to change patient management in each category. If the unsuspected HIV prevalence among admitted patients is sufficiently high, a hospital may find that it is in its institutional self-interest to offer voluntary testing to all patients in certain clinical categories.

Unfortunately, the "hospital self interest" argument is less likely to apply in Africa than in the U.S.A. Improving efficiency of diagnostic procedures and development of ambulatory alternatives to inpatient treatment has led to falling hospital censuses in the U.S.A., such that few hospitals now operate at their functional capacity. When a hospital is not full, a diagnostic test that hastens diagnosis and reduces hospital stay will reduce the services the hospital provides and thus reduce expenditures. In U.S.A. hospitals that do operate at capacity, a decrease in average length of stay may not decrease expenditures, but is likely to increase revenue as hospital reimbursement is often linked to number of admissions (DRG system) rather than number of days. Regardless of how full a hospital is, it is always in its interest to reduce expenditures on non-compensated care, of which AIDS patients comprise a disproportionate share in many cities.

In most of Africa, recent population increases have outstripped increases (in some cases, decreases) in the capacity of health facilities. Hospitals (especially in areas of high HIV prevalence) are much more likely to operate at functional capacity, although capacity may be limited by staff size or equipment rather than physical plant. The range of services offered by the hospital is likely to be limited, with most internal medicine patients receiving little more than a bed, nursing care, and intravenous hydration. Drugs must commonly be bought by the patients' families either from a hospital pharmacy or from private pharmacies. The limited services provided by the hospital suggest that the cost of a hospital day does not differ very much by diagnosis. Operating at capacity suggests that shortening average length of stay will not influence total hospital days, but rather total number of admissions. Unless hospital revenue is related to total number of admissions or to diagnosis, there would be little financial benefit, to the hospital, associated with using an HIV test to shorten hospital stay. The benefit must instead be measured in the reduction of opportunity cost, which is the cost to patients who

otherwise would have access to hospital services if the hospital stays of HIV positive patients were shorter.

Not only may a hospital not have a financial interest in using HIV tests to reduce length of stay of HIV positive patients, in some cases the financial incentives may be reversed. We performed a short retrospective study in a rural Zaïrian hospital to examine the impact of HIV positive patients on the hospital's financial health.[12] The hospital recovers approximately 70% of its operating costs from patient fees. We postulated that a high census of HIV positive patients would financially threaten the hospital because it would have difficulty recovering costs from HIV positive patients who are more likely to be indigent because they are chronically ill and unable to work; and/or because they come from households that have recently had or currently have other seriously ill members.

Instead, we found the opposite. Patients with HIV-related disease were much more likely to be young adults than patients with other diagnoses. They were therefore much more likely to be employed. Large employers in Zaïre are required by law to provide health benefits to employees and their families. Because the hospital had a sliding scale fee structure, the average revenue from employed patients (for the same services) was 3 to 10 times greater than for non-employed patients. Thus, on average, it was in the hospital's financial interest to *maximize* the length of stay of HIV positive patients. Employed patients had a longer average length of stay, but the sample was not large enough to permit us to differentiate employed from non-employed HIV-positive patients with respect to length of stay.

The hospital studied was private, not-for-profit, and administered by the Protestant church. If its revenues increase without an increase in fees, it is able to provide more services to the local population or able to decrease its fees so that access is more equitable. Since employed HIV positive patients effectively subsidize the care of other, non-employed patients, it may not even be in the community's interest to reduce the length of stay of employed patients. Doing so, the community would forego a transfer of funds from large national or international companies into their community.

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12 Bertozzi S; Mposo N; Green S; Mandiyangu M; Walker D; Ryder R: Increased hospital revenue associated with admitting HIV positive patients to a rural Zaïrean hospital. in *Abstract Volume, Sixth International Conference on AIDS* San Francisco: June 1990, 2:283.

There should be no implication that the rural hospital described is representative of other African hospitals, or even of other Zaïrian hospitals. On the contrary, it is probably very unrepresentative. It is located on the only road between Kinshasa, the capital, and Matadi, the country's only major port. Any company that is importing or exporting goods is likely to operate on that road. Thus, the percentage of patients who are employed by a large company is likely to be uncharacteristically high. However, it illustrates the need to consider the costs and benefits of diagnostic testing from the perspective of the individual or the institution that must make the decision to test. Whether diagnostic HIV screening reduces total expenditures at a hospital is not nearly as important to the hospital as what net effect it will have on the institution's balance sheet.

In spite of low average access to health services in Zaïre, large firms are legally mandated to provide health care for employees and their families. Thus the average annual health expenditures per employee are much greater than the average for the entire population. Correspondingly, the amount that employers are able to spend to avert a lost HLY is much greater than the national average—both by providing better treatment for infected employees and by preventing new infections. HIV testing may be an important part of a campaign to improve treatment of HIV infected persons and to reduce HIV transmission. However, it also has the potential to be used by the firm to identify HIV infected individuals for the purpose of reducing the firm's exposure to medical costs. The former is of clear benefit to the employee and probably also to the firm. The latter may be of benefit to the firm but is harmful to current or potential employees.

2) Improved "rationing"

One of the most perplexing and interesting issues raised by the HIV epidemic is the question of when may an HIV test result (positive or negative) appropriately be used to deny access to services.

Those readers who find unethical under any circumstances the notion of conditioning access to medical services upon a person's state of health are referred to the literature on ethics of medical triage (patient selection).[13,14] Without discussing the strengths of the supporting arguments, criteria governing access to scarce resources have

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13 Winslow GR: *Triage and Justice.* 1982, UC Press, Berkeley.

14 Kilner JK: *Who Lives? Who Dies?* 1990, Yale U Press, New Haven.

included (a) how likely is the patient to derive medical benefit from the treatment? (b) would the patient otherwise die imminently? (c) what is the likelihood the patient will benefit from treatment? and (d) how long is the patient likely to benefit? In the U.S.A., choosing between patients occurs, for example, when we decide who will receive transplant organs and who will be admitted to (or discharged from) an intensive care unit. In 1972, the need to choose patients for renal dialysis brought to the forefront of public debate the question of how to allocate scarce medical resources. Unfortunately,

> . . . curiously, no congressional hearings were held on the matter [federal funding of renal dialysis], and less than thirty minutes of debate took place on the Senate floor. Federal funding apparently presented a way of avoiding uncomfortable life-and-death decisions altogether, especially those involving evaluations of the social worth of patients. The arguments voiced by a majority of the senators during the brief floor debate confirm this interpretation. As a result, the opportunity to develop carefully considered approaches to medicine's inevitable patient selection decisions was lost.[15]

In developing countries, where resources are scarcer, the problem of choosing between patients might be expected to be even more common. For example, parts of Africa have high rates of female infertility with resulting high demand for medical evaluation. It is possible that hospitals able to accept a limited number of women for such evaluations may want to condition access on HIV status.

This is a very difficult topic both ethically and practically. Because HIV positive patients are already vulnerable to irrational discrimination that can affect all aspects of their lives it seems dangerous to set any precedent for 'justifiable' discrimination. It is also difficult as a non-African to comment on policies which are so intimately linked to culturally determined value systems. But, it is important to recognize that the value system we take for granted in the U.S.A., especially as regards the rights of handicapped persons, may be seen as a luxury that is not affordable in much of Africa. It is not reasonable to insist that buses have handicapped access when there is a great shortage of buses; it may not be reasonable to expect that there will be special classes for the developmentally disabled when there are not enough regular classes; and it may not be reasonable to expect that HIV positive persons have equal access to specialized training or medical services. In the United States, we have decided to pay the cost of ensuring

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15 Kilner JK, *op cit* , pp4-5.13

equal access for HIV positive persons, but we cannot expect that countries with different values and scarcer resources will reach the same conclusion.

In the USA and in African countries, persons suspected of being HIV infected have been subjected to unjustifiable abuse from their families, their employers, their communities and their governments—often in the name of advancement of the public health. Loss of employment, travel restrictions, loss of housing, and suspension from school are just some examples. This history of unfair treatment of a group that is already greatly disadvantaged has lead to an understandable tendency to protest almost any attempt to distinguish HIV positive persons from HIV negative persons. However, we are unfair to the very persons whose rights we seek to protect if we refuse to address the question of when may the HIV test appropriately be used to condition access to services. By refusing to address the issue and lumping all "testers" together, we render suspect persons and institutions who use the test justifiably and legitimize those who unjustifiably discriminate. Would that it were easy to tell the difference.

Preventing HIV positive African students from traveling internationally, in absence of credible evidence that such restrictions are effective in reducing spread of disease (especially if HIV positive American students do not face similar restrictions) is clearly not ethical. However, consider the example of an African government that is able to finance advanced engineering studies overseas for 10 students per year. Is it reasonable for the government to accept applications only from persons under 55 years of age? or only from persons who would be expected to return and work in their field for at least ten years? If yes is the answer to either, then an argument could be made that accepting applications only from HIV negative applicants is also reasonable.

Although each culture must set its own priorities, if rationing guidelines are explicit then they are more likely to be applied in a consistent way and more likely to benefit from informed debate. It is far better to have a national policy that excludes HIV positive persons from government university scholarships than to accomplish the same end by having the admissions office subtly interfere with the applications of people they suspect to be infected.

Discrimination is an obvious concern of any patient undergoing HIV testing for diagnostic purposes. The test results may not only help to identify which is the optimal treatment, but may also determine whether the patient is permitted access to treatment. If a hospital explicitly or implicitly denies access to treatment to HIV positive patients, then

it would be very difficult to describe the relationship between diagnostic HIV testing and cost of care. This is not only a theoretical concern. Many African health facilities are operating at capacity. They are forced to ration care. If they believe that HIV positive patients are less likely to benefit from care (because of their high mortality, low life expectancy, or both) then the care will be given preferentially to HIV negative patients.

Whether or not such differentiation/discrimination can be defended, it unquestionably encourages HIV positive patients to conceal their infection and to refuse HIV testing.

HIV testing to limit access to services may also be used to reserve certain services exclusively for HIV infected persons. Social service programs are always faced with the problem of determining eligibility for benefits in a way that is fair and reasonably impervious to corruption. Although it is not very difficult to falsify an HIV test result, HIV negative persons have significant reason to want to avoid being labeled HIV positive. As a result, HIV tests might be useful in targeting assistance to HIV positive persons. In Africa, a marked disparity between the HIV prevalence rate among women who sell sex and that of the similarly aged general population suggests that women who sell sex play a major role in propagation of the virus. Thus, donors should strongly consider supporting a pilot program to provide financial support or guaranteed employment to women who choose to reveal that they both sell sex and are infected with HIV.

HIV Testing for Epidemiological Monitoring

A consistent theme that underlies the discussions in the preceding chapters is the overarching importance of the prevalence and/or incidence of a disease in the evaluations of the cost-effectiveness of interventions to combat it. This importance is the result of the extreme variability of prevalence and incidence relative to other parameters. More than a thousand fold difference in HIV prevalence rates exists in sub-populations across the African continent and even within many individual countries. This variability is normally much greater than that of other variables, such as costs of inputs, response to therapy, willingness to change behavior, etc. In addition, prevalence and/or incidence are likely to enter into models in several ways. For example, a model of behavioral response to prenatal HIV screening might incorporate not only the probability that the woman to be screened is HIV infected, but also the probability that she has witnessed HIV-related disease among her first degree relatives. Or, a model that incorporates reproduction rate

(the expected number of secondary cases infected by an index case) is likely to use the distribution of prevalence and incidence rates to estimate reproduction rates for different sub-populations.

If one accepts the importance of incorporating prevalence and incidence estimates into cost-efficiency models and thus into decisions about resource allocation and targeting of interventions, then it is clearly important to gather serologic data to be able to describe the pattern of incidence and prevalence across the populations.

Epidemiological information is expensive to obtain and thus serious consideration must be given to:

- what and how much information is necessary and to
- what are most cost effective ways of obtaining the information.

In an environment where there are insufficient HIV tests to test blood donors, to use thousands of the available tests to perform epidemiological surveys requires that the epidemiological information will result in more infections being prevented than would have been prevented by testing blood donors.

For the purpose of targeting interventions, large differences in prevalence and incidence rates are important, accuracy of the absolute values is much less important. Although, an average national HIV prevalence of 3% in a country of 20 million people represents 400,000 fewer infected persons than a prevalence of 5% , revealing the difference between a 0.5% prevalence in one area and a 10% prevalence in another is much more important for targeting interventions than the absolute precision of those figures or even the national average. This suggests that many efforts to precisely describe HIV serologic distribution are costly overkill. However, precise surveys have an important double purpose: they permit estimation of the effectiveness of interventions by documenting a change in the incidence of infection. Because of the long average period between infection and death, a change in incidence will only be slowly reflected in a change in prevalence.

Directions for future research

Early research on the economic aspects of the HIV/AIDS epidemic in developing countries, as in industrialized countries, focused on estimates of the present and future cost of the epidemic measured in direct medical care costs and indirect costs of lost

production. Such studies proved invaluable as advocacy tools to convince policy makers, especially those in areas other than health, that HIV/AIDS was a multisectoral problem and that slowing its spread and alleviating its impact required a multisectoral response. They also helped to redefine the debates about both public health and health economics in developing countries by highlighting the fact that young adult deaths have disproportionately negative impacts on their households, employers and their communities.

Despite the benefits that have come from the direct cost/indirect cost studies, they have been of little use to planners responsible for either programs to prevent HIV transmission or to those responsible for alleviating the impact of the epidemic, except as advocacy tools for mobilizing resources. Although this thesis has focused on the relatively narrow domain of HIV testing, it highlights the need to shift the economic research focus away from studies of the magnitude of the national cost impact toward research that can inform the decisions of planners confronted with the epidemic.

It is becoming increasingly clear that economics may play as large a role in understanding what drives the epidemic as in understanding what its impact will be. Despite the greater visibility of migration because of strife or natural disaster, most migration is a result of economic pressures and the opportunities offered by distant labor markets. To the extent that migrants are away from their families, relatively anonymous in a foreign culture, and have money to spend, then they are in a situation where they are especially likely to engage in high risk behaviors. To design interventions that respond to these pressures, research must be done to better understand the linkages. Similarly, commercial sex workers enter their trade, which was a high-risk occupation even before the advent of HIV/AIDS, because of the economic return.

If policy makers and planners hope to decrease HIV transmission via commercial sex then they need to better understand the supply and demand characteristics of the market as well as what determines the ability of workers to insist upon a safe working environment, i.e. safe sex. Thus, the economic determinants of HIV transmission is a major area of research that has received inadequate attention.

A second under-explored area is the application of economic tools to assist planners to allocate resources among different interventions to prevent HIV transmission. Despite the urgent need to investigate and develop novel preventive interventions, several "accepted" interventions have been widely implemented and consume the bulk of

HIV/AIDS prevention resources in developing countries. These include education via mass media, schools and via peer educators for sex workers and out of school youths; condom promotion via subsidy and social marketing; provision of clean needles to intravenous drug users; and screening of blood for transfusion. Unfortunately, most countries have been unable to fully fund even these basic preventive activities and are thus forced to choose among them. Chapter 4 discusses cost-effectiveness models for evaluation of screening of blood for transfusion and makes reference to the issues underlying voluntary confidential testing, a preventive strategy aimed at encouraging behavioral change. Additional efforts are urgently needed to develop methods for evaluating the effectiveness of the other "accepted" interventions.

Finally, as the pattern of the epidemic in the countries affected earliest shifts from one of rapid epidemic growth to one of a major endemic disease, then the relative importance of efforts to alleviate the impact of the epidemic will increase. Despite a plethora of hypotheses about how the loss of young adults to AIDS will affect the welfare of households, the economic viability of sectors of the economy, or the stability of communities, there has been inadequate attention to quantifying the relative importance of these hypothesized impacts. This quantification is especially important now that alleviation programs are being designed and implemented in areas that had high levels of poverty even before HIV/AIDS. If the goal of such alleviation programs is poverty alleviation, then they should target the neediest in a community, not necessarily those that joined the ranks of the poor most recently. At the same time, additional information about who in a community is most affected—and how they are affected—may permit the design of interventions that respond to problems specific to HIV/AIDS. For example, the orphaning of children can often be anticipated by many years. This may provide an opportunity to strengthen coping mechanisms to prevent dissolution of the household or impoverishment of the children—rather than just responding once it has occurred.