

PN-ARV-394 98466

**selected themes
from the
Berlin Conference**

Berlin

June 6-11 • 1993

**IXth
International
Conference**

**On
AIDS**

**IVth
STD
World
Congress**



1993 **AIDS** BERLIN

a report on

- Selected themes from the IXth International Conference on AIDS/IVth STD World Congress

This report is based on a debriefing given by AIDSCAP at the U.S. Department of State in July 1993. It is not a comprehensive report on the Berlin Conference, but a summary of some of the meeting's most important themes from the perspective of the AIDSCAP staff.

- by the AIDS Control and Prevention Project (AIDSCAP),
Family Health International

**in
collaboration
with**

- The Center for AIDS Prevention Studies, University of California, San Francisco
- John Snow, Inc.
- Ogilvy, Adams and Rinehart
- Population Services International
- The Program for Appropriate Technology in Health
- Prospect Associates
- The Institute of Tropical Medicine, Antwerp
- The University of North Carolina at Chapel Hill
- The University of Washington

funded by

- United States Agency for International Development

table of contents

Introduction	1
Conference messages	1
Communication interventions	3
Targeting	3
Women, youth, and AIDS orphans	5
Women	5
Youth	7
Orphans	8
HIV testing and counseling	9
Workshop presentations	9
Round table discussions	10
Vaccines, therapies, and the impact of tuberculosis (TB) on HIV/AIDS	13
Current vaccine investigations	15
Current therapies	16
Tuberculosis (TB) and HIV/AIDS	17
Economics, the response of governments and donor response	21
Economics	21
The response of government	22
International donor response	23
Program considerations	25
Program design	25
Program implementation	25
External messages	26

introduction

The IX International Conference on AIDS, in affiliation with the IV STD World Congress, was held in Berlin, Germany, 6-11 June 1993. The Berlin Conference marked the second consecutive year that the international AIDS conference was successfully combined with the STD congress.

Over the nine years that the international conference has been convening, more has been learned about HIV than any other single pathogen in medical history. As a result, there have been widespread unrealistic expectations of where HIV knowledge would lead, spurred in part by the extensive media coverage of each conference. The Berlin Conference reflected a continuing media interest: of roughly 14,000 conference participants, some 1,500 were journalists. No dramatic reports emerged from Berlin, however, and no substantive breakthroughs are expected during the next several years. Instead, it is increasingly clear that the battle against HIV infection and AIDS will proceed as a process of learning from proven successful preventive interventions and methodically pursuing promising biomedical therapies.

The format for the Berlin Conference was somewhat different than in the past, with 24 plenary sessions, none of which overlapped. In addition, more roundtables were offered, providing additional opportunities for discussions between participants. While consideration of biomedical aspects continues to dominate the international AIDS conference proceedings, greater attention is being given to the social sciences and behavioral aspects of HIV infection and AIDS; hence, at Berlin prevention issues and the epidemic in the developing world were more highly profiled than ever before. During the opening ceremonies, Conference President Professor Karl-Otto Habermehl proclaimed effective prevention a priority issue and drew attention to the Berlin Conference's emphasis on AIDS in the developing world. Discussion of prevention was highlighted by the plenary session presented by AIDSCAP Director Dr. Peter Lamptey, who identified inadequate resources and lack of supportive policies as the most important hindrances to the prevention of AIDS. [PS-02-2, P. Lamptey, *HIV prevention: is it working?*]

conference messages

Four messages emerged from Berlin which are of primary importance to those working to prevent and control HIV in the developing world:

- **The epidemic keeps spreading into Asia and previously unaffected areas of Africa. Prevalence rates of 36-40% are now being reported in some parts of southern Africa, and AIDS adult mortality has become the leading cause of death in some western Africa cities, as documented by Dr. Michael Merson, Director of the Global Programme on AIDS, World Health Organization (WHO/GPA) in his opening plenary. [PS-01-1, M. Merson, *The HIV pandemic — global spread and response.*]**

-
- **Usable and practical HIV/AIDS vaccines and cures are a long way off, and the hope that a vaccine or cure can stop the epidemic is no longer realistic.** The development of any therapeutic vaccine — that is, effective vaccine given after infection has occurred to prevent disease — is a rare biomedical event. As knowledge of the complexities of HIV infection expands, there is actually less reason to believe that therapeutic HIV vaccines will be a feasible option in the foreseeable future. Optimism regarding the development of a preventive vaccine — to prevent HIV infection from occurring in exposed individuals — has likewise been shaken. The complexity of the viral agent, plus the existence of various strains and the mutability of the virus are primary factors in the new pessimistic assessment. In addition, as pointed out in Dr. Lamptey's plenary session [PS-02-2, P. Lamptey, *HIV prevention: is it working?*], an ideal therapeutic or preventive vaccine would have to be inexpensive, stable, single-dose, orally administered, effective against all HIV strains, and offer life-long immunity to have a significant worldwide impact on HIV infection and AIDS.
 - **Effective prevention is now and will continue to be the key factor in successfully slowing the global AIDS epidemic.** Even if there were a technological breakthrough on vaccines and cures tomorrow, the complex social, sexual, and behavioral factors that place individuals at risk for HIV infection and disease would remain.
 - **The success of some well-conceived and implemented community-based, general population-based, and institution-based prevention programs has now been documented, but successes to date have all been implemented on a small scale.** The plenary on whether or not HIV prevention efforts have in fact worked offered the first internationally available overview of programs reviewed by the World Health Organization (WHO) to evaluate the prevention of sexually acquired HIV through projects that employed one or more of three strategies: reducing high-risk behavior; better management of STD cases; and increased availability and use of condoms. If the epidemic is to be slowed globally, successful prevention interventions must be replicated on a much larger scale with comprehensive scope, overall policy support, recognition of condom and STD drug needs, and substantially increased resources.

The next international conference will be in 1994, in Yokohama, Japan. Subsequent international conferences will be held every two years; however, smaller and more frequent regional meetings will continue to provide valuable, effective forums for productive networking to share information and lessons learned.

communication interventions

The process involved in enabling people to recognize, acknowledge, and act upon their high-risk behavior, and sustain this action over time, offers a key challenge to those working in HIV/AIDS prevention programs. Changing human behavior often confounds researchers and program implementors, and the Berlin Conference offered no new practical breakthroughs. However, a review of the current trends and controversies on the impact of communication interventions presented in Berlin does offer some insights relevant to the development of sustainable, effective prevention programs.

targeting

Long-standing controversies in the HIV/AIDS communication field on whether or not to target specific audiences continued in Berlin. The arguments in favor of targeting center around two main factors: effectiveness and efficiency.

- Targeted messages and programs are more cost-effective and appropriate.
- Targeting is key to the assessment of priorities and disbursement of limited resources for prevention and control of HIV infection. Dean Jamison of the World Bank offered the economist's view that there is: "greater cost-effectiveness with interventions with high-risk populations." [PS-01-2, D. Jamison, *Health economics and progress in health.*]

Reported drawbacks to targeting included:

- Targeting can engender social ostracism and stigmatization of individuals who fall into defined high-risk groups. Countries that lack national policies, programs, and general education for the population at large are seen as especially vulnerable to this phenomena.
- Those in the population who are not targeted when, in fact, they may be practicing high-risk behavior (but not as members of a "high-risk group") may perceive themselves as "safe" from HIV transmission; thus, targeting may encourage complacency and reduce the likelihood that "majority" un-targeted individuals will engage in adequate preventive activities.

The individual's perception of risk does provide a core construct for health behavior change, and potentially counterproductive effects must always be seriously considered when designing, implementing, and evaluating targeted HIV/AIDS prevention initiatives. In Berlin and at previous international AIDS conferences, the stigmatization argument has gathered support in some industrialized countries where attempts have been made to target gay communities and, to a certain extent, prostitutes. These groups generally have been the object of long-standing societal

stigmatization for other reasons. While fear and misperceptions about AIDS may exacerbate stigma in some situations, accurate targeted HIV/AIDS preventive messages and interventions have not been shown to be a primary cause of ongoing stigmatization.

There was limited concern about targeting non-stigmatized groups, such as the military and long-distance truckers. However, questions were raised about the groups left out of such efforts, such as women (other than prostitutes) and youth. In order to effectively reach these large, potentially complacent populations, calls were made to focus attention on high-risk behavior without adhering to rigid notions of high-risk groups.

From a global perspective on the effectiveness of prevention efforts and the efficient use of available resources, appropriate and well-integrated targeting represents a key factor in HIV/AIDS prevention. Each of the 15 prevention programs reviewed at the WHO/GPA consultation on effective approaches to AIDS prevention held in May of 1992 and identified in the "HIV Prevention: Is It Working?" plenary as successful included targeting — with examples from both industrialized and developing countries. Moreover, WHO has estimated the costs of launching and sustaining a worldwide prevention effort at between \$1.5 and \$2.9 billion dollars. The amount actually available globally per year is approximately \$220 million dollars when World Bank loans are subtracted. Considering the reality of known available resources, basic decisions need to be in place on whether to focus on identifiable groups at risk of contracting and spreading HIV infection, or to promote efforts aimed at reaching more general populations.

women, youth, and AIDS orphans

Some attention was focused on two groups often overlooked: women in the general population and youth. In addition, a few sessions touched on a subset of youth made up of AIDS orphans — a group of concern in an increasing number of developing countries.

women

The conference revealed an increasing interest in women and the AIDS epidemic, and not only as vectors of transmission to offspring or sex partners. However, very little is known about the natural history of HIV infection and AIDS in women, and very little emerged from Berlin indicating this issue is being studied.

- One Walter Reed study, however, found no difference in most cohorts studied between U.S. women and men with regard to progression of HIV infection to AIDS, nor from AIDS to death. [WS-CO3-5, L.I. Levin, *Preliminary analysis: Comparison of HIV-1 disease progression between men and women who are clinically evaluated in U.S. Army medical centers.*]
- A number of presentations reinforced the importance of STDs as a co-factor in HIV transmission, particularly in women whose STDs are often asymptomatic. Information on reproductive tract complications in HIV-infected women was presented (including PID, HPV, and cervical problems). These complications often lead to significant morbidity in women before the official onset of AIDS. [WS-B17-3, W. Friedmann, *Opportunistic diseases in HIV-infected women.*]
- One paper was presented on malaria, and how HIV infection diminishes a pregnant woman's biologic capacity to limit the impact of falciparum on fetal growth. [PO-BO5-1041, R.W. Steketee, *Plasmodium falciparum malaria and HIV infection among pregnant women in rural Malawi.*] This and other discussions on infectious diseases may indicate a trend towards looking at AIDS in relation to other health problems — especially tuberculosis (TB) infection.
- Regarding pregnancy and AIDS, European studies which were presented further dispelled the earlier supposition that pregnancy hastens the progression of HIV infection to AIDS, and from AIDS to death. [PO-BO1-0906, E. Raise, *The role of pregnancy in the evolution of HIV asymptomatic women*; PO-B23-1940, A. Schäfer, *The role of pregnancy in the development of HIV infection.*]

-
- The existence of perinatal transmission of HIV has, by now, been well-documented. A presentation by Dr. Catherine Peckham revealed average rates of about 15% in Europe and 30-35% in African countries. She further outlined factors that appear to be associated with increased rates of perinatal transmission, including advanced maternal clinical and immunological status, p24-antigenaemia, premature delivery, and breast feeding. [PS-04-2, C. Peckham, *Mother-to-child transmission of HIV: risk factors and timing.*]

Very little is known about identifying women's health-seeking behavior with respect to STDs, the response of the health care system to women with AIDS, or the implications of AIDS for maternal and child health (MCH) systems, including pharmaceutical supplies.

The identification of palliative care which would be simple, effective, affordable, and able to improve the quality of life of infected women will be important in the future.

Most of the presentations on the social and behavioral aspects of AIDS and women and families focused on women in developed, industrialized countries. Interventions with commercial sex workers did attract attention at Berlin, with presentations ranging from the results of KAP (knowledge, attitudes and practices) surveys, to identification of risk factors and descriptions of condom use and other prevention efforts. Reproductive rights were discussed, but largely within an industrialized country context. Some sessions looked at women as vulnerable partners, including partners of bisexual men. Many women at the conference were outspoken about the need to be included in HIV/AIDS programs. They implored programs to include components to raise the status of women through programs such as female literacy and income generation. Developing country women also called for training in partner communication, especially techniques for sexual negotiation.

Several studies reported at Berlin found that women were more likely than men to inform their partners about an STD. [PO-C20-3082, M. Wettrich, *Partner notification beliefs of persons presenting to STD clinics by gender and select client risk behavior-U.S. 1991*; PO-D20-4014, A. Ingegno, *AIDS patients in Abidjan: social dynamics and care process*; WS-D29-2, E.K. Njeru, *STD partner notification and referral in primary health care clinics, Nairobi, Kenya.*] One study in Zambia found that while men were worried about their own risk, women worried about their partner's behavior and risk. [WS-D21-6, E. Faxelid, *Partner Notification in Lusaka.*]

Only one session looked specifically at women as care givers of AIDS patients in developing countries, which was surprising considering what is known about women's roles as caretakers of the ill in general in the developing world. [WS-B33-5, M. Ssemukasa, *Women - the key to caring for the sick at home.*] A more general study found that health care workers, regardless of their sex, are considerably more likely to acquire HIV from their patients than vice-versa. [WS-C12-4, L. Robert, *Update: evaluating the risk of HIV transmission from health-care workers (HCWS) to patients.*]

The risks of infection among female health workers (particularly nurses and midwives) have tremendous implications for developing countries, where health workers are exposed to large quantities of blood during deliveries and work with a general lack of protective equipment. A WHO study reported an HIV seroprevalence rate of 22% among midwives and 11% among nurses in Uganda. [WS-C12-2, I. Kanyama, *Risk of occupational exposure to HIV among nurse-midwives and traditional birth attendants.*]

Overall, the conference did confirm two important current emphases for women and AIDS: a focus on STDs and the need for female-controlled protective methods (including microbicides, spermicides, and the female condom) to address a wide range of STDs.

youth Youth were perhaps the only group at risk for HIV infection not among the active constituent participants at Berlin. Although still controversial, the evidence is overwhelming that strategies for reaching young people must include family life/sexuality education. Dr. Anke Ehrhardt of Columbia University proclaimed sexuality education a basic human right. [PS-02-1, A. Ehrhardt, *Young people and sex education.*]

- Encouraging alternatives to sexual intercourse for young people can be effective, but only if they are introduced before the initiation of first sexual intercourse. There appears to be no documented effect once adolescents initiate sexual intercourse.
- Sexuality education programs must be gender- and age-specific, include the acknowledgement of women's rights, and foster tolerance for diversity of lifestyle and a positive attitude towards sex.
- On a closely-related subject of special interest to policy makers and politicians, a number of studies and one plenary presentation overwhelmingly refuted the commonly held notion that early sexuality education leads to increased promiscuity. [PS-02-1, A. Ehrhardt, *Young people and sex education*; PO-D02-3444, M. Baldo, *Does sex education lead to earlier or increased sexual activity in youth?*; PO-D02-3445, R. Beazley, *The effects of a sexuality/AIDS/STD educational program on knowledge, attitudes and behaviours of Canadian grade 9 students.*]

Other presentations focused on communication strategies for reaching youth, including an emphasis on self-esteem building and, as with women, a need to focus on communication strategies and techniques with partners, especially sexual negotiation. [PO-D02-3455, J. St. Lawrence, *Social support as a factor in African-American adolescents' risk for HIV infection*; PO-D02-2459, V. Paiva, *Sexuality, gender norms and condom negotiation among teenagers.*]

orphans Reports on AIDS orphans reflected problems found specifically in Tanzania, Uganda, Kenya, and Zambia. [WS-D26-1, *Trends in assisting future orphans programs*; WS-D26-2, I. Semali, *The impact of adult deaths from AIDS and other causes on the nutritional status of children in northwestern Tanzania*; WS-D26-3, G. Lwihula, *Cultural aspects of adult fatal illness from AIDS and other causes: Funeral costs, child fostering, inter-household transfers*; WS-D26-4, R.W. Nduati, *A survey of orphaned children in Kibera Urban Slum, Nairobi*; WS-D26-5, U. Sharpe, *Orphans' sexual behavior in Masaka Diocese, Uganda*; WS-D26-6, E.N. Mataka, *Children in developing countries — children in distress.*] However, little attention was paid to lower seroprevalence developing countries in earlier stages of the epidemic that will eventually also experience AIDS orphan problems. Research on the conditions of AIDS orphans largely document what makes intuitive sense:

- Orphans fare worse in nutritional and educational status than children living with their biologic parents.
- Orphan-related needs that must be taken into account by policy makers and potential service providers include clothing, school fees, food, and housing.
- The original cohort of uninfected grandparents that has been taking care of AIDS orphans since the beginning of the epidemic is dying out.
- Orphanages must continue to be resisted as a solution to the problems of orphans, as orphanages isolate children from communities.
- Adolescent orphans are themselves at high risk of HIV infection, and as a group often remain outside the reach of traditional prevention messages.

Private voluntary organizations (PVOs) and non-government organizations (NGOs) will be the major institutional providers of care for AIDS orphans, and models of care need to be developed.

HIV testing and counseling

There were two sessions in Berlin on HIV testing and counseling : a roundtable [RT-16, *HIV testing: Is it necessarily a good thing?*] and a workshop in which presentations were given on counseling and testing experiences in industrialized and developing countries. [WS-C16-1. S. Pretet, *Anonymous tests and prevention*; WS-C16-2. P. Lurie, *Routine HIV testing of inpatients: costs, benefits, and problems*; WS-C16-3. A. Russell Gerber, *HIV counseling and testing at publicly funded sites in the United States, 1990-1991*; WS-C16-4. M. Moore, *Impact of HIV counseling and testing (CT) in Uganda*; WS-C16-5. E. Salame, *Predictors of suicidal attempts/ideas among HIV test petitioners*; WS-C16-6. W. Kirschner, *Frequency of HIV tests in the German population by gender, age, social class, and risk behaviour*.] The former resulted in a heated debate about the advantages and disadvantages of HIV testing, especially in developing countries.

workshop presentations

Data were presented at the workshop from an evaluation conducted by the Centers for Disease Control and Prevention (CDC) of the AIDS Information Centre (AIC), a facility offering free voluntary counseling and testing in Kampala, Uganda. [WS-C16-4, M. Moore, *Impact of HIV counseling and testing (CT) in Uganda*; PO-C25-3214, N. Kabashira, *Gender differences before and after HIV counseling and testing in Kampala, Uganda*; PO-C25-3215, N. Frank, *HIV counseling and testing (CT) in young Ugandans*.] Risk reduction behaviors were studied in 3,000 AIC clients after pre-test counseling and at three and six months. The results showed:

- As reported by the clients, substantial and significant increases were found in certain risk-reducing behaviors, including faithfulness and condom use with steady and non-steady partners. These changes were reported by both seropositive and seronegative individuals, although to different degrees: seropositives showed greater increases in condom use than seronegatives.
- In addition, an increased proportion of seropositive individuals reported that they were abstinent after the intervention. On the other hand, seronegative individuals reported abstinence less often after the intervention.

Although this was an uncontrolled study, large differences in reported behaviors were shown, and risk reduction strategies differed for seronegative and seropositive individuals, lending support to the claim that the program was able to induce behavior change among its clients.

Impact of HIV counseling and testing (CT) in Uganda

Source: (Abstract WS-C16-4)

	HIV positive (percent)			HIV negative (percent)		
	T ₁	T ₂	T ₃	T ₁	T ₂	T ₃
Faithfulness	49	41	30	48	56	63
Condom with steady	10	79	89	15	39	36
Condom with non-steady	28	87	100	29	89	95
No sexual activity	45	57	69	45	37	33

roundtable discussions

During the roundtable discussion, the bases for counseling and testing programs were emphasized. These include:

- early detection of HIV infection can lead to referral to clinical care, including specific drug therapy where available, and other support services;
- knowledge of serostatus can relieve anxiety and help people make major life decisions (e.g., enter a new relationship, get married, or have children);
- counseling with HIV serostatus information can facilitate behavior change;
- every person who wishes to know his/her serostatus has the right to know.

However, a number of concerns were raised about the drive to develop counseling and testing programs in developing countries. [PO-D29-4254, H. Curtis, *What is the role of HIV testing in developing countries?*]

- A number of participants pointed out that early diagnosis does not necessarily lead to medical advantages in developing country settings, as required medical services and drugs are largely unavailable.
- Learning of infection has at times been associated with severe psychological distress, which might offset any medical advantage. [WS-C16-5, E. Salame, *Predictors of suicidal attempts/ideas among HIV test petitioners.*]

-
- The counseling and support services required to deal with this problem are usually not in place.
 - HIV testing has also been associated with discrimination. A participant from Brazil suggested that for Brazilians, there are very few advantages and many problems associated with knowing one's HIV status.

While roundtable participants generally acknowledged that people have a right to knowledge of their serostatus if they so desire, they agree that testing services should not operate in a vacuum, but should be part of a comprehensive control program:

- referral services should be in place to provide clinical, social, and psychological care and support;
- condoms should be widely accessible;
- the community should be fully supportive so that persons are not coerced into obtaining their test results, and seropositive individuals are not faced with discrimination.

Unfortunately, there are still very few settings in the developing world where all these conditions apply. It was also argued that it might be difficult to develop and enforce mechanisms to ensure that the test would be provided on a voluntary basis and that the results would be treated as confidential.

One of the strongest criticisms leveled at counseling and testing programs concerned their high cost. While it was suggested that counseling and testing might be provided through the private sector at cost, even this may not be simple to organize. A roundtable participant from India described a situation in which private clinics have sprung up offering anonymous HIV testing; no counseling is offered, and discrimination against persons with HIV or AIDS is rife.

In sum, voluntary counseling and testing can have an important role to play within a comprehensive program for the care and support of persons with HIV/AIDS, in settings where preventive and supportive measures are available, and where the social environment does not discriminate against persons with HIV/AIDS. However, the contribution of voluntary counseling and testing activities to the prevention of HIV/AIDS, especially in developing countries, is still unclear. Further research and evaluation is under way to provide the information required for guiding public health policy in this area.

vaccines, therapies, and the impact of tuberculosis (TB) on HIV/AIDS

The problems associated with developing vaccines against HIV infection have not abated with the ever-increasing knowledge and scrutiny of HIV. The basic question of what constitutes protection in terms of immune response remains unanswered, nor is it clear how HIV causes disease. Indeed, it is postulated that some immune responses to HIV vaccines could cause disease.

There are six requirements for an optimal HIV vaccine's availability, application, and distribution:

- the provision of safe and effective prevention or quick eradication of initially infecting HIV strains regardless of the type of HIV exposure (blood, sexual, milk);
- practical application that provides protective anti-HIV immunity, such as an oral dose or established protection after one or two injections;
- possession of heat-stable characteristics and no need for sophisticated preservation measures;
- simple steps for administration;
- affordable cost for all countries;
- compatibility with other vaccines being administered.

Even before these requirements are met, however, there remains complex scientific and medical barriers to vaccine development. There remains a lack of knowledge of the correlates of protective immunity, with no satisfactory animal models of HIV infection on which to test possible vaccines. Vaccines are currently designed to induce some or all of the types of immune responses that are surmised, but not known, to be protective against HIV. [PS-05-01, D. P. Bolognesi, *Development of Human HIV Vaccines.*]

Because there is no animal model, researchers are studying specific groups of individuals to try and understand what part(s) of the immune response protect from infection or disease:

- Individuals who have lived for several years with HIV infection are one such group. These long-term survivors appear to have a specific component of the immune system, called cell-mediated immunity, that is strongly reactive to the HIV virus. [PS-05-2, J. Levy, *HIV pathogenesis and long-term survival*; PS-01-3, A. Fauci, *Immunopathogenic mechanisms of HIV infection: implications for therapeutic strategies*; WS-A07-6, D. Mann, *Selected HLA class I and II alleles are*

associated with relative rates of disease progression in HIV-1 infection; WS-A09-4, G.M. Shearer, HIV exposure in long-term non-seroconverting homosexual men at risk for HIV infection; WS-A15-5, S.H. Weiss, Evidence of Immunologic and virologic responses to HIV exposure among a high risk but long-term HIV antibody seronegative (HIV-) cohort of injection drug users (IDU); WS-A21-6, D. Schwartz, Immune response without HIV in the blood of a long-term survivor; WS-B03-1, H. Sheppard, Characterization of long-term HIV-1 infection without CD4+ cell loss (non-progressors); WS-B03-2, S. Buchbinder, Healthy long-term positives (HLPs): genetic cofactors for delayed HIV disease progression; PO-A22-0490, Z. Bentwich, HIV specific immunity in seronegative individuals.]

- A second group of individuals of interest are those who are known to have had multiple exposures to HIV infection, such as prostitutes in Africa and sexual partners of AIDS patients who continue to have negative HIV tests. Some of these individuals have an immune response to HIV, implying that the immune system had been exposed to the virus although they have no antibody to HIV. [WS-A07-3, F.A. Plummer, Evidence of resistance to HIV among continuously exposed prostitutes in Nairobi, Kenya.]
- A third group under study are individuals with new HIV infection. In acute HIV infection the body's immune response is able to quickly contain but not eliminate the virus. [WS-A15-2, A. Vyakarnam, HIV replication by TH1 but not TH2 CD4+ T cell clones specific for HIV-1 gag p24.]
- Pregnant women are the fourth group being studied in the hope of determining what factors in the mother protect the infant from HIV infection. [WS-B06-3, M. Lallemand, Antibody response pattern and prediction of perinatal transmission of HIV-1 in African women; WS-B06-4, J. Puel, Maternal viral cell load is related with mother-to-infant transmission of HIV-1; WS-B06-5, U. Bredberg Rådén, Predictive markers of mother-to-child transmission of HIV-1 in Tanzania; PO-A11-0188, N. Remy, Identification of viral isolates involved in mother to child transmission of human immunodeficiency virus; PO-A21-0459, B.M. Polliotti, Maternal neutralizing antibodies on the transmission of HIV from mother to infant.]

The mechanism by which HIV destroys the immune system is not well understood. It is thought to include direct destruction of the immune system by the virus; the immune system destroying HIV-infected cells; and an effect of HIV on the cell to induce programmed cell death at an inappropriate time. In the laboratory there is also some evidence that some kinds of antibodies to HIV enhance rather than inhibit HIV's growth. It is therefore important to assure that vaccines induce beneficial and not pathogenic immune response. [OP-01-1, R.C. Gallo, Perspectives for the future control of HIV; PO-A19-0374, L. Meygaard, Contribution of programmed death of T cells to HIV pathogenesis.]

HIV mutates in an infected person to escape the immune system. This promotes the emergence of resistant strains. One of the major questions in vaccine development is

whether a vaccine can be prepared that will be effective against the many mutated forms of HIV. It is also not known whether there is an area or site of the virus that is so important to its survival that it is conserved and does not mutate, and whether a vaccine could be made to be effective at such a conserved site.

The vast majority of HIV infections in the world are acquired sexually, so it is important that a vaccine protect against mucosal exposure (vaginal and urethral). Very little is known about the nature of mucosal immunity required for protection from HIV, or whether protection from HIV at mucosal sites is possible at all. [PS-05-1, D.P. Bolognesi, *Development of human HIV vaccines.*]

**current
vaccine
investigations**

The vaccines currently under investigation consist of genetically engineered parts of the virus, mainly from proteins of the outer coat. These would be administered by injection, and it is not known whether these systemically administered HIV immunogens will induce mucosal immunity. There are four main types of vaccines currently being considered. [PS-05-1, D.P. Bolognesi, *Development of human HIV vaccines.*]

- Subunit and peptide, using small pieces of the outer coat of the virus: these vaccines initially did not provide a high nor a persistent antibody response. More recent genetic engineering has resulted in subunits that more closely resemble the three-dimensional structure of the proteins on the actual virus. Adjuvants, or vaccine enhancers, have also improved; consequently, antibody responses are now higher and more persistent. There is still some question as to the degree of cell-mediated immunity that these vaccines elicit against HIV.
- Vector vaccines: these vaccines are made by inserting the genetic material of the proteins of the outer coat of HIV into larger viruses like the smallpox vaccine virus. The theoretical advantage of this method is that there is a component of cell-mediated immune response to these larger viruses. Introducing HIV proteins on a larger virus may help the body develop cell-mediated immunity to HIV.
- Whole killed virus: this vaccine is made by taking the whole virus and treating it such that it will not be infectious. It was not originally tested because there were worries that if the preparation of killed vaccine was not adequate and some of the HIV was still infectious, the vaccine would cause AIDS. However, some recent lab experiments where African Green monkeys were given whole killed SIV vaccine (SIV is a virus related to HIV) showed good results.
- Live attenuated virus: this vaccine is made by taking out a section of the virus' genetic material so that the virus cannot cause a complete infection. This approach was also dismissed earlier because of the fear that HIV itself might cause certain cancers even if it did not cause AIDS. Because of the disappointing results of peptide and subunit vaccines and the success of the whole killed virus in monkeys, this concept is being re-examined.

To date, no human trials have occurred to test whether these vaccines prevent infection with HIV (efficacy trials), although many small safety tests have occurred [PS-05-1, D.P. Bolognesi, *Development of human HIV vaccines*; OP-02-1, W. Dowdle, *Future HIV vaccine policy and implications for future efficacy trials*]. In all likelihood, efficacy trials in humans are at least two years away.

**current
therapies**

There are two basic approaches to HIV therapy: decrease the amount of virus and hence destruction of the immune system; or boost the immune system to counter the effects of HIV infection. While no major breakthroughs in either approach were announced at Berlin, an ongoing controversy concerning Zidovudine (AZT) became more heated, and the debate over the effectiveness of KEMRON was resolved.

The only licensed drugs that decrease the amount of HIV virus — Zidovudine (AZT), DDC, didanosine (DDI) — all work in the same way in the virus and act to prevent the virus from entering the genes of the infected person. While the virus appears to become resistant to these drugs, some evidence was presented indicating that treatment with two drugs appears to work better than treatment with one drug. [PS-03-2, J.M.A. Lange, *Antiretroviral treatment*; WS-A19-4, J. Balzarini, *Appropriate treatment modalities prevent emergence of virus resistance to HIV-1-specific inhibitors in vitro*.]

The most highly publicized issue at Berlin concerned the Concorde Trial: a European trial started in 1988 of AZT therapy in early, asymptomatic infection. [WS-B24-5, M. Seligmann, *The Concorde Trial: First Results*.]

- The main conclusions of the trial stated that there was no benefit in using AZT early in HIV disease rather than deferring treatment until later in the disease.
- Furthermore, CD4 cells commonly used as a marker of disease progression did not correlate with the outcome; that is, a decline in CD4 cells was not associated with death or the development of AIDS.

There are some methodologic problems with the Concorde Trial: a significant number of patients originally randomized to placebo (32% overall and 56% of patients with low CD4 cells [less than 500]) switched to AZT one year into the three-year study. AZT was offered to them after it was approved for therapy in HIV infection. This large number of patients switching to AZT might have introduced a bias in the observed results. Moreover, the overall clinical benefit of AZT may wane over time, possibly due to resistance of HIV to the drug. There is some data from the US indicating that the risk of developing AIDS in patients using AZT was significantly reduced if the patient was switched to DDI. [PO-B26-2024, T. Evans, *Switching to DDI is superior to continued ZDV for patients with progressive symptoms. Results of Bristol study 010*.]

Preliminary progress on other approaches to decreasing the amount of virus presented at Berlin include:

- Blocking the enzymes that break up large virus proteins before virus assembly (protease inhibitors). This may be the next class of drugs licensed. [PO-B26-2023, J.P. Vacca, L-735,524, *An oral bioavailable HIV-1 protease inhibitor*; WS-B26-3, J.F. Delfraissy, *A phase I-II dose ranging study of the safety and activity of Ro 31-8959 (HIV-Proteinase inhibitor) in previously Zidovudine (ZDV) treated HIV-infected individuals*; WS-A18-6, K.Y. Hostetler, *HIV protease inhibitor lipid prodrug exhibits greatly prolonged plasma residence time in vivo*; WS-B26-6, S.A. Danner, *Phase-I study of A-77003, an HIV protease inhibitor, in man*; WS-A18-3, M.J. Otto, XM323, *a novel non-peptidyl inhibitor of HIV protease with potent in vitro antiviral activity*; WS-A18-4, C.H. Chang, *Novel non-peptide inhibitors of HIV protease: three dimensional structure of the complex by X-ray crystallography.*]
- Blocking a protein that helps make more HIV-infected cells (transactivating protein inhibitor). [PO-A07-0099, E. Vives, *Effects of the basic domain on HIV-1 TAT transactivation using chemically synthesized TAT protein and TAT peptides.*] The possible advantage of this approach lies in its potential to stop the spread of HIV infection to other cells after the HIV has infected one cell.

Efforts to boost the immune system focus on understanding the complex ways that immune cells communicate with each other (cytokines) and developing drugs that mimic their activity in order to boost parts of the immune system that appear to keep the virus in check. [PO-B26-2077, M. Robles, *Comparative study of three treatment schemes vs. HIV: AZT 300 mg/day plus alpha-interferon 2B; AZT 300mg/day and AZT 500 mg/day: preliminary report*; PO-B26-2073, J. De Créé, *A phase-I study of R 89439, a potent alpha-APA RT-inhibitor on HIV-1 negative and HIV-1 positive volunteers.*] Oral administration of low-dose cytokines (alpha-interferon) had been touted as a treatment for HIV in Kenya. A WHO study of the effectiveness of "KEMRON," the name given to this low-dose oral treatment, concluded that KEMRON has no therapeutic effect. [PO-B26-2056, E. Katabira, *Low-dose oral interferon alpha in the management of symptomatic HIV-1 infection.*] The other effort involves ways to reconstitute the immune system that has been destroyed by the HIV virus. [PO-A19-0394, S.K. Stanley, *Delineation of cell types infected by the human immunodeficiency virus (HIV) in the thymus of the SCID-HU mouse*; PO-A18-0362, B.D. Greenstein, *Regeneration of immune tissues with inhibitors of estrogen biosynthesis*; PO-A17-0350, L. Su-ling, *Thymic changes in SIVsm infected cynomolgus monkeys.*]

**tuberculosis (TB)
and
HIV/AIDS**

Dr. Kevin De Cock highlighted the increased importance of TB infection to the HIV/AIDS epidemic worldwide. [PS-04-3, K. De Cock, *Tuberculosis and AIDS: Treatment, prophylaxis, and public health issues.*] While interventions strategies have lead to a marked decrease of morbidity and mortality from TB in developed countries, it remains a major problem worldwide. One-third of the world's population is infected

with the tubercle bacilli and is at risk of getting TB disease. Eight million new TB disease cases occur annually, 95% in the developing world. TB disease accounts for three million deaths annually, or 9% of all worldwide deaths and 26% of all avoidable deaths in adults.

Currently, 3% of global TB cases are associated with HIV infection. It is estimated that this proportion will increase to 10% by the year 2000. Although this represents a relatively small percentage on a global scale, in certain areas the rate is dramatic: In Abidjan, Côte d'Ivoire, 39% of adult TB cases are considered to be attributable to HIV infection. Four to five million people are estimated to be co-infected with HIV and TB, with 80% of this total living in Africa.

Dr. De Cock presented several lines of evidence that TB is an opportunistic infection in the setting of HIV infection. Evidence includes: clinical observations and data from TB and HIV surveillance, HIV testing of TB patients, cohort studies, and chemoprophylaxis in HIV-infected people. In Abidjan, 32% of 247 adult AIDS deaths had disseminated TB as the cause of death, which often was not realized antemortem. This represents a rate three times higher than other causes of death in AIDS and 16 times higher than TB in HIV-seronegative patients.

Surveillance data from the US indicates that TB cases had leveled off until 1985, but are on the rise again in those US cities with an HIV infection problem. In Abidjan the TB incidence between 1985 and 1991 was highest in 30-39-year-old males and in 20-29-year-old females — both age groups that have the highest HIV infection rates in these populations. HIV seroprevalence studies among TB patients indicate that the HIV seroprevalence is two to five times higher than in the general population.

In terms of biologic interaction between HIV and TB, it appears that HIV may:

- increase re-activation of TB;
- increase risk of primary infection and mortality from TB;
- increase risk of re-infection;
- be accelerated by TB infection.

In developing countries, the vast majority of TB infections precede HIV infection. HIV infection, however, alters the 10% lifetime risk of TB to a 10% annual risk of TB in the setting of HIV infection.

The diagnosis of TB is more difficult in HIV-infected patients because of decreases in smear positivity, atypical X-rays, and increased false positive x-rays. Therapy is also more difficult because of increased adverse effects from medications, increased mortality, and questions about increased relapse rates. Overall, 18-20% of HIV infected patients have adverse reactions from TB chemotherapy. In a study from Africa, the odds of dying with TB were 16 times higher in HIV-infected people compared to HIV-uninfected people. [WS-B09-1, J. Batungwanayo, *Impact of HIV infection in Tuberculosis in Kigali, Rwanda: One year study of 377 cases.*]

De Cock's plenary closed with a comparison of the control measures that we have for TB and for HIV:

TB	HIV
vaccine 0-80% protective against severe disease in children	no vaccine
preventive therapy 90% effective	no preventive therapy
therapy cures 90% of patients	no curative therapy

In spite of effective modalities of control, TB is still the leading cause of adult preventable death. This illustrates the lack of political will for global disease control, and calls into question what the future may hold when advances are made in HIV vaccines and therapies.

economics, the response of governments and donor response

economics Speakers at an economics symposium [WS-D23-1 through D23-6, *Societal response: economic issues*] predicted that AIDS will impose enormous burdens on the health care systems of both developed and developing countries. Speakers also emphasized that the cost of caring for HIV-infected persons must be presented in the context of its societal impact. A symposium presentation by Steve Forsythe of AIDSCAP reported the results of work in Malawi. [WS-D23-2, S. Forsythe, *Projecting the socio-economic impact of HIV/AIDS in Malawi.*] The direct AIDS-related costs to the health system in Malawi currently stand at 20% of the annual recurrent costs, and are expected to rise as the epidemic expands. In addition, the indirect costs in lost productivity are expected to range between 14-21% of GNP in the formal sectors of the Malawi economy by the year 2000. Other studies suggest that such estimated costs are but one part of a much larger social cost which also will continue to rise throughout the developing world:

- An ongoing study in northwest Tanzania found that less than one-fourth of people who died of AIDS visited hospitals. In most cases, the cost of AIDS is borne by the household. [WS-D23-1, P. Mujinja, *The impact of AIDS on health care utilization and expenditure by the fatally ill in northwest Tanzania.*]
- A study in Zaire found that patients were able to pay for only half of their hospital expenses. The burden for the other half fell on families and health facilities. [WS-D23-6, N. Mposo, *The HIV positive patients' ability to support health care cost and the impact on the hospital.*]

The costs of AIDS are likely to be larger than can be currently documented. In many cases, costs will be carried by a health system already vastly overburdened and with too few resources to deal with numerous public health and medical problems. AIDS also will create a burden on families that lose the income and support that those with AIDS had brought to the household. For people in poverty, the stress of carrying for dying relatives and the loss of income is likely to intensify their already difficult living conditions.

**the
response
of
governments**

It is clear that government policy and program priorities can play a major role in determining the course of the AIDS epidemic:

- Robert Hanenberg of AIDSCAP discussed the decisions by the government of Thailand to emphasize use of condoms in the CSW network. As a result of this policy and subsequent programs, there has been a significant decline in the rates of STDs in Thailand. [WS-C21-4, R. Hanenberg, *The use of sexually transmitted disease (STD) statistics to evaluate Thailand's HIV prevention program.*]
- Zambia's 54 STD clinics have contributed to a significant decline in STD rates in that country. The University Teaching Hospital in Lusaka, Zambia, saw a 72% decline in STD cases from 1983 to 1991 as a result of enhanced STD detection and management in Zambia. [WS-C22-6, S. Hira, *Zambian national STD control program: a model program.*]

However, government policies may also exacerbate HIV transmission. One presentation attributed an increase in STD rates, in part, to the government's decision to direct national resources to carry on its war against Tamils rather than to needed social service. [PO-C08-2758, D. Fernando, *The civil war in the northern & eastern provinces & STD & HIV infectivity in Sri Lanka*; PO-C10-2808, I. Abeyewickreme, *Sexually transmitted diseases and HIV in Sri Lanka.*] Elsewhere, several studies found National AIDS Control Programs (NACPs) to be weak and ineffective. One study argued that the NACPs were not strong advocates within the political priority setting process, in large part because they had little experience in that process. [PO-D28-4233, B. Olivier, *Cost of national AIDS programmes in developing countries: Cost analysis and trends.*] Essentially, the NACPs were created out of what had been technical components of the health bureaucracy, and when these technical units were elevated into a policy role, they were not prepared or equipped to successfully serve an AIDS program advocacy role within political systems.

Government responses can also be examined from the standpoint of evaluating those cases where government was essentially passive, or uninvolved, and did not become a barrier to innovative prevention initiatives. It is within this context that many NGOs have flourished. For example, in South Africa 7,000 traditional healers have received training in HIV prevention. The training included explicit discussions of sex with clients, how to use condoms, and appropriate referrals as needed. [WS-D13-2, M. Mancini, *Organizing South African traditional healers to mount sexually explicit AIDS prevention initiatives.*]

Although NACPs may often be weak, and governments erratic in their responses, the evidence from Berlin does appear to confirm that worldwide, the range of groups trained in AIDS prevention is far wider than that of other recent international development or health programs. People with HIV, schoolchildren, healers, barbers, CSWs, pharmacists, businesses, unemployed people, and others have all been trained in various aspects of prevention activities.

**international
donor
response**

As previously noted, Dr. Michael Merson urged international spending of \$2.5 billion per year on prevention: the estimated cost of a minimal package of HIV/AIDS prevention measures in all developing countries. [WS-D24-6, N. Soderlund, *Estimating the cost of HIV/AIDS prevention strategies in developing countries.*] Merson, Soderlund, and others maintained that this amount would buy a minimum but effective package of prevention measures. Dr. Peter Lampthey reinforced this message with a number of examples of effective prevention interventions during the "Prevention: is it working?" plenary. However, a World Bank panelist referred to its 1993 *World Development Report* on world health to question whether \$2.5 billion could be effectively used by countries, especially those with weak infrastructure and management. [ME-02, *Meet the experts panel: Priorities and impact of international donors.*]

A representative from the World Bank asserted that its structural adjustment programs over the past 13 years do not undermine social service spending or lead to greater vulnerability of low-income people and thus increase their risk of HIV. The World Bank representative called for greater efficiency in the use of health resources; however, one panelist questioned the relevance of this call when African countries spend about \$4 per capita per year on health — a figure too low to establish meaningful preventive and curative programs.

From a policy and economic point of view, the Berlin Conference pointed to the need for coherent studies of the cost-effectiveness of various prevention intervention to help policy makers determine the most appropriate policies and programs. Together with other prevention-related issues, AIDS must be viewed as a development issue that overlaps with poverty, income, gender, and processes of empowerment.

program considerations for prevention efforts

The Berlin Conference reinforced a universal need to synthesize the many ideas and prevention-based initiatives and programs into a larger framework for understanding and subsequent action. Worldwide efforts can be grouped into three overlapping active categories: program designs, program implementation, and external messages on prevention.

program design

- What has proven successful must be meshed with new initiatives.
- Movement toward regional planning needs encouragement and support.
- Assistance must be offered with HIV/AIDS policies to enhance and support prevention efforts.
- Through policies and programs, efforts need to be in place that discourage discrimination and eliminate other unethical practices. Certain groups within society need continued and increased attention, especially women (not limited to CSWs) and youth inclusive of AIDS orphans.
- HIV/AIDS prevention efforts need to be increasingly integrated into family planning and MCH programs.
- The projected rapid growth of AIDS in Asia must become a world concern of highest priority.
- The movement of HIV infection and AIDS into rural areas requires planning and program implementation action.
- Care management and STD control initiatives need support and integration into HIV/AIDS prevention programs.

program implementation

- In areas where incidence is on the increase, various program components must be integrated. The importance of community involvement must be recognized, and appropriate actions taken.
- Projects in areas with low but increasing incidence should focus on high-risk behaviors and develop targeted interventions based upon the high-risk behavior of targeted groups.

-
- There is a need to expand small-scale projects of proven effectiveness while maintaining community involvement.
 - Prevention programs must look closely at human sexuality and effective means for modification of high-risk sexual behavior.
 - Innovative schemes for reaching people with STD treatments and prevention will be of increasing importance to HIV prevention.
 - Voluntary HIV counseling and testing projects should be evaluated from a prevention perspective to assess their ability to cost-effectively sustain decreased high-risk behavior in developing countries.

**external
messages**

Preventive themes must continue to be developed regionally within the developing world and promoted globally. The lessons learned via evaluation of successful interventions must be incorporated into all prevention initiatives in the developing world. The results from WHO's evaluation of prevention programs used in the "HIV Prevention: Is It Working?" plenary are of great significance to prevention in the developing world: 12 out of the 15 successful programs presented came from prevention programs in developing countries where the epidemic is most severe. The Berlin Conference provided substantial support of the need for increased prevention efforts. If this trend continues, those working in this field may find new opportunities to expand the reach of viable prevention initiatives, as well as opportunities to maintain and increase the visibility, credibility, and status of established programs.