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TURNING POINT IN HIV/AIDS RESEARCH : VISION OF HOPE

Perhaps for the first time since the start of the HIV pandemic the results of biomedical research in HIV/AIDS are providing rays of cautious hope through the dark clouds of despair and helplessness. The new knowledge are the windows of opportunity for developing effective therapy and prevention strategies.

In any disease control programme, more so for HIV/AIDS, an element of hope is essential. Without hope people with HIV will have no reason to face up to the dramatically changed circumstances of their lives. They would have no cause to believe that elegant advances made in biomedical science can contribute to building a world in which AIDS would no longer be a threat to the health and survival of millions. It is only within the climate of hope—not one of fear and anxiety, that the threat of HIV/AIDS epidemic can be confronted and overcome.

Unfolding of the Epidemic

By the end of 1995, a total of 1.3 million cumulative AIDS cases had been reported from 193 countries to the WHO. After allowing for under diagnosis, delays and under-reporting, and based on estimated number of HIV infections, there are 6 million cumulative AIDS cases world-wide. Currently 20.1 million adults are estimated to be alive and infected with HIV or have AIDS. There are at present 3 men infected for every 2 women. Globally nearly 10,000 new infections occur each day. Of the total prevalent infections, the majority remain concentrated in eastern, central and southern Africa. But the epidemic is evolving with spread of infection from urban to rural areas as well as to West and South Africa, India and South-East Asia and to a lesser extent (with proportional shifts to heterosexual infections) in North America, western Europe and Latin America. WHO currently projects that there will be 26 million persons infected with HIV by the year 2000, representing a cumulative total of over 40 million infections; more than 90 per cent will be in developing countries. The projected cumulative total of AIDS cases will be close to 10 million[1].

The economic and demographic consequences of the spread of HIV/AIDS are inexorable and awesome. The challenge is to act speedily and effectively to limit the further spread of the epidemic and to minimize its impact by harnessing the results of rapid progress in biomedical research on HIV/AIDS that has taken place over the last 15 years.

Turning Point in HIV/AIDS Research

Though there are many areas of biomedical research which hold promise/hope for the future, there are some which have immediate relevance and application. Discussed here are four such areas. Taken together, they

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could be described as the turning point of HIV/AIDS research. They have generated hope in our struggle against HIV. These are (i) a clearer understanding of biology of HIV and host response, (ii) availability of several new and promising drugs, (iii) strategies to reduce perinatal transmission of HIV, and (iv) successful interventions for behavioural change.

Estimated Global Burden (in million) of HIV/AIDS: End of 1995	
North America	0.79
Latin America & Caribbean	1.47
Western Europe	0.47
North Africa, Middle East	0.21
Sub-Saharan Africa	12.90
Eastern Europe & Central Asia	0.03
East Asia & Pacific	0.03
South and South-East Asia	4.17
Australasia	0.01
Total	20.08*

**including persons living with AIDS*
Source : Mertens & Low-Beer, 1996

Biology of HIV and Host Response

Dynamics of HIV replication

The replication of HIV in the human body controls the natural history and pathogenesis of HIV infection. It multiplies mainly in the lymph nodes, spleen, gut-associated lymphoid cells, and macrophages. Despite the obvious importance of clearer understanding of viral replication relatively little quantitative information was available regarding the kinetics of virus-production and clearance. This quantification has now become possible because of availability of retroviral agents with sufficient potency to abrogate HIV-1 replication and sensitive polymerase chain reaction (PCR) based methods to quantify the virus. These assays are able to pick up HIV RNA throughout the course of the disease of all patients, regardless of the clinical stage.

By using drug inhibitors of HIV-1 (protease and/or reverse transcriptase inhibitors) that block *de novo* infection of cells, the rate of elimination of plasma virus has been determined. From serial measurements of the subsequent changes in plasma viraemia (and CD4 lymphocyte counts) it has also been possible to infer kinetic information about pre-treatment steady state.

It is now known that the composite lifespan of plasma virus and virus-producing cells is remarkably short ($t_{1/2} = 2.0 \pm 0.9$ days). This holds true for patients with CD4+ lymphocyte counts ranging from 18 to 355 cells/mm^3. Extrapolating from changes in blood it could be shown that between 10^8 and 10^9 virions are being cleared every day, equivalent to about 30 per cent of the total. As the levels of blood-borne viraemia show only gradual changes over many months, the daily rates of virus destruction and production have been taken to be roughly equal, that is HIV production must be around 10^8-10^9 per day[2]. That the mean half-life of virus producing cells is around 2 days, indicates that turnover of the actively infected cells is both rapid and continuous. It could also be inferred that nearly all of plasma virus must come from recently infected cells.

Several of the more potent combinations of antiretroviral drugs are capable of inducing such a dramatic fall in viral replication that the virus may no longer be detectable in plasma with the currently available techniques. Though studies of the relationship between changes in viral RNA in plasma and changes in levels in fixed lymphoid tissue are fragmentary, those that have been completed suggest that viral RNA levels in plasma

Situation of HIV/AIDS in India		
AIDS cases in India	Male	Female
Total no of AIDS cases	2284 (76.2)	712 (23.8)
Probable source of infection in India		
Hetrosexual promiscuous	2205(73.6)	
Blood transfusion	209(7.0)	
Blood product infusion	23(0.8)	
Homosexual contact	23(0.8)	
Spouse of AIDS patients/ seropositives	37(1.2)	
Intravenous drug addicts	239(8.0)	
Others	260(8.6)	
Total	2996	

Figures in parentheses are the percentages
Source : NACO, Period of report upto 31st October, 1996

is an indirect reflection of the number of productively infected cells in the body as a whole, and that most viral replication occurs in extra-vascular fixed lymphoid tissues. It is this viral replication in lymphoid tissues rather

than circulating virus *per se* that is mechanistically linked to the progressive immunologic depletion that characterizes the illness[3,4].

Surveillance Data for HIV Infection in India

Details of seropositive individuals

Group	Seropositive
Hetrosexually promiscuous	18350(38.2)
Homosexuals	181(0.4)
Blood donors	3939(8.2)
Dialysis patients	241(0.5)
Antenatal mothers	435(0.9)
Recipients of blood/blood products	822(1.7)
Suspected ARC/AIDS cases	8409(17.5)
Intravenous drug users	2375(4.9)
Others	13281(27.7)

Seropositivity rate 16.5 per thousand

Figures in parentheses are the percentages
Source : NACO, Period of report upto 31st October, 1996

The rate of virus replication stabilizes after primary infection at a particular level or 'set point' in each individual. This level appears to be 10^2 to 10^6 HIV RNA copies/ml of plasma and remains relatively stable in asymptomatic patients over months and possibly years. The 'set-point' is strongly associated with rate of disease progression and time to death, with a continuum of increased risk with increased plasma HIV RNA levels[5].

These results coupled with the demonstration that the level of plasma viraemia at 6 months to one year following primary infection is an accurate predictor of the rate of disease progression leave little doubt of the importance of virus replication to the pathogenesis of HIV diseases.

Measurements of viral burden may now form the basis for decisions concerning initiation and modification of anti-retroviral therapeutic regimens, and this will be of practical consequence. HIV RNA levels appear to be more predictive of progression than CD4+ counts particularly in asymptomatic individuals with cell counts higher than 0.35 x 10^9/l. In addition to the usefulness in assessing prognosis and guiding the initiation of therapy, HIV RNA levels are of potential value in assessing response to therapy.

As an estimated 10^8 to 10^9 virions are produced daily, it is very likely that HIV-1 replication continues in lymphoid tissues though at a significantly lower rate. Even at these lower replication rates it would be expected that viral variants with reduced susceptibility to anti-retroviral drugs will evolve over time. An asymptomatic individual can harbour at least 10^6 mutants of HIV, and for an AIDS patient the figure is more than 10^8, among which one may find drug-resistant mutations. Thus, even in the absence of any selective pressure, a sub population of viral variants that is resistant to anti-retroviral drugs evolves. The prevalence of such mutants in the population of virus prior to the initiation of anti-retroviral therapy is dependent on the number of prior rounds of viral replication, the mutation rate, and the selective advantage possessed by wild-type virus over variants that have incorporated mutations confering drug resistance. Recent studies have shown that there is almost complete replacement of wild-type virus by drug-resistant variants in plasma within 14-28 days[2].

Turnover of CD4 cells

The concomitant recovery of CD4 cells following drug treatment has also been studied. If it is assumed that dynamics of blood lymphocytes reflect events throughout the body, and that the blood lymphocyte pool is about 2 per cent of the total population, the overall mean CD4+ lymphocyte turnover is about 2x10^9 cells/

Projection and Estimation (in million) for 2000

Cumulative number of HIV infected	40
Persons infected with HIV	26
Cumulative number of AIDS cases (adults)	>10
Children <5 years infected through mother	5
HIV related death (adults)	>8
Children <10 years orphaned as a result of AIDS related death	5-10
New cases/year	
Africa	0.7
Asia	0.5
Prevalent HIV infections in India	5
AIDS cases in India	>1

Source : Mertens & Low-Beer, 1996; Quinn, 1996

day. The number of CD4 lymphocyte destroyed and replenished each day is of the order of 10^9 , which is strikingly close to estimates of total number of HIV-1 RNA expressing lymphocytes in the body as determined by using *in situ* PCR and hybridization methods[6].

This rapid and on-going recruitment of CD4+ cells into a short-lived virus expressing pool probably explains the abrupt increase in CD4+ lymphocyte numbers that is observed immediately following initiation of potent anti-retroviral therapy.

The CD4 lymphocyte depletion in advanced HIV-1 infection has been likened to a sink containing a low water level, with the tap and drain both open equally wide. As the regenerative capacity of the immune system is not infinite, it is not difficult to see why the sink eventually empties. It is also evident that the primary strategy to reverse immuno-deficiency should be to target virally mediated destruction, rather than to emphasize lymphocyte reconstitution[6].

Other developments

Two other significant breakthroughs, though they do not qualify to have immediate application, deserve mention. These are the identification of HIV suppressive factors and co-factors.

HIV suppressive factors: The CD8+ lymphocytes are believed to be involved in the control of HIV-1 infection *in vivo*, by cytotoxic mechanisms and/or by release of HIV suppressive factors. The levels of production of these factors correlate with the stage of disease and show a progressive decline in parallel with the decline of the immune system. For several years, many groups tried to identify these elusive CD8+ suppressive factors.

The chemokines RANTES, MIP-1α and MIP-1β have now been identified as the major suppressive factors produced by CD8+ T cells[7]. A combination of monoclonals antibodies to these chemokines could block the activity of CD8+ suppressive factors. It has been shown that these 3 chemokines are the major HIV-suppressive factors secreted by CD8+ cells.

Clinical studies on the production of RANTES, MIP-1α and MIP-1β *in vivo* will be critical to define their role in the natural history of HIV infection, especially whether high levels of these chemokines are associated with delayed progression of HIV disease. Chemokines levels may also provide a reliable correlate of protection in monkeys treated with experimental vaccines. The identification of HIV-suppressive chemokines may open new perspectives for the development of effective therapeutic approaches to AIDS.

HIV co-factor: It is known that HIV enters cells by docking onto a receptor protein known as CD4. By itself CD4 is not sufficient for HIV infectivity, some unknown 'co-factor' found only in human cells is also required. Researchers have reported the discovery of a membrane protein called 'fusin' which together with CD4 permits cells to fuse with HIV's surface—a key step in the infection process[8].

Interpreted in the light of the earlier findings, chemokines could be suppressing HIV infection by blocking the fusin receptor directly or by sending signals that make cells produce fewer receptors. If so, then together the two sets of findings might help to explain why a small percentage of people have been able to resist HIV's ability to destroy the immune system even after being infected with HIV for a decade. They may have higher levels of these chemokines, fewer fusin like receptors or both[8].

This discovery could help clear up several puzzles about HIV, including how it destroys cells and why it appears not to harm some infected people. The work could also lead to an animal model; by stitching the fusin gene into a small animal such as rabbit, it would be possible to develop a relatively inexpensive laboratory model for testing AIDS vaccine and study exactly how HIV destroys the immune system. And it also raises the prospect of new therapies that, by blocking binding to fusin would limit HIV's ability to infect cells[8].

Thus, clear messages for management of HIV/AIDS emerge from improved understanding of the biology of HIV and the host response. Given that the virus is replicating 24 hours a day and from day one, anti viral treatment is called for at all stages of the disease. Any means to reduce viral spread will ultimately be beneficial. Treatment strategies, if they are to have a dramatic clinical impact, must therefore be initiated as early as possible in the course of infection, perhaps even during sero-conversion.

The demonstration that there is complete replacement of wild-type virus by drug resistant virus in plasma within 14-28 days is a striking example of the capacity of the virus to evolve in response to selection pressure.

Against this background, monotherapy cannot succeed. Only a combination of drugs has the potential to outwit the virus.

The recovery of the CD4+ count, even in symptomatic infection, implies that immune reconstitution may be possible as long as replication of the virus can be held in check.

Novel Therapies for HIV/AIDS

Early studies on pathogenesis and the ability to better quantify plasma HIV load have established the dynamic nature of HIV infection. Also established has been the fact that an aggressive therapy instituted early in infection is not only desirable but also essential.

The presentations made at the III Conference on Retroviruses and Opportunistic Infections, Washington and the XI International Conference on AIDS, Vancouver, earlier this year have sparked enthusiasm in developing drug regimens for the prevention and treatment of HIV/AIDS.

Till recently only one family of drugs (nucleoside analogues) had shown to be promising after extensive clinical trials. Zidovudine (AZT) was the first of such drugs that was developed. It worked by interfering with an enzyme—reverse transcriptase (RT), which is essential for HIV replication. The drug prevented successful transcription of viral DNA into viral RNA. AZT increased survival and decreased the frequency and severity of opportunistic infections in advanced cases of infection. However, AZT failed to show much benefit when given to HIV infected people who had not yet developed symptoms. This happened, because HIV mutants that were resistant to AZT mushroomed. Other nucleoside analogues such as didansine (ddI), zalcitabine (ddC), stavudine (d4T) and lamivudine (3TC) have the same drawback and this has limited their use. It had become evident that monotherapy with these drugs would not have a long lasting effect.

Shape of HIV/AIDS Epidemic in India

- India is experiencing a rapid and extensive spread of HIV. This is particularly worrysome since India has more people than the continents of Africa, Australia and Latin America combined.
- There are estimated 2 to 5 million people infected with HIV, and 50,000 to 1,00,000 cases of AIDS may have already occurred.
- The epidemic is fueled by both married and unmarried men visiting sex workers.
- The most rapid spread of HIV has occurred in Bombay (read Mumbai) and the State of Tamil Nadu. In Bombay HIV prevalence has reached 50% in sex workers, 36% in STD patients and 2.5% in women attending antenatal clinics.
- Certain regions, such as eastern India (Calcutta area) and northern India (New Delhi region) still show a lower prevalence of HIV (1-2%) among sex workers.
- Contrary to traditional belief, sexually transmitted diseases and sex with multiple partners are common in the country, both in urban and rural areas. An estimated 3-4% of some rural population have a STD.
- Injecting drug use is a problem in Manipur, which is in the North-East region, where 55% of drug users are HIV infected.
- HIV is rapidly spreading to rural areas through migrant workers and truck drivers. Surveys show that 5-10% of some truck drivers in the country are infected with HIV.
- An estimated 1-2 million cases of TB occur in India every year. In Bombay 10% of patients presenting with TB are HIV+ve. Tuberculosis is the presenting ailment of AIDS in over 60% of AIDS cases.

Source: AIDS Analysis Asia 2(5): 11, 1996

Several clinical trials using combination of two nucleoside analogues have shown promising results. The success of US AIDS Clinical Trial Group 175 study, European-Australian trial-Delta and other studies have shown that combination therapy had sustained clinical benefits and plasma HIV RNA and CD4+ counts improved. The nucleoside analogue combinations with the most demonstrated clinical benefits include zidovudine/didanosine and zidovudine/zalcitabine.

There are limited data on other combinations of nucleoside analogues that do not contain zidovudine. Thus, combinations of nucleoside analogues compared to zidovudine alone have been shown to have clinical benefits in terms of prolonged survival and fewer AIDS defining events, when given to asymptomatic individuals with relatively early

stage disease. These results have demonstrated that an intervention regimen used in patients with early stage HIV disease could actually be clinically beneficial[9].

At Vancouver, experiences with non-nucleoside reverse transcriptase inhibitor used in combination with nucleoside analogues have rekindled hope. These non-nucleoside drugs are similar to nucleoside analogues in that they change the function of reverse transcriptase but unlike the nucleoside drugs they do not have to be activated by cellular enzymes, but disarm reverse transcriptase by binding directly to it. However, like nucleoside analogues, there is quick development of resistance against them.

These appear to act synergistically with drugs like AZT, and because they affect RT by a different mechanism, fear of cross-resistance is not much. They have strong anti-retroviral activity but patients develop resistance within weeks. Nevirapine, loviride, and delavirdine are some of the non-nucleoside reverse transcriptase inhibitors which are undergoing additional safety and efficacy studies.

In an international study comparing a combination of nevirapine, AZT and ddI with a two drug regimen of AZT and ddI, and a third treatment group receiving nevirapine and AZT, patients in all the 3 treatment arms experienced a reduction in plasma RNA of 90 per cent or more within a few days. But those taking triple drug regimen experienced a 96.8 per cent viral load reduction that persisted for a year. About 35 per cent of patients taking nevirapine and AZT achieved undetectable levels of virus in blood, but the effect gradually waned off. About 30 per cent taking AZT and ddI sustained undetectable viral loads for a full year. However, 80 per cent in the triple-drug arm reached undetectable levels, about three-fourth of them maintained the effect. Similar results have also been obtained in preliminary studies in paediatric patients[10].

Despite the drawback of quick development of resistance associated with non-nucleosides, their potency combined with rapid absorption make them ideal candidates for situations that call for short term therapy. They have the potential of playing a role as a "morning after" pill for preventing infection following unprotected sex. They also qualify for use in post-exposure prophylaxis at the work place.

In Washington and later at Vancouver, researchers presented findings of clinical trials with another class of drugs that act by blocking the activity of a protease enzyme needed for AIDS virus replication. In combination with other anti-HIV drugs, these protease inhibitors have helped to decrease the viral load substantially among patients, as compared to those receiving other anti-HIV drugs.

Interim results of a study using indinavir (protease inhibitor), alone or in combination with other nucleoside analogue(s) indicated that after 24 weeks, the viral RNA had plunged about 200-fold and was undetected in 86 per cent of patients who received indinavir, AZT and 3TC. Forty per cent of the patients receiving indinavir alone had undetectable virus levels. While the virus was detected in all who were taking AZT and 3TC.

In a large trial in patients with very advanced HIV disease the addition of ritonavir to an existing regimen (including no current therapy) reduced progression to AIDS, and morbidity by almost 50 per cent[11]. Even in a population with severe HIV infection (CD4 counts between 50 and 250 cells/mm^3), it has been possible to reduce circulating HIV to undetectable levels with a combination regimen of ritonavir, ddC and AZT. This reduction could be maintained for over a year. The results also suggested that the development of resistance is certainly minimal when reduction in viral load is high[12]. Combination of zidovudine, lamivudine and indinavir resulted in a greater than 90 per cent reduction in HIV RNA levels to fewer than 500 HIV RNA copies/ml at 6 months.[13] However, as yet, there are very few data from long-term (more than 52 weeks) and large (more than 250 patients) controlled clinical trials of any protease inhibitors.

The use of this new class of drugs in combination with the first generation nucleosides and non-nucleoside reverse transcriptase inhibitors hold promise for a level of control of established HIV disease that has so far eluded patients. Use of these regimens in primary HIV infection holds promise for interfering with the establishment of chronic persistent infection and dramatically altering the subsequent course of HIV disease.[10] Seen in the light of the findings of other studies which showed that individuals who had less HIV in their bodies fared better than those with higher viral loads, it promises to reshape the way clinicians manage HIV infected persons[14].

Preventing Perinatal HIV Infection

It is estimated that by the beginning of this year over 1.5 million children have been infected with HIV-1 through mother-to-child transmission. By the turn of the century it is feared that as many as 5 million children under the age of 5 years will be infected through their mother[1].

As HIV infection among women spreads more widely, perinatal transmission likewise would continue to increase in areas where heterosexual transmission is most common. Transmission rates have varied from 13 to 52 per cent.

There are several factors associated with transmission of HIV from mother-to-child (Table). Of the interventions available to prevent this transmission the use of zidovudine has been shown to be most promising[15] The other interventions are non-nucleoside RT inhibitors, immunoprophylaxis, vaginal disinfection, alternatives to breast feeding, caesarian section and vitamin A supplementation.

Table. Selected factors associated with mother-to-child transmission of HIV-1.

Proved or possible (relationship not fully determined)
• Maternal immune deficiency
• Chorioamnionitis
• Breast feeding
• Vaginal delivery
• Low maternal serum vitamin A concentration
• Instrumentation during labour and/or delivery (episiotomy, forceps, *etc*)
• Premature rupture of membranes
• Prematurity
• Prolonged labour
Controversial
• Maternal immune response against HIV
• Viral strain characteristics

The results of AIDS Clinical Trial Group (ACTG) Protocol 076 are considered as a turning point in strategies for preventing perinatal HIV transmission. In 1994 it was demonstrated that zidovudine administered to a group of HIV infected women (with CD4+ cell count above 0.2×10^9/l) during pregnancy and labour and to their new borns reduced the risk of perinatal HIV transmission by two-thirds (from 24.9% to 7.8%). The zidovudine regimen consisted of antipartum zidovudine (100 mg orally five times daily) plus intrapartum zidovudine (2 mg/kg intravenously for 1 hour followed by 1 mg/kg/h until delivery) plus zidovudine for new born (2 mg/kg orally every 6 h for 6 weeks) beginning 8-12 h after birth[16]

The observation that the risk of transmission of HIV-1 from mother to infant increases when the foetal membranes rupture more than 4 h before delivery, may lead to precautions as simple as not intentionally rupturing the membranes in the hope of inducing or accelerating labour. Though this suggests that every effort should be made to shorten the time between rupture of membranes and delivery, this does not mean using interventions that could increase morbidity for the mother or child[17]

A lower incidence of mother-to-infant transmission has also been attributed to the mode of delivery. In several retrospective reports, caesarean section has been said to lower the risk of transmission. An observational study of over 1200 mother-child pairs by the European Collaborative Study showed, after controlling for potential confounders, that caesarean section halved the rate of mother-to-child transmission of HIV[18]. Nevertheless the risk of morbidity and mortality to both mother and child with caesarean section precludes the use of this method as a sole alternative in preventing mother-to-child HIV transmission especially in developing countries.

Similarly the advantages of breast feeding outweigh the risk of transmission of HIV. The role of other potential interventions is still under evaluation. A randomized trial of routine delivery vs caesarean section is underway in Europe.

The breakthrough provided by the use of zidovudine has offered the hope of controlling the HIV epidemic in children. In countries where zidovudine is available and affordable, these results have drawn attention to the importance of expanding prenatal HIV testing and of improving the care of the infected women during pregnancy. For countries where the cost of this regimen is prohibitive, trials of modified timing and doses of zidovudine are needed to find the most efficient method of reducing perinatal transmission. The more potent and shorter acting preparations against retroviruses now becoming available, such as non-nucleoside reverse transcriptase and protease inhibitors, may augment the

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Genetic Diversity of HIV: Implications for India

Two major types of HIV in humans have been characterized HIV type 1 and type 2. Presence of both have been reported from India. HIV-1 isolates can be classified into eight subtypes, based on *env* sequences. These subtypes designated A through H, constitute the major group named M. In addition, a ninth subtype I has been described recently. Divergent strain of HIV-1 outside group M have been reported and are provisionally categorized as group O. Within O group, isolates may differ from each other. HIV-2 has also been phylogenetically classified into subtypes, though the number of sequenced isolates are limited.

There have been very few investigations of HIV-1 strain variation in India. Available data indicates that subtype C is most predominant in India. Subtypes A,B and E also co-exist[1]. Genetic subtyping studies have revealed that majority of the C subtype were homologies to C3 genotype while remaining (34%) were closest to C2 genotype. Greater degree of divergence observed within C2 genotype as compared to C3 indicates earlier introduction of C2 in India. The C3 genotype may be a recent mutational variant of subtype C unique to India[2].

There appears to be a relationship between the subtypes and mode of transmission. Though HIV E and C have been reported to spread predominantly through heterosexual transmission and HIV B transmission occurs amongst homosexuals and intravenous drug users, recent reports indicate that this relationship is not very rigid.

Development and evaluation of diagnostic tests for HIV have been based primarily on subtype B strains of North America & Europe. Sensitivity of these tests in detecting GpM subtypes other than subtype B is a source of concern.

As with diagnostic tests for HIV-1 most vaccine candidates are based on subtype B. It is known that vaccine efficacy is subtype specific. Hence evaluation of these candidate vaccines in areas where other subtypes predominate or where multiple subtypes are circulating, like in India will pose considerable challenges.

1. Bollinger, R.C., Tripathy, S.P. and Quinn, T.C. The human immunodeficiency virus epidemic in India. Current magnitude and future projection. *Medicine 74:* 97, 1996

2. Gadkari, D.A. Moore, D., Sheppard, H., Mehendale, S., Kulkarni, S. and Bollinger, R. Viral subtype analysis of HIV-1 infected patients from Pune, India. XI International Conference on AIDS, July 9-12, 1996; Vancouver, Canada. Abstract TuA 374.

available strategies as these are tested for safety and efficacy in pregnancy.

Successful Interventions for Behavioural Change

Since the start of the HIV epidemic, scientific knowledge about AIDS and HIV has continuously expanded and evolved. However, one thing has remained unchanged. The only means to prevent HIV is by behaviour change. Essentially all new HIV infections associated with risk behaviour can be prevented if people can be helped to make changes in sexual and drug use practices that create risk for contracting HIV. Although the two behaviours that confer risk—having unprotected sex with a potentially infected partner and needle sharing by injecting drug users (IUDs)—are very easy to specify, these are also behaviours which are difficult for many people to change.

Several success stories in slowing down the spread of HIV provide encouragement and hope for wider use of these strategies to create an enabling environment which will facilitate and support behaviour change.

Development of programmes with an integrated approach to inducing behavioural change, promoting condom use and controlling STDs may reduce the infectivity of HIV transmitters and the susceptibility of HIV-exposed persons. In Kinshasa, Zaire, it has been shown that intensive STD diagnosis and treatment coupled with a condom distribution programme for female sex workers successfully decreased the incidence and prevalence of STDs including HIV infection. A

community-based syndromic approach to the treatment of symptomatic STDs led to a 42 per cent decrease in HIV incidence compared with control villages in Mwanza, Tanzania. Needle exchange programmes have helped stabilize and in some instances reduce HIV incidence among IDUs in Australia and Europe. Similarly the steep decline in HIV incidence among homosexual men through educational efforts aimed at changing sexual behaviour has been very encouraging[19].

Candles of Hope

A programme for care of HIV/AIDS should offer a vision of:

- hope that they can live normal, healthy lives for several years after being infected with HIV
- hope that they will receive a decent standard of health care, without discrimination.
- hope that they will receive the understanding and support of their families, friends and other members of the community.
- hope that they can maintain or recover their sense of self-worth and self confidence.
- hope that they can make a meaningful, positive contribution to society as a whole.

Source: Candles of Hope: The AIDS Programme of the Thai Red Cross Society, Actionaids, British Council, UNDP, 1994

In the South-East region of Asia, prevention strategies, (approaches and interventions) adopted by countries so far, are now showing the impact. The '100 per cent condom use' programme in Thailand has received world-wide attention. Started in 1991, the strategy of 100 per cent condom use for men has been promoted all over the country to ensure condom utilization in the commercial sex setting. The availability of condoms and well publicized messages on HIV transmission have resulted in a decrease of 80 per cent in STD rate in Thailand from 1989 to 1994. From 1991 to 1995, the men's reported use of condoms during the most recent sexual contacts with sex workers increased from 61 to 92.5 per cent. In 1995 15.2 per cent of men had a history of a sexually transmitted disease as compared with 42.2 per cent in 1991[20].

The success of the 100 per cent condom campaign suggests that environmental interventions may be more effective public health strategies in preventing HIV infection in developing countries than strategies that rely solely on health education targeted at the behaviour of the individuals. The campaign in northern Thailand provided condoms to every establishment where sex was sold and encouraged and enforced their use, as well as educated people to reduce the sexual behaviour that could place them at high risk. The dramatic success of this public health intervention in quickly reducing the very high rates of HIV infection in a general population of heterosexual adolescents and young men within a few years after their first sexual activity is unprecedented. One reason for the success of the 100 per cent condom programme was that it concentrated on a limited goal, the use of condoms in commercial sex. The programme used sanctions and threats of sanctions against sex establishments where condoms were not used in every encounter. Violations were detected by asking men who came to government clinics with STDs other than HIV where they had contacted their infection. The programme worked as it did not reduce the income of the brothel owners and the commercial sex workers[21].

The Sonagachi project in Calcutta is another success story, and qualifies to be a model for successful peer education programme among sex workers. The project also includes provision of health care, literacy programme and schooling for children of sex workers. An external evaluation of the Sonagachi project revealed that the level of syphilis in the community is showing a downward trend, from 28 per cent at baseline (1992) to 25 per cent at first follow up (1993) survey to 13 per cent in second follow up (1994) survey. The condom use by clients has increased from 2 per cent in 1992 to 85 per cent in 1994 (personal communication HPO, ODA, New Delhi, 1996).

The interventions among injecting drug users including needle exchange programme, are being implemented successfully in Nepal. In Myanmar, the IDUs have begun to personalize the risk as a result of IEC programme. The peer education activities seem to have contributed to a decline in HIV infection among IDUs from nearly 75 per cent in 1993 to 50 per cent as of late 1995[22].

The National AIDS Control Organization (NACO), India in collaboration with an international donor agency is supporting five Non-governmental Organisations (NGOs) in Assam, Manipur and Nagaland in conducting out-reach interventions with injecting drug users. The NGOs have also linked up with NACO, WHO and the Govt of Manipur to develop a model project on home- or community-based care of persons with AIDS[23].

A number of NGOs have responded very positively to the HIV epidemic in India. Many of them have played a major role in raising awareness and have helped to remove the veil of secrecy and hypocrisy surrounding sexual attitudes and behaviour. The experience of some of these organizations demonstrate the potential of NGOs to respond in a constructive way to the multi-faceted challenges and problems posed by the HIV epidemic.

In a recent publication, pioneering work of some of such organizations has been documented[24]. They have shown success in at least three fronts.

- They have shown how to reach and support sections of the population such as women in prostitution and injecting drug users.
- They have illustrated how community-based organizations such as women's groups can help economically and socially disadvantaged people gain greater control over their lives and so protect their health and well being.
- They have shown that NGOs working in such diverse fields as legal aid, rural development and women's health have a common interest in HIV epidemic.

Not only have the NGOs broadened the front against HIV/AIDS, but they have shown how HIV/AIDS programmes can promote development by enabling the poor and disadvantaged to gain some control of at least some important aspect of their lives.

Conclusions

It has been 15 years since AIDS was first recognized and given a name. It has taken these many years of struggle, to discover and learn about the virus and the disease caused by it, and methods to control it. Recent studies on the dynamics of HIV-1 replication have enhanced our understanding of disease pathogenesis. It is now clear that even during the period of clinical latency there is continuous high-level viral replication, CD4 cells infection, cell death, and new CD4 lymphocyte production. The magnitude of viral and CD4 cell turnover is phenomenal—on an average 10^8 - 10^9 virions and approximately the same number of CD4 are produced and destroyed each day. This suggests that sensitive measurement of viral load may be useful in identifying those individuals in whom the disease will rapidly progress, and those in whom the disease will progress slowly. This has re-defined the aim of the therapy. The debate over whether to treat early or late in the course of diseases has become insignificant when viral load is used as a marker.

There is a reasonably good chance that of all modes of transmission mother-to-child transmission may soon become the most amenable to effective preventive intervention. Trials have opened new opportunities and raised hopes. A group of useful anti-retroviral drugs are on the horizon. The good news is that a whole range of new drugs would become available for use singly or in combination for those infected with HIV. The downside of the good news is the cost. They would be 'breath takingly' expensive. There are strategies for behavioural changes with proven track record, waiting to be adapted to local needs for control of HIV. These and many other developments in research ring in an era of hope.

Until now the world has shown solidarity against HIV/AIDS. The 'haves' and 'have-nots' have stood together. Hand in hand, shoulder to shoulder. United by common fear, despair and hopelessness. It may soon change for the 'haves'. HIV may become like any other chronic disease—more or less manageable, but at a cost. For the 'have-nots' HIV may continue to be killer No.1.

Take for example the simple concept of using a drug to prevent HIV transmission from mother to her new born. Implementing an effective programme based on this intervention may require several steps, many of which may not be feasible in less developed countries. Institutional procedures need to be established, doctors and other staff must be trained about HIV counselling and testing and about utilizing zidovudine therapy for HIV-infected women and their children. For this intervention to be useful it requires that all pregnant women have access to antenatal care, and they are offered HIV counselling and voluntary testing. Further, those found HIV positive are offered zidovudine and also access to other important medical, social and psychological services needed. To facilitate informed decision making appropriate educational material may also need to be prepared and provided.

For countries like India, which have sparse resources for even the most basic public health measures, major limitations in care, little or no option for anti-retroviral treatment, inefficient methods of public education, inability to utilize the results of research may widen the gap between the 'haves' and the 'have-nots'.

Then, is the hope limited to the 9 per cent (1.29 million) people with HIV/AIDS living in the developed world?

In their wake, these advances have brought challenges to the national and international community to ensure that the gains of research reach the people who need them most. The people of the world need to reach out to each other. There should be no 'them' and 'us', if this pandemic is to be overcome. It is time to demonstrate that our capacity for compassion matches our capacity for scientific progress. We should continue to be all together in this voyage of hope. A journey through the dark side of the pandemic. A journey of change. A change for the better. A hope that stigma, fear, and despair are replaced by optimism, equity and compassion. A hope that tomorrow may not be just more of yesterday.

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This write-up has been contributed by Dr. Lalit Kant, Deputy Director-General, and Dr. Q.B. Saxena, Asstt. Director-General, Indian Council of Medical Research, New Delhi.

ICMR NEWS

The following meetings of various technical committees/ groups of the Council were held:

Meetings of the Scientific Advisory Groups (SAGs)/ Scientific Advisory Committees (SACs):

SAC of the Centre for Advanced Pharmacological Research on Selected Traditional Remedies, Lucknow	October 28, 1996 (at Lucknow)
SAG of the Division of Reproductive Health and Nutrition	November 5-6, 1996 (at New Delhi)
SAC of the Centre for Advanced Research on Standardization, Quality Control and Formulation of Selected Traditional Remedies/ Natural Products, Jammu	November 15, 1996 (at Jammu)

Meetings of the Toxicology Review Panel/Project Advisory Committees (PACs)/ held at New Delhi :

Toxicology Review Panel of the Division of Reproductive Health and Nutrition	November 7, 1996
PAC on Management of Glaucoma	November 15, 1996

Participation of ICMR Scientists in Scientific Events:

Dr. U. Sengupta, Director, Central JALMA Institute of Leprosy, Agra, participated in the autumn meeting of the project entitled Peptides for Early Detection and Vaccination Against Tuberculosis and Leprosy at London (November 4-7, 1996).

Dr. G.V. Satyavati, Director-General, ICMR, participated in the X meeting of the Directors of Medical Research Councils or Analogous Bodies and Concerned Research Foci in the Relevant Ministries at Bandung, Indonesia (October 21-25, 1996).

Dr. C.P. Puri, Dy. Director, Institute for Research in Reproduction (IRR), Mumbai, participated in the meeting of the Regional Advisory Panel of the WHO for Asia and the Pacific at Vanuca Island, Fiji (October 24-27, 1996).

Dr. Z.M. Patel, Officer-in-Charge, ICMR Genetic Research Centre, Mumbai, participated in the VI World Congress on Ultrasound in Obstetrics and Gynaecology at Rotterdam (October 27-31, 1996).

Dr. Kamala Krishnaswamy, Dy. Director (Senior Grade), National Institute of Nutrition, Hyderabad, participated in the VII Expert Panel meeting of the Diet and Cancer Project at Washington D.C. (November 6-8, 1996).

Dr. U.M. Donde, Dy. Director, IRR, Mumbai, participated in the National Conference of the Vietnamese Association of Clinical Biochemists at Ho Chi Minh city (November 13-15, 1996).

Dr. G.B. Nair, Asstt. Director, National Institute of Cholera and Enteric Diseases, Calcutta, participated in the XXXII Joint Conference of the US-Japan Medical Programme at Nagasaki (November 14-16, 1996).

Dr. Kalyan Banerjee, Director, National Institute of Virology, Pune; Dr. K.N. Panicker, Dy. Director, Vector Control Research Centre, Pondicherry; and Dr. G.B. Nair, Participated in the XIV International Congress for Tropical Medicine and Malaria at Nagasaki (November 17-22, 1996).

Dr. V.P. Sharma, Director, Malaria Research Centre, Delhi, participated in the IV Neem Awareness Workshop on How to Grow and Use Neem at Mbita, Kenya (November 17-19, 1996).

Dr. M.A. Khan, Senior Research Officer, Institute of Cytology and Preventive Oncology, New Delhi, participated in the V Western Pacific Congress on Chemotherapy and Infectious Diseases at Singapore (December 1-4, 1996).

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
XX National Conference of the Indian Society for Surgery of Hand.	December 7-8, 1996; (at Agra)	Dr S. Husain, Organising Secretary, Department of Plastic and Reconstructive Surgery, Central Jalma Institute for Leprosy, Agra-282001.
Guha Research Conference.	December 23-26, 1996; (at Darjeeling)	Prof. N.C. Mandal, Convenor of the Conference, Bose Institute, Calcutta-700054.
Symposium on Frontiers in Biology and Biotechnology.	January 6-8, 1997; (at Vellore)	Dr. Anna Oomen, Organising Secretary of the Symposium, Department of Neurological Sciences, Christian Medical College, Vellore-632004.
XX All India Cell Biology Conference and Symposium on Recent Trends in Cell Biology.	January 13-15, 1997; (at Mumbai)	Dr. R.A. Bhisey, Organising Secretary of the Conference, Cancer Research Institute, Mumbai-400012.
Symposia on (i) AIDS and Cancer Victims: Quality of Life, Psychosocial Interventions and Issues Related to Caregivers; and (ii) Divorce: A Grief Process.	January 23-24, 1997; (at Manipal)	Dr. K.B. Kumar, Department of Psychiatry, Kasturba Hospital, Manipal-576119.

INDIAN COUNCIL OF MEDICAL RESEARCH

The following areas have been identified as thrust areas for research in the field of HIV/AIDS and its associations with sexually transmitted diseases and tuberculosis:

(i) Basic research like culture, identification and characterization of various isolates of HIV.

(ii) Prevalence of other communicable diseases and opportunistic infections in subjects with HIV/AIDS.

(iii) Studies of HIV/AIDS and tuberculosis and chemotherapeutic trials.

(iv) Exploration of new drugs specifically anti-retroviral in Allopathy and traditional systems like Homeopathy, Ayurveda, Siddha, *etc.*

(v) Studies on the effectiveness of AZT in:

  (a) asymptomatic HIV positive cases.

  (b) persons with accidental needle prick injury while handling HIV positive cases as a measure of preventive AIDS therapy.

(vi) Epidemiological research using more advanced techniques like mathematical modelling, clinical research and drug development, studies related to the vaccine development, diagnostics, surveillance and forecasting.

(vii) Behavioural research related to the prevention/control of HIV/AIDS.

(viii) Development of indigenous kits for diagnosis of HIV.

(ix) To generate prevalence/incidence data on STDs in individuals practicing high risk behaviours in urban/rural areas.

ICMR PUBLICATIONS

	Price (Rs.)
Nutritive Value of Indian Foods (1985), by C. Gopalan, B.V. Ramasastri and S.C. Balasubramaniam, Revised and Updated (1989), by B.S. Narasinga Rao, K.C. Pant and Y.G. Deosthale (Reprinted 1995)	23.00
Growth & Physical Development of Indian Infants and Children (1972, Reprinted 1989)	10.00
Studies on Weaning & Supplementary Foods (1974, Reprinted 1996)	15.00
Studies on Pre-School Children (1974, Reprinted 1984)	6.00
A Manual of Nutrition (Second Edition 1974, Reprinted 1995)	6.00
Low Cost Nutritious Supplements (Second Edition 1975, Reprinted 1994)	4.00
Menus for Low Cost Balanced Diets and School Lunch Programmes Suitable for North India (Second Edition 1977, Reprinted 1994)	4.50
Some Common Indian Recipes and their Nutritive Value (Fourth Edition 1977, Reprinted 1995) by Swaran Pasricha & L.M. Rebello	10.00
Nutrition for Mother & Child (Third Edition 1978, Reprinted 1994) by P.S. Venkatachalam & L.M. Rebello	9.00
Japanese Encephalitis in India (Revised Edition 1980)	5.00
Some Therapeutic Diets (Fourth Edition 1988, Reprinted 1995) by Swaran Pasricha	4.50
Nutrient Requirements & Recommended Dietary Allowances for Indians (1990, Reprinted 1995)	16.00
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Diet & Diabetes (Second Edition 1993) by T.C. Raghuram, Swaran Pasricha & R.D. Sharma	18.00
Dietary Tips for the Elderly (1992) by Swaran Pasricha & B.V.S. Thimmayamma	3.50
Diet and Heart Disease (1994, Reprinted 1996) by Ghafoorunissa and Kamala Krishnaswamy	26.00
*Depressive Disease (1986) by A. Venkoba Rao	58.00
**Medicinal Plants of India Vol.2 (1987)	136.00

* 10 per cent discount allowed to individuals.

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A TRIBUTE
TO
DR. VIJAY DHANDA
(1938-1996)

Dr. Vijay Dhanda, Director, Vector Control Research Centre, Pondicherry and one of the foremost Medical Entomologists and Zoologists of the country, passed away on 21st August 1996 at the age of 58 years.

Dr. Dhanda was born at Izatnagar, Uttar Pradesh, on 26 January 1938 and had his school and college education at Mukteshwar and Nainital respectively. He obtained his Masters and Doctorate degree in Zoology from Lucknow University in 1958 and 1963 respectively and a Diploma in Applied Parasitology and Entomology from the London School of Hygiene and Tropical Medicine, London in 1966.

He joined the National Institute of Virology (NIV) at Pune, then called the Virus Research Centre of the ICMR in 1962 as a Senior Research Fellow and subsequently rose to the position of Director Grade Scientist in 1984. He was appointed as the Director, Vector Control Research Centre (VCRC), Pondicherry in October 1990 and led the research activities of the Institute till his death.

During his active research career, Dr. Dhanda made commendable contributions in various aspects of Medical Zoology particularly in taxonomy of ticks, arthropod tissue culture and parasitology. His research has resulted in better understanding of the natural history of viral and parasitic diseases as well as their vectors and has been directed towards the disease control.

He has published over 130 research papers in prestigious Indian and International journals.

Dr. Dhanda had actively participated in numerous national and international scientific conferences and meetings and had been a member of numerous scientific organisations. He was awarded Dr. M.O.T. Iyengar award of the ICMR in 1984 for his contributions in Medical Entomology.

Dr. Dhanda was not only an excellent scientist, but also a fine human being. He was soft spoken, suave and well read. He will be remembered with profound respect and affection by all at NIV, Pune and VCRC, Pondicherry for his honesty, sincerity and conviction to scientific research.

Dr. H.R. Bhat
&
Dr. K. Banerjee
National Institute of Virology, Pune

ICMR BULLETIN INDEX
VOL. 26, 1996

Main Feature	Page No.	Month
Highlights of Research at the Tuberculosis Research Centre, Madras	1	January
Neuritic Leprosy	13	February
Highlights of Tribal Research under Indian Council of Medical Research	21	March-April
Health Care for the Elderly	33	May
Control of Iodine Deficiency through Safe Use of Iodised Salt	41	June
Highlights of Research on Diarrhoeal Diseases under the Indian Council of Medical Research	49	July
Studies on Noise Pollution	61	August
Prospects of Using Monomolecular Surface Films in Mosquito Control	77	September
Research in Infertility	97	October
ICMR Completes 85 Years: PM Launches the Concluding Ceremoney and Gives Away ICMR Awards	109	November
Turning Point in HIV/AIDS Research Vision of Hope	121	December

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