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The evidence base for interventions to prevent HIV infection in low and middle-income countries

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The views expressed are those of the authors, and not the CMH, the Working Group, or WHO.

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Summary

Over the last two decades, HIV has infected more than 50 million people worldwide and killed and more than 16 million people. Most infections have occurred and continue to occur in the developing countries. While care issues have attracted most attention, the overwhelming priority for countries is to prevent additional people from being infected. In this paper, we systematically review the evidence base for interventions that reduce sexual and non-sexual transmission.

We examine interventions by centrality to the HIV epidemic, their amenability to effect change, and their cost-effectiveness. Highly effective interventions that may reduce HIV incidence by up to 80% exist, including peer-based programs targeted to sex workers and high-risk heterosexual or homosexual men and management of sexually-transmitted infections. In addition, effective interventions to reduce transmission from injecting drug use, and from mother to child are also available.

While accelerating vaccine development, HIV/AIDS programming needs to give the highest priority to these interventions. However, these interventions have not been implemented with the scale and vigor necessary to have a sustained impact at national level in any developing country except Thailand. Spending on the implementation of interventions needs to increase by several multiples of its current level and more spending on intervention research is needed.

Control of the HIV epidemic is possible provided the highest impact prevention interventions are implemented on a much wider scale.

Section I. Introduction

Since its recognition in 1981, AIDS has devastated lives worldwide. UNAIDS estimates that over 50 million people have become infected with HIV, primarily in Africa and Asia, of whom 22 million have already died. In several sub-Saharan African countries the prevalence of HIV in the young adult population exceeds 20%, with the vast majority resulting from heterosexual transmission. Each day more than 15,000 new infections occur, 1,600 of them in children. Perhaps more ominous for the future of the hardest hit countries, AIDS affects more people than it infects. It impoverishes families as they try to meet the costs of care and funerals. It leaves behind orphans with a dim future. The epidemic is rolling back many of the hard-won development gains of the past 40 years in parts of Africa – life expectancy has declined by as much as 10 years in several sub-Saharan African countries - and is threatening to do so elsewhere. Yet the epidemic has not been homogenous. Half of the African population lives in countries where (as yet) less than 5% of the adult population is infected. In other parts of the world, seroprevalence is lower, often below 1% of the adult population. For all populations, prevention of new infections remains a key strategy to reduce the consequences of HIV/AIDS.

The global response to the HIV/AIDS epidemic has been complex. In spite of the grim picture described above, there have been many important achievements in the HIV/AIDS field. One of the main and largely unsung achievements of the past two decades is that we have developed effective prevention interventions. They can reduce HIV incidence and risky behaviors by up to 80% and can be applied *now*.

A lack of accurate information has and still does frustrate efforts to predict the ultimate size of the epidemic and to identify priority areas for intervention. For example, predictions have ranged from the extreme suggestion that HIV would die out as quickly as it arose (1), to

pessimistic scenarios such as projections for Mexico that suggested 260,000 cumulative AIDS cases by 2000 (2) that were about four-fold higher than UNAIDS estimates for 1997. Even careful early projections by the Global Program on AIDS (3) underestimated by over 50% the actual global prevalence of HIV/AIDS in 2000. The 1993 World Development Report's baseline scenario predicting 2.5 million new infections and 1.8 million AIDS deaths in 2000 turned out to be a drastic underestimate (4).

A major reason for the enormous error in estimates and projections has been the lack of systematic and reliable surveillance to estimate trends and levels of infection. India only achieved national coverage of most states with at least two rounds of sentinel surveillance in 1998. Using data from the UNAIDS website, we have calculated that 1988 was the median year in which countries in sub-Saharan Africa implemented at least two consecutive years of sentinel surveillance. Several still do not have data yearly. Moreover, data on AIDS and other causes of deaths are unavailable for most of sub-Saharan Africa. Finally, serial sentinel surveillance provides an accurate picture of HIV prevalence trends, but it can be unreliable at estimating HIV incidence, especially in high prevalence settings (5). To track incidence and risk behaviors, representative population cohort studies are required in at least a few places. These are central to information-based planning and evaluation. Yet, there are few such studies in developing countries.

Here, we consider the scientific evidence for effective interventions to reduce transmission of HIV accumulated over the last two decades and ask several key questions. What is the strength of the evidence of effectiveness of interventions? What were some of the key reasons for gaps in their implementation?

Our paper is organized as follows. Section II reviews the criteria for prioritizing interventions. Section III discusses the dominant type of HIV transmission worldwide- namely heterosexual transmission. Section IV discusses transmission between men who have sex with men. Section V describes transmission from HIV infected mother to newborn and infant children. Sections VI and VII address non-sexual transmission through injecting drug use and blood transfusion, respectively. For each type of transmission, we briefly describe the epidemiology and interventions to interrupt transmission, ranked broadly by effectiveness of the intervention. Clearly there is some overlap of interventions across transmission routes, such as voluntary counseling and testing. Section VIII briefly reviews the state of the art on HIV vaccines. Section IX discusses some of the key reasons for gaps in implementation. Finally, the last section provides options for the way forward.

Section II. Criteria for prioritizing preventive interventions

Although HIV causes AIDS, the causes of the epidemic are the behaviors and circumstances that lead to the transmission of HIV – chiefly commercial sex, unprotected sex with multiple partners, high levels of sexually transmitted infections, and injection drug use. Social and economic factors such as poverty, social disruption, marginalization, inequity of gender and race, and migrant labor practices foster some of these behaviors and underlie the epidemic (6). This has spawned the view that AIDS is a development issue that must be addressed through social and economic improvement (7).

AIDS is certainly a development issue. However, the developmental roots of the epidemic are not easily amenable to intervention in the short term. Sound macroeconomic policies, improved education for girls, labor force participation by women, and good governance reduce poverty, but take decades to have a sustained impact. With millions becoming infected annually, waiting for

poverty and inequality to end will do little to mitigate the growth of the epidemic. (8;9). High impact interventions that interrupt HIV transmission need to be implemented now (10). Several key elements in the chain of transmission of HIV have proven to be amenable to intervention. Such interventions interrupt transmission relatively rapidly.

Over the past 15 years there has been a substantial effort to identify ways of altering behavior or reducing susceptibility to HIV. Despite sometimes less than rigorous scientific methods (11), consistent patterns in what works and what does not work are becoming clear. This body of work has shown HIV transmission can be reduced by as much as 80%. Thailand's experience shows that it is possible to do so at a country level. However, these interventions have not been implemented with adequate scale and vigor. There are many reasons for this, perhaps the overriding one being that the competing needs of the HIV and AIDS epidemics make prioritization difficult. Given the range of interventions, how does a program prioritize? We suggest the following public health criteria for prioritizing preventive interventions, in order of importance: centrality to the epidemic, amenability to change, and cost-effectiveness. While these criteria are most relevant to heterosexual transmission, they are also applicable to other modes of transmission.

- **Centrality to the epidemic**. The behavior or factor addressed should be an important cause of HIV spread. For sexual HIV spread, unprotected sex with multiple partners is clearly the most important factor in promoting transmission. Yet how sexual behavior drives HIV transmission is often misunderstood. In a population, sexual behavior is very heterogeneous. Most individuals have few sex partners, while a few have many. Evidence from Nairobi, for example, shows that most individuals report a few sex partners, whereas a few report substantially higher numbers of sex partners (12) (see figure 1). This is key to the spread of

sexually transmitted infections (STI). The concept of the high frequency transmitter core group has been applied to STIs for the last 25 years (13) and is discussed more below. In this paper we use the term vulnerable groups when referring to core groups and groups at high-risk of acquiring or transmitting HIV.

- **Amenability to change.** The second criterion relates to the feasibility of success of the intervention in accessible populations. Some factors may be very important to the epidemic but difficult to alter. To reduce sexual HIV transmission, for example, it is usually simpler and more acceptable to make sexual contacts safer than it is to avoid them in the first place. Similarly, it is considerably more difficult to ensure regular condom use among stable partners than among casual ones (14). In many countries, the dependence of a given intervention on a well-functioning peripheral health delivery system may limit the ability to implement it.

- **Cost-effectiveness**. Many HIV prevention interventions are orders of magnitude less expensive than the cost of caring for persons with AIDS – they are cost beneficial. Typically, one HIV infection prevented saves 20 disability-adjusted life years (DALYs), while in contrast, preventing one HIV infected person from developing AIDS results in one year of life saved (15). However there is tremendous variability in their relative cost-effectiveness-- the cost to prevent one HIV infection. Relative cost-effectiveness analysis is helpful for governments and other funders of HIV/AIDS control programs in choosing the interventions that prevent the largest number of infections per dollar spent. Besides costs, criteria such as the number needed to be reached by an intervention to prevent one HIV infection (which we term the intervention efficacy ratio) can be used to prioritize interventions. However, while there has been a marked increase recently in cost-

effectiveness studies for HIV prevention, most of the evidence comes from industrialized countries. In addition, the complexities of an epidemic may make it hard to assess cost-effectiveness with great precision, as many effects accrue over a prolonged time span. Mathematical modeling may provide additional insights into costs and effects (16-18). In this paper all cost figures presented are in US dollars ($).

Section III. Interrupting heterosexual transmission

Heterosexual transmission accounts for more than 70 percent of all HIV infections worldwide, and is the primary mode of transmission in several regions, including sub-Saharan Africa, south and southeast Asia, the Caribbean, and North Africa and the Middle East (19;20).

It is worthwhile to briefly review the sexual transmission of HIV and other STIs (21;22). In order for an epidemic to occur, each infected individual must on average make infectious contacts with more than one individual—an infectious contact is a contact that would result in transmission if his/her partner would be uninfected. A R_0 greater than one implies a growing number of infections. R_0 (the basic reproductive rate) is the product of three factors: transmissibility (β), rate of partner change (C), and duration of infection (D). R_0 must be reduced in order to lower the prevalence of the infection, and brought below 1 to eliminate it from a population. Thus, interventions can be directed at any of these three parameters. Interventions directed at β enhance resistance to infection or decrease susceptibility. Barrier methods such as condoms, treatment of co-existent STIs, use of antiretrovirals to decrease transmission, circumcision and HIV vaccines would reduce β. Interventions directed at C aim to alter sexual behavior, including decreasing the rate of partner change, increasing the age of initiation of sexual activity, or decreasing high risk behavior. Interventions directed at D aim to

reduce period of infectivity, such as through use of antimicrobials and antiretrovirals, or via contact tracing or partner notification (23).

HIV transmission is a biological event. Transmission depends on the infectiousness of the individual who is the index case and the susceptibility of the subsequent individuals exposed. (24;25) The rate of transmission is dependent on viral load. In Rakai, Uganda, an assessment of HIV-1 serum viral load on the rate of transmission per act of heterosexual intercourse was examined retrospectively among 174 HIV-discordant couples. When viral load was less than 3500 copies/ml, transmission was estimated at 0.9 per 1000 episodes of intercourse, and increased linearly to 2.98 per 1000 when the serum viral load was at or above 50,000 copies/ml (26;27). Differences in viral load have been noted between serum and semen (28;29). Actual concentration of HIV in the genital tract, may in fact be the most important determinant of transmission (30).

For HIV, the contribution of each individual to the value of R_0 is not proportional to his/her number of (unprotected) sex partners but to the *approximate square* of that number (31). For example, a man with a concurrent number partners is a more efficient transmitter than a man with serial partners even thought the number of lifetime partners remains the same. In no national population yet studied, including in Africa, is the *mean* rate of C in the *general* population high enough to keep R_0 at 1 or higher (i.e. C=1/BD). However, C can be high enough in vulnerable groups to increase the epidemic above a R_0 of 1. Vulnerable groups are therefore key in the chain of infection and important candidates for targeted interventions (32).

Centrality of vulnerable groups also implies relative efficiency. "Upstream" interventions (see definitions in next section) are substantially more efficient than "downstream" interventions.

Ensuring condom use by one core group member with 1000 sex partners per year is more than 1000 times as efficient as ensuring condom use by someone who has one sexual partner. The number of individuals that an intervention needs to affect to prevent one infection, "the intervention efficiency ratio", quantifies the concept of centrality.

Over the last decade or so, research has focused on two new areas: sexual networks and phase-specific epidemics. The knowledge base is nascent and based mostly in developed countries. Sexual network structures, the mixing patterns between different risk populations, are believed to be largely pre-existing "social" structures. There are crucial determinants of spread of STIs (33). Overlaying such networks, Wasserheit and Aral have defined four stages through which STI epidemics evolve—growth, hyperendemic, decline, and endemic—with each stage corresponding to a stage of evolution of sexual networks, vulnerable populations and control programs (34). High levels of mixing within vulnerable populations fuel the rapid spread of the epidemic within the group. A study in Seattle, Washington, for example, noted that mixing patterns among heterosexuals across race/ethnicity, age, and educational categories were significantly associated with risk of infection with gonorrhea and chlamydia (35). Bridge populations allow for the spread of the epidemic from core populations to low-risk groups. Overall growth depends on mixing between vulnerable and lower-risk populations. A study of sexual networks in Cambodia identified several factors associated with being likely to be a "bridge" among men who had unprotected sex with high and low risk partners. These included younger age at sexual debut, peer influences, geographic residence, and past history of STIs (36).

Wasserheit and Aral's phases were tested empirically by Blanchard et al in their study of geographic patterns of gonorrhea and chlamydia over time in sub-areas of Winnipeg, Canada. Blanchard found that both appeared to be moving through different stages of the epidemic, with

chlamydia, in an earlier phase, becoming more dependent on vulnerable groups, and gonorrhea transmission, in a later phase, to be more sporadic (32). In addition, analysis of sexual network structure of community-wide chlamydia over a 4 year period in Colorado Springs, USA, showed that it was a potentially faster and more reliable way to determine STI epidemic phase, which can be used to design better interventions. (33). More applications of network structures are required in developing country settings.

There is a belief that a focus on vulnerable groups only applies to early stages of the epidemic and is no longer true in a "mature" epidemic, when much transmission occurs outside vulnerable groups. For example, some have cited the forthcoming four-city study in Africa (37) to question the relevance of vulnerable groups to the African epidemic. The study is a ecological comparison of about 2000 adults in four areas: two areas with lower HIV prevalence in West Africa (Cotonou, Benin, averaging 3% and Yaoundé, Cameroon, averaging 4%), and two in Central/East Africa with generalized epidemics (Kisumu, Kenya, averaging 25% and Ndola, Zambia, averaging 27%). The study finds that differences in the rate of partner change, concurrent sexual partners, use of sex workers or overall condom use did not explain the ecological variation. The only behavioral variables that explained the differences between high and low prevalence settings were the age at which girls became sexually active, and the age at which men and women first married. The study also found higher rates of ulcerative STIs and lower rates of circumcision to explain the variation.

This study, while useful, has fundamental flaws. First, ecological studies are useful at showing differences across populations, but are poor at explaining these differences. Given the study had only *four* comparison units, its power to detect differences would be low. Ecological studies

suffer numerous other problems of inference of their results (38). Complicating matters, the comparisons of sexual behavior do not take into account that sexual behavior is not normally distributed (Figure 1 from Kenya, one of the high prevalence settings, demonstrates such variation). Second, the study did not report the differences *between HIV positive and HIV negative individuals*. Studies of individuals are far more informative to understand the chain of transmission (i.e., if the infected individuals were one, two or several contacts away from a putatively infected vulnerable group individual, and what co-factors of transmission, such as STIs, might be). Even if the study chose to do so *post-hoc*, it has too small a sample size to be reliable- only about 60 to 80 HIV positive cases would be available for analyses in the each of two low-prevalence areas. The ecologic finding of higher rates of ulcerative STIs and lower rates of circumcision itself supports underlying sexual transmission. Thus, the study does not definitively refute the importance of vulnerable groups in high prevalence settings. Further epidemiological studies focusing on individual differences are required to confirm the suggestion that vulnerable groups are not central to generalized HIV epidemics. Its worth noting that the totality of the mathematical and conceptual work noted above suggests that "memory" of the epidemic is of limited duration and in the long run, the major determinant of the epidemic is sexual behavior.

III. 1. Interrupting heterosexual HIV transmission: interventions with strong evidence of effectiveness

Effective interventions to interrupt heterosexual transmission include peer-group interventions among sex workers and interventions for high-risk heterosexual males.

a) Peer Group Interventions Among Sex Workers

In countries with high rates of HIV infection, women in sex work are at enormous risk of acquiring and transmitting HIV, and unsafe sex for money has fueled the HIV epidemic in many developing countries. Sex workers rapidly become HIV infected and transmit infection to their clients, who in turn transmit HIV to their other female sex partners, and who in turn transmit to their children. Each infection prevented "upstream" among female sex workers prevents all "downstream" ones, except in situations where the transmission risk is high from other risk behaviors. The centrality of unprotected sex within vulnerable populations is perhaps best illustrated by the observation that major heterosexual HIV epidemics *only* occur in societies where unprotected commercial sex is common. The first effective prevention intervention to be described in this context (39), and the one with the highest impact, is peer education programs directed at safer sexual behavior among women in prostitution.

Peer education programs typically use well-trained peers such as former sex workers to disseminate information and safer sex supplies, conduct skills building sessions, and provide referrals. Around the world, it has been possible through peer programs to increase condom use by sex workers to high levels, maintain high levels of condom use over long periods, reduce the incidence of HIV and other STIs among sex workers and prevent further spread of infections (Figure 2) (40-43). One intervention project among 2000 sex workers in the Pumwani area of Nairobi has been estimated to prevent some 6,000-10,000 infections annually (44). Thailand acted upon this insight with national-scale multiple interventions of which the key was a 100% condom program for sex workers and their clients; a significant decline in HIV incidence resulted (45) and HIV-1 prevalence has stabilized at approximately 2% of the adult population. Cambodia has begun to replicate the 100% condom program and preliminary reports suggest

increases in condom use and decreases in HIV incidence between 1997 and 2000 (46). India has adopted this approach as a central element in its new national AIDS control strategy. Sex worker interventions are typically low-technology and are relatively replicable in the presence of NGO capacity (see Box 1). They can work in the absence of peripheral health delivery capacity, although referral and treatment of STIs do require such capacity. The intervention ratio, effect size and cost effectiveness of this type of intervention are compared to others in Table 1.While the efficacy of these programs has long been understood, they have only been implemented at a national scale in Thailand. Contrary to some beliefs, peer-mediated education programs generally reduce the stigmatization associated with the sex trade, spark community development, and also contribute to the control of other STIs (41). Another fallacy is that these interventions promote prostitution. In Nairobi, for example, the number of women in the community reporting sex work declined during implementation of sex worker peer group interventions (12).

Box 1: Interventions Targeting Commercial Sex Workers

Commercial sex work takes place in many parts of the world. Commercial sex workers (CSWs) may work in more formal settings such as brothels, massage parlors, and bars, as well as in less formalised settings, such as homes, truck stops, restaurants, and the streets. High levels of vulnerability to HIV infection, coupled by the opportunity to have large downstream impacts on HIV transmission, have spurred efforts to prevent HIV infection among this population.

Successful prevention programs have been developed in several parts of the world, including Calcutta and Tamil Nadu (India), Nairobi (Kenya), and Thailand that have focused on reducing HIV risk among CSWs. While no two programs are alike, they do have certain components in common: the use of peer educators in the dissemination of information, condom distribution, the development of condom negotiation skills, and referrals for additional needed services.

Peer education efforts involve the recruitment and training or individual CSWs, either currently active or retired, to bring about individual level changes in knowledge, attitudes, beliefs and/or behaviors among members of their cohort. Because they are members of the community that they serve, are acquainted with the particular issues facing the women and generally have the trust of the individuals being targeted by the intervention; they can therefore more successfully access and engage CSWs in HIV prevention efforts than other health providers. Peer educators are also perceived as being role models, and as such as having greater influence in changing community norms. The definition of a peer varies across projects to include other key gatekeepers or stakeholders, such as brothel madams, pimps, bar owners, and security personnel (246). Peer-based efforts are often linked to other efforts for HIV prevention, including STI management, volunteer counseling and testing, primary health care services, as well as additional services including education, vocational training, legal assistance, and advocacy.

Peer-based CSW interventions have been successful in both developing and developed country settings, in urban and rural areas, and across countries with the full spectrum of legal status for commercial sex work. Examples of successful programmes include work in Nairobi, Kenya (247), the Sonagachi Project in Calcutta, India, outreach efforts in Tamil Nadu, India, and the 100% condom programme in Thailand (61; 247- 249). Peer-based CSW interventions are often coupled with peer education efforts with CSW clients through outreach or work-based strategies. These efforts can enhance the impact of CSW programs but are not necessary for their success. CSW programs, properly implemented, by themselves can have a significant impact on HIV transmission.

The challenges to developing and sustaining peer-based CSW interventions are several (246). The often illicit nature of commercial work means that the numbers of people, their location, and their needs are unknown. Community mapping, participatory processes, training and support, and building trust with these traditionally marginalised communities are crucial components in the successful implementation of these interventions. Pre-existing working relationships between NGOs, community leaders and political leaders, either local or national, are important to facilitate access and delivery of interventions; without them, efforts can become highly constrained and ineffective. Support and incentive structures must also be in place to assist peer educators while at the same time not removing them from their place within their cohort. However, the success of existing programmes demonstrate the feasibility of their implementation, despite the challenges.

b*) Interventions Among Males With High-Risk Heterosexual Behavior*

High-risk male behavior, notably having unprotected sex with a sex worker, is also central to the heterosexual spread of HIV. Intervening among high-risk men is more complicated than intervening among sex workers. High-risk men are not as readily identifiable as are high-risk women. Many men in occupations involving long absences from steady partners (truck drivers, miners, plantation workers, the police and military) practice unsafe sex with multiple partners, but not all of them do. This reduces the efficiency of any interventions. These men are often amenable to interventions (47-49) through the workplace, although the effect size may be modest. One effective strategy for intervention has been through workplace peer education. A randomized trial of this type of intervention in Zimbabwe found a 30% reduction in HIV-1 incidence (49).

Unfortunately, many high-risk men do not belong to readily identifiable groups. Alternate strategies, therefore, need to be used to reach males involved in high-risk heterosexual behaviors. A recent randomized trial in an urban setting in Latin America targeted motels with condom and information programs for both commercial and non-commercial sex (50). It showed 30% to 50% increases in condom use in commercial and non-commercial sex contacts when condoms where placed in the motel rooms. While directly handing condoms to couples was similarly effective for commercial sex, it was less effective for non-commercial sex; surprisingly, the presence of health education materials reduced the frequency of condom use.

Approaching sex workers to make sex worker-client contacts safer is often more efficient than approaching their clients, as there are many fewer of them. For sex workers in the Pumwani cohort in Nairobi, two orders of magnitude more men would need to be reached and their

behavior affected if the intervention were to target men rather than women. This is less efficient and more costly, even if it were to have an equivalent effect on behavior (Table 1).

III. 2. Interrupting heterosexual HIV transmission: interventions with some evidence of effectiveness

Possibly effective interventions to interrupt heterosexual transmission include management of STIs, voluntary counseling and testing and male circumcision.

a) Improved Management Of Bacterial Sexually Transmitted Infections

Piot and colleagues first hypothesized that conventional STIs were a risk factor explaining the high frequency of heterosexual transmission of HIV in Africa in 1984 (51). Since then, the presence of an STI has been shown to increase susceptibility to HIV infection, perhaps by disrupting mucosal surfaces or modulating mucosal immunity (52;53). STIs also increase HIV shedding in the genital tract, thereby increasing the infectivity of an infected person (54-56). These considerations prompted the landmark randomized community trial in Mwanza, Tanzania, which showed that providing simple STI management to the general population could reduce HIV incidence by 38% (95% CI 15-55%) ; absolute risk was 1.9% in the control group versus 1.2% in the intervention group (57). Another randomized community trial, conducted in Rakai, Uganda, based on periodic mass STI treatment of adults, failed to reduce HIV incidence (58). Neither study appeared to have a substantial impact on STI prevalence, sparking much debate about their interpretation. However, more recent and longer term follow-up of the Mwanza study does suggest a reduction in STIs (59). In addition, observational studies have clearly demonstrated the presence of STIs to be a risk for HIV infection. Thus, while STIs definitely contribute to the spread of HIV, the best strategies for controlling them, particularly in generalized epidemics, still need further study. Since having an STI is a marker for risky

behavior, STI patients are an important target for interventions. While this is widely recognized and has proven to be successful (60), few systematic studies have been conducted. STI interventions among sex workers have also been shown to contribute significantly to HIV control (61-64).

In view of the debates surrounding these interventions, assessing cost-effectiveness of STI control is difficult. For improved case-management we only have the Mwanza study, which suggests favorable cost-effectiveness (Table 1) (65).

b) Voluntary Counseling and Testing

There is growing enthusiasm for voluntary counseling and testing (VCT) as an HIV prevention strategy to be used across different populations. VCT has been discussed as a gateway to the provision of other interventions, including prevention of mother-to-child-transmission and administration of antiretrovirals. Thus, its benefits as a prevention measure by itself are hard to measure.

The direct effect of VCT alone on HIV risk behaviors remains uncertain despite several studies, including some randomized trials (66;67). The most consistent behavioral change effects have been observed among HIV discordant couples (68-71). A randomized control trial of 5758 individuals presenting at STI clinics in the United States examined the impact of enhanced counseling versus didactic messages typical of current care. At twelve month follow-up, 20% fewer new STIs were observed among individuals receiving counseling as compared to the didactic control group (72). In the didactic control arm 211 participants had developed new STIs, as compared to 165 of those receiving enhanced counseling and 173 receiving brief counseling; differences versus the control group were all statistically significant. There are fewer

studies of the efficacy of VCT in developing countries (73-76), where there are many impediments to their implementation (77). One randomized multicenter trial of VCT showed a decrease in risky sexual behaviors at six months and one year following counseling (14). The main effect overall effect was decreased unprotected sex with non-primary partners, and in some sub-groups there was no effect on non-regular partner sexual contacts. There was no overall effect on the incidence of STIs. It is unclear how sustainable the behavioral changes were, as long-term follow-up was not reported. Cost per healthy year of life gained ranged from $346 in Tanzania to $249 in Kenya (78); however, the transmission rate used in modeling the effect size was very high (67), which would significantly underestimate the costs per infection prevented. It is also unclear who would seek counseling and testing, as high-risk individuals might avoid such services (79). Even if effective, it is likely that this type of intervention only becomes relatively efficient and cost-effective at higher HIV prevalence.

b) Male Circumcision

A wealth of evidence has accumulated indicating that uncircumcised men are at higher risk of HIV infection (80). This association is likely causal. Male circumcision could significantly reduce HIV susceptibility of men permanently, assuming that there is no effect of circumcision on increasing risky sexual behavior. In a recent cohort study among male partners of HIV infected women in Uganda, none of the 50 circumcised male partners seroconverted during 106 person-years of follow-up compared to 40 seroconversions among 137 uncircumcised men during 239 person-years of follow-up (81). Given the epidemiology, there is renewed interest in performing intervention trials. One such trial is being planned in South Africa, introducing male circumcision in a region where it is not traditionally practiced (82). A larger trial in Kenya is being planned that will randomize 2800 males to either early or delayed circumcision (83).

III. 3. Interrupting heterosexual HIV transmission: Interventions with limited evidence of effectiveness

Interventions with limited evidence of effectiveness in interrupting heterosexual transmission include microbicides, mass media education, education programs for youth, use of highly-active antiretrovirals to disrupt general population transmission and reducing the supply of sex workers.

a) Microbicides

There is a critical need for female controlled-methods of protection against HIV and other STIs. Vaginal microbicides have been suggested, along with female condoms, as potentially feasible alternatives. Vaginal microbicides would need to respond to a range of STIs, allow reproductive capacity, be limited in their toxicity, and be acceptable for sexual behavior (30).

The only microbicide currently in widespread use in nonoxynol-9 (N-9), a detergent. It's effectiveness in HIV and STI control has been examined in several randomized control trials (54;84-87). While one study showed that N-9 might slightly reduce the risk of gonorrhea and chlamydia transmission (84), recent results of a large four-year, four-country randomized control study indicate that N-9 appears to increase HIV acquisition, perhaps as a result of increased vaginal inflammation resulting from frequent use (87). Other products being tested as potential microbicides include other detergents, polymers designed to block HIV attachment, compounds expected to change the pH of vaginal fluids, and suppositories aimed at increasing lactobacilli in the vaginal area, in the belief that the bacteria contribute to resistance of other STIs (30).

b) Mass Media Education

A hard lesson of the first two decades of AIDS prevention programming is that while information, education and communication approaches are highly effective *in increasing*

knowledge of HIV/AIDS and creating an environment conducive to other interventions, they have by themselves little effect on behavior. Studies from several industrialized countries have shown improvements in levels of HIV-related knowledge following mass media campaigns, but little effect on behavior (88-92). Even where behavioral change follows a mass media intervention program, the impact may be short-lived (93). There are very few studies of the effects of mass media campaigns in developing countries. It has been observed in India that the mass media are an important source of knowledge regarding HIV, but that this knowledge is inadequate and contains misconceptions (94). Thus, mass media can be used effectively to disseminate knowledge about HIV and create an environment that is permissive for more focused interventions, but is unlikely to have much direct impact on behavior by itself.

c) School-Based Programs For Youth

As high incidence rates of HIV infection are frequently observed among young people in developing countries (95), protecting youth is a goal of all HIV prevention programming. Age differentials between male and female sex partners are used to justify the need to target youth. There is, however, little evidence that general school-based interventions for youth reduce HIV or STI incidence. Studies which have examined impact of such interventions, chiefly those focused on curriculum changes, or school-based information campaigns, for the most part have found that, while knowledge often improves, there is little evidence for sustained adoption of safer sexual behaviors (96-101). The mean age of initiating sexual intercourse may fall somewhat (102), but this will have little effect on the progression of the HIV epidemic. Some programs, however, have shown some evidence of positive behavioral change (103), often in the context of peer education approaches vulnerable youth (104). A recent randomized HIV risk reduction intervention among Namibian adolescents in schools indicated again that knowledge

improved considerably, but a modest change in behavior was observed only among youth who were sexually inexperienced at baseline; it is not clear whether the effect was sustained (105). While it is clearly necessary to provide youth with accurate information on protecting themselves against HIV, particularly in areas with high HIV prevalence, general youth education programs alone have limited impact on behavior. More focused programs that use more peer education are less well tested, but an ongoing randomized trial in Tanzania should provide more useful data. The new trial will evaluate primary school-based health education with a peer education component, youth-friendly sexual health services, and community mobilization. Twenty rural communities have been randomized into either the set of interventions or routine school lessons; all will receive syndromic management for STIs as well as family planning services (106).

c) Population Impacts Of Transmission From Highly Active Anti-Retroviral Therapy

The advent of highly effective anti-retroviral therapy (HAART) has been a major advance in the therapy of HIV infection and AIDS (see related CMH papers on AIDS care and the impact of prevention and HAART interventions). HAART prolongs and improves life but is not curative. The effect of using treatment as a prevention strategy is uncertain. Most studies have suggested that HAART reduces viral load (81) and therefore probably transmissibility. However, as mentioned earlier, some studies show differences between serum and semen HIV viral load (28; 29). The currently recommended "late" entry into HAART –namely beginning treatment when AIDS symptoms appear-- might not materially reduce transmission, as viral load is highest early in HIV infection and drops over time. It may in fact take people who were out of the transmission pool and put them back in, albeit at lower infectivity.

Risky behavior appears to be increasing among men who have sex with men in some North American cities (107-109), perhaps because of the availability of HAART. The US-based

Young Men's Health Study found high rates of HIV infection among young men who have sex with men (110). There are also recent reports of increasing rates of HIV and STI among men who have sex with men in San Francisco and Ontario, Canada, areas that had declining or stabilized epidemics for many years (107;111). Mathematical modeling of HAART coverage among gay men in San Francisco suggests that even a 10% increase in risky behavior would negate the transmission benefits 50-90% coverage levels of the population with HAART (112). In Nairobi, 100% condom use among commercial sex workers decreased and HIV incidence increased on two separate occasions when "quack cures" received wide media coverage (12) (See Figure 4). It is worth noting that actual coverage with HAART does not exceed 30% in most western communities.

Despite these caveats, HAART as a prevention strategy cannot be ruled out in the future. Using HAART early in infection to boost immune response, possibly along with a low efficacy vaccine, is possible. Some mathematical models have suggested that targeting HAART to vulnerable groups might be highly effective in reducing overall transmission (113, see also the related CMH paper on the impact of prevention and HAART).

d) Reducing The Supply Of Sex Workers As An HIV Prevention Measure

Some have proposed programs to reduce the supply of sex workers as a strategy to reduce HIV transmission(114). Several such programs have been carried out in Thailand (115), but they have not achieved their objective. As long as there is demand for paid sex, preventing entry of one person into sex work will often result in substitution by another. In contrast, interventions that raise the legal costs of exploitation of child sex workers or rape, and enforcement of legal sanctions, may be effective (116) by raising costs for all parties and reducing the possibility of substitution. Cross sectional studies also suggest that high urban male-to-female ratios may

predict HIV susceptibility; thus, interventions that lower the urban male-to-female ratio, such as increased job opportunities for women in urban areas, could decrease HIV infection rates (117). Overall, attempts to reduce supply are unlikely to be effective, and would certainly be very costly to implement on a wide scale.

Section IV. Men who have sex with men (MSM)

While much of the HIV transmission in industrialized countries is between men who have sex with men (MSM), infections in this group is estimated to contribute only 5-10% to the global HIV pandemic (118). The prevalence of HIV in MSM varies geographically. Significant rates of homosexual transmission have been reported in several low and middle income countries, predominantly in South East Asia and Latin America. UNAIDS estimates that 48% of HIV infections in Latin America and the Caribbean are among MSM (119) and several Asian countries such as Thailand (10%) (120), Indonesia (32%) (121), and Taiwan (34%) (122) have also measured significant rates.

In many developing regions, the initial detection of HIV was in the homosexual population, but over time on the proportion of HIV positive MSM decreased as heterosexual and injection drug use transmission began to rise (118; 123-126). This was especially evident in Eastern Europe as HIV rapidly spread among the injecting drug using population (127).

Preventing homosexual and bisexual transmission is important to reducing the overall epidemic even in countries with relatively low HIV prevalence (128). A study in India estimated that 29% of the male prisoners had engaged in sex with other men. Most of these men also reported having sex with women (129). In assessing the sexual practices of military personnel in northern Thailand, one study found that 16% of the sexually active soldiers had reported having had anal

or oral sex with other males (130). Significantly, all of these men also reported having vaginal intercourse with females. Other men who are at high risk include men and boys who live in economically depressed areas where sex tourism is carried out (121). MSMs can therefore serve as bridges between vulnerable groups and general populations.

MSM may or may not identify themselves or their sexual practices as homosexual, making targeting of interventions to them difficult. Additionally, cultural taboos and denial of the existence of such behaviors may add to the complexity of reaching this group of men. Authorities often reject the possibility that sex between men occurs in their communities. Furthermore, in some regions, male homosexuality may be considered criminal activity; MSM in countries such as Malaysia, India and many African countries are breaking the law (118). Although the laws are not always enforced, some countries, such as Yemen, respond to sodomy law-breakers with a death penalty. This complicates efforts to identify MSM and engage them in HIV prevention programs.

The highest risk for sexual transmission of HIV occurs during unprotected, receptive anal sex (131-134). A recent study from the US estimated that the risk of acquiring HIV from unprotected, receptive anal sex intercourse was 0.82 % per-contact when the partner was known to be HIV positive (135). The virus is able to gain access to the bloodstream efficiently through minute tears in the thin rectal mucosa. The presence of STIs can increase the risk of becoming infected with HIV (136-140).

IV. 1. Interrupting MSM HIV transmission: interventions with some evidence of effectiveness

Interventions with some evidence of effectiveness to interrupt MSM-based transmission include peer outreach. Interventions with limited evidence include STI treatment, and mass media campaigns. More research on VCT and circumcision among MSM is required.

a) Peer Outreach

Although little has been written on HIV prevention interventions for MSM in developing countries, they are likely to be similar to those that are directed at the heterosexual population. Peer led prevention programs for MSM have been found to be initially effective at reducing high-risk behavior in the US (141; 142). Peer interventions include outreach activities as well as those that bring men together in informal and familiar places to discuss safe sex issues. A review by Choi and Coates in 1994 of formally evaluated intervention programs found increases in condom use (range 55-80%) and decreases in unprotected anal sex among participants of small group interventions, whether single or multiple session in format (143). Separate studies by Kelly and Kegeles of peer outreach among MSM in the United States found reductions in the mean frequency of unprotected anal sex during the previous 2 months (1.68 at baseline, 0.59 at follow-up, p=0.04), reductions in the proportion of men engaging in any unprotected anal intercourse (from 41% to 30%), and increases in the mean percentage of occasions of anal intercourse protected by condoms (44.7% to 66.8%, p=0.02) (141;142). Sustained peer education programs for male sex workers and other high frequency transmitters such as prisoners or men in the military would likely be effective in developing countries.

Programs that provide condoms, lubricants and information in places where high-risk homosexual sex is likely to take place (bars, brothels, prisons etc) could be a strategic use of

resources. Family Health International studies evaluating the effectiveness of condom social marketing projects with MSM measured an increase in reported condom use during last sexual intercourse in Jamaica (from 51% at baseline to 78%) and in Brazil (from 21% to 76%) (144).

IV. 2. Interrupting MSM HIV transmission: interventions with limited evidence of effectiveness

a) STI Treatment

Studies from industrialized countries show a correlation between a history of an STI and HIV infection, suggesting that STI treatment for MSM might be effective at reducing HIV transmission (137; 145; 146). Health service providers would need to be trained to examine for, recognize and treat anal and rectal STIs. Counseling and testing must be held in appropriate venues to reach areas with high prevalence of HIV in MSM.

b) Mass Media Programs

As with the heterosexual population, mass media programs alone for HIV prevention in MSM are likely to be an ineffective use of resources. A study in the UK found that although 80% of MSM remembered being exposed to an HIV prevention media campaign, less than 13% could correctly relay the message (147). Other studies show increases in knowledge and awareness of HIV/AIDS, but do not assess changes in behavior.

Section V. Mother-to-child transmission

UNAIDS estimates that in 1998 nearly 600,000 children acquired HIV infection from their mothers. Worldwide, WHO estimates that there were about 470,000 HIV deaths annually among children under age 5, or about 4% of all under-5 deaths (148). HIV transmission rates from untreated breastfeeding HIV-infected mothers to their newborns range from 25% to 48% (149-

151). Up to half of these infections are believed to be due to breastfeeding, the rest to intrauterine and intrapartum transmission (152).

V. 1. (i) Interrupting Mother-to-child HIV transmission: interventions with strong evidence of effectiveness

Intervention trials have shown that it is possible to prevent a significant proportion of mother-to-child transmission through use of antiretrovirals to disrupt transmission or replacement feeding.

a) Antiretrovirals (ARV)

Several studies have demonstrated that short courses of zidovudine (AZT) or nevirapine during pregnancy, sometimes in combination with other antiretrovirals, reduce transmission from 37-50% in low-income countries (151). Economic analyses have found that interruption of mother-to-child transmission is cost-effective (153;154), with costs well below $100 per healthy life year gained (Table 2). However, the number of mothers that the intervention needs to affect to prevent one infant HIV infection varies with the type of intervention, efficacy of intervention, and duration of breastfeeding. The number of women in the population who would need to be screened in order to identify one HIV infected women is dependent on the population HIV prevalence. This in turn affects the cost-effectiveness of these interventions (Table 2 and Figure 3).

While these interventions are undoubtedly effective, health systems capable of delivering them are lacking in many high-prevalence countries (151). All currently effective means of prevention of infant HIV infection require identification of HIV during pregnancy. Thus, VCT for HIV during pregnancy is one bottleneck in implementation of these interventions. While antenatal testing offers a unique point for intervention and identification of individuals who may otherwise

not seek testing, it presents several issues that are distinct from VCT in settings where clients perceive themselves to be at some risk for HIV. This includes issues such as partner involvement and notification, maintenance of confidentiality in a high volume obstetric setting, and dissemination of several complex messages regarding mother-to-child transmission of HIV prior to delivery, in addition to disclosure of results to women who perceive their risk for HIV to be minimal.

To avoid the complexity of antenatal VCT, it has been suggested that nevirapine be given without HIV testing to all pregnant women in high-prevalence settings (155). This approach bypasses the difficulties of VCT and may be the most expeditious way to rapidly decrease infant HIV in high prevalence settings. It certainly requires early evaluation. Evaluation would also need to address concerns such as that the danger that nevirapine would be perceived as a potential cure for HIV, or that mass treatment may lead to widespread viral resistance to nevirapine, rendering a whole class of highly effective treatment drugs unavailable. Additionally, such a system, in not identifying HIV infected women as part of its provision, would miss an important opportunity to counsel HIV infected women appropriately for decision-making about subsequent pregnancies or to counsel them on shortening or cessation of breastfeeding.

b) Replacement Feeding

Perhaps the most challenging aspect of prevention of infant HIV in high prevalence areas has been to identify feasible methods to decrease breastmilk transmission of HIV. Breastmilk transmission of HIV contributes to 30-50% of infant infections among breastfeeding infants of HIV infected mothers (152). Complicating the issue, breastfeeding may also have adverse effects on maternal mortality (156). Although there is not 'rebound' increased viral load in

mothers who have received short-course antiretrovirals, there is persistent breastmilk HIV transmission over the duration of lactation. Thus, breastfeeding does not eliminate the benefit of peripartum antiretrovirals but the overall efficacy of short-course antiretrovirals is substantially lower among breastfeeding mothers (~25%) than among non-breastfeeding mothers (~50%) (157;158).

The majority of breastmilk HIV transmission appears to occur in the early postpartum period (152). Although the two regimens have not been compared in a single study, the HIVNET 012 regimen appears to have more sustained efficacy for prevention of late transmission (39%) than short-course zidovudine (27%) in breastfeeding populations (159;160). This may be because nevirapine more effectively reduces maternal breastmilk HIV or provides better infant prophylaxis during the first week postpartum, a critical time for transmission, or because nevirapine results in production of a more effective infant immune response that protects against recurrent breastmilk HIV exposure. Cofactors for breastmilk HIV transmission include maternal HIV RNA load, primary HIV infection, maternal immunosuppression, mastitis, and breast abscess (161-163). One study has suggested that early introduction of weaning foods may increase breastmilk HIV transmission and this has been the basis for increased promotion of exclusive breastfeeding among HIV infected women who choose to breastfeed (164).

The most effective way to prevent breastmilk HIV transmission is to recommend that HIV infected mothers not breastfeed their infants. A randomized trial in Kenya demonstrated that the use of replacement feedings prevented 44% of mother-to-child HIV transmission, and led to a 21% higher rate of HIV-free child survival at 2 years (152).

Several authors have expressed concern that the benefits of breastfeeding, which protects against mortality from respiratory disease and diarrhea, may outweigh the risks of HIV transmission (149;165). Replacement feeding may be difficult to implement in areas with poor sanitation, limited access to breastmilk substitutes, unsafe water supply or high prevalence of childhood infections, where there is concern regarding the competing mortality risk of formula feeding. In urban centers of sub-Saharan Africa, replacement feeding has been implemented with evidence of efficacy in prevention of HIV without competing mortality risk, and such a model is being evaluated in operations research for feasibility and large-scale implementation in several pilot sites in the region (152;166;167) Outcome measures including infant mortality, community breastfeeding practices, and stigmatization are being evaluated in these feasibility studies. Among women who choose to breastfeed, promotion of good breastfeeding practice, exclusive breastfeeding, and avoidance of feeding from breasts with mastitis or abscess may decrease risk of breastmilk HIV transmission.

c) Emerging Intervention Approaches

In the future, breastmilk transmission of HIV will be approached in several ways. First, feasibility and safety of replacement feeding are influenced by regional practice, preferences, and competing infectious diseases risk; operations research is therefore currently being used to define practicable public health approaches that are regionally appropriate (164). Breastmilk pasteurization, pooled treated breastmilk, and wet nursing have all been suggested as options for prevention of breastmilk HIV transmission, however, there is no feasibility or efficacy data on these methods. It will be important to determine the efficacy and risks of antiretroviral prophylaxis during lactation. Studies evaluating infant antiretroviral prophylaxis with either zidovudine or nevirapine during the breastfeeding period are planned or underway in several

sites, and the results of these studies are necessary before recommending this approach. UNAIDS is conducting a multicenter study to determine the risk of mixed feeding and the feasibility of exclusive breastfeeding. As perinatal HIV intervention programs are implemented on a wide scale, resistance to either zidovudine or nevirapine may require altered approaches both to perinatal and breastmilk HIV transmission. Finally, vaccine-generated immune responses that confer protective immunity to breastfeeding infants may be the most sustainable, feasible approach to prevention of breastmilk HIV transmission, but unfortunately this is also approach that will require the longest time for development. There are over 20 ongoing or planned perinatal HIV intervention studies in breastfeeding populations in Africa and India. Interventions to be evaluated include antiretroviral prophylaxis, infant feeding pattern, vitamin A, chlorhexidine, immunotherapy, and vaccines. Results from these studies will become available during the next 5 years.

In sum, the most effective way to avert both HIV infections in infants, and to prevent children from becoming AIDS orphans, is to prevent infection in their mothers. In low-prevalence settings the absolute number of infant infections prevented by interrupting mother-to-child transmission is small (154), and the costs of screening and counseling per case averted are relatively high. In high-prevalence settings (>10%), antenatal VCT with delivery of ARVs and replacement feeding offers the opportunity to cost-effectively avert infant HIV and to provide important education and counseling to women who would otherwise not receive counseling on HIV prevention or testing for identification of HIV. Identification of asymptomatic HIV in young women will be important for prevention of further pregnancies and infant infection, and enable women to access interventions that may prolong maternal health and survival.

Counseling and testing HIV uninfected women also provides an important opportunity to promote messages for prevention of HIV in women at risk.

Despite the fact that mother-to-child transmission is highly amenable to intervention programs, their large-scale delivery is complex. Thus, for most developing countries with prevalence below 5% among adults, including many African countries, greater emphasis should be placed on preventing upstream infections, for example through sex worker programs. In countries where perinatal transmission interventions are affordable and practicable, their cost-effectiveness seems to be a compelling ground for implementing them.

Section VI. Injection drug use and HIV infection

Injection drug use (IDU) is a major source for HIV transmission in many parts of the world. In Asia, injection drug use has been the main mode of transmission in Malaysia (75% of all cases), Vietnam (65% of all cases), the Yunnan province of China, and the northeastern states of India (168-170). In Latin America, injection drug use has been a key factor in the HIV epidemic in the several countries, including Argentina, Brazil, and Chile (171). Parts of Eastern Europe are seeing rapidly growing HIV epidemics driven primarily by injection drug use. In still other regions including North Africa, parts of Western Europe, the Middle East, and the United States, injection drug use is a significant contributor to the HIV epidemic (168). IDU populations have served as entry points for HIV into other risk groups and to general populations.

The illicit status of injection drug use makes it difficult to accurately estimate the numbers of individuals involved or the full spread of the practice. Ball et al estimated that in 1998 there were at least 5.5 million IDUs worldwide, spread across at least 129 countries and territories, up from a total of 80 in 1992 (168). HIV infection among IDUs has been reported in 103 of these

areas (see Figure 5). The increase in the reported prevalence of injection drug use is due primarily to its spread along newly established trade routes, although increased awareness and public acknowledgement of the issue is also a factor (171-174). Worldwide, heroin is the main illicit substance injected; other substances injected include cocaine and buprenorphine.

HIV can be transmitted through multiple-person use of injection materials including needles, syringes, filters, cookers, and rinse water (collectively known as "works") (175). Sharing occurs between individual drug users as well as through communal injectors who both provide the drug as well as inject the substance for the user often using makeshift equipment. The shared use of drug paraphernalia can lead to the explosive spread of HIV within injection drug using populations, with dramatic increases in short periods of time, increasing from 0 to 50% sometimes in as short a period as six months (169). The risk of transmission of HIV through shared "works" depends on the background prevalence of HIV infection within the population as well as on the sharing behavior. The higher the prevalence of HIV within a community, the more likely an instance of sharing can result in HIV transmission (176). For example, in a population with 10% HIV seropositivity, a new user shooting up once a day has a 90% chance of using an infected needle within 21.5 days from onset of injecting. If the user shoots up three times a day, the number of days drops to seven; at a rate of five times a day, a new user has a 90% chance of using an infected needle within four days (169). Abdala et al showed that HIV-1 can survive for more than 4 weeks in used syringes kept at room temperature (177).

Interventions to reduce injection-related HIV transmission are based on an approach known harm reduction. The approach acts on the belief that individuals who are not prepared to abstain completely from drug use can still undertake measures to reduce their risk of HIV infection (178). Harm reduction strategies span from efforts to reduce the risk of HIV infection (cleaning

and reduced sharing of works) across efforts to reduce injection drug use (reduced injecting, use of alternate noninjectable substances) to cessation in overall illicit drug use (176).

Injection drug use also contributes to sexual transmission of HIV. Evidence from China indicates that younger IDUs have more sexual partners and are unlikely to use condoms (179). There is an association between injection drug use and commercial sex work for women (176). Its spread among injection drug user populations to their non-IDU sex partners and their offspring is dependent on the mixing patterns between populations as well as safer sex behavior practices. HIV prevention efforts targeting individuals injecting drugs should therefore include efforts aimed at reducing risks resulting from unprotected sex.

VI. 1. Interrupting IDU HIV transmission: interventions with strong evidence of effectiveness

Several strategies have been shown to be effective in reducing HIV risk behaviors among IDUs. While there is some difficulty in teasing out which components are most effective, there is clear evidence that needle exchange programs, peer outreach, and methadone maintenance programs are effective.

a) Needle Exchange Programs (NEPs)

NEPs are programs that increase access to sterile syringes and needles, and have been proven to reduce sharing, thus reducing the risk of HIV infection (180). NEPs not only provide sterile injecting syringes and needles, usually in a one-to-one exchange for used ones, but also provide participants with information on safer injection practices and on how to clean works, referrals for drug treatment, and information and condoms to prevent sexual transmission of HIV.

There is strong evidence through studies, mostly from developed countries, that the existence of NEPs decrease the shared use of equipment. An ecological study of HIV seroprevalence in the United States found that HIV seroprevalence in 27 cities with established NEPs decreased an average of 5.8% among injection drug users, whereas in 52 cities without NEPs, HIV seroprevalence rates among injection drug users increased 5.9% (181). Limited information is available on the effectiveness of NEPs in developing countries. One study in Nepal showed a significant reduction in unsafe injection practices; however, HIV prevalence remained low, and the study was not able to measure impact on HIV seroconversion (182). Another similarly sized study in Madras, India showed reduction in needle use and sharing, but did not demonstrate any differences in the numbers of casual or commercial sex partners (182;183). A recent review concluded that 10 of 14 studies reviewed suggest decreased needle sharing resulting from NEPs; the review concluded also that NEPs are effective in getting IDUs into drug treatment programs (184). As of yet, there has not been a formal meta-analysis conducted of the effectiveness of NEPs. A New York City study of 1752 IDUs found that participation in needle exchange saw a 59% relative risk reduction in borrowing needles and a 73% reduction in renting or buying used needles from onset of participation in the NEP. The study also saw a significant decline in needle reuse, from 12% to 4% (66% reduction in relative risk (185). In a review of five studies, Simonsen et al found the median point estimate of infection from an HIV-infected needle to be 0.3%, with a range of 0.2-0.5% and the caveat that the transmission rate may vary considerably with the stage of infection and the age of the person infected (186). Therefore about 333 injections with shared needles by an HIV uninfected individual must be averted to prevent one case of HIV transmitted by infected needle. Since much needle sharing takes place between two uninfected or two infected individuals, the required number of injections with shared needles per

infection must be much larger. Assuming an individual injects 3 times a day, that averages to reaching approximately 110 HIV infected individuals to prevent one HIV infection.

NEPs can be controversial, with critics arguing that they endorse injection drug use and will increase its prevalence. Data available provide no evidence that they increase the amount of drug use by clients, change overall community levels of drug use, or increase the numbers of discarded syringes in the community (176;180;187). Median costs per participant contact range from $1.35 in the United States to $3.21 in Nepal (169). In their review for the US Centers for Disease Control and Prevention, Lurie et al calculated cost-benefits of NEPs and found ranges of the cost per HIV infection averted in the US to be between $3800 to almost $100,000, below the estimated lifetime cost of treating an HIV-infected person (180).

b) Peer Outreach

Peer-based community outreach uses trained IDU peers to disseminate information, education, and safer injecting materials, but may or may not include needle exchange activities. Peer outreach is effective in accessing IDUs not in treatment. Several models of outreach have been tested to provide IDUs with information on how to clean their works and provide them with the necessary cleaning supplies, encourage users not to share their equipment, and use sterile equipment whenever possible. A review of 36 publications found that peer outreach can reduce drug use risk behaviors and is effective in providing referrals for drug treatment entry (178). A review of outreach-based strategies showed a decrease of 16-34% at follow-up in the reuse of non-syringe injection materials across four studies, a decrease of 14-43% in syringe reuse at follow-up across four studies, and that 24-31% of IDUs across five studies had stopped injecting between baseline and follow-up. The review also revealed that outreach activities across seven studies resulted in 11 to 62 fewer injections per IDU reached per month (188).

c) Methadone Treatment

Oral methadone is the most commonly used method to maintain individuals who inject heroin but who are not ready to abstain from drug use. Most programs include other services including counseling and social services (187). It has been widely evaluated as a form of drug treatment in developed countries, and is associated with reduced rates of injection and sharing of injection equipment for individuals in treatment (176;178). Methadone maintenance has been shown to reduce injection frequency between 60-84% and reduce sharing of syringes or needles by 50-81% (189). Annual costs of methadone maintenance in the United States run at $5250 per person, based on an analysis of 600 programs conducted by Barnett *et al* (190).

VI. 2. Interrupting IDU HIV transmission: interventions with some evidence of effectiveness

Possibly effective interventions to interrupt HIV transmission due to injection drug use include programs promoting alternate substances, detoxification, and abstinence and programs targeting risky sexual behaviors of IDUs.

a) Alternate Substances, Detoxification, And Abstinence Programs

Methadone is not the only opiate used in therapy programs. Other drugs used include levo-alpha-acetylmethadol, buprenorphine, tincture of opium, and pentazocine. These programs operate under similar premises as methadone programs and could potentially be equally as effective in reducing HIV risk behaviors. Programs designed to eliminate individual dependence on drugs not only eliminate HIV risk associated with drug injecting but could also reduce risky sexual behaviors related to sex work, the exchange of sex for drugs, and unprotected sex while under the influence of drugs. Several programs, particularly in Asia, promote rehabilitation before detoxification. In Asia and Africa, community organizations and traditional healers

provide forms of treatment that incorporate abstinence and individual engagement in rehabilitation activities (176;191). Anecdotal reports indicate that these programs are effective; formal evaluations have not yet been conducted (176). Alternate methods need to carefully introduced to avoid the substitution of abuse of one injectable substance for another, without any changes in HIV risk behaviors. In India, for example, use of intramuscular injections of buprenorphine to treat individuals withdrawing from heroin has triggered the spread of illicit buprenorphine injecting in some communities; in other communities, some IDUs have shifted to injecting dextropropoxyphane, which is cheap and easily available (168;192).

b) Interrupting Sexual Transmission Among IDUs

Most programs targeting IDUs also incorporate efforts to reduce sexual transmission of HIV (168;178;188). Preliminary results of a meta-analysis of 33 US-based, behavioral and social HIV risk reduction programs among IDUs show barely significant changes in any sexual risk behavior resulting from all interventions (odds ratio 0.86, 95% CI 0.76-0.98) (193). The results of 27 studies show a smaller non-significant change in behavior, avoidance of unprotected sex (OR 0.93, 95% CI 0.83-1.03). For the six studies that examined the use of male condoms while having sex, the change was barely significant (OR 0.62, 95% CI 0.38-0.99). The overall weighted average effect size of the intervention studies showed that 202 more people in the interventions groups reduced their unsafe sex behaviors after an intervention compared to the control/comparison groups, a risk difference of 2.9% within the intervention group or 4.1% of those in the intervention group at risk at baseline. The small levels of change demonstrated indicate that sexual risk behaviors of IDUs have been difficult to alter. More studies are needed to identify how best to affect these behaviors.

VI. 3. Interrupting IDU HIV transmission: interventions with limited evidence of effectiveness

a) Measures To Reduce Drug Supply

Efforts to halt drug trafficking through increased surveillance, stiffer criminal penalties for suppliers and users, and other measures in the "war against drugs" generally have not been successful. New drug trafficking routes emerge as existing ones are patrolled or cut. A consequence of market globalization has been the diffusion of drugs into countries that heretofore had no history of injection drug use (171). Day et al report an increase in heroin use in West Africa and other parts of the continent following the development in the early 1980s of transshipment routes from Southeast Asia via West Africa to Europe and North America (173). Likewise, as reported by Stimson et al, heroin use in the Indian state of Manipur and the Chinese province of Yunnan is attributed to their location on heroin trade routes from neighboring Myanmar (171). The supply control strategies being employed in many African countries, for example, have demonstrated only limited effectiveness based on reports of increasing trading activities and drug availability (191).

Section VII. Transmission of HIV from the blood supply

It is estimated that the global proportion of HIV transmission due to contaminated blood and blood products is between 5 and 10% (194). In sub-Saharan Africa, less than 30% of countries have enacted a national policy on blood transfusion (195). African transfusion-associated HIV is thought to account for up to 10% of all cases of HIV/AIDS (196;197) and 25% of HIV infections in women and children. HIV efficiently establishes infection when HIV infected blood is transfused. At least ninety percent of patients who receive these transfusions eventually become

HIV positive themselves (198). Progression to AIDS may be relatively rapid when HIV is acquired through a blood transfusion owing to the large amount of virus that is introduced (199).

While virtually all blood products in industrialized countries undergo testing for HIV anti-bodies, many people in developing countries are receiving unscreened, HIV infected blood. It is estimated that only 20-30% of the world's health services provide blood that is free of pathogens and in adequate supply (194).

In several countries blood screening facilities are not available (195). In others, substandard test sensitivity has permitted HIV transmission during blood transfusions. Often tests are inaccurate due to the unrefrigerated storage of reagents, the use of kits beyond their date of expiry, and human error (196;200). The level of risk for contracting transfusion-acquired HIV depends upon the capabilities of the health care system to screen for antibodies, the overall prevalence of HIV in the donor population and the frequency of exposure to the blood products.

In Myanmar, the proportion HIV/AIDS cases that are believed to be transfusion-acquired was 0.3% in 1995 but increased to 4.6% in 1997 (201). In India, there has been a serious attempt to improve the blood system by supporting voluntary, unpaid blood donations and licensing blood banks (202). Despite this effort, a routine annual inspection of blood transfusion centers in Delhi found that over half of them were "unsatisfactory" (203). Unsatisfactory blood transfusion centers pose an increasing threat to the overall epidemic as the prevalence in the donor population rises. In North India between 1989-1996, the rate of HIV antibodies from donors increased from 0.04% to 0.55% (204). Those rates are relatively small, but considering that 3 million units are collected, this means that 1,650,000 units of HIV infected blood would be transfused if all the blood was unscreened. The screening of blood for HIV is mandatory in

India; however, there are reports that quality control for these tests is not being maintained in most of the blood transfusion centers (205).

VII. 1. Interrupting HIV transmission from blood supply: interventions with strong evidence of effectiveness

There are three main interventions that have been used to reduce the risk of HIV transmission through the blood system. These include HIV antibody screening, avoiding unnecessary blood transfusions, and excluding high-risk donors (206).

a) HIV Antibody Screening

There are a number of different tests that can be used to screen blood for HIV antibodies. Blood banks that process a large amount of blood product typically use Enzyme-linked Immunosorbent Assays (ELISA). ELISA are the most commonly used tests to screen for HIV infection because of their high sensitivity, comparatively simple methodology, and appropriateness for testing sizeable samples at once. When used properly, these tests can detect virtually all HIV positive blood. However, there is still a small risk of transmission despite the type of antibody test used. If the donor acquired the virus within the last one to three months, it may not be detected (207;208).

Screening blood for HIV can be an expensive component of the overall health care system. The costs are difficult to gauge depending upon the setting, volume produced and equipment used. A study in Brazil was able to show a 16% decrease in price using two different ELISA tests ($1.15) over the more complex Western Blot test ($1.80) (209). Another study reviewed the estimations of resources that would be required to strengthen blood transfusion systems in sub-Saharan Africa and found the cost to be between $5.30 and $18.20 per unit of blood (210). Still another

study in Zambia in 1995 found that the total cost of averting a case of HIV through screening was $31.62 (211).

b) Avoiding Unnecessary Blood Transfusions

Although blood transfusions can be necessary for survival during surgery, childbirth or trauma, unnecessary bloods transfusions are often given to "revitalize" patients for a range of conditions, such as anemia (211;212). Studies from the early 1990's reported high levels of unnecessary blood transfusions in Africa (206;211;212). Encouragingly, a recent report from Zambia demonstrated much closer adherence to international requirements for blood transfusions than was seen in the last decade (213).

Rational transfusion guidelines must be drawn up and adhered to so that those people who require blood can get prompt access to a safe product. Alternatives to blood such saline, iron, crystalloids and colloids should be considered, depending upon costs and availability (194;214). Autologous transfusion could be an alternative for people that are expecting to have elective surgery (208). Similarly, reduction of childhood and maternal anemia could be addressed through iron supplementation and treatment of helminthic infections (see related CMH paper.)

c) Excluding High-Risk Donors

Excluding high-risk donors reduces the level of risk within the blood system. A study from Cote d'Ivoire found that the most important risk factors in their study area were contact with a prostitute and being aged 30-39 years (215). The study found that excluding people that had had contact with a prostitute in the last five years would have excluded 31% of the donors but reduced 73% of the HIV infected blood.

Excluding paid donors is likely to reduce the risk of transfusion-acquired HIV. During the early 1990's, Thailand recognized that the blood donor seropositivity was highest among paid donors. In 1993, a policy was enforced that restricted blood donation to volunteers. Partly owing to this policy, HIV-1 antibody prevalence decreased from 4.04% in 1991 to 3.34% in 1993 (216).

In countries that test all blood, HIV-infected blood donations are often made prior to seroconversion and before high levels of viral replication occur (217). Potential donors who have engaged in high-risk behavior in the three months prior to the testing date should therefore be excluded.

A cost-effectiveness analysis was carried out in Zimbabwe in 1995 to estimate the cost of averting a case of HIV through deferral of high-risk donors (197). Compared to not screening at all, deferring of blood donors using the history of a genital ulcer cost $94 per HIV infection, $102 when using a history of contact with a commercial sex worker and $147 using history of multiple partners. Compared to testing alone, testing and deferral using a history of a genital ulcer resulted in cost savings while a history of paying for sex or multiple partners resulted in a cost of $259 and $1,578 per case averted respectively.

Recruiting volunteer, low-risk donors can be challenging. Often blood services attempt to recruit volunteers from schools, clubs or workplaces (218). However, volunteer blood donation is not "free" in the economic sense. The cost per unit of voluntarily donated blood in Africa can still be about $30-50 for materials and labor (206). Social marketing studies could reveal the most effective ways of recruiting and retaining low-risk blood donors and national blood donor registries could be established.

VII. 2. Interrupting HIV transmission from blood supply: interventions with some evidence of effectiveness

Research continues on the possibility of other interventions that would reduce the risk of HIV transmission through the allogenic blood system. Post-collection viral inactivation has been attempted through solvent and detergent treatment and ultraviolet blood irradiation (UBI) (208;219). Unfortunately, as blood is living matter, treatment that is intended to kill pathogens in the blood tends to kill the delicate blood cells themselves. However, a recent study has shown promise in heat treatment of blood. Fresh frozen plasma that is heated to 50 degrees Celsius was shown to completely inactivate HIV (220). The procedure takes less than an hour and was able to preserve plasma protein integrity. Sophisticated equipment is not required but the procedure must be monitored carefully to guarantee quality. Efficacy and cost-effectiveness of this strategy have yet to be analyzed.

Section VIII. Current state of HIV vaccines

As with other viral epidemics, an HIV vaccine offers the best method for ending deaths from the AIDS epidemic. No HIV vaccine is available today. Here, we quickly review the scientific challenges faced in developing an effective vaccine, describe current and forthcoming trials of various vaccines and briefly discuss delivery issues. The reader is referred elsewhere for more in depth discussion on biology (221-223) or innovative public private partnerships to accelerate vaccine (www.iavi.org), and their political economy issues. Working Group 2 of the CMH describes economic issues of supply and incentives to vaccine development.

VIII. 1. Scientific challenges to HIV vaccine development

Vaccine design and clinical testing of HIV vaccines face several challenges. These include: a lack of clarity regarding which types of immune responses (e.g. cellular or humoral) are

necessary for protection against HIV; and a lack of information regarding the specific composition of HIV antigens necessary to confer protective immunity and the absence of a validated animal model (224;225). The durability and breadth of immune responses necessary to achieve protection under field conditions, where highly variable subtypes of HIV are circulating, is also unclear and will remain so until human field trials with a candidate HIV vaccine demonstrate a sufficient level of protection that studies assessing correlates of protective immunity may be undertaken. Without animal models, testing vaccines on humans through a range of interventions is required. Such a strategy is expensive and difficult to implement but will lead fastest to creating a viable vaccine.

Early attempts at HIV-1 vaccination had a goal of sterilizing immunity (226). However, when one considers vaccines against many other pathogens such as influenza virus, the goal has been to prevent clinical disease. In fact many conventional vaccines do not prevent infection per se but rather, prevent clinically apparent disease. Thus, the perceived potentially positive outcomes of vaccination against HIV-1 have broadened over the 14 years since the first clinical trials. We have come to realize that there may be other positive benefits even for vaccines that do not confer sterilizing immunity (224;227). For an individual vaccine, the benefit may be an attenuated infection with a lower viral load and long term slow or non-progression. For the population, the benefit may be lower rates of secondary transmission to sex partners or infants due to the lower viral load (228;229).

HIV-1 is one of the most mutable virus known. Within an individual the virus mutates quickly producing a swarm of quasi-species that are constantly being selected by the immune or drug milieu in that person. At the population level, multiple strains called clades of virus exist, and recombination between clades creating even more diverse hybrid viruses has now been found to

be commonplace. To put things in perspective, there is now as much diversity within each clade of HIV-1 as there was between clades at the beginning of the epidemic. HIV-2, a related virus has had a less explosive spread and appears to be less transmissible and virulent but also shares the properties of mutability and is sufficiently different from HIV-1 that vaccine approaches for each virus will likely need to be considered separately. Consequently, in terms of vaccines we are aiming at targets that are dynamic and unpredictable, although the significance of this variability is unclear and will be partially dependent on the type of immune protection achieved.

During the past two years, a number of new scientific advances have had a significant impact on the strategies now being undertaken for HIV vaccine design and development. The recent development of more specific and sensitive assays for assessing cellular immune responses have significantly enhanced natural history studies (230). Similarly, demonstration of cross-reactive cellular immune responses have provided renewed optimism that cross-reactive preventive vaccines may be designed against HIV subtypes circulating in different geographic locales (222). Recent structural biological data of specific stable HIV envelope proteins have provided new leads for design of immunogens focused on neutralization of HIV primary (231). In addition, a specific "dendritic" cell receptor that binds stable envelope proteins has been discovered (232). Vaccine induced antibodies which block receptor binding may inhibit the capacity of HIV to establish a persistent infection. Finally, data from several laboratories studying the roles of HIV regulatory and accessory genes have collectively suggested that one or more HIV regulatory and/or accessory genes (e.g. *nef*, *tat*, *rev*) may be important as components of an effective HIV vaccine (233).

Finally, there are other challenges facing HIV vaccine testing. There are very few well-characterized cohorts suitable for HIV vaccine efficacy trials thus constraining multiple and

parallel efficacy trials. Regulatory strategies for critical path development of candidate HIV vaccines are not sufficiently harmonized among the major national/international regulatory bodies, to allow for parallel development of similar vaccine designs in different parts of the world.

VIII. 2. Ongoing and forthcoming clinical trials of HIV vaccines

Although the majority of candidate vaccines currently in clinical trials still focus on strains of HIV circulating in industrialized rather than developing countries, the past two years have yielded significant advances for a number of products. The first Phase III efficacy trials of HIV vaccines are now well underway. VaxGen's bivalent recombinant gp120 vaccines directed against HIV-1 subtypes B and E (AIDSVax) is likely to report results before 2002. In addition, both the U.S. National Institutes of Health and Department of Defense are preparing for potential Phase III efficacy trials of a prime-boost regimen consisting of recombinant canarypox expressing *env*, *gag*, protease and *pol* and *nef* epitopes developed by Aventis-Pasteur for priming followed by a subunit HIV-1 glycoprotein boost. Phase I/II trials of the prime-boost approach are currently ongoing in efforts to optimize dosing and scheduling regimens, with these Phase III trials targeted for potential launch in 2002. Preliminary Phase I trials of new vaccine strategies are continuing, including but not limited to DNA vaccines (Merck & Co., and Wyeth-Lederle), viral vectors (e.g. Recombinant vaccinia- Therion, Inc.), bacterial vectors (e.g. Recombinant salmonella- University of Maryland), HIV core structural subunit protein (p24, Chiron) and synthetic peptide vaccines (HGP-30), and prime-boost combinations of these products.

During the past two years, the pipeline of new HIV vaccine designs has significantly widened, with a greater emphasis on vaccine designs applicable for use in the developing world, through a series of innovative public-private sector partnerships. The IAVI Vaccine Development

Partnerships are currently developing the following multigenic HIV vaccine designs: DNA priming plus recombinant MVA boosting; Venezuelan equine encephalitis replicon particles; Single-dose recombinant adeno-associated virus; and orally administered salmonella for delivery of DNA vaccines. The European Union (EU) HIV vaccine effort (EuroVac) in collaboration with Aventis-Pasteur is focusing on development and comparative testing of different pox virus vectors containing multiple HIV-1 genes. In addition, the U.S. National Institutes of Health and Department of Defense are supporting the development of a broad spectrum of HIV vaccine strategies, including but not limited to recombinant MVA, oliogomeric subunit proteins, prime-boost and virus-like particles.

Thus, the current themes that underlie the new push in HIV-1 vaccine development are: First, to investigate a broad array of strategies, not just those that are the most promising. Second, to employ a variety of immunogens and vectors in combination, to enhance immunity. Third, to push ahead with human trials of imperfect vaccines earlier rather than later since these will give us important immune correlates of protection or the lack thereof on which to design the next generation of vaccines. Finally, to use non-human primate models to investigate novel strategies but, recognizing their limitations, not allow non-human primate studies to unnecessarily delay human trials. Finally, it is clear that even with the most optimistic forecasts, a relatively effective and safe vaccine that can be widely distributed is a number of years away.

VIII.3. Delivery strategies

The extraordinary infrastructure that is in place to deliver immunization services can serve as a base for HIV vaccination, but by itself it is inadequate because an HIV vaccine will not, at least at first, be delivered to infants and children, who are the targets of most current vaccination campaigns. Initial HIV immunization is likely to be targeted at vulnerable groups such as sex

workers, highly sexually active adults and truck drivers as well as soon-to-be-sexually-active adolescents—groups we do not currently have mechanisms to reach for vaccination, or in fact for most other health interventions. As a result, we will need to create, validate and cost-out systems to reach out to these groups. Furthermore, those who are dispossessed are more likely to be at risk so not only will routine systems need to be used (like schools, the army, religious gatherings, etc.) but we will need to create new delivery systems to reach out past those normal social places, to reach the most vulnerable groups (234).

Even a vaccine that did not completely protect against infection, but that did provide enough immunity to reduce initial burden could make a significant contribution to limiting epidemic by making transmission to next sexual partner less likely. Conversely, there is concern that a vaccine that is less than 100% effective could increase overall rates of HIV transmission if accompanied by an increase in risk-taking behavior (235).

It is unlikely that any HIV vaccine will be 100% effective. Furthermore, even if a vaccine were fully effective for HIV, persons would still be at risk for other STIs, pregnancy and other reproductive health issues. As a result, HIV vaccine distribution and use will need to be accompanied by full implementation of other prevention and behavior change education modalities also a challenge in implementation. As a result, a simultaneous effort needs to be created now to assure that systems and political will is in place to assure simultaneous access for a vaccine in both North and South.

Section IX. Why is coverage with effective interventions so low?

The challenges of HIV prevention in developing countries are considerable. Of the evidence-based interventions that have been shown to prevent HIV transmission, enhanced STI

management has perhaps been implemented most widely, but even then rarely on a national scale. The coverage of these interventions in many countries is still only a fraction of what is needed. The reasons for low coverage are complex. We point to a few.

First, there is lack of advocacy for the most effective interventions. Such interventions involve programs in partnership with the poorest, most marginalized and most stigmatized groups. This can be politically unpopular, as evidenced by recent experience of India, where women's groups protested the emphasis on sex workers in the national AIDS control program (45). The needs of AIDS patients often compete for attention and resources. While their needs should be addressed, in most countries the majority of HIV/AIDS resources are already directed at care, and there must be a clear focus on preventing further spread of infection.

Second, total spending on HIV prevention interventions has been too low. UNAIDS recently estimated that total HIV/AIDS-related expenditure in 1996-1997 from domestic and foreign sources in 64 developing countries where three-fourths of the world's HIV population live, was only $549 million. Of this, $280 million (which also funded AIDS care) was spent in Brazil and Thailand. Only $141 million of country-level spending was in sub-Saharan Africa, or about 20 cents per capita. Of this, Uganda accounted for $37 million, whereas Nigeria, the most populous country, only spent $4 million in 1996. The World Bank is the largest external financier for health and other programs in the world, including $233 million in cumulative disbursement for HIV/AIDS (236). Yet, its cumulative disbursement per capita since 1990 on HIV/AIDS in Africa has only been 32 cents.

Several costing studies suggest prevention requirements are an order of magnitude greater than what is currently spent. The 1993 World Development Report (4) estimated that with 1993's

tools, comprehensive HIV/AIDS and STI prevention services for all developing countries would cost $1.5 to 2.9 billion per year and would avert an estimated 9.5 million new adult HIV infections between 1993 and 2000. Attaran and Sachs estimate that around $5 billion to $10 billion a year is required from rich countries in the next decade to battle AIDS in Africa. According to their estimates, prevention and community support would probably cost around $3 billion a year, and between $2 billion and $7 billion a year would be needed for treatment (237). This assumes that the price of HAART treatment in the hardest-hit areas in Africa of $500 per patient. Schwartländer et al estimate costs of an expanded response to HIV/AIDS in Sub-Saharan Africa to reach $9 billion annually by 2005 with about $4.8 billion required for prevention interventions focusing on youth, workplace programs, mother-to-child transmission and condom distribution (238).

Thirdly, it is not only the level of spending, but the lack of priority accorded the most effective interventions that has contributed to the epidemic. Scientific findings have had an insufficient impact on policy (239;240). Lack of priorities among external partners adds to confusion within countries. An early review of 60 World Bank projects (241) found that only 48% financed condom promotion and 57% financed STI treatment, while 38% financed treatment of AIDS and opportunistic infections. The World Bank's most recent document on scaling up interventions in Africa (242) barely discusses targeting groups important in transmission, provides no criteria for priority setting and suggests that all interventions may be possible at any time. Finally, although in many countries health systems are at or near collapse, coverage of other interventions such as immunization has increased, even in times of economic stagnation (148).

Lastly, other constraints to scaling up HIV prevention exist. These include the lack of mapping information on geography or occupational transmission hot spots, poor condom availability and

quality, low access to STI treatment services, limited coverage of NEPs, limited NGO capacity, and lack of training in outreach services. To some extent, these are amenable to correction with higher spending, but broader system strengthening will be required, especially for STI services.

Section X. Future directions

HIV/AIDS is a problem that threatens to overwhelm many developing countries. Although the first battles were lost long ago, the world has powerful interventions that can prevent HIV. Future actions could include the following:

Advocacy for evidence-based interventions

Much of the emphasis of AIDS programming and spending has been on trying to meet the needs of HIV-infected people. This is understandable; individuals with HIV need the best care possible and have organized themselves so that their demands are heard. However, spending extensively on learning how to prevent HIV, either through public health programs or through the development of vaccines, remains a priority. Perhaps this did not happen because the constituencies that need these programs – HIV uninfected people worldwide – either do not know they need them or, because of their marginalization, do not have sufficient political voice to be heard. Changing this situation will require sustained advocacy for a clear focus on the highest impact interventions, directed at the general public, policy makers and those that fund programs (243).

Spending more and spending better

Spending on effective interventions at scale throughout Africa and Asia is key. Spending more would achieve economies of scale, reaching efficiencies not possible in small projects. As mentioned earlier, different estimates have been made as to the spending needed to adequately

address the epidemic. The exact amount varies, but all agree that the amounts needed are multiples of what is currently being spent. Cutting incidence by half would seem an attainable objective in view of what has been achieved in Thailand. This would imply that the 5.3 million new infections seen globally in 2000 could be halved to 2.6 million by 2007 (20). With the Thai national AIDS control program budget of approximately $1.00 per capita, it was also achieved cheaply. Spending also needs to be largely directed at interventions that have been shown to work rather than dissipated in questionably effective efforts. It is encouraging that the recent Group of Eight summit set the goal of reducing HIV-1 prevalence among youth by 25% by the year 2010 (244). A necessary, but perhaps insufficient requirement is to achieve high coverage (at least 90%) of evidenced-based interventions that target transmission from vulnerable groups.

Research on new interventions

While we have compelling evidence for high impact of some interventions, more are needed. HIV/AIDS research and programming has been directed largely at understanding the disease and how to care for patients. Prevention research requires increased emphasis and funding. A research agenda should include studies of male circumcision, STI treatment in high prevalence settings and vaginal microbicides, as well as cost-effective behavioral interventions for high-risk men and high-risk youth.

Vaccine development

As discussed above, there is renewed optimism that HIV vaccines are ultimately possible. IAVI (221) has energized the HIV vaccine research field and has catalyzed several vaccine development initiatives. This work needs to be supported, strengthened and moved forward as rapidly as possible. The groundwork for deployment of HIV vaccines, such as research on the highest impact vaccination strategies and their cost-effectiveness also needs to begin now.

Evaluation of impact and monitoring progress

We propose international, independent monitoring of coverage of key effective interventions (245), which would report each year to a virtual forum of NGOs, civil society and the United Nations. This would include the requirement for every country or major state to provide reliable HIV surveillance data, mapping of transmission hot spots, estimates of coverage for key interventions and evaluation of intervention impacts. It would also involve transparent goals such as ensuring that at least 90% of transmission hot spots are covered by effective interventions within 5 years. Such programs would in addition create an environment for epidemiological and operational research and, with access to vulnerable groups, provide a setting for testing candidate vaccines.

The experience of the first two decades of the HIV epidemic has taught us that control of the epidemic is possible if the highest impact interventions are implemented at scale. The rapid and widespread implementation of such interventions must be given the highest priority. Too much time and effort has been wasted on insufficient and often ineffective action. It is past time to act decisively and effectively.

Table 1. Comparison of Efficiency, Effect Size and Cost Effectiveness of Different Evidenced Based Interventions for HIV Prevention for Developing Countries: Sexual Transmission

	Sex Worker Interventions	STI Management	High Risk Heterosexual men[1]	Voluntary Counseling and Testing	MSM Peer Outreach[2]
Efficiency Ratio[3]	0.6-1 (41;42)	48 (57)	116 (49)	9-11	-
Effect Size- (Relative Reduction in HIV Incidence)	80% (41;42)	44% (57)	25-33% (49)	50% (78)	-
Cost per HIV infection prevented[4]	$8-12 (42)	$218 (65)	-	$249-346 (78)	-
Dependence on the health delivery system	Low	Medium	Low	High	-

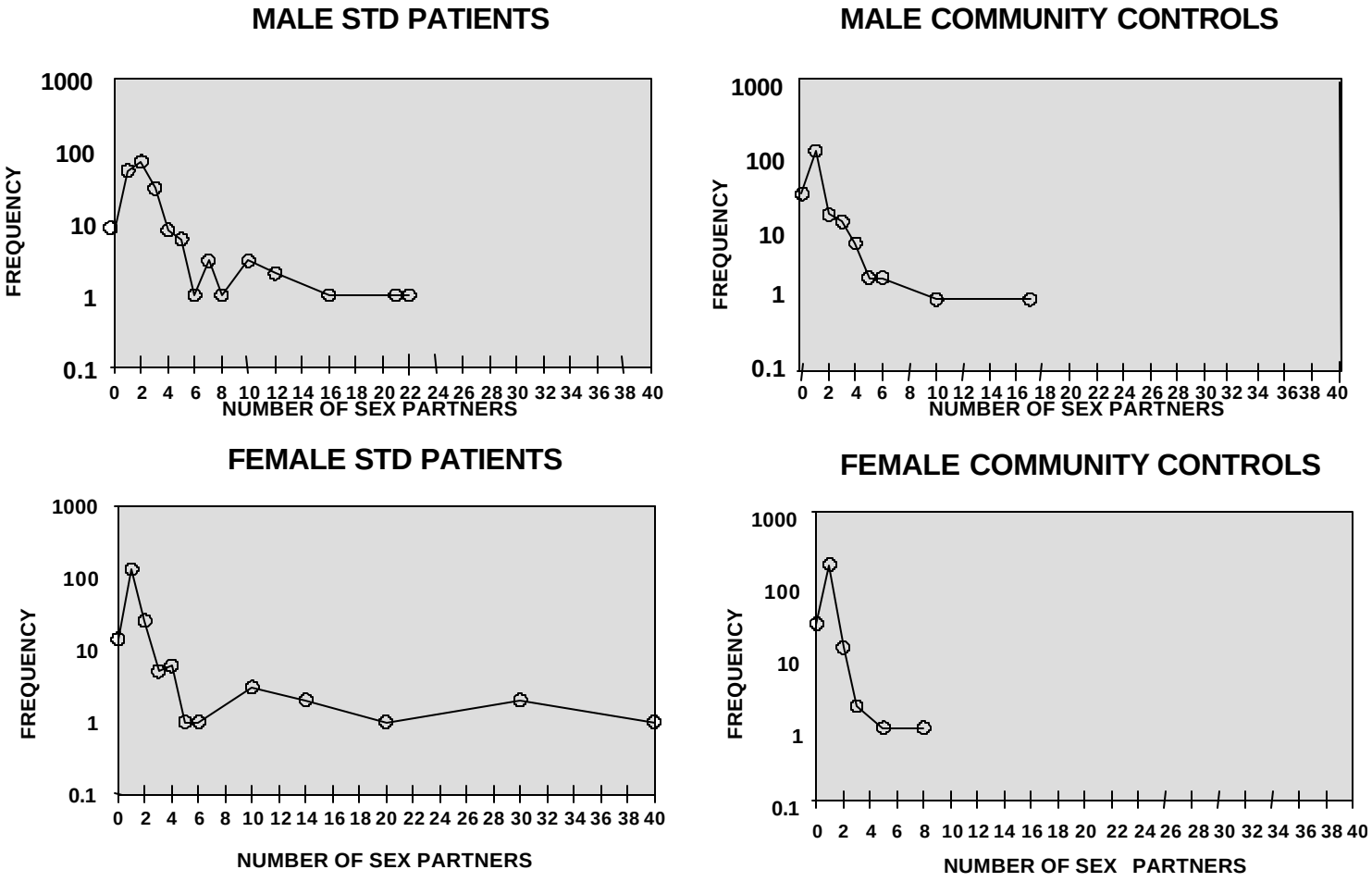
[1] The efficiency ratio and the effect size are taken from a randomized trial of a workplace peer education intervention in Zimbabwe (50). No cost effectiveness studies have been published on interventions to reduce HIV incidence in heterosexual men.
[2] Figures not available for peer outreach activities for MSM.
[3] The intervention efficiency is the number of individuals who must be affected by an intervention to prevent 1 HIV infection. These were calculated from published intervention studies.
[4] Where cost effectiveness analysis has not been done the cell is blank.

Table 2. Comparison of Efficiency, Effect Size and Cost Effectiveness of Different Evidenced Based Interventions for HIV Prevention for Developing Countries: Non-Sexual Transmission

	Needle Exchange Programs	Antiretrovirals in pregnancy	Replacement feedings	Screening of Blood[1]
Efficiency Ratio	110	44 (154)	51 (152)	~2470 (198;203)
Effect Size-(Relative Reduction in HIV Incidence)	5.8% (181)	37-50% (154)	44% (152)	
Cost per HIV infection prevented	$3,800-$100,000 (180)	$276 (155)	-	$32 (211)
Dependence on the health delivery system	Low	High	Medium	High

[1] Efficiency ratio calculated by assuming 1 per cent of units not screened, 5 per cent of units are HIV-contaminated, implementation of screening is 90 per cent effective, and risk of infection through transfusion of HIV-contaminated blood is 90 per cent.

Figure 1: Number of Reported Sex Partners in Previous Three Months in Nairobi
Source: (46)



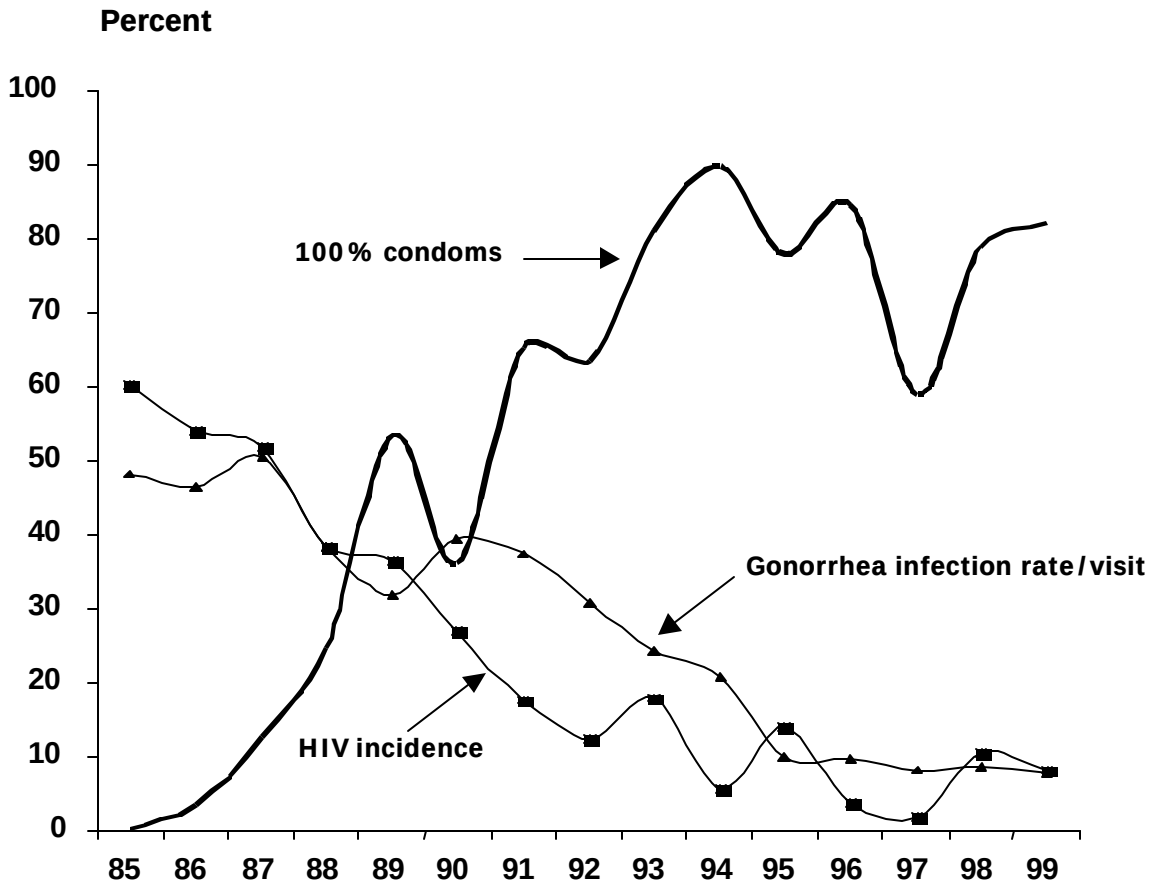


Figure 2. Sustained increased condom use and reduced HIV and gonorrhea incidence in the Pumwani sex worker cohort over 15 years. The Pumwani sex worker cohort was started in 1985 as a research project on the epidemiology of sexually transmitted diseases (37;42). Interventions to reduce HIV-1 and STI incidence consisted of peer education and condom promotion within the sex worker community and appropriate management of bacterial STI. The percentage of sex workers reporting the use of condoms with all paying sex partners (heavy black line), the percentage of clinic visits during which sex workers tested positive for gonorrhea (triangles) and the percent annual incidence of HIV-1 seroconversion (rectangles) is plotted against calendar year.

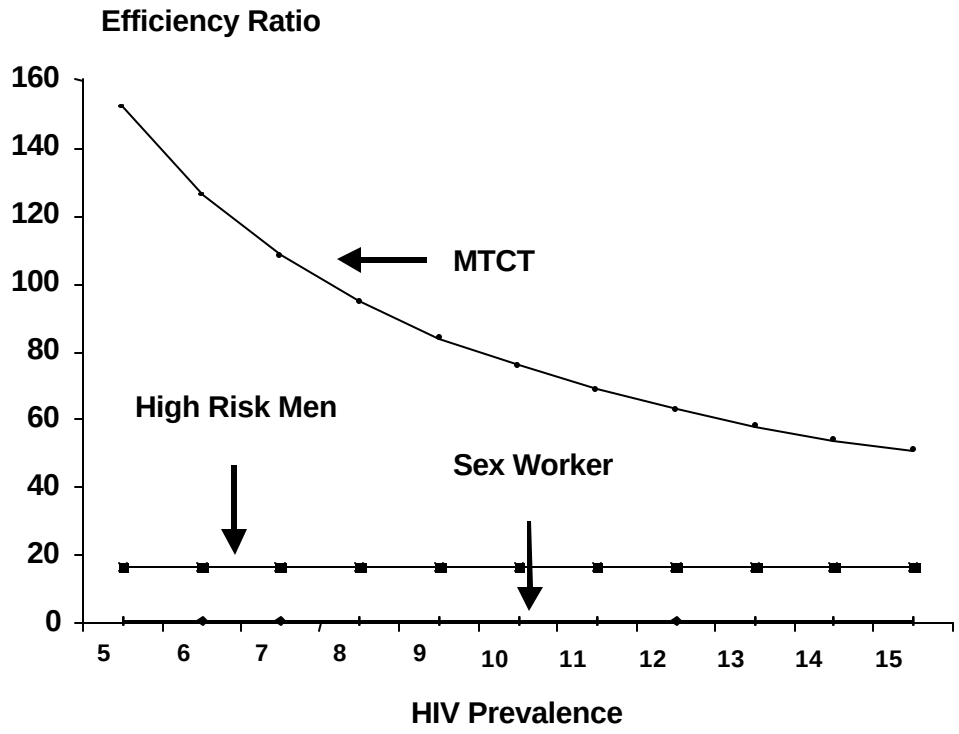


Figure 3. The efficiency ratio for different interventions to prevent one HIV infection. The efficiency ratio is defined as the number of individuals that need to be affected by an intervention to prevent one HIV infection. Estimates were derived from a simple spreadsheet model with the following assumptions. Female sex workers: HIV prevalence among sex workers is 50%, sex workers have 1000 partners annually and the HIV transmission rate per sexual contact is 0.001. The number of infections is adjusted for prevalent infections among sex worker partners. Each infection in men from sex worker contacts results in 2 other infections in the population. Intervention results in an increase in condom use to 80% of contacts. **High risk men:** High-risk men are the sexual partners of sex workers. Men average 50 contacts with sex workers annually. The other assumptions are as described under the sex worker scenario above. For both sex worker and high risk men interventions there is little effect of population prevalence on intervention efficiency since sex workers rapidly reach a high prevalence of HIV even when general population prevalence is relatively low. **MTCT:** Interventions to reduce mother to child transmission using HIV screening in pregnancy, anti-retrovirals and formula feeding. The baseline transmission rate is assumed to be 30% and the intervention effect a 50% reduction in transmission.

Source: (46)

Figure 4. Change in HIV incidence and rate of 100% condom use in response to reporting of quack cures, Nairobi.
Source: (46)

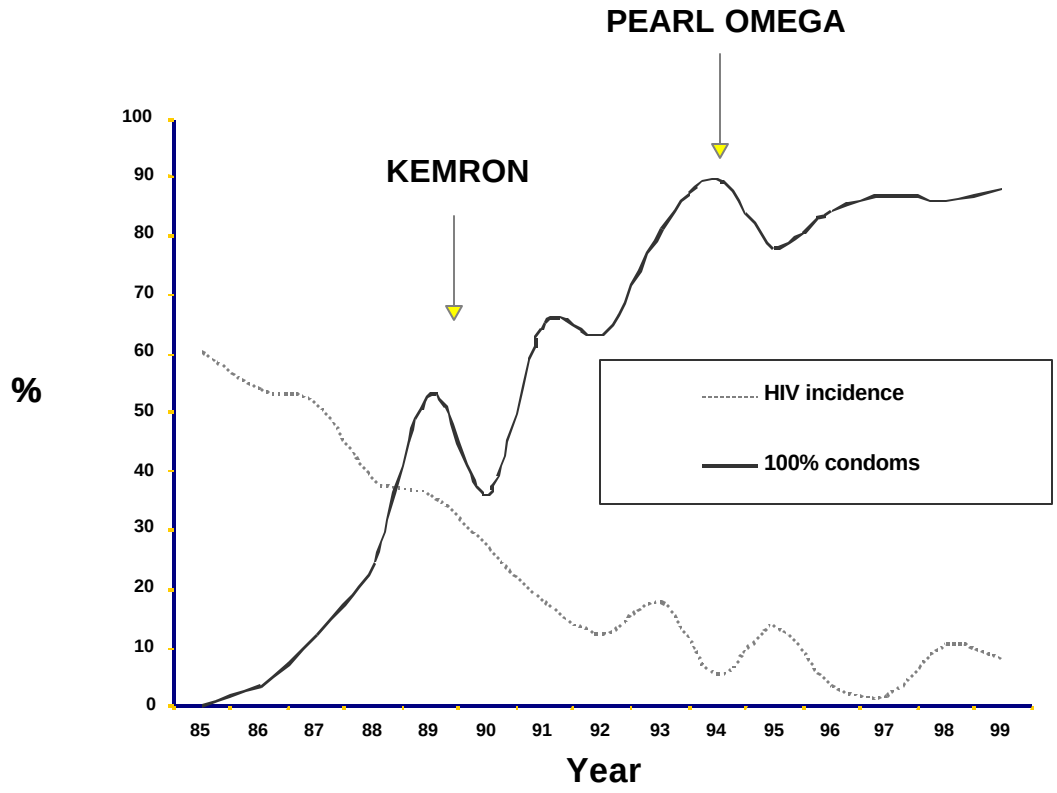
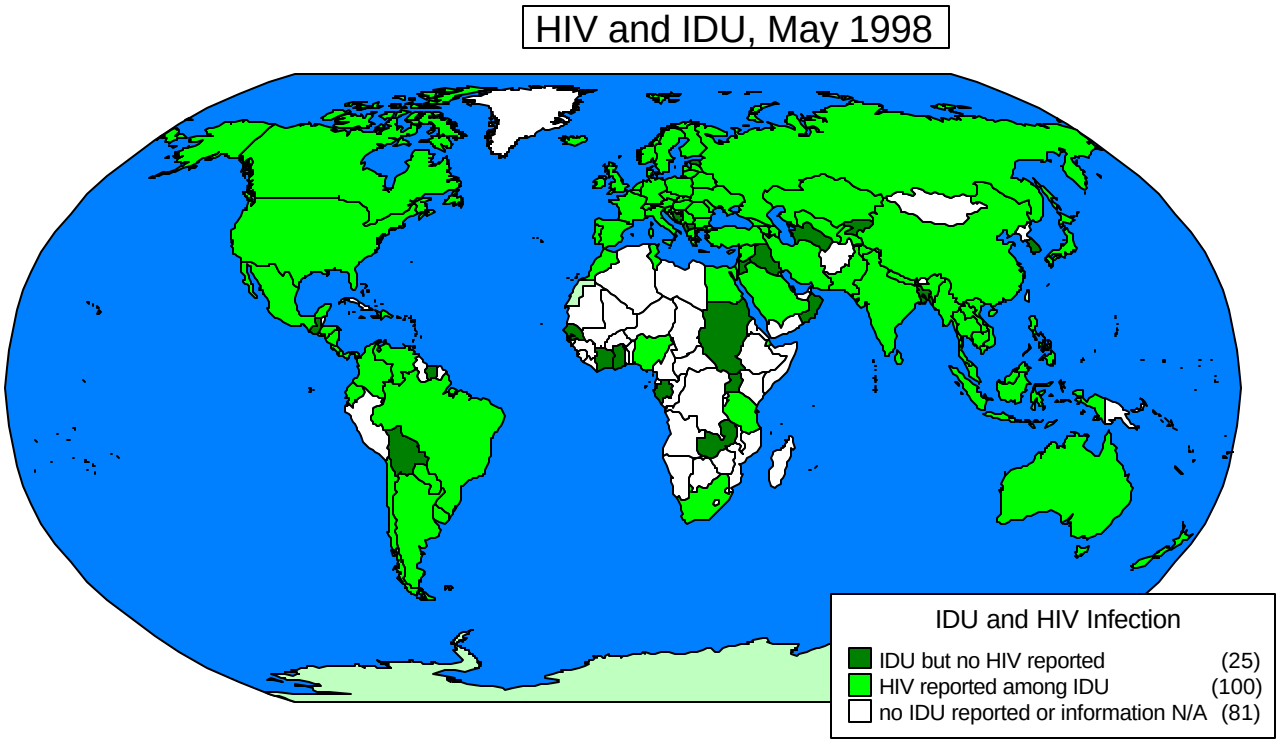


Figure 5: Global Distribution of Injection Drug Use and HIV
Source: (168)



map only shows 100 countries with HIV among IDU instead of 103… missing are West Bank, Macao, and American Samoa.

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