Viral infections in solid transplant patients

B. Hostettler, E. Jordan, G. Cathomas, R. Attenhofer, E. Reusser.

μM DHPG combined with 5U/ml IFN α and 95 ± 5% inhibition with 11.1μM DHPG in combination with 0.2 ng/ml IFN γ (n = 3).

Conclusions: IFN α and IFN γ decrease HCMV infection in monocyte-like cell line THP-1 and may lead to an improvement of the available chemotherapy against this important human pathogen. Combination of IFNs with DHPG after infection showed a synergistic effect.

P1032 Activity of Penciclovir (PCV) in vitro against Cytomegalovirus (CMV) Wild Strains (WS) and against Strain AD169

B. Hostettler, E. Jordan, G. Cathomas, R. Attenhofer, E. Reusser. University Hospital, Basel, Switzerland

PCV has a well-documented inhibitory activity against herpes simplex virus and varicella-zoster virus. By contrast, data on its activity against CMV are limited. We evaluated the in vitro activity of PCV against 3 CMV WS (#1 and #2 from marrow transplant recipients, #3 from a neonate) and against CMV strain AD169, and compared the results with those obtained in parallel with acyclovir (ACV), ganciclovir (GCV), and foscarnet (FOS). A plaque reduction assay was used to determine the inhibitory drug concentration reducing plaque numbers by 50% (IC50). The drugs were tested in 6 human fibroblast cell lines. The results were as follows:

| WS#1 | WS#2 | WS#3 |
|------|------|------|
| PCV 138 (134-148) | 232 (29-366) | 87 (72-102) |
| ACV 43 (29-68) | 31 (28-54) | 26 (24-27) |
| GCV 2 | 3 (2.6-5) | 2 (1-3) |
| FOS 75 (47-114) | 73 (47-116) | 106 (72-140) |

| Strain | IC50 μM |
|--------|---------|
| AD169 | 75 (47-119) |

The pooled IC50 of PCV (all CMV strains) were significantly higher than those of ACV, GCV, and FOS (P < 0.0001 for each comparison). However, the IC50 values obtained must also be considered in the context of the pharmacokinetic and toxicologic properties of the drugs tested, and the activity of PCV against CMV should be further investigated in vivo.

Viral infections in solid transplant patients

P1033 Infection in Immunosuppressed Patients after Bone Marrow Transplantation (BMT)

V. Tchebovtkivich, S. Moiseev, K. Abdukalladin. Russian Institute of Haematology and Transfusiology, St.-Petersburg, Russia

Twelve patients with different forms of haematological malignancies underwent autologous (n = 6) or allogeneic (n = 6) BMT were tested. The materials (blood sera and nasal swabs) were collected each 2 weeks during 6 months in pre- and post-transplantation period. Nasal swabs were washed with 1 ml PBS and the material was subjected to sedimentation. The sediments nasal epithelium cells were used for direct immunofluorescence (IF) microscopy, which was performed with fluorescence-conjugated antibodies (Abs) to respiratory viruses and Mycoplasma pneumoniae (Mp). The supernatant was used for detection of mucosal Abs. The detection of these Abs as well as Abs in blood sera was performed in Indirect Haemagglutination Test (IHA) with viral (Influenza types 1, 2 and 3, Adenovirus, Respiratory syncytial virus, Coronavirus) and Mp antigens. Bacterial and fungal infections were diagnosed microbiologically. In all 56 episodes of infection were diagnosed. In 54 of these episodes mixed Mp-viral infection was demonstrated. Twenty five (45%) episodes were detected in immunosuppressed patients during the period of profound neutropenia immediately after BMT. The clinical manifestations of invasive bacterial infections caused by Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa were more severe in the episodes of preexisting respiratory viral- Mp infection. So the viral- mycoplasmal respiratory infection decreases the resistance to bacteria in immunosuppressed patients. The immune response in the patients was characterized by dramatic decrease in blood Abs level whereas the mucosal Abs changed similarly to those in immunocompetent patients. We conclude that viral- mycoplasmal infection enhances the immunodepression in immunosuppressed patients especially the general immune response rather than the local one and these infections must be carefully controlled.

P1034 CMV Management to Prevent Related Allograft Deterioration

U. Jacobs, D. Niese, H.-U. Kleiter. Medical Dept, University Hosp. Bonn, Germ

Objectives: Enhanced allograft by CMV may induce acute rejection as well as chronic transplant (TF) damage via endothelial and myogenic lesions.

Methods: In a subset of 113 renal allografted patients (P) we analysed CMV incidence, onset, risk profile and evaluated earliness and sensitivity of cytotoxic (lymphocyte subsets defined by FACS) and viral diagnostic work-up weekly after TX (pp65-early antigen, CMV-IgM and IgG-ELISA techn.) + virus isolation in urine and throat swabs, as well as the impact of early virostatic intervention on acute and long-term TP function and survival. CMV disease defined as combination of one viral parameter plus organ deterioration.

Results: Incidence of CMV disease was 31% posttransplant, 58% of all associated with monoconal antibody therapy (OKT3) for acute rejection. Independently of recipient status pretransplant positive donor CMV IgG increased risk of disease up to 70%. In addition earliness and sensitivity of CD4/CD8 inversion (93%) was > pp.65 early antigen (56%) > IgM seroconversion (33%) > virus isolation (10%). In P with recurrent CMV disease PCR was more a marker for infection regardless of disease. Leucocytes decreased from 8.6 ± 1.4 to 4.2 ± 1.8/ml. Clinically the predictive value of a characteristic nocturnal hyperhidrosis all P with CMV disease complained about was accompanied with the CD4/CD8 inversion-decrease of CD4-lymphocytes and increase of CD8-lymphocytes resulting in a ratio <1-even preceding acute organ deterioration.

The degree of infection reflected severity of CMV disease course and the diagnostic parameter of this parameter was not impaired even in P on monoconal antibodies. Consequent virostatic therapy contributed to improvement of transplant function with decrease of serum-creatinine from 3.2 ± 1.2 to 1.6 ± 0.5 mg/dl. There were no adverse effects associated with ganciclovir and no drug resistance. One year graft survival was improved up to 97% without any CMV complication. Statistical analysis after 2.7 ± 1.2 yrs follow-up period excluded any remaining impact of previous CMV disease on longterm TF function (actuarial creatinine and proteinuria).

Conclusions: Despite high incidence and varying time of onset esp for primary CMV posttransplant adequate CMV monitoring guarantees earliest diagnosis. The trias of symptoms: CD4/CD8 inversion, nocturnal hyperhidrosis and leucocyte decrease are reliable and most sensitive predictors. Consequent virostatic treatment contributes to improve amelioration of transplant survival and even prevention of long-term graft damage as it might result from undetected CMV disease on a chronic base.
**P1035** Human-Herpes-Virus-6 Associated Severe Allograft Dysfunction

U. Jacobs, H.-U. Klehr. Medical Department, University Hospital, Bonn, Germany

**Objectives:** Renal transplant survival rate could be improved up to 96% throughout the last 3 years in our transplant care unit due to efficacy of OKT-3 in steroid resistant acute rejection episodes and early intervention in CMV infection often linked to this strong immunosuppressive regimen. But there is only small experience with reactivation of HHV-6 infection in transplantation esp. for its treatment.

**Case Report:** We therefore report on a 66 y old male patient (p) suffering from a severe infection with fever up to 41°C, leucopenia, fatigue and transplant dysfunction 13 weeks after allografting. He had overcome 3 rejection episodes treated with cortisone, ATG and OKT-3 twice resp. A primary CMV infection transmitted by positive donor transplant manifested after the first OKT-3 course requiring ganciclovir. Now by weekly viral work-up CMV reactivation could be excluded. But there was evidence for a strong viral infection from continuously decreasing CD4/CD8 inversion within lymphocyte subsets. By means of standardized weekly viral monitoring HHV-6-IgM antibodies were detected fluorescein-spectroscopically.

**Conclusion:** The results obtained by PCR in blood of patients without acute onset of CMV-disease, don’t coincide with that in urine and saliva. CMV DNA present in different biological materials. In urine and in saliva the amount of viral DNA was essential, but in blood the levels of CMV DNA without symptoms of CMV-disease in patients were very low. The semiquantitative detection of CMV DNA in blood is more successful for disease diagnosis than in urine and in saliva.

**P1036** Cytomegalovirus Infection in Renal Transplant Recipients

A.M. Vedjakov, M.S. Dolgikh, E.S. Baranova. Institute of Transplantology & Artificial Organs, Moscow, Russia

**Objectives:** To compare the results of cytomegalovirus (CMV) DNA detections in blood, saliva and urine, anti-CMV antibodies IgM for prognosis of CMV disease.

**Methods:** DNA from leukocytes was isolated by glass beads. A semiquantitative nested polymerase chain reaction (PCR) with two sets of primers to MIE region was used. The sensitivity of PCR was 5-10 copies of viral DNA. IgG and IgM were determined by ELISA.

**Results:** Samples (blood, saliva and urine) of 16 patients after transplantations (1-3 months) were investigated. These patients had no acute symptoms of CMV-disease, but had minor unclear clinical symptoms. 8 patients had CMV DNA in blood by PCR. <100 copies in 10^6 leukocytes. 6 (75%) from these had CMV DNA in urine and 5 (62%) also in saliva. 2 of these fell in CMV-disease later with rising of CMV DNA level. Among 8 others PCR-negative in blood patients 4 had CMV DNA in urine and in saliva. 3 of these 4 patients were after effective ganciclovir therapy. Others 4 had no CMV DNA neither in urine nor in saliva. That patients, who had no or very low DNA signal in blood, had intensive DNA signal in urine or saliva, if it was. IgM positive were 2 patients, who had anti-CMV drug therapy early.

**Conclusions:** The results obtained by PCR in blood of patients without acute onset of CMV-disease, don’t coincide with that in urine and saliva. CMV DNA present in different biological materials. In urine and in saliva the amount of viral DNA was essential, but in blood the levels of CMV DNA without symptoms of CMV-disease in patients were very low. The semiquantitative detection of CMV DNA in blood is more successful for disease diagnosis than in urine and in saliva.

**P1037** Monitoring of Cytomegalovirus Infected Patients after Renal, Heart and Bone Marrow Transplantation by PCR and ELISA.

M.S. Dolgikh, A.M. Vedjakov, E.S. Baranova. Institute of Transplantology & Artificial Organs, Moscow, Russia

**Objectives:** The diagnosis of active cytomegalovirus (CMV) infection and monitoring of therapy by polymerase chain reaction (PCR) and ELISA.

**Methods:** DNA from leukocytes was isolated by glass beads. A semiquantitative nested PCR with two sets of primers to MIE region was used. The sensitivity of PCR was 5-10 copies of viral DNA. IgG and IgM were determined by ELISA.

**Results:** 72 patients (67 renal, 3 heart, 2 BMT) were investigated. 29 patients were CMV-positive by PCR. The quantity of CMV DNA correlated with clinical manifestations. 9 patients with more than 1000 copies of viral DNA in 10^6 leukocytes had acute CMV disease. The blood samples from patients with active CMV-infection were drawn in intervals 4-14 days after transplantation. 6 from 8 patients with 100-1000 copies had subfebrile temperature and/or gastroinestinal symptoms. After effective ganciclovir therapy viral DNA cleaned as a rule. But in 4 patients without clinical symptoms CMV DNA was detected 2-4 months after. IgM and IgG antibodies correlated with CMV disease badly. Among anti-CMV IgM-positive samples 42.3% were PCR-positive, and among IgM-negative samples 31.8% were PCR-positive (p > 0.05). IgM antibodies and CMV DNA in blood of the patient with BMT were detected during 2 months after finish of drug therapy without rise of IgG antibodies titre and without clinical symptoms. These IgM antibodies also appeared 4 weeks later, than CMV DNA at the onset of disease.

**Conclusions:** PCR is direct and very sensitive method for diagnosis of active CMV infection. The amount of CMV DNA >1000 copies in 10^6 leukocytes correlated with CMV disease. IgM and IgG detection had low diagnostic value.

**P1038** Do Children with Lymphoproliferative Diseases during Chemotherapy Acquire Hepatitis C Virus Infection?

J.S. Nowak, D. Januszkiewicz. Institute of Human Genetics, Polish Academy of Sciences, Poznań, Poland, Institute of Pediatrics University of Medical Sciences, Poznań, Poland

**Objectives:** To estimate the incidence rate of HCV infection and to analyze the HCV genotypes in three-year-follow-up study of children with leukemias and lymphomas undergoing chemotherapy.

**Methods:** The studied group consisted of 148 children, without HCV antibodies (HCVAb) at the time of the diagnosis. HCVAbs were estimated with EIA test of IInd generation (Organon Teknika). Presence of HCV-RNA particles and their genotypes were detected by nested PCR method and line probe assay (Inno-Lipa HCV II).

**Results:** The appearance of HCVAb during therapy was observed in 42 patients (28.4%), in median time 14 months after diagnosis.
Among 42 children with positive HCV-RNA, in 36 patients (85.7%) RNA-HCV was confirmed by PCR. result in every examination. 34 of HCV-RNA positive cases were infected with HCV with a single genotype, including type 1a in 31 children and type 1b in 2 patients. Coinfection with two genotypes of HCV was observed in two patients (1a+1b). None of the HCV-RNA positive children has become negative during 3-year-follow-up study.

Conclusions: Persistence of virremia in the HCV-infected patients can be explained by the therapy-induced immunosuppression. The same HCV genotype in almost 90% of analyzed children strongly suggests the common source of HCV infection. The infectivity of those children should be seriously considered during chemotherapy.

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**P1039 Influence of Prolonged Antiviral Prophylaxis in the Detection of CMV after Allogeneic BMT**

P. Valdejo, L. Cadecho, S. López, R. Cámara, L. Román, M. López-Bera. Hospital de la Princesa, Madrid, Spain

Cytomegalovirus (CMV) infection remains the most frequent infection after allogeneic bone marrow transplant (ABMT). Demonstration of CMV in clinical samples is the principal approach for the diagnosis of CMV infection.

**Objective:** To determine whether the use of prolonged antiviral prophylaxis affects the detection of CMV by shell vial assay (SVA) and conventional cell culture (CC) in surveillance specimens after ABMT.

**Methods:** A total of 72 patients with ABMT (CMV sero+ and/or donor sero+) were prospectively monitored during 22 weeks for the detection of CMV in blood, urine, throat and bronchoalveolar lavage (BAL) by SVA and CC in MRC-5 cell line. Of these, 42 received high dose acyclovir (HD ACV) (500 mg/8 h) from day −5 to +30 after BMT (Group A); and 30 received HD ACV from day −5 to +30 and then, or valaciclovir (2/6 g/h) or ACV oral (800 mg/6 h) up to the week 18 post BMT (Group B). These 30 patients were enrolled in a prospective trial to compare both antiviral prophylaxis.

**Results:**

| Patients | Samples | Samples CMV+ | SVA+ | CC+ |
|----------|---------|--------------|------|-----|
| Group A  | 42      | 1313         | 40 (3%) | 26 (60%) | 29 (72.2%) |
| Group B  | 30      | 1751         | 15 (0.94%) | 9 (60%) | 7 (46.7%) |

Conclusions: The prolonged use of prophylaxis antiviral after ABMT reduces significantly (p < 0.05) the detection of CMV in surveillance specimens. Sensitivity of CC decrease in specimens from patients with prolonged antiviral prophylaxis.

**P1040 Viral Complications after Renal Allotransplantation**

P. Lazarova 1, K. Metodiev 1, H. Ben-Basat 2, N. Kolesnik 3.

1Medical University, Varna, Bulgaria. 2Hadassah Medical Center, Jerusalem, Israel. 3Inst. Urology & Nephrology, Kiev, Ukraine

Major problem after renal allotransplantation are both, rejection crises and infectious complications, requiring rather different therapeutic behaviour. The infections could be of various origin; however, those with viral etiology are biggest problem for transplantologists. The authors of present study examine dynamically 78 recipients of renal allografts by using the method of immunologic monitoring, also microbiologic, virologic and biologic tests, as well as the influence of immunomodulation and antiviral therapy. Altogether 64 infectious complications are registered during the first 3 months after transplantation for all patients. 38 of 64 (59%) infections have viral origin and their etiology is as follows: 13 (of 38) hepatitis, 11 influenza, 6 CMV, 2 adenoviral, 2 ECHO, 2 herpes, 2 HIV (1 seropositive and 1 virus-carrier). It is worth-mentioning that our long-term study covers a period of recent 10 years and the 2 patients with HIV etiology of their viral infection complications are registered in the first period of investigation, in the time when AIDS-testing had just been considered as obligatory examination in haemodialysis centers. The immunoreactivity type of 38 patients with viral infections after renal allotransplantation shows lower activity which could explain the easy-to-develop infectious process from one hand, but from the other hand, it is obvious that those recipients show considerably less number of rejection episodes, compared to other patients with preliminary higher immunoreactivity status. Our model of immunologic monitoring allows a reliable prediction and differentiative diagnosis of both, infections and rejections after renal allotransplantation.

**P1041 Association of Cytomegalovirus (CMV)-specific Cytotoxic T-Cell (CTL) Activity with PCR-based Detection of CMV in Blood and with CMV Disease after Renal Transplantation (RTx)**

P. Reusser, R. Attenhofer, G. Cathomas, M. Tamms, G. Thiel. University Hospital, Basel, Switzerland

CMV-specific HLA class I-restricted CD8+ CTL are thought to play an important role in controlling CMV infection and disease. PCR-based detection of CMV DNA in blood specimens permits recognition of CMV infection at an early stage. We studied 20 patients (pts) during the first 3 months after RTx who were CMV-seropositive before RTx (18 pts) or seronegative with a seropositive kidney donor (2 pts). The CMV-specific CTL response in peripheral blood was assessed at 1, 2, and 3 months after RTx. Blood mononuclear cells were co-cultured with CMV-infected autologous fibroblasts for 2 weeks, and then tested by C7-release assay for cytotoxicity against CMV-infected or uninfected autologous or HLA-mismatched fibroblasts. The PCR was used for detection of CMV DNA in blood leukocytes once a week. The assay was considered positive if ≥2 consecutive blood specimens were PCR-positive. In the first 3 months after RTx, a CMV-specific CTL activity was demonstrable in 11/20 pts (55%), and CMV DNA was detectable in the blood of 18/20 pts (90%) at a median (range) of 23.5 days (8-46). There was no association between the presence of CMV-specific CTLs and of CMV DNA in blood during the month of first CTL detection (P = 0.2). CMV disease developed in 7/20 pts (35%). There was an inverse correlation between the presence of a specific CTL response and of CMV disease after RTx (P = 0.04). In conclusion, CMV-specific CTLs do not appear to suppress CMV infection as detected by PCR in peripheral blood during the first 3 months after RTx. By contrast, a CMV-specific CTL response mediates protection from CMV disease during this period after RTx.

**P1042 Significance of EBV Status and PTLD in Adult Cardiac Transplantation**

R. J. Koerner, J.S. Harwood, E.K. Gould, A. McMaster, R. Freeman, A.A. Codd, J. Forry, J.H. Dark. Freeman Hospital, Newcastle upon Tyne, United Kingdom

**Objective:** Determination of the relation of Epstein-Barr virus (EBV) matching between heart transplant donor and recipient and the incidence of EBV associated post-transplantation lymphoproliferative disorder (PTLD).

**Method:** The initial EBV status of both donor and recipient of 378 adult heart transplants was determined by testing the EBV viral...
capid antigen (VCA) IgG status retrospectively. The EBV IgM status was determined from 6 weeks post transplant in EBV IgG negative recipients.

**Results:** 366 donor/recipient pairs were tested for EBV IgG. 12 patients lacking sufficient specimens for testing were excluded. Of the 366 cases tested, 330 (90%) both recipient and donor were found to be EBV IgG positive, 27 (7%) recipient EBV IgG positive and donor EBV IgG negative, 2 (1%) both recipient and donor EBV IgG negative. 7 (2%) were EBV IgG negative but received organs from EBV IgG positive donors. 3 patients sero-converted to EBV IgM, 2 patients remain EBV IgM negative. PTLD was diagnosed in 12 (3%) of the 366 patients of which only 1 was EBV IgG negative but received an organ from a EBV IgG positive donor. This patient sero-converted to EBV IgM positive 4 months post transplant, shortly before the diagnosis of PTLD. Of the 11 patients with PTLD who were EBV IgG positive pretransplant, 9 received organs from positive donors. Serological evidence of EBV reactivation could be demonstrated in 7 (53%) of these patients shortly before the diagnosis of PTLD. No significant difference in the incidence of PTLD was found between both groups (p > 1).

**Conclusions:** 1. EBV matching does not reduce the incidence of PTLD. 2. Changes in EBV serology are not predictive of subsequent PTLD.

**P1043** Infections in the Intrathoracic Organ Transplantation

P. Suwangool, P.P. Suwangool. Chulalongkorn University Hospital, Bangkok, Thailand

**Objective:** To study the cause of death due to infection in intrathoracic organ transplantation.

**Methods:** Prospective study all cases, by cultures, biopsies, necropsies or autopsies.

Infection is a major complication and cause of death in organ transplantation. By December 1996, 36 heart transplantations, 13 heart-lung and 6 lung transplantations had been performed at Chulalongkorn Hospital. In study of infections in the biopsies, necropsies and autopsies of these patients, disseminated tuberculosis was seen in 2 patients, one in heart transplant who lived 20 months after operation, the other was a lung transplant who survived 2 years and 2 months following operations. Nocardia brain abscess was seen in one heart transplant patient. The other had severe-extraventricular bronchopneumonia. Severe pneumonia was seen in 5 heart-lung transplant, 3 of these had CMV. Aspergillus was present in 3 patients, 2 of which also associated with CMV. Five of 6 lung transplant patients died of severe bacterial pneumonia, one of these had associated aspergillosis.

**Conclusions:** CMV and bacterial pneumonia was the common cause of death.

**Advances in HIV**

**P1044** Induction of Immune Responses Against HIV-1 Reverse Transcriptase by DNA Immunization

M. Iagudina 1, 6, S. Gudim 2, M. Lev 1, O. Ivanova 1, D. Pokholok 2, M. Ganer 1, S. Kochevka 2, U. Rudden 2, B. Wahner 2, I. Immovenko Institute of Virology, Stockholm, Sweden, 2 Engelhardt Institute of Molecular Biology, Moscow, Russia, 3 Swedish Institute for Infectious Disease Control, Stockholm, Sweden

**Objective:** To induce immune responses against HIV-1 reverse transcriptase.

**Methods:** Plasmid DNA was constructed encoding HIV-1 RT (66 kDa) under the control of CMV promoter (RT-DNA). Rabbits were immunized by intramuscular injection of RT-DNA. A reference immunization was done with p66 expressed in E. coli. Immune responses were studied by ELISA, immunoblot, and PBMC proliferation tests using p66 and synthetic peptides.

**Results:** DNA immunization induced potent humoral and celluar anti RT responses. After 2 months anti RT sera reached 1:7000. Anti RT sera reacted with RT in immunoblot. Purified anti RT IgG inhibited up to 30% of RT activity. Similar responses were induced by p66, but their fine specificity was different.

| Epitope type | Aa | B-cell response | T-cell response | Comments |
|--------------|----|-----------------|-----------------|---------|
|               |    | RT-DNA p66      | RT-DNA p66      |         |
| CD4*         |    | +++++           | late early common |
| Th           |    | +++            | late early common |
| 276-290      |    | +++++          | early unique    |
| 375-389      |    | +              | late unique     |
| 411-425      |    | +++            | late early common |
| CTL          |    | +              | late unique     |
| 514-528      |    | +              | late unique     |
| B-cell       |    | +              | late early common |
| 284-289      |    | +              | late late common |
| 291-305      |    | +              | late common     |
| 347-356      |    | +              | late common     |
| 442-425      |    | +              | late late unique |

**Conclusions:** Potent anti HIV-1 immune response of unique fine specificity was induced by immunization with DNA encoding HIV-1 reverse transcriptase.

**P1045** The Effect of Hib Immunization on HIV Viremia in HIV Seropositive Adults

D. Dockrell 1, G. Poland 3, P. Mitchell 1, P. Wollan 1, T. Smith 1, S. Strickland 3, P. Ponem 1, D. Persing 1, Mayo Clinic, USA, 1 University of Minnesota, USA, 2 University of Kentucky, USA

**Background:** Cellular activation may increase HIV viral replication and therefore viremia. Immunization of HIV-positive persons is recommended against influenza, pneumococcus and Haemophilus influenzae type b (Hib). Recent reports suggest that antigenic stimulation caused by vaccines may lead to increased HIV viral replication and viral load. In this study we examined whether Hib immunization had any significant effect on HIV RNA copy number, CD4 count or p24 antigen levels one month after receiving one of three licensed Hib-conjugate vaccines.

**Methods:** We retrospectively analyzed sera from 53 HIV-positive individuals enrolled in a Hib-conjugate vaccine study. Subjects randomly received one dose of one of three licensed Hib-conjugate vaccines (Connaught, Merck or Lederle). HIV RNA copy number was determined by RT-PCR using the HIV Monitor assay (Roche). CD4 counts and p24 assays (Coulter) were also performed. Samples were analyzed pre-immunization (baseline) and one month post-immunization. We had 90% power to detect a 1.23 log rise in RNA copy number.

**Results:** 38/53 (72%) of those enrolled were receiving anti-retroviral therapy.

| HIV-1 RNA copies/ml | Pre-immunization (mean) | Post-immunization (mean) |
|---------------------|-------------------------|-------------------------|
| CD4 T-cells/ml      | 15,506                  | 15,073                  |
| p24 pg/ml           | 289                     | 296                     |

**Conclusion:** No statistically significant differences were seen in HIV RNA copy number, CD4 count or p24 antigen level one month after Hib-conjugate immunization. Subgroup analysis ac-