

Epidemiology of HIV/ AIDS in India

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India witnessed first case of HIV/AIDS in the year of 1986 in Chennai (Tamil Nadu) among female commercial sex worker – the core group of transmitters. This was almost a decade later its appearance in the globe. Thereafter, cases were reported from Mumbai and northeastern state of Manipur. The number of cases of HIV/AIDS continues to spread from these three “epicenters”. As of 31st January 2006, officially, a total of 120,000 full blown cases of AIDS have been reported from India. It is realized that there is a wide gap between the reported and estimated figures because of the absence of epidemiological data in major parts of the country. Of the 120,000 cases of AIDS, 78.6% are reported in men and 21.4% in women. The seropositivity rate is 0.91% in adult population. More than 90% of the infections in India is due to HIV 1 sub-type C.

Over the years, the HIV infection has spread from high-risk group to general population, from urban to rural area, and from high prevalence states to all states. During the course of the epidemic, the proportion of HIV infected women has kept on increasing. Data suggests that HIV vulnerability among youth is high. The surveillance figures estimate that 5.134 million people are living with HIV in India. So far, six states namely, Andhra Pradesh, Tamil Nadu, Maharashtra, Manipur, Nagaland and Karnataka have entered in to the generalized epidemic / high prevalence category [$>1\%$ in Antenatal cases (ANC)] Gujarat, Goa and Pondicherry are designated as medium prevalence states ($>5\%$ High Risk Group). The rest of the country is still in low prevalence category ($<5\%$ High Risk Group).

Predominant mode of HIV transmission among AIDS cases has been hetro-sexual route, other routes being intravenous drug (4%). Mother to Child Tansmission [MTCT] (3.5%) and through blood (2.3%). In the northeastern states, the predominat mode of transmission is through intravenous drug use.

Most of the AIDS cases are in the age group 30-49 years. About 2% of females and 12% of males in the age group 15-49 years are reported to have non-regular sex partner. There was no difference in non-regular sex partner between urban and rural areas.

The national response to HIV/AIDS started before the first case of HIV/AIDS was reported in India. In 1985, screening of high-risk groups was carried out at Pune (Maharashtra) and Vellore (Tamilnadu) by Indian Council of Medical Research (ICMR). National AIDS Control Organization was formed in 1986 to formulate National AIDS Control Programme (NACP). Phase I of NACP (1992-99) focused on prevention with surveillance to track the epidemic, Information Education and Communication (IEC) through mass media, blood safety, strengthening of Sexually Transmitted Diseases (STD) services and social mobilization through NGOs. The programme was revised in 1999. The Phase II (1999-2004) has clear-cut objectives. The strategies in Phase II are strong political advocacy, decentralization and leadership at the state level, care and support to people living with HIV/AIDS, participation of non health sectors and communication for behavior change.

In India, HIV/AIDS epidemic is now two decades old. Within this short period, it has emerged as one of the most serious public health problems in the country. HIV/AIDS, therefore must be seen as a national calamity and can only be fought unitedly by forging coordination and convergence in respect of HIV/AIDS prevention control strategies between civil society, non-governmental (voluntary) organizations and government sectors.

Bacterial Diarrhea in Patients with HIV/AIDS

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Various opportunistic infections have been described in patients with HIV/AIDS. Enteric infections in such patients are an important cause of morbidity/mortality. It has been estimated that 30-50% of patients with AIDS in USA and about 90% in Africa and Haiti suffer from chronic diarrhea.

As compared to bacterial diarrhea in these patients parasitic diarrhea is more common and at times life threatening.

A study from the US revealed that the mean annual incidence of bacterial diarrhoea was 7.2 cases per 100 person per year. The study also revealed *C. difficile* was the most common recognized bacterial pathogen. In another study, the bacterial pathogens that were identified included *Escherichia coli* particularly Enteropathogenic *E. coli*. Enteroadherent *E. coli* has also been found to be an important cause of bacterial diarrhea in AIDS patients.

Other bacterial pathogens include Salmonella, Shigella and Campylobacter. Proper identification of bacterial enteric pathogens in HIV/AIDS patients may help in rational and effective treatment.

Pneumocystis Carnii Pneumonia in AIDS Patients

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Pneumocystis carinii has been recognised as a cause of pneumonia since the 1940's when epidemics of "plasma cell pneumonia" were diagnosed among malnourished neonates in Eastern Europe. Thereafter, with the use of immunosuppressives becoming more common in the 1960's, *P. carinii* pneumonia (PCP), emerged as a potentially lethal cause of pneumonia in this group of patients. Despite its increasing recognition, PCP, remained a rare infection; a review from the CDC in 1974 reporting only 194 episodes of PCP in the entire US over a 3 year period. (1). It was of course, only in the 1980's, with the advent of the AIDS epidemic that every physician was forced to familiarize himself with this previously obscure pathogen.

A remarkable change has occurred, over recent years, in the incidence of PCP infection in patient's with HIV infection. Regular PCP prophylaxis with daily septran has resulted in the frequency of PCP declining from 48% in hospitalised patients to 29%.(2). Indeed, the emergence of safe, effective and cheap prophylaxis against PCP has emerged as our main victory in the war against AIDS. Effective treatment has brought the mortality of this once dreaded infection down to around 5%, even in these immuno-suppressed patients, a figure not much different from the mortality in any bad community- acquired pneumonia. A large recent study on the trends in the prevalence of infectious diseases in patients dying of HIV in the USA between 1987 to 1992 showed the percentage of HIV-related deaths from PCP declined from 32% to 13% in this 5 year period.(3). The pulmonary complications of HIV study, a prospective study that recruited 1353 HIV infected patients and followed them up over a mean period of 53 months also confirmed the declining incidence of PCP in recent years.(4). In this study, bacterial pneumonias were a more common pulmonary complication in HIV +ve patients than PCP. With the recent emergence of highly effective anti-retroviral therapy further dramatically reducing the incidence of opportunistic infections there is room for cautious optimism.. There are even recent reports claiming that it may be safe for patients doing well on antiretroviral therapy to discontinue their primary prophylaxis against *P. carinii* if the CD4 count exceeds 200 cells per cubic mm for a sustained period of time.(5).

What about the situation in India and the developing world? There is a paucity of data on the incidence of PCP infection in Indian's infected with HIV and there are many who feel, that PCP is not seen with the same frequency in our part of the world as it was in the developed world, where at the start of the AIDS epidemic, PCP was consistently the most common index diagnosis. Several reasons have been put forth for this. Is the organism less frequently present in our tropical environment? Are there racial differences in host susceptibility? Were Indian patients dying earlier from more pathogenic organisms like *M. tuberculosis*? Or finally are we not diagnosing this pathogen as often as we should because of lack of diagnostic facilities. I favour the last two of these hypotheses for the perceived reduced incidence of PCP in our country. It is increasingly clear that patients with PCP may present with normal chest radiographs; this has been reported to occur with incidences ranging from 2- 34 % in different western series. (6). Also since these patients often do not produce sputum, or are too feeble to cough it out, there is no doubt that bronchoscopy and analysis of bronchoalveolar lavage is the best way to make a positive diagnosis of PCP. The skill and experience of a good cytologist is also vital if PCP is not to be missed. Unfortunately very few hospitals in our country can lay claim to having the combination of a good-quality HRCT scanner, a skilled bronchoscopist, and an experienced cytologist, and I am convinced many patients with PCP must therefore be dying undiagnosed and un-recognised. . Empirical treatment for PCP is thus clearly justified in the HIV +ve individual, with a low CD4 count, respiratory symptoms, hypoxia, and an abnormal chest radiograph, in whom bacterial and mycobacterial infections have been ruled out with reasonable certainty.

Several recent advances have been made in the diagnosis and management of PCP and it would not be out of place to mention some of them here; DNA amplification techniques have improved diagnostic sensitivity thousand to ten-thousand fold. Rapid diagnosis of PCP from a saliva or oral-rinse sample may be the tests of choice in the future. Atovaquone has emerged as a safe and effective form of therapy for mild to moderate forms of the disease. Whilst this drug is not easily available here, another combination that has emerged is the combination of clindamycin (600 mg every 8 hours) with primaquine (15 to 30 mg a day.) I have found this an effective, safe and relatively inexpensive combination in the Indian patient who cannot tolerate trimethoprim / sulfamethoxazole (septran).. A final advance well worth mentioning is the realisation that corticosteroids are vital adjunctive therapy in all patients with PCP and a PaO₂ below 70mm Hg. A consensus statement on the role of steroids as adjunctive therapy for PCP recommends starting these drugs early (within the first 24 – 72 hours of antipneumocystis therapy). (7). The simple regimen currently recommended is 40 mg of oral prednisolone twice a day on days 1 through 5, 40 mg daily on days 6 through 10, and then 20 mg daily on days 11 through 21. Alternatively, intravenous methylprednisolone can be given with equal success at 75% of the above doses if a parenteral route is necessary. There is now no doubt that this simple intervention saves lives in even the most sick patients with PCP. Our improved survival in ventilated PCP patients may be a reflection of this fact.

Thus to conclude we seem to be making advances in our battle against this most dreaded pathogen in patient's with AIDS. In these days of highly effective but highly expensive anti retroviral therapy it is heartening to note that a daily tablet of oral septran costing less than a rupee a tablet can have a profound impact on this epidemic. A lot remains to be resolved however; basic questions like whether PCP is contagious or not, whether acute PCP results from de novo infection or reactivation of latent infection, and finally why, despite decades of trying we are still unable to reliably cultivate the organism reliably. With newer technology helping us address these dilemma's, we will continue to make advances in our battle against this deadly pathogen.

A study of the relationship between HIV infection and Mycobacterial Diseases : the JALMA experience

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Association between HIV and mycobacterial diseases has shown varying associations. Our Institute has pursued studies to understand the trends and also possible mechanisms. HIV surveillance studies carried out in our Institute among Leprosy patients and patients with active Tuberculosis disease showed that the trend of HIV infection, over a decade, is low among the leprosy patients. There has been a slight rise in HIV-positivity from 0.124% (5/4025) during 1989-1993 to 0.376% (8/2125) during 1999-2004. Follow-up of these patients at an interval of six months, revealed that the incidence of downgradation in clinical spectrum into a severe form of leprosy as well as reversal reactions and neuritis (both chronic and acute) was not observed among these HIV positive leprosy patients. None of them developed Erythema Nodosum Leprosum (ENL) reactions. HIV-positive leprosy cases did not develop either AIDS related complex (ARC) or AIDS. The underlying mechanism by virtue of which the severity of both the diseases is lowered is not known. This study indicated that contrary to some other reports, there does not appear to be significant association of HIV infection with leprosy. Another study (2001-2004) showed that the incidence of HIV infection among adult patients with active Tuberculosis disease was 4.3% (26/600) and among paediatric TB patients was found to be 8.5% (23/270). The progression to ARC/AIDS among HIV-TB co-infected patients was faster/ rapid when compared with HIV-leprosy co-infected cases. This indicated differential susceptibility/ relationship of Leprosy and Tuberculosis patients to HIV infection or vice versa.

Other studies carried out at this Institute showed cross-reactivity of HIV-negative leprosy sera with HIV structural antigens. When Western Blot was performed with HIV-negative leprosy sera, it was observed that sera from leprosy patients across the spectrum showed high reactivity with p18, Gp41 and p55 in addition to lower reactivity with other proteins. On the other hand, sera from normal healthy individuals as well as patients with leishmaniasis did not show any reactivity to any of the structural proteins. Bio-Informatics approach was applied to explore the similarities. BLASTP analysis revealed that envelope group of antigens of HIV (Gp41, Gp120 and Gp160) had sequences similar to *M.leprae* ML0470, putative integral membrane protein, Rv0740, mmpL9 (*M.tuberculosis*), core (gag) antigens (p18) had similarities to ML0406 but polymerase group of antigens (p52) had similarities to PE_PGRS (*M.tuberculosis*, H37Rv). Nucleotide sequence analysis, on the other hand did not reveal any significant homology between *M.leprae* and HIV and / or between *M.tuberculosis* and HIV. The results, therefore, suggest that these similarities could be responsible for immune modulation and could probably be the reason for differential susceptibility/ association to these two important mycobacterial infections.

Immune Restoration Syndrome in Tuberculosis and HIV Co-infected Patients: prospective analysis of the cellular and humoral immunological parameters.

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Background: Simultaneous antiretroviral and anti-mycobacterial treatments in patients co-infected with HIV and tuberculosis (TB) frequently cause Immune Reconstitution Syndrome (IRS). To test the hypothesis that an acute exacerbation of mycobacteria-specific Th1 response after HIV-infection control by Highly Active Antiretroviral Therapy (HAART) causes IRS, we prospectively analysed the kinetics of TB-specific Th1 immune response in TB-HIV co-infected patients receiving anti-TB then anti-HIV therapy. In addition, analysis of the kinetics of specific antibodies was performed.

Methods: Prospective, multicenter study of 22 consecutive untreated HIV-TB coinfecting patients included when initiating antimycobacterial therapy and sequentially evaluated during HAART and at time of IRS. IRS was defined according to classical clinical diagnostic criteria. Patients were declared IRS-negative if no IRS occurred within 3 months after HAART initiation. Mycobacteria-specific (tuberculin/PPD, ESAT-6, Ag85B) Th1 IFN-g producing cells were quantified by ELISPOT, intracellular cytokine analysis (ICS) and in-vitro production of 25 cytokines/chemokines in antigen-stimulated PBMC-supernatants quantified by chemoluminescence. Free and immune complexed circulating antibodies against ESAT-6/CFP10, PGL-Tb1 and LAM were measured with ELISA. Kinetics of specific circulating secreting B cells was performed using measurements of in vitro antibody production. Comparisons between groups were made using non-parametric Fischer exact and Mann-Whitney tests.

Results: Nine patients (41%) experienced IRS (IRS+) within a median of 23 days after HAART onset (M0). M0 median CD4 counts were 37/mm³ for IRS+ vs. 56/mm³ for IRS- ($p=0.09$) and rose at M3 by 97/mm³ vs. 62/mm³ in IRS+/IRS- patients ($p=0.1$). PPD-specific Th1 IFN-g-producing CD4 cells increased sharply during IRS from a baseline median of 56 up to a maxima of 3462 SFC/106PBMC, but not CMV-specific responses tested as control. Those PPD-specific cells represented up to 35% of CD4 cells by ICS and all expressed activation marker (HLA-DR). Only 3 IRS+ patients had ESAT-6- but no Ag85B-specific responses at time of IRS. IRS-negative patients did not develop acute PPD-specific responses except in one case. In addition, at time of IRS a peak of PPD-specific Th1 cytokines/chemokines (IL-2, IL-12, IFN- γ , IP10 and MIG) without Th2 cytokines (IL-4, IL-5, IL-13, IL-15), and a peak of non-specific inflammatory cytokines/chemokines (TNF- α , IL-6, IL-1b, IL-10, RANTES and MCP-1) occurred. The kinetics of antibodies showed that IRS-positive patients presented a significant lower level of anti-PGL-B1 antibody at enrolment and before developing IRS, such low level was not associated with circulating complexed antibody. No difference was found with other antibodies between IRS-positive and IRS-negative patients. Absence or low levels of anti- PGL-Tb1 free antibody in IRS+ patients were associated with a low counts of circulating secreting specific B cells.

Conclusion: Immune restoration concomitant to CD4 T-cell exposure to mycobacterial antigens contained in tuberculin but not in living TB pathogens appears to cause IRS in patients co-infected with HIV and TB. This key event provides new evidence valuable for the diagnosis and treatment of IRS. Moreover, the presence of significant levels of anti-Pgl-Tb1 seems to be associated with some protection against the development of IRS, since they were detected only in patients who did not developed IRS.

Tuberculosis : Understanding the Enemy

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Tuberculosis has reemerged with vengeance as major killer due to a single infectious organism *Mycobacterium tuberculosis*. It is a unique intracellular pathogen because only 10% of the infected people clinically manifest the disease and in rest, it can remain latent and may become active if the immune system becomes compromised by HIV. People who are infected with TB and are HIV positive are 3 to 10 times more likely to develop full blown TB. One-third of HIV-infected people worldwide are co-infected with TB, and TB is responsible for the death of one out of every three people with HIV/AIDS worldwide.

The profile of TB changes in association with HIV. It is harder to diagnose, progresses faster in infected people, is fatal if undiagnosed or left untreated. While efficient diagnosis, new drug targets and a vaccine is important for effective management of TB, there are some major issues which need to be addressed. It is of utmost importance to understand the fundamental biology of latency, the nature of the metabolic shift from replicating state to latency, macromolecules required to maintain state of latency and switch from latency to active infection. This study would lead to identification of metabolic markers for latent TB which can be used as biomarkers and targets for developing drugs that are effective against latent TB. Identification of disease specific proteins found in sputum or blood of *M. tuberculosis* infected HIV patients can become useful tool to indicate active infection in the human body. These will also serve as biomarkers to monitor disease progression, response to treatment in patients with TB regardless of the immune status of the host and can significantly reduce the length of clinical drug trials. Another issue requiring attention is to identify differences in immune system between people carrying latent infection and those with active TB and HIV and to understand the mechanisms that allow TB bacteria to escape the natural immune responses that help some people keep the disease under control while others succumb to serious illness, particularly people with HIV. The acquired information could help design a therapeutic vaccine that can stimulate the immune systems of people with latent TB to eliminate the infection. It is equally important to understand why some TB strains are more virulent than others. Focus has been laid on the impact of transposition of the insertion element IS6110 into various locations on the bacterial genome, polymorphisms of immunologically important genes and identification of mycobacterial interspersed repetitive units if they have a role in virulence of *M. tuberculosis*. The variability in the intergenic region in the mycobacterial genome appears to be intriguing. While some investigators are exploiting the variability in molecular epidemiology, its functional role has not been addressed. We have found polymorphism in the promoter region of a gene which appears to protect *M. tuberculosis* from oxidative stress and thus determines the virulence of tubercle bacilli. The promoter region contains a repetitive sequence which shows extensive polymorphism in clinical isolates of *M. tuberculosis*. The functional role of polymorphism has been addressed by fusing the variable region containing the promoter elements with the reporter gene and assaying for its expression. The results reveal that the variability in repeat numbers affect the gene expression thus opening a novel mode of gene regulation in *M. tuberculosis*. Answers to these unexplored questions is likely to yield comprehensive information on therapeutic and immunological intervention of TB with and without HIV.

GL-07

HIV and Tuberculosis co-infection in children

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Tuberculosis is increasing in prevalence in many countries and is now the leading infectious cause of death worldwide, being responsible for three million deaths annually. HIV infection has emerged as the most important predisposing factor for developing overt tuberculosis in people co-infected with *M. tuberculosis* and an important reason for the recent worsening of the global tuberculosis epidemic.

Epidemiology of HIV-Tuberculosis: Pediatric HIV infection today represents a major setback to child health. At the end of December 2004, it is estimated that approximately 39.4 million (potential range 35.9- 44.3 million) people are living with HIV/AIDS worldwide. Of these 2.2 million (potential range 2- 2.6 million) are children under 15 years of age. In the year 2004, it is estimated that there were 4.9 million people newly infected with HIV, of which 0.6 million were children and there were 3.1 million deaths (1). Latest estimates show that about 5.1 million [2.5–8.5 million] people were living with HIV in India in 2003 (2). Serious epidemics are underway in several states. In Tamil Nadu, HIV prevalence of 50% has been found among sex workers, while in each of Andhra Pradesh, Karnataka, Maharashtra and Nagaland, HIV prevalence has crossed the 1% mark among pregnant women.

GL-08

Cytokine response in co-infection

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Leishmaniasis currently threatens 350 million men, women and children in 88 countries around the world with an overall prevalence of 12 million. HIV-leishmania co-infection was reported to the World Health Organization (WHO) from 33 countries worldwide up to 1998. The majority of cases are reported from southern Europe with up to 9% of HIV-infected persons developing leishmaniasis in these regions. While most *Leishmania*/HIV co-infections in the Americas are reported in Brazil, there are few reports from Africa and Asia since no active surveillance exists. However, the frequency of co-infection is bound to rise and India needs to be vigilant in the regions of kala-azar endemicity.

Since both HIV and *Leishmania* infect mononuclear cells and dendritic cells and by themselves cause impaired cell mediated immunity, it can be expected that co-infection will have serious consequences. It has been shown that leishmania infection accelerates the replication of HIV in vitro and also adversely affects the course of the disease in patients. The response of leishmania to therapy, which is dependent on an intact immune response, is adversely affected by HIV. Since a Th1 cytokine profile is beneficial to both these infections, the role of cytokines in the outcome of co-infection has been investigated by a number of groups. These issues will be presented and discussed.

GL-09

Host genetic factors and HIV infection

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The problem of AIDS pandemic in India is alarming since more than 5.1 million people are infected and those infected tend to progress rapidly to AIDS, thereby leading to its vicious spread. Our immunogenetic studies on 180 HIV+ Asian Indians have shown that (i) CCR2 allele 64V, that is associated with faster progression to AIDS is highly prevalent in more advanced type C HIV-1 infected symptomatic patients and in those coinfecting with pulmonary tuberculosis, (ii) absence of CCR5D32 allele, known to provide resistance against HIV infection, (iii) Of the five CCR5 promoter haplotypes, HHC was most frequently observed in healthy controls, (iv) HHF*2, associated with HIV-1 disease retardation was rare, (v) HHAB and HHE haplotypes of CCR5 were observed as homozygous genotypes in higher frequencies, particularly in the type C HIV-1 infected patients, suggestive of an increased likelihood of infection and accelerated course of infection. These results alongwith our additional data on HLA diversity and cytokine gene polymorphism are indicative of a possible faster and easy spread of AIDS in the Asian Indian population. HIV-1 clade C dominates global AIDS pandemic and stands a great challenge for India. We have carried out extensive studies on molecular diversity of HLA, in depth analysis of peptide binding motifs and identified most common HLA supertypes with maximum population coverage. Based on this background information, we have initiated studies to predict HLA based HIV-1 clade C gag derived CTL epitopes that could be immunodominant and could be incorporated in vaccine design.

GL-10

Modulation of Macrophage Signalling Machinery By A Mycobacterial Secretory Antigenic Protein, MTSA-10

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Mycobacterium tuberculosis (Mtb) Secretory Antigen (MTSA-10), a 10- kDa secretory protein encoded by RD-1 region of the Mtb genome putatively plays an important role in the mycobacterial virulence and intracellular survival. Our study focuses on delineating possible role of MTSA-10 in modulation of the host macrophage functions.

The *mtsa-10* gene was cloned in *E. coli* expression vector and the purified recombinant protein was used to stimulate the murine macrophage cell line J774.1. Using proteomics approach, we found that recombinant MTSA-10 could induce J774.1 cells to undergo major de-phosphorylation of the total phospho-proteome. About two-thirds of the proteins analysed get de-phosphorylated within 20 minutes of stimulation as compared to those in the unstimulated cells. This dephosphorylated state persisted without any significant change for 1 hr. This might be the key effect pursuant to stimulation with mycobacterial protein, that prevents macrophage activation.

Macrophages are known to produce robust amount of reactive oxygen species (ROS) when encountered by antigens. However, we observed that MTSA-10 caused a reduction in ROS production by J774.1 cells when administered alone or simultaneously with the known ROS producers like LPS or IFN-g. Furthermore, we found that MTSA-10 stimulation activated the membrane-associated phosphatases, which might be the cause for global de-phosphorylation of macrophage proteins.

Our results indicate that MTSA-10 plays an important role in modulating the overall signalling process by changing the cellular equilibrium of kinases and phosphatases. ROS is known to inactivate phosphatases and thereby activate the kinases. MTSA-10 appeared to keep the phosphatases in active state. This implies that potentially MTSA-10 could activate phosphatases by lowering down the ROS production in infected macrophages. Thus, it might give *Mycobacterium* an advantage over macrophages not only to evade destruction but also survive happily within it. (Work in the Sharma Lab is supported by R&D grants from DBT (Govt of India); SKB and NG are SRF supported by CSIR)

GL-11

Genetic analyses of host genes that affect progression of HIV-1 and gene therapy approaches

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Several host genes are now known to be involved with HIV-1 infection, replication and pathogenesis. Prominent among them are the chemokines, chemokine receptors and all other genes that influence their expression, especially the interleukins. HIV-1 resistant mutation CCR5-delta-32 is extremely rare among North-Indians and individuals who are homozygous for this deletion have not been found. Disease modifying mutations of other genes that are linked with progression like SDF-1, Rantes, Mip-1-alpha, CCR2 and CX3CR1 were undertaken and some common and some unique mutations were observed. DC-SIGN is important in the early stages of HIV-1 infection. DC-SIGNS are also involved in modulating infections by M.tuberculosis and several other pathogenic bacteria. We observed three unique substitutions in the intronic region between third and fourth exon and one insertion between fourth and fifth exon among all the 16 normal individuals in our study. We designed novel ribozymes, DNA-enzymes and small interfering RNAs (siRNAs) against host genes (CCR5) and some viral genes (HIV-1 Tat/Rev and Gag) and show protection against HIV-1 challenge in tissue culture condition. We exploited the lentiviral based vectors to express our transgenes in the appropriate host cells, that is lymphocytes and macrophages.

GL-12

Understanding Immune Restoration Disease (IRD) through Immunological and Immunogenetic Studies

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Immune Restoration Diseases (IRD) are a collection of atypical inflammatory and autoimmune diseases seen after HIV viraemia is suppressed by antiretroviral therapy (ART). IRD probably reflect dysregulated immune responses against pre-existing pathogens, with different immunopathological mechanisms for different pathogens. For example, mycobacterial IRD are associated with restored delayed type hypersensitivity (DTH) responses to mycobacterial antigens, whereas patients who experience CMV IRD have elevated plasma levels of soluble CD30, a marker of a T2 cytokine environment. As IRD are often compartmentalized, monitoring plasma levels of antigen-specific IgG antibody may be more informative than peripheral blood T-cell responses, as demonstrated for CMV and HCV-associated IRD. Genetic studies have provided evidence of distinct immunopathological mechanisms and inherited susceptibility to IRD associated with mycobacterial and herpesviridae infections. For example; most patients (92%) who experienced an IRD associated with herpesviridae carried IL-12B+1217*1, compared with 42-54% of patients with other or no IRD. Many herpesviridae-IRD patients carried TNFA-308*2 as part of the HLA-A2,B44 haplotype, rather than the disease-associated haplotype, HLA-A1,B8,DR3. IL6-174*C was rare and TNFA-308*2 was absent in patients with IRD arising from Mycobacterium sp. Thus distinct immunopathological mechanisms lead to the various IRD. The expansion of ART in the developing world where HIV patients have low CD4+ T-cell counts and high rates of concomitant infections, will place a large number of patients at-risk of developing IRD. It is therefore important to understand the immunopathology so that prevention, diagnosis and treatment can be improved.

HIV infection and Dermatological and Venereal diseases

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India is considered to be a low HIV prevalence country with an overall <1% prevalence. There are more than 5.1 million HIV infected cases in the country. Often these patients have skin and sexually transmitted diseases, depending on the stage of the infection, host immune response and number of CD4 cell count in the blood. The occurrence of these manifestations also vary in different regions due to varying prevalence of various microbial agents. Various studies have reported different mucocutaneous manifestations with varying frequencies.

We studied 302 HIV positive patients for their skin and sexually transmitted diseases. Majority of our patients were males between 20 – 40 years of age. Large majority of them had acquired the infection from commercial sex workers through heterosexual unprotected sexual intercourse. Amongst the sexually transmitted diseases; at the time of presentation 46 patients had herpes simplex infection, 37 genital warts, 27 syphilis, 19 molluscum contagiosum, 8 chancroid, 7 vulvovaginal candidiasis, 6 scabies, 5 non-gonococcal urethritis, 2 gonococcal urethritis and 1 patient had candidial balanoposthitis. However amongst the skin diseases 28 patients had dermatophytosis, 24 oral candidiasis, 22 each had folliculitis and insect bite hypersensitivity, 8 patients each had seborrhoeic dermatitis and generalized ichthyosis/xerosis, 4 acneiform eruption, 3 each tubercular lymphadenitis and post-herpetic neuralgia, 2 patients each had toxic epidermal necrolysis, miliria, verrucae, hidradenitis suppurativa, Behcet's disease and oral hairy leukoplakia. One patient each had fix drug eruption, polymorphous light eruption, melasma, urticaria, sebaceous cyst, neurofibromas, asteatotic eczema, IED, fibromas and erythroderma. Majority of our patients had manifestations of infectious etiology while some were coincidental associations.

Parasitic Infections in AIDS

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Coccidia, Microsporidia and certain helminthes have been incriminated as causative agents of diarrhoea in immune compromised patients (ICP). To study this association, 100 ICP with diarrhoea: comprising of 20 HIV infected patients, 40 malnourished children and 40 patients with malignancy were investigated. Fifty ICP, without diarrhoea, consisting of 10 HIV seropositive individuals, 20 malnourished children and 20 malignant cases served as controls. Modified cold Kinyoun's acid fast staining was suitable, as a routine technique, for demonstration of oocysts of *Cryptosporidium*, *Isospora* and *Cyclospora*. Immunofluorescence for *Cryptosporidium* occyst was economically unsuitable as a routine diagnostic technique. *Cyclospora* was cultivable in 5% aqueous Postassium dichromate medium. Modified trichrome blue staining was suitable for demonstration of *Microsporidia*. Formolether concentration technique was suitable for demonstration of cysts of *Giardia intestinalis*, *Entamoeba histolytica*, *Entamoeba dispar*, *Entamoeba coli*, *Iodamoeba butschlii*, *Endolimax nana*, *Trichomonas hominis*, *Strongyloides stercoralis* and ova of *Hymenolepis nana*. *Cryptosporidium* was demonstrated in 30, 21.5 and 2.5 percent of patients with HIV infection, malnutrition and malignancy respectively. As compared to controls the observed incidences in patients with diarrhoea in HIV and malnourished patients were significantly higher ($p < 0.01$). *Isospora*, *Cyclospora* and *Microsporidia* were demonstrated in five, three and one percent of ICP with diarrhoea, respectively. *Blastocystis hominis* was demonstrated in 16 and six percent of cases and controls respectively. The incidence is significantly more in cases as compared to controls ($p < .01$). *G. intestinalis* was demonstrable in 22.5, 15 and 10 in cases of malnutrition, malignant and HIV infected groups respectively. *E. histolytica*, Helminthes, *Salmonellae* and *Shigellae* were conspicuous by their rarity in the test and control groups. However *Candida* species was isolated in significantly higher number from malignant group with diarrhoea. It was concluded that *Cryptosporidium* and other intestinal *Coccidia* could be the commonest aetiological agents of enteritis in HIV patients and malnourished children with diarrhoea.

Entamoeba Histolytica, E.dispar and E.moshkovskii Infections in Patients with HIV in India

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Entamoeba histolytica is one of the non-opportunistic protozoa, commonly found in HIV infected people regardless of immune status with or without diarrhoeal symptoms. *E.histolytica* is indistinguishable in its cyst and trophozoite forms from those of *E. moshkovskii* and *E. dispar*. *E. histolytica* as a non-opportunistic protozoa have been documented in patients with HIV, but informations are scanty regarding the prevalence of *E. dispar* or *E. moshkovskii* in patients with HIV. In our laboratory we have reported *E. histolytica*, *E. dispar* and *E. moshkovskii* in stool samples by nested PCR. Out of 746 stool samples screened, 68 stool samples showing cyst or trophozoite stage of *E. histolytica*/*E. dispar*/*E. moshkovskii*, were subjected to SSU rRNA (small subunit rRNA) gene-based polymerase chain reaction which revealed the presence of *E. moshkovskii* and *E. dispar* in Pondicherry,India. Our report of *E. moshkovskii* was first such report from India. The study reveals that only 19% of 68 stools samples resembling *E. histolytica* by microscopy were really *E. histolytica*, implying that the 81% of suspected infection were misdiagnosed and would have been treated unnecessarily with antiamebic drugs. The results of the study also shows that there is a high rate of colonization of nonpathogenic *E. dispar* and *E. moshkovskii* amongst the patients which indicate an increased chance of misdiagnosis when diagnosed based on morphological findings alone. The present paper will review the status of *E. histolytica* , *E. dispar* and *E. moshkovskii* infections in patients with HIV in India and the need for the evaluation and development of the tests for their accurate detection in stool specimens.

Coccidian parasites in HIV infected individuals in south India

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In the absence of readily available retroviral therapy in India, opportunistic infections of the gastrointestinal tract have been a major cause of morbidity in HIV infected individuals. In a five year study from 1998 to 2002, between one and three samples from 258 HIV infected patients with diarrhea were examined. Enteric parasites were diagnosed in between 53 and 61% of the HIV patients seen each year. Protozoan parasites were common, with *Isospora belli* (19.7%), *Cryptosporidium* (15.5%), *Giardia lamblia* (5.0%) and *Cyclospora cayatenensis* (3.8%). Microsporidia were seen in 4.6%. The helminths seen were *Strongyloides stercoralis* larvae (8.5%), *Ascaris lumbricoides* ova (2.3%) and hookworm ova (4.3%). Enteric parasites were identified in 5.8% of samples received from HIV-negative patients, with *Giardia* the most commonly identified parasite (2.6%). However, a later study (2003-2004), demonstrated the difference in parasitic infection patterns after the introduction of co-trimoxazole prophylaxis with a lower rate of *Isospora* infections and a relative increase in cryptosporidial infections. Cryptosporidial infection in patients with AIDS may cause severe and often fatal diarrheal disease. Very little is known about the molecular epidemiology of *Cryptosporidium* in the developing world, where standards of hygiene and prevalence of enteric pathogens differ significantly from developed countries. We have reported the identification of *Cryptosporidium* spp by microscopy from HIV seropositive patients with (28/111, 25.2%) and without diarrhea (20/423, 4.7%) in southern India. DNA was extracted from *Cryptosporidium* positive fecal samples and species determined by the small subunit rRNA (SSU) polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP). Multi-locus genotyping was carried out by PCR-RFLP analysis at the thrombospondin-related adhesive protein of *Cryptosporidium* (TRAP C1) *Cryptosporidium* oocyst wall protein (COWP) and glycoprotein 40/15 (*Cpgp40/15*) loci. *Cryptosporidium hominis* (31/48, 64.6 %), *C. parvum* (9/48, 18.8 %), *C. felis* (5/48, 11.6%) and one isolate each of *C. muris* and *C. meleagridis* were identified. *Cpgp40/15* PCR-RFLP identified six subgenotypes, with subgenotypes Ib and If most commonly seen. Five isolates of *C. parvum* had discordant genotyping results. Cryptosporidial diarrhea was associated with decrease in CD4 count below 200 ($p=0.009$), but not with high viral load. There was no significant association between genotype and symptoms. This first report of molecular typing of *Cryptosporidium* spp from HIV infected individuals in India documents the high incidence of potentially zoonotically transmitted strains in humans.

GL-17

Toxoplasmosis in AIDS Patients

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Toxoplasma gondii is a coccidian protozoan, which is widely prevalent. It infects a wide range of vertebrate hosts including humans. Even though in immunocompetent individuals infection remains largely asymptomatic and latent, it causes severe and life threatening disease. In most of the cases it is due to reactivation of latent infection and the parasite has special predilection to central nervous system. In developed world before Highly Active Anti-retroviral Therapy (HAART) toxoplasmic encephalitis (TE) was reported in upto 39% HIV infected cases. However, after HAART the incidence of TE has come down to only 3-10% cases. Even, though low-dose co-trimoxazole-pyrimethamine prophylaxis is not effective, high dose treatment with these drugs is highly effective. Rifampicin, used as prophylaxis and treatment of tuberculosis, is reported to reduce the efficacy of anti-toxoplasmic treatment. HIV infected patients can best minimize the fresh active infection of toxoplasma by using precautionary measures.

GL-18

Penicilliosis Marneffeii and its Current Knowledge

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Penicilliosis marneffeii is the third most common opportunistic infection in AIDS patients in northern Thailand, after tuberculosis and cryptococcosis. It afflicts patients residing in the endemic areas which include Southeast Asia, India and China. Cases have also been reported from other countries. Early diagnosis by serologic and molecular assay-based methods have been developed and are proving important in diagnosing infection. The occurrence of natural reservoirs and the molecular epidemiology of *P. marneffeii* have been studied, however the natural history and mode of transmission of the organism remain unclear. Soil exposure, especially during rainy season, has been suggested to be a critical risk factor. Using a highly discriminatory molecular technique, MLMT, to characterize this fungus, several isolates from bamboo rats and humans were shown to share identical multilocus genotypes. This data suggests that either transmission of *P. marneffeii* may occur from rodents to humans, or that rodents and humans are coinfecting from common environmental sources. Studies on the fungal genetics of *P. marneffeii* have been focused on the characterization of genetic determinants that may play important roles in asexual development, mycelial-to-yeast phase transition, and the expression of antigenic determinants. Molecular studies have identified several genes involved in germination, hyphal development, conidiogenesis, yeast cell polarity and yeast phase transition.

Cryptococcosis in AIDS

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Cryptococcosis caused by the encapsulated basidiomycetous yeast, *Cryptococcus neoformans* is an important opportunistic infection in AIDS patients. AIDS associated cryptococcosis accounts for 50% of all cryptococcal infections reported annually and usually occurs in HIV patients when their CD4 lymphocyte count is below 200/mm³. Meningitis is the predominant clinical presentation with fever and headache as the most common symptoms. Extraneural sites include lungs 20(%), skin, bone, urinary tract including prostate, and others. Pulmonary disease presents as fever, cough, headache, lymphadenopathy and hepatosplenomegaly. Histology shows multiple granulomas composed of histiocytes and epithelioid cells along with numerous cryptococci. Secondary cutaneous infections occur in up to 15% of patients with disseminated cryptococcosis and often indicate a poor prognosis. About 5–10 % of AIDS patients develop cryptococcosis in the United States, Europe and Australia, the incidence is much higher in sub-Saharan Africa (15–30 %). Numerous cases of AIDS associated cryptococcosis have been reported from several parts of India. The data are scanty to give an estimate of its prevalence; however, a few studies indicate about 5% prevalence of cryptococcal meningitis in AIDS patients with a median duration of survival of about two years. It is estimated that 10–25 % of AIDS patients with cryptococcosis die in spite of antifungal therapy, and 30–60 % succumb within the first year of onset. AIDS associated cryptococcosis accounts for 50% of all cryptococcal infections reported annually. Currently *C. neoformans* is referred to as two species, viz. *C. neoformans* and *C. gattii* with different ecologic niches. *C. neoformans* infects predominantly AIDS patients and it has two varieties, var. *grubii* (serotype A) being very common world wide, and var. *neoformans* (serotypes D) being very less frequent, both with the sexual stage *Filobasidiella neoformans* var. *neoformans*. *C. gattii* infects predominantly immunocompetent patients. It has two serotypes, viz. B and C both with the sexual stage as *F. neoformans* var. *bacillispora*. Serotype B is very common while serotype C is rare, except recently recorded to occur very frequently in Sub-Saharan Africa. Molecular studies on *Cryptococcus* isolates have shown them to be comprised of eight major types, viz., molecular types VNI and VNII corresponding to *Cryptococcus neoformans* var. *grubii*, serotype A, molecular type VNIV corresponding to *C. neoformans* var. *neoformans*, serotype D and molecular types VGI, VGII, VGIII and VGIV corresponding to *C. gattii* serotypes B and C. Culture and isolation of *C. neoformans* is the gold standard method having greater specificity and almost 100% sensitivity for diagnosis of cryptococcosis. Direct examination of CSF sediment prepared with India ink has a sensitivity of about 96% in AIDS cases. The detection of polysaccharide antigen by latex particle agglutination in body fluids such as: CSF, serum and urine is a rapid and presumptive method of diagnosis of cryptococcosis and is positive in about 90–95% cases with a high specificity. Antifungals used in cryptococcosis treatment are amphotericin B, 5-flucytosine and fluconazole. PCR has been tried successfully for detecting cryptococci in clinical specimens by some investigators.

Candidosis and HIV/AIDS: Indian experience

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Mucocutaneous candidosis is probably one of the commonest opportunistic infection with which most of the HIV-positive patients presents in the clinic with oropharyngeal candidosis (OPC) being most widely reported. In India, its incidence has been reported from 50 to 100 per cent. Type of lesions may vary and some of the patients may lack classical picture of oral thrush especially when CD4 count is quite high. In our recent study on OPC in HIV-positive patients, we found that patients can present with gingivitis, glossitis, while the unusual manifestations like generalized cutaneous lesions, non healing cutaneous ulcers, perineal cutaneous lesions or disseminated candidosis were first reported in our initial studies with agent isolated mainly *C. albicans*. Several studies since 1992, with increased number of patients with OPC, still show the prevalent isolate as *C. albicans*, though emergence of non albicans *Candida* species, in concordance with experience of other investigators, has also been reported. Surprisingly, *C. dubliensis*, one important species of *Candida* reported in OPC mainly from abroad is still not seen in Indian HIV positive population with infection; barring only one report from a carrier. The reason for this discrepancy is difficult to explain, however, the type of oral hygiene in different groups of patients along with their flora before active infection may have some role. Our present study also revealed good correlation of extent of oral lesion along with CD4 count.

Candida oesophagitis, one of the AIDS defining infections, scarcely reported in Indian HIV-positive patients. Same also applies on *Candida* vulvovaginitis. Probably it may be due to the cumbersome procedure of collection of sample and lack of enthusiastic investigator specifically looking for this type of lesion.

Inexpensive conventional diagnostic test can differentiate majority of common pathogenic species of *Candida*. Species identification is essential and has therapeutic impact hence need to be adopted in any diagnostic setup.

In contrast to wide application of the *in vitro* antibacterial susceptibility test, development and adoption of *in vitro* antifungal susceptibility test is still in infancy in India. This test system is essential for therapeutic guidance in fungal OI in HIV disease, particularly in case of fluconazole, widely used triazole, which is being used for prophylaxis of OPC and life long maintenance therapy in patients who have been treated for chronic meningitis with amphotericin B. Few institutions have adopted the guidelines laid down by the National Committee of Clinical Laboratory Standards while others are using indigenously developed test. AIIMS has optimized NCCLS macro- and micro-broth dilution and conventional agar dilution techniques especially for *Candida* species. We observed that in contrast to the worldwide report of appearance of growing population of fluconazole resistant *C. albicans*, only 6 per cent of our isolates from OPC were resistant against fluconazole. Situation though is not alarming at this point, surveillance programmes need to continue, to forecast the advent of a resistant population.

CMV as a Cofactor Enhancing Progression of AIDS

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Since the first cases of AIDS were defined in 1981, CMV end organ disease has been an AIDS defining opportunistic infection. I will give a historical perspective to suggest that throughout all of this time, including the current era of highly active antiretroviral therapy (HAART), CMV has also acted as a co-factor, driving the pathogenicity of HIV.

In 1989 we reported that haemophiliacs who were seropositive for CMV developed AIDS more rapidly than those who were CMV seronegative and that this difference remained significant once age was controlled for statistically(1). We collaborated to study another large group of haemophiliacs but did not find a similar effect(2); this difference remains unexplained.

Detels and colleagues(3) reported that patients with persistent excretion of CMV in serial samples of semen had a significantly increased relative hazard of developing AIDS once differences in CD4 counts were controlled statistically.

When studying the responses of patients with first episode CMV retinitis to ganciclovir therapy using quantitative competitive PCR, we reported that those who presented with a viral load higher than the median for the whole group had a significantly shorter survival than the remaining patients(4). At that time, we could not be certain that this was not just an indirect measure of HIV since HIV viral load measurements were not then available. However, Steve Spector's group answered this question in 1999 by showing that the death rate among patients enrolled in a randomised trial of oral ganciclovir was driven largely by the CMV viral load rather than the HIV viral load(5).

Also in 1999, Kovacs and colleagues reported 440 infants born to HIV positive mothers whose CMV status was known because of culture or serology results. HIV disease was increased significantly amongst the children who were positive for CMV. A raised HIV viral load was a risk factor for disease progression only among the CMV seronegatives(6).

The availability of HAART has dramatically controlled HIV replication, so delaying the development of immunocompromise. In addition, we showed in 1999 that HAART also reduced asymptomatic CMV viraemia, presumably because HAART gave back protective immune functions against CMV(7). Thus, the availability of HAART has both decreased HIV replication and the replication of CMV so potentially impairing its ability to act as a cofactor. To determine if CMV still has a role to play in the era of HAART we decided to follow a cohort of patients given HAART and observe if those who progress to new AIDS defining conditions or to death were more likely to have evidence of CMV infection than the remainder. We recruited any patient whose CD4 count had ever been less than 100 and followed them for a median of 36 months as they received the best available HAART therapy. We collected blood samples for CMV PCR whenever they attended the clinic and found that 375/2969 (13%) of these were positive for CMV DNA. Of the 374 patients who were followed, 69% were consistently CMV negative throughout, 4% were consistently CMV positive and 27% of patients were intermittently CMV positive or negative. We examined the group for the two end points of new AIDS defining conditions or death and looked at CMV, CD4 counts and HIV viral load as covariates both at baseline and time updated(8).

To summarise the covariates measured over follow-up using multivariable analyses, i) progression to a new AIDS defining event was significantly associated with HIV RNA level, CD4 count and CMV DNA thus showing that CMV is an additional risk factor for progression which is independent of CD4 count and HIV level, ii) CD4 count and CMV DNA were persistently associated with mortality but, once these two factors had been controlled, HIV viral load was no longer significant so showing that mortality is driven by CMV and the CD4 count not by HIV(8).

I conclude that CMV remains important in the era of HAART and that CMV has been underestimated as an important cofactor since the beginning of the AIDS epidemic.

GL-22

Surgeon and HIV Positive Patient

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The story of HIV started with identification of *Pneumocystis carinii* pneumonia in 5 young homosexuals about 25 years back in USA. But since then number of HIV positive/AIDS patient is continuously increasing and now disease is a global health problem of enormous magnitude.

A surgeon can encounter a HIV positive patient in different settings. In most of the cases he is asked by his medical colleagues to perform screening tests for HIV before supportive or therapeutic surgery in a HIV positive patient but sometime surgeon may be the first clinician to see a HIV positive patient presenting with the problems of oral ulcers, dysphagia, or ulcers in anorectum etc. Most other if not always there is under fear in surgeons for managing HIV positive persons. But on the same time if proper precautions are not adopted by the surgeon he may get HIV infection.

GL-23

Organ Transplantation In HIV positive patients

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AIDS is a major health problem in India with a current estimated prevalence rate of 0.9%. Most transplant units routinely have excluded patients with HIV infection from consideration for solid organ transplantation. However most of the data in the literature regarding transplantation of HIV sero- positive patients pertains to the time prior to the administration of Highly Active Anti-Retroviral Therapy. This data provides little evidence to the management of these patients in the current era.

The other main concern has been the immunosuppressive medications to a population already at risk of opportunistic infections. Also the medications may accelerate the progression to AIDS through decreased immunosurveillance and increased viral replication. There is also the concern whether scarce organs should be utilized in HIV positive patients who may have a worse prognosis than HIV negative patients

As a result of improved outcomes in transplantation and HIV interest has developed in solid organ transplantation in HIV infected individuals. With prolonged survival HIV positive patients face end stage organ disease from HIV associated nephropathy, (HIVAN), HCV and HBV infections.

Recent understanding of treatment and monitoring strategies in HIV/AIDS in India

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Recent understanding of treatment and monitoring strategies can be divided into following:

Pre-ART care: This is care provided during the period when a HIV positive person is well and does not require initiation of ART. With the scaling up of the national programme and increase in the number of counseling and testing centers, It is expected that, a shift from AIDS patients to HIV persons will occur. These persons should be advised and counseled to maintain healthy/positive living. However, in order to properly follow up and monitor these patients such as early detection of opportunistic infections (OIs) and initiation of ART before the CD4 declines to below 200, a comprehensive pre- ART workup of HIV persons including clinical and laboratory workup must be done. Laboratory workup includes mandatory baseline screening CD4, CBC, ALT/AST, ALP, serum Creatinine, CXR, VDRL/TPHA; urinalysis. For women annual PAP smear screening and HBsAg and HCV screening for IDUs/ transfusion-associated infections or those with liver enzyme elevations and any other relevant investigations (symptom driven). Due attention should be given to screen them for TB. CD4 counts should be monitored every 3 months if CD4 <350 and every six months if CD4 > 350.

ART Care: All symptomatic patients and patients with CD4 counts less than 200 should be initiated on ART. It is important to initiate treatment before CD4 cell counts drop below 200. If CD4 is between 200-250, this should be repeated in 4 weeks and treatment to be considered in asymptomatic patients. First line drug regimens include AZT or d4T + 3TC + NVP or EFV or TDF + 3TC + NVP or EFV. Second line drug regimen include one of these RTI regimens i.e. TDF + ABC +3TC or ddI + ABC +3TC or TDF + AZT+3TC and one of boosted PI i.e. 1st: LPV/r or 2nd: ATV/r when available or 3rd: SQV/r or 4th: IND/r (cold chain needed for Ritonavir) or NLF when cold chain not available.

Monitoring and follow up patients on ART: Frequent follow up during the initial months is necessary to diagnose and efficiently manage acute adverse events, work with the patient on adherence issues, and diagnose clinical conditions like IRIS and new occurrences of OIs. Once a patient is on an effective and stable regimen at 6 months, quarterly follow up is recommended where adherence is reasonably ascertained. Estimation of CD4 count is recommended at 6 months to document immunological improvement on ART and every 6 months thereafter where possible. A Plasma Viral load (PVL) at 6 months is essential to determine efficacy of the ARV regimen.

Managing failure: Antiretroviral treatment failure can be defined in 3 ways: virological, immunological or clinical, in most instances one follows the other. Progression of disease with occurrence of OIs or malignancies after 3 months or more of ART initiation is defined as clinical failure. A drop of greater than 30% in CD4 counts from peak value or a return to pre-ART baseline or lower is defined as immunological failure. Virological failure is defined as PVL value of >400 copies/ml at 6 months after ART initiation. Identifying the cause of failure is important before deciding to modify the ART regimen. Following points need to be assessed: a) Adherence: A detailed assessment of adherence needs to be done. The reasons for non-adherence need to be explored. Unless these reasons are identified, a patient may also find it difficult to adhere to the second-line regimen. b) Drug interactions: Assessing whether the patient is concomitantly taking medications which interfere with ARV activity is important. Many patients may not reveal that they take herbal treatments along with the prescribed ART regimen and c) Continuing high risk behavior: If a patient continues to practice high risk behavior, superinfection with a drug resistant virus may lead to treatment failure. Once failure is documented a second-line ART regimen should be designed for the patient wherever available.

Drug Resistance and Monitoring in HIV/AIDS

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In the developed countries administration of ARV Therapy has remarkably reduced mortality. However, the emergence of resistance to these drugs remained to challenge this unique achievement. The contributing factors have been administration of suboptimal doses and poor adherence. The potential for transmission of resistance strains has been recognized and has shown to impact on the efficacy of the ARV regimens.

In the past five years several patients in the developing countries, including India are receiving ARV therapy since the world opinion has changed to link prevention with Care. In resource constrained settings individual monitoring of drug resistance is not practical. Even though the technology is available it requires expensive equipment and trained manpower. As nations begin to scale up ARV treatment, understanding patterns of HIV drug resistance and the success and failures of regimens will be critical to choose the best regimens. HIV drug resistance is the single most important factor that influences the long term success of ARV scale up. We have been conscious of HIV drug resistance and have undertaken studies on the emergence of drug resistance in HIV/AIDS patients who have been treated with dual therapy, mothers who received single dose of Nevirapine as ARV prophylaxis for reduction of mother to infant transmission, in patients receiving triple ARV therapy and ARV Naïve patients. In Our studies we have used two techniques; DNA sequencing and the Oligoligase Chain Assay (OLA). The results will be presented and discussed.

Lastly, it is important to build national capacity for laboratory testing, (including networking) clinical monitoring, a quality assurance program to help ensure the accuracy and consistency of genetic analysis undertaken by participating laboratories and policy development in order to sustain the monitoring and surveillance efforts over the long term.

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