DIVISION OF CLINICAL SCIENCES

Division Of Clinical Sciences

The Department of Clinical Sciences at NARI has been carrying out research related to the improving the clinical management of HIV infected individuals. Antiretroviral therapy has been one of the corner stones in the management of HIV infection and ART related research is one of the priorities in clinical research at NARI.

In the ACTG 5175 study, where once daily and twice daily administered ART regimens are being studied to determine whether once daily regimens are non-inferior to the gold standard twice daily regimens. A total of 120 subjects have been enrolled in the study and follow up of the enrolled subjects is ongoing.

Tuberculosis is one of the commonest opportunistic infections occurring in HIV infected individuals in India and research related to HIV and tuberculosis has been another area of focus of the Clinical Sciences Department at NARI. In the smear negative pulmonary tuberculosis project, the algorithm for improved diagnosis of pulmonary tuberculosis in HIV infected individuals is being evaluated. This project is being done in collaboration with the Tuberculosis Research Centre at Chennai and so far, 68 subjects have been enrolled in the study.

NARI has been identified as an ART Link Centre by the National AIDS Control Organization to provide Anti-Retroviral Therapy (ART) to NARI research study participants. During the last one year from April 2007 to March 2008, 72 participants have been enrolled in the free ART programme at the NARI Clinic located at NIV. A total of 264 subjects have been receiving free ART from the NARI clinic located at the National Institute of Virology by the end of March 2008.This centre has been identified by NACO as one of the 10 training centres for training of medical officers and specialists from various ART centres in India. Till date two 12 day trainings were conducted for medical officers and 25 medical officers were trained for National ART programme and 30 specialists were trained in a 4 day specialist training programme.

In addition to carrying out clinical studies, the clinics attached to NARI provide various diagnostic and counseling services to referred patients and provide treatment and prophylaxis for opportunistic infections.

A. Evaluation of a diagnostic algorithm for HIV positive pulmonary TB suspects who are initially smear negative

[Lead Investigators: Dr. Padma Priyadarshini (TRC, Chennai) and Dr. S. P. Tripathy (NARI, Pune)]

Evaluation of Diagnostic algorithm for HIV positive Pulmonary TB suspects who are initially smear negative a multicentric study.

The sample size for the study would be 540 HIV positive TB suspects (270 patients each from Chennai and Pune)

Primary Objective of the study was to develop and evaluate a diagnostic algorithm for HIV

positive persons suspected to have tuberculosis, but who are smear negative for acid-fast bacilli during the initial screening for TB.

Secondary Objective was to determine the utility of initial chest x-ray (CXR) and sputum culture, in the RNTCP diagnostic algorithm, in identifying TB cases among the initial smear negative HIV positive patients

Inclusion Criteria

1. Age > 15 years
2. HIV positive individuals with cough > 2 weeks and/ or fever > 2 weeks regardless of prior ATT or ART
3. Initial 3 sputum smears are negative for acid fast bacilli by Ziehl-Neilsen (ZN) technique
4. Willing to participate in the study

Exclusion Criteria

1. Patients with smear positive tuberculosis
2. Unable to expectorate
3. Seriously ill and moribund patients
4. Unwilling to participate

So far, 68 eligible subjects have been enrolled in the study. These included 48 males and 20 females. The mean age of the study participants so far has been 35.06 years [(median 35 years + 6.29 (2SD)]. Of the 68 subjects enrolled, three study subjects had a positive culture within the subsequent two months after the culture was carried out for M tuberculosis. Oral thrush was seen in 5 of the 68 study subjects. Enrollment into the study and follow up of the enrolled subjects is still ongoing.

B. Nevirapine V/s Efavirenz-based highly active antiretroviral therapy regimens in antiretroviral-naive patients with HIV and Tuberculosis infection in India"

[Lead Investigators: Dr. Sinha (AIIMS, New Delhi) and Dr. S. P. Tripathy (NARI, Pune)]

The staff recruitment in the project was initiated in September 2007 and completed by January 2008. Subsequently, the training of recruited project staff was carried out at NARI in Pune and enrollment of subjects was initiated after the training was completed.

Objectives of the study:

1. To compare clinical, virological and immunological responses to nevirapine (NVP)-based and efavirenz (EFV)-based highly active antiretroviral therapy (HAART) regimens in antiretroviral-naive patients with HIV and Tuberculosis infection on anti-TB treatment (ATT).

2. To determine the safety of nevirapine based and efavirenz based highly active antiretroviral therapy regimens in antiretroviral-naive patients with HIV and Tuberculosis infection on ATT.

3. To study the response of switching back to nevirapine based regimen from efavirenz based regimen once anti-TB treatment will has been completed.

4. To characterize drug-associated toxicities of nevirapine based and efavirenz based regimens in HIV and Tuberculosis patients on ATT (especially hepatic, cardiac and hyperlipidemia).

Sample Size:

150 HIV infected TB patients would be randomized to the following two groups after obtaining informed consent: Group I-75 patients with NVP-based highly active antiretroviral therapy regimen with anti-TB treatment.

Group II-75 patients with EFV-based highly active antiretroviral therapy regimen with anti-TB treatment.

Inclusion Criteria:

1. HIV infection, documented licensed ELISA test kit.
2. Confirmed or probable TB.
3. Antituberculous treatment with standard therapy according to guidelines for less than 14 days.
4. CD4+ cell count (As per NACO guidelines)
5. The following laboratory values obtained within 30 days prior to or at study entry:
   - Absolute neutrophil count (ANC) **500 cells**/mm^3.
   - Hemoglobin 8.0 g/dL.
   - Platelet count 50,000/mm^3.
   - Creatinine 3 x ULN.
   - AST (SGOT), ALT (SGPT), alkaline phosphatase 5 ULN.
   - Total bilirubin 2.5 x ULN.

6. Female subjects of reproductive potential must have a negative serum or urine pregnancy test performed within 7 days before or at study entry. Male and female subjects who are participating in sexual activity that could lead to pregnancy and who are receiving EFV must agree to use reliable methods of contraception.

7. Men and women age 18 years.

8. Ability and willingness of subject or legal guardian/representative to give written informed consent.

Regimen:

All eligible TB patients were categorized according to the RNTCP and WHO guidelines for anti-TB treatment (ATT) thrice weekly (DOTS) therapy. DOTS is being provided by concerned DOTS center free of cost.

Antiretroviral therapy is being started between 2-8 weeks after starting ATT as per NACO guidelines. ARV therapy is being provided free of cost by the ART clinic, NARI, Pune. Once ATT has been completed, the patients will switch back to nevirapine based regimen from the efavirenz based regimen.

Initially, enrollment was started at Talera Hospital in the Pimpri Chinchwad area in February 2008. Subsequently, enrollment was also started at the Aundh Chest Hospital in Pune. By end of March 2008, a total of eight subjects have been enrolled in the study.

C. AACTG 5175 Study: A phase IV, randomized, open label evaluation of the efficacy of once daily protease inhibitor and once daily non-nucleotide reverse transciptase inhibitor containing therapy for initial treatment of HIV-1 infected subjects from diverse areas of the world.

[Principal Investigator: Dr.S. P. Tripathy]

This is a multicentric collaborative study sponsored by the AIDS Clinical Trials Group (ACTG) of the National Institutes of Health (NIH), USA. The primary objective of the study is to demonstrate the non-inferiority of a once-daily PI- and once-daily NNRTI-containing regimen as compared to standard twice-daily ARV therapy for the initial treatment of subjects infected with HIV-1 from diverse areas of the world.

For the study, at entry into the study, subjects are randomized (in 1:1:1 ratio) to one of the following three treatment arms:

1. Arm 1A: Lamivudine (3TC) / Zidovudine (ZDV) 150 / 300 mg 1 tablet BID + Efavirenz (EFV) 600 mg QHS

2. Arm 1B: Emtricitabine (FTC) 200 mg QD + Aatazanavir (ATV) 400 mg QD + Didanosine Enteric-coated (ddI-EC) 400 mg orally QD for subjects who weight > 60 kg and 250 mg QD for subjects who weight < 60 kg

3. Arm 1C: FTC 200 mg QD + Tenofovir (TDF) 300 mg QD + EFV 600 mg QHS

The enrollment of 120 subjects in the study was completed on 4th June 2007. Thirty-five patients were randomized to Arm A, 43 to Arm B and 42 to Arm C.

There were two deaths and one study subject lost to follow up so far. One death was due to suicide and the other due to disseminated pulmonary tuberculosis. Thirteen Expedited Adverse Events occurred during follow up of the study subjects. The SAEs included IRIS with Efavirenz induced severe depression, severe gastritis (2 cases), acute gastroenteritis with shock (2 cases), severe anemia (3 cases), pleural effusion, abdominal TB, encephalitis and diffused cerebral edema. Six subjects developed virological failure and had to be placed on a Step 2 regimen.

Table 2.1: Virological failure in A5157 Study

Sr. No.	Step 1Arm	Sex	Time since enrollment*
1	1C	M	Week 30
2	1B	M	Week 58
3	1B	M	Week 25
4	1B	M	Week 38
5	1B	M	Week 46
6	1B	M	Week 40

* For shift on step 2 regimen

A5199 study participant's details:

The onset and progression of HIV associated neurological disease in A5175 study subjects is documented by A5199 study. The follow up of the subjects enrolled so far is still ongoing. Of the 120 subjects enrolled in ACTG 5175 study, 100 (52 males and 48 females) are co-enrolled in the neurological substudy (A5199) and their neurological assessment is being carried out during their follow up visits.

D. HIV-1 DRUG RESISTACE SURVEILLANCE AND MONITRING

[Lead Investigators: Dr. R. S. Paranjape, Dr. S. P. Tripathy]

Using internationally standardized methodologies recommended by the World Health Organization, NACO had proposed to undertake two types of HIV drug resistance surveys. First, Threshold Survey to evaluate transmitted HIV drug resistance in recently infected, ARV-naïve population and Second, Monitoring Survey to monitor the emergence of HIV drug resistance in population starting first-line ART.

For threshold survey in the Mumbai region, VCT Centre, KEM Hospital and VCT Centre LTM Hospital at Mumbai are the sites for specimen collection. PPTCT centre, Kakinada , Andhra Pradesh is the site for another threshold survey among Primi Para Antenal mothers aged 15 to 24 years.

ART center, J J Hospital, Mumbai and ART centre, Govt. Hospital of Thoracic Medicine, Tambaram, Chennai are the two sites for the Monitoring survey. National AIDS Research Institute, (ICMR) Pune is the central laboratory where genotyping is being performed.

Under Threshold project total 70 specimens from consecutive eligible clients were collected at sites LTM and KEM hospitals, Mumbai during 25/06/2007 to 27/12/2007. New clients accessing services at two VCTCs in Mumbai were included in the survey if they were 15-24 years old, asymptomatic, permanent residents of Mumbai, and found to be HIV-positive. Those who had a past history of treatment with ART or PMTCT were excluded. HIVDR testing was conducted on collected plasma specimens at the National AIDS Research Institute using the Viroseq RT-PCR method (Abbot®). Protease and RT genotypes were generated using the Stanford University

HIVDR database. Out of 70 samples, initial 49 samples were processed to obtain 34 successfully amplified and analyzed specimens. No resistance-associated mutations were seen from these 34 samples. However, several polymorphisms have been noted at the protease and RT gene sequences studied. Phylogenetic analysis revealed that all samples belonged to HIV-1 subtype C. This survey at Mumbai sites indicates that the prevalence of transmitted HIVDR among recently infected VCTC clients is low (<5 %) in Mumbai. However, continued monitoring is needed to monitor the emergence of transmitted HIVDR at the site.

At PPTCT centre, Kakinada, Andhra Pradesh which is the other site for threshold surveillence, 17 samples have been collected and sent to the Central Laboratory NARI, Pune till now. Discussions are ongoing at present as to how to complete the collection of the remaining samples as soon as possible.

Under the HIV Drug Resistance Monitoring component of the project, a total of 149 samples have been collected during 21/11/2007 to 12/12/2007 at ART Centre at J J Hospital, Mumbai and are being processed at the Central Laboratory at the NARI, Pune. Another 150 samples have been collected from the second site for the HIVDR Monitoring project located at the ART Centre, Goverment Hospital of Thoracic Medicine, Tambaram, Chennai and transported to the Central Laboratory at NARI, Pune for further testing.

E. NARI ART Link Centre

[Lead Investigators: Dr. M.V. Ghate, Dr. S. P. Tripathy]

Total 264 patients were registered in the NACO ART link centre of NARI by March 2008 out of which 72 were enrolled during April 2007 to March 2008. The regimens for all the enrolled patients are shown in figure 2.1. Out of 72 participants covered on ART during this year, 41 were males and 31 were females. Five patients had side effects due to ART like lactic acidosis, AZT induced anemia, nausea, vomiting and acidity. Twelve were diagnosed with the opportunistic infections like Pulmonary tuberculosis, Oral candidiasis and Herpes zoster. There was increase in six monthly CD4 counts in these patients after initiation of ART as shown in figure 2.1.

Figure 2.1: ART regimen in NACO ART NARI link Center till March 2008

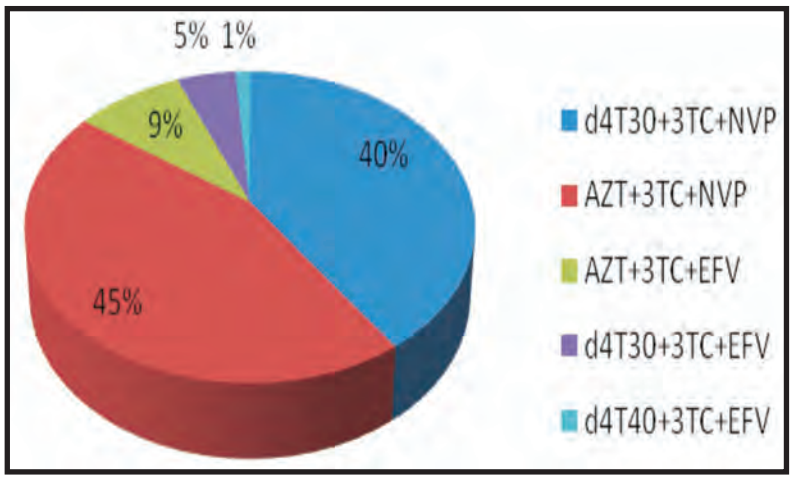
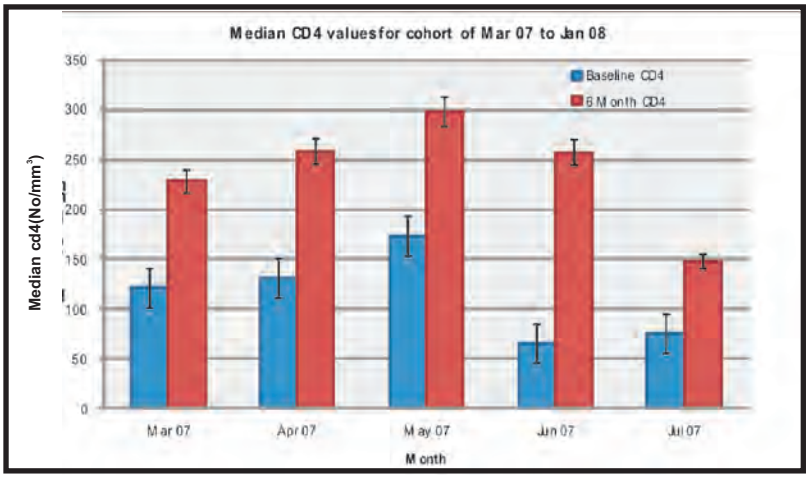


Figure 2.2: Median CD4 count of patients at baseline and at 6 months follow up for NACO ART patients



Median cd4 counts at baseline and at 6 months for the same patients

F. Neuro AIDS Study:

[Lead Investigators: Dr. S. M. Mehendale and Dr. M. V. Ghate]

The objectives of this study are

1. To determine the prevalence and nature of HIV associated neurocognitive impairment (HNCI) in treatment naïve individuals who are infected with clade C

2. To determine the impact of antiretroviral (ARV) treatment on HNCI

3. To assess the viral genetics associated with HNCI in individuals infected with clade C HIV 4.

To determine the relationship between host factors and HNCI in individuals infected with clade C HIV-1infected people in Pune, India.

This study has been approved for funding by National Institute of Mental Health, NIH, USA. The case report forms have been generated and neuropsychological test battery translations have been done in local language.

A bridge neuroAIDS study has been initiated as a NARI intramural study with the same objectives in July-August 2007. Under this bridge study, only participants from HPTN 052 study have been co-enrolled in neuroAIDS study and 30 participants have been enrolled till date.