HIV/AIDS: epidemic update, new treatment strategies and impact on autoimmunity

F. Croce[1], S. Piconi[3], F. Atzeni[4], P. Sarzi-Puttini[4], M. Galli[1], M. Clerici[2]

[1]Infectious Diseases Unit, Department of Clinical Sciences L. Sacco, University of Milan, Milan;
[2]Chair of Immunology, Department of Biomedical Sciences and Technologies, University of Milano and Laboratory of Molecular Medicine and Biotechnology, Don C. Gnocchi ONLUS Foundation IRCCS, Milan;
[3]Allergy and Clinical Immunology Unit and [4]Rheumatology Unit, L. Sacco, Milan, Italy.

Francesco Croce, Stefania Piconi, Fabiola Atzeni, Piercarlo Sarzi-Puttini, Massimo Galli, Mario Clerici.

Please address correspondence to: Piercarlo Sarzi-Puttini, MD, Rheumatology Unit, L. Sacco University Hospital, Via G.B. Grassi 74, 20157 Milano, Italy.
E-mail: sarzi@tiscali.it

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ABSTRACT

Human Immunodeficiency Virus (HIV) infection represents one of the most serious challenges to global public health, since more than 30 million people are living with HIV/AIDS worldwide. Highly active antiretroviral treatment (HAART) introduction has dramatically changed the mortality and morbidity of HIV-affected subjects in industrialized countries but has implied an evolution of many HIV-related aspects, both in the utilisation of new antiretroviral drugs options and in the newly-observed spectrum of HIV-associated diseases, including the rheumatic pathology.

Current epidemiological, therapeutic, autoimmune and rheumatic aspects of HIV-1 infection are here discussed.

Current epidemiology of HIV/AIDS

According to the latest UNAIDS statistics, people living with HIV/AIDS worldwide were 33.2 million in 2007, with a significant reduction if compared with the 39.7 million estimated in 2006 (1).

Unfortunately, the difference cannot be ascribed to a declining trend of the pandemic itself but mainly to the revision of the HIV/AIDS estimates in India, where HIV-affected persons varied from 5.7 million in 2006 to 2.5 million in 2007, and in some other countries of sub-Saharan Africa. The progressive increase in the number of sentinel sites involved in HIV/AIDS surveillance in each country, as well as the results of recently conducted population-based national surveys, favoured a more tailored picture of the overall prevalence.

Even the incidence and mortality rates of HIV infection have been significantly reduced. This is due to the fact that these parameters are mathematically derived by combining together HIV prevalence and the median survival of an HIV-positive patient in absence of any treatment, which is much longer than previously calculated (2,3).

Access to the diagnosis, care and treatment of HIV infection still remains very limited in developing countries, where thousands of people become infected or die everyday. Sub-Saharan Africa maintains the sad primacy of the region mostly hit by the epidemic, with respectively 68% and 90% of HIV-positive adults and children worldwide living in this area. The prevalence rate greatly varies across sub-Saharan Africa, ranging from less than 2% in some countries of West Africa to above 15% in most of Southern Africa. Unprotected sex accounts for the majority of new HIV infections in the African continent.

There is evidence of a slope of epidemic trends in the Russian Federation, Ukraine and other ex-Soviet republics, where the increasing intravenous drug abuse represents the most important transmission pathway. China, Pakistan, Indonesia and Vietnam are also experiencing increasing rates of both parentally- and sexually-transmitted HIV/AIDS infections. Nonetheless, encouraging epidemiological elements have been locally registered both in sub-Saharan Africa and in South-East Asia, since HIV/AIDS prevalence is continually decreasing in Cote d'Ivoire, Kenya, Zimbabwe, Cambodia, Myanmar and Thailand. Instead, the number of new HIV infections in the Caribbean, Latin America, the Middle East and North Africa remained approximately stable in the last year. The unvaried rate of HIV incidence together with the prolonged lifetime of treated patients might explain the increasing number of HIV-affected patients observed in North America and Western Europe.

Finally, the recent scaling up of treatment access in resource-constrained areas could explain the reduction of worldwide HIV-associated deaths.

In Italy, 58,400 AIDS cases have been notified to the national register of the

Ministry of Health since the beginning of the epidemic (4). The trend is declining, as the number of AIDS cases was 5653 in 1995 and 1200 in 2007. Thirty-five thousand, three hundred (35,300) subjects have already died from AIDS and nearly 23,000 are currently on antiretroviral treatment; 20-25% of AIDS patients are females and 20% are foreign-born. Socio-demographic characteristics of HIV-infected subjects have changed over time, since the most frequent way of transmission is now heterosexual contact, the mean age is over 40 years and 53.4% of the patients finds out they are HIV-positive at AIDS diagnosis. The numbers of newly HIV-affected subjects and people living with HIV/AIDS in 2007 were 3,500-4,000 and 110,000-130,000 respectively. Considering that nearly 60,000 HIV-positive patients are regularly followed at Italian health centres, 1 out of 2 persons with HIV/AIDS living in Italy might be unaware of their serological status, clearly exceeding the median percentage around 30% observed in other Western countries.

Therapy of HIV-1 infection

Since the occurrence of the first AIDS cases in 1981, remarkable efforts have been made to learn more about HIV/AIDS and to discover effective drugs to contain the dramatic consequences of the pandemic.

So far, more than 20 compounds have been officially registered for the treatment of HIV/AIDS. They have classified in five categories in relation to their target within the replication cycle of the virus (5): [1] Nucleoside Reverse Transcriptase Inhibitors (NRTIs): zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC) and emtricitabine (FTC); [2] Nucleotide Reverse Transcriptase Inhibitors (NtRTIs): tenofovir disoproxil fumarate (TDF); [3] Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): nevirapine (NVP), delavirdine (DLV) and efavirenz (EFV); [4] Protease Inhibitors (PIs): saquinavir (SQV), ritonavir (RTV), indinavir (IDV), amprenavir (APV) and the prodrug fosamprenavir (fAPV), lopinavir (LPV), atazanavir (ATZ), tipranavir (TPV) and darunavir (DRV); [5] Fusion Inhibitors (FIs): enfuvirtide (T20).

Some of these compounds are no longer used in clinical practice because of low antiviral potency or unsustainable side effects, while a low dose of ritonavir is currently used as a booster of other PIs.

A cocktail of three or more compounds from different classes has been proven as extremely effective for the therapy of HIV-positive subjects and is generally known as HAART (highly active antiretroviral therapy). The widespread introduction of HAART in industrialised countries has greatly reduced the mortality and significantly improved the quality of life of treated patients (6). Initially, HAART was charged with being a high pill burden and of multiple daily dosages, which negatively affected the patient compliance. Progressively, new treatment schedules have been developed and fixed-dose combinations are currently used worldwide. An all-in-one pill, which contains TDF, FTC and EFZ to be taken only once daily, has become available since this year (7).

Instead, in resource-constrained nations, the high cost of the drugs, the lack of adequate health care infrastructures and the scarcity of specialised human resources have limited HAART adoption to only 20% of HIV-positive people needing the treatment (8). Recently, international campaigns and new strategies have been implemented to scale up treatment access in developing countries. The most important are the "3 by 5" WHO initiative, which aimed at reaching the objective of 3 million HIV-affected patients on treatment before 2005, the Global Fund to fight AIDS, tuberculosis and malaria (GFATM), sponsored by the G8 countries, and the President's Emergency Plan for AIDS Relief (PEPFAR), funded by the US Government. Even if the goal of universal access to HIV care and treatment is still far from being achieved, these interventions significantly increased the number of HIV-positive patient being treated in developing countries and proved to be highly effective also as a prevention tool (9-12).

Many treatment guidelines on prophylaxis and treatment of HIV/AIDS and opportunistic infections are available for clinicians (13-20). Viro-immunological parameters (HIV-RNA and $CD4^+$ T-cell count) and clinical manifestations are taken into consideration in order to decide when to start HAART. Treatment should be always recommended in the presence of AIDS-defining illnesses or with a CD4 count less than 200/mmc, and it should be considered if the CD4 range is 200-350/mmc (recommendation of US Department of Health and Human Services, December 2007). For asymptomatic patients with $CD4^+$ T cells >350 per μL and HIV-RNA<10^5 copies/mL, available clinical data are insufficient to define the best option between the "early" and the "late" approach (20). In favour of the former hypothesis, there is concern about the early depletion of gut $CD4^+$ T lymphocytes (21), the increasing viral diversity and the limited regenerative capacity of the immune system after many years of infection in the absence of any treatment; on the other hand, drug-related side effects, limited number of available therapeutic options and drug costs may suggest a later HAART introduction.

Anatomical spaces defined as "immunological sanctuaries" (*e.g.*, central nervous system) and a small pool of infected long-lived memory T lymphocytes represent the most important viral reservoirs. The viral latency in long-lived cell populations blocks the eradication of HIV-1 infection, since HAART cannot eliminate integrated proviruses from resting cells, and patients are thus condemned to assume the treatment lifelong. Immuno-modulatory molecules (interleukin 2, anti-CD3 mAb, interleukin 7) and the histone deacetylase-1 inhibitors (*e.g.*, valproic acid) have been used respectively to reactivate or to reduce the number of latently infected $CD4^+$ T cells in patients on HAART, but many doubts remain regarding their real efficacy (22, 23).

HAART combination aims at obtaining the maximum synergistic effect of different drug classes to favour the immune reconstitution, with increasing of absolute and relative number of $CD4^+$ T-lymphocytes, and to avoid, or at least delay, the risk of emerging of drug resistance.

Drug resistance is the most common reason for treatment failure. Low patient adherence, ARV-related side effects or drug-drug interactions may lead to sub-optimum pharmacological concentrations, and, in the end, to viral rebound. Viral resistance has been ascribed to every currently used antiretroviral drug and represents both a clinical and a public-health threat (24). The sequence of mutations conferring drug resistance may appear through different patterns and some naturally occurring polymorphisms might actually modulate resistance (25, 26). What is more, viral strains harbouring resistance-conferring mutations are transmissible and are tracked in up to 20% of newly infected individuals in developed countries, where the access to HAART is common (27). On the other hand, the prevalence of drug resistance in untreated populations remains low in regions with poor access to the treatment. The widespread utilisation of mono- or dual-NRTI therapy in past decades has led to the emergence of viral species with reduced susceptibilities to many, if not all, available drugs. Researchers are trying to discover novel compounds whose action is directed to points of the viral replication cycle different from those traditionally targeted.

Recently FDA-approved drugs are maraviroc and raltegravir, respectively an entry and an integrase inhibitor. Maraviroc specifically binds to the CCR5 receptor of the CD4 T-cell, thus competing with HIV for cellular entry, while raltegravir blocks the final step of viral integration in host cell DNA. Phase III clinical studies, enrolling heavily treatment-experienced patients, showed that adding maraviroc or raltegravir to an optimised antiretroviral treatment obtained a significantly better virologic response over 24 weeks if compared with placebo; both drugs were safe and usually well tolerated (28-31).

Etravirine is a NNRTI which maintains an *in vitro* activity against viral species resistant to other compounds of the same class (32). A significant HIV-RNA reduction was observed when etravirine was added to the antiretroviral regimen in treatment-failing patients who had at least one NNRTI-associated drug resistance mutation (33, 34).

Other investigational drugs, showing short-term antiretroviral activity in patients with documented resistance to NRTIs, NNRTIs or PIs, are under investigation in clinical trials (35-37).

New insights have recently been gained into long-term HAART-related toxicities, which include metabolic changes (*e.g.*, lipodystrophy, diabetes mellitus) and serious damage occurring to the renal, hepato and mitochondrial compartment. The studies have demonstrated their role on clinical impact in terms of HAART efficacy, life quality, compliance to the treatment and, in last analysis, the survival of HIV-affected patients (38).

Finally, it has also been observed that the proportion of deaths attributable to non-AIDS diseases in HIV-affected patients, including liver, cardiovascular and pulmonary diseases and non-AIDS malignancies, has progressively increased (39).

HIV-1 infection and rheumatic disease

A wide spectrum of rheumatic diseases is observed in HIV-infected individuals. Most of these are classical autoimmune conditions (soft-tissue rheumatism, reactive arthritis, vasculitis and polymyositis), others represent entities that may be specific to the setting of HIV (diffuse infiltrative lymphocitosis syndrome (DILS), HIV associated arthritis) (40).

HAART (highly active antiretroviral therapy) has had a profound beneficial effect on survival in HIV-infected patients but has also contributed both to an altered frequency and a different nature of rheumatic complication: arthralgia, rhabdomyolisis, osteonecrosis as well as inflammatory syndromes associated with immune reconstitution (41).

Animal model and clinical experience have demonstrated that lymphopenia itself contributes to the pathogenesis of autoimmunity (42). At the same time, because most lymphopenic hosts do not develop autoimmune diseases, important co-factors must also be required to break self-tolerance. (43).

Many studies clearly demonstrated the role of Treg lymphocytes in maintaining host tolerance (44, 45). McHugh and Stevach (46) showed that autoimmune colitis was induced by inoculation of specifically depleted $CD4^{-}CD25^{+}$ Treg into nude mice, but not by injections of these cells in immuno competent animals. Therefore, concomitant T cell lymphopenia is a critical co-factor required for the development of colitis following Treg depletion. It is interesting to observe that lymphopenia alone is not sufficient to induce autoimmunity even if, in this condition, the absolute number of Treg is clearly diminished. This is likely due to the fact that Treg themselves effectively undergo homeostatic peripheral expansion (HPE) *in vivo*, a feature that tends to actually enrich for Treg during lymphopenia.

Indeed, humans rendered lymphopenic by cyclophosphamide-based chemotherapy regimens (47) demonstrate a relative increase in the frequency of Treg compared to normal individuals; this increase results from the efficient HPE of CD4CD25hi Treg lymphocytes, which appears to out-compete the non-regulatory $CD4^{+}$ pool (48). Together, these data suggest that lymphopenia itself is not likely to result in functional regulatory T cell depletion and autoimmune phenomena.

Indeed, Treg expansion itself appears to be an important safeguard that has evolved to limit autoimmune reactivity during lymphopenia. Thus, in animal models, induction of non-selective lymphopenia is associated with HPE of both Treg and non-Treg subsets and, as a consequence, results in a normal or even increased Treg/non-Treg ratio, which effectively inhibits self-reactive T cells. If, however, Treg are specifically depleted, the ratio of Treg/non-Treg drops dramatically, resulting in unrestricted proliferation of self-reactive T cells that ultimately induce autoimmune disease.

HIV-associated immune reconstitution inflammatory syndrome (IRIS) is the most well defined autoimmune syndrome associated with lymphopenia in humans. This clinical entity illustrates the potent interplay between lymphopenia and organ-specific autoimmunity. IRIS is a relatively common phenomenon during HAART therapy and typically occurs shortly thereafter the initia-

tion of therapy, during the rapid rises in $CD4^+$ counts that occur via HPE (49). The typical clinical scenario of IRIS involves an HIV infected patient with a previous history of localized viral infections or infection-associated inflammation that is well controlled at the time of HAART initiation. The rapid rise in $CD4^+$ counts that follows HAART induces a site-specific inflammation, resulting in the relapse of the previous clinical scenario, most often without evidence for re-infection. Although the inflammatory process can be quite severe, it most often remains localized to the tissue where the initial infection occurred and usually does not result in systemic autoimmunity. Lymphopenia associated with altered homeostasis clearly plays an important role in IRIS because a more prolonged duration of lymphopenia; a greater degree of $CD4^+$ depletion; and a faster $CD4^+$ increase following HAART all predispose to this syndrome (50). Inflammation appears to be a critical co-factor because elevated serum IL-6 levels; IL-6, TNF-α and IL-12 polymorphisms; persisting microbial antigen burden; and/or high level inflammation at the tissue site at the time of HAART initiation all predispose to IRIS.

To conclude, IRIS can be described as an autoimmune syndrome that results in localized inflammation during immune reconstitution in a site of previous infection. The immune response is clearly exaggerated during immune reconstitution and can result in tissue destruction despite the absence of uncontrolled infection. Thus, IRIS may result from a loss of immune self-tolerance to tissue-associated antigens that are presented to cells undergoing HPE in the context of an inflammatory environment.

References

1. 2007 AIDS epidemic update. December 2007. UNAIDS, Geneva
2. UNAIDS Reference Group on Estimates, Modelling and Projections. 2002. UNAIDS, Geneva
3. UNAIDS Reference Group on Estimates, Modelling and Projections. 2006. UNAIDS, Geneva
4. Aggiornamento dei casi di AIDS notificati in Italia e delle nuove diagnosi di infezione da HIV. Centro Operativo AIDS, Dicembre 2007
5. DE CLERCQ E: Anti-HIV drugs. *Verh K Acad Geneeskd Belg* 2007; 69: 81-104.
6. SIMON V, HO DD, ABDOOL KARIM Q: HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006; 368: 489-504.
7. KILLINGLEY B, POZNIAK A: The first once-daily single tablet regimen for the treatment of HIV-infected patients. *VDrugs Today (Barc)* 2007; 43: 427-42.
8. UNAIDS, 2006 report on the global AIDS epidemic: a UNAIDS 10th anniversary special edition http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp (accessed July 20, 2006).
9. CALMY A, KLEMENT E, TECK R, BERMAN D, PECOUL B, FERRADINI L: Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling-up. *AIDS* 2004; 18: 2353-60.
10. KOBER K, VAN DAMME W: Scaling up access to antiretroviral treatment in southern Africa: who will do the job? *Lancet* 2004; 364: 103-7.
11. LIBAMBA E, MAKOMBE S, HARRIES AD *et al*.: Scaling up antiretroviral therapy in Africa: learning from tuberculosis control programmes – the case of Malawi. *Int J Tuberc Lung Dis* 2005; 9: 1062-71.
12. GUPTA R, IRWIN A, RAVIGLIONE MC, KIM JY: Scaling-up treatment for HIV/AIDS: lessons learned from multidrug-resistant tuberculosis. *Lancet* 2004; 363: 320-4.
13. RATHBUN RC, LOCKHART SM, STEPHENS JR: Current HIV treatment guidelines – an overview. *Curr Pharm Des* 2006; 12: 1045-63.
14. DYBUL M, FAUCI AS, BARTLETT JG, KAPLAN JE, PAU AK: Panel on Clinical Practices for Treatment of HIV. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. *Ann Intern Med* 2002; 137: 381-433.
15. CAROSI G, TORTI C, ANDREONI M *et al*.: Key questions in antiretroviral therapy: Italian Consensus Workshop (2005). *J Antimicrob Chemother* 2006; 57:1055-64.
16. YENI PG, HAMMER SM, CARPENTER CC *et al*.: Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *JAMA* 2002; 288: 222-35.
17. EACS – Guidelines for the clinical management and treatment of HIV-infected adults in Europe/Version 2. Dec 2007 (http://www.eacs.eu/guide/1).
18. DHHS – Guidelines for the use of antiretroviral agents in HIv-1 infected adults and Adolescents. December, 1, 2007 (http://www.aidsinfo.nih.gov/guidelines).
19. HAMMER SM, SAAG MS, SCHECHTER M *et al*.: International AIDS Society-USA panel. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *JAMA* 2006; 296: 827-43.
20. GATELL JM: Early antiretroviral therapy: rationale, protease inhibitor-sparing regimens and once daily dosing. *Antivir Ther* 1998; 3: 49-53.
21. MEHANDRU S, TENNER-RACZ K, RACZ P AND MARKOWITZ M: The gastrointestinal tract is critical to the pathogenesis of acute HIV-1 infection. *J Allergy Clin Immunol* 2005; 116: 419-22.
22. YLISASTIGUI, NM ARCHIN, G LEHRMAN, RJ BOSCH, DM MARGOLIS: Coaxing HIV-1 from resting CD4 T cells: histone deacetylase inhibition allows latent viral expression. *AIDS* 2004; 18: 1101-8.
23. LEHRMAN G, HOGUE IB, PALMER S *et al*.: Depletion of latent HIV-1 infection *in vivo*: a proof-of-concept study. *Lancet* 2005; 366: 549-55.
24. SG DEEKS: Treatment of antiretroviral-drug-resistant HIV infection. *Lancet* 2003; 362: 2002-11.
25. KANTOR R, KATZENSTEIN DA, EFRON B *et al*.: Impact of HIV-1 subtype and antiretroviral therapy on protease and reverse transcriptase genotype: results of a global collaboration. *PLoS Med* 2005; 2: 112.
26. PARKIN NT, SCHAPIRO JM: Antiretroviral drug resistance in non-subtype B HIV-1, HIV-2 and SIV. *Antivir Ther* 2004; 9: 3-12.
27. STEAIN MC, WANG B, DWYER DE, SAKSENA NK: HIV-1 co-infection, superinfection and recombination. *Sex Health* 2004; 1: 239-50.
28. NELSON M, FÄKENHEUER G, KONOURINA I *et al*.: Efficacy and safety of maraviroc plus optimised background therapy in viremic, ART-experienced patients infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-week results. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 104aLB
29. LALEZARI J, GOODRICH J, DEJESUS E *et al*.: Efficacy and safety of maraviroc plus optimised background therapy in viremic, ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of a phase 2b/3 study in the US and Canada. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 104aLB.
30. COOPER D, GATELL J, ROCKSTROH J *et al*.: Results of BENCHMRK-1, a Phase III Study Evaluating the Efficacy and Safety of MK-0518, a Novel HIV-1 Integrase Inhibitor, in Patients with Triple-class Resistant Virus. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 105aLB.
31. STEIGBIGEL R, KUMAR P, ERON J *et al*.: Results of BENCHMRK-2, a Phase III Study Evaluating the Efficacy and Safety of MK-0518, a Novel HIV-1 Integrase Inhibitor, in Patients with Triple-class Resistant Virus. 14th Conference on Retroviruses and Opportunistic Infections, February 25-28, 2007; Los Angeles, CA. Abstract 105bLB.
32. ANDRIES K, AZIJN H, THIELEMANS T *et al*.: TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2004; 48: 4680-6.
33. LAZZARIN A, CAMPBELL T, CLOTET B *et al*.: Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; 370: 39-48.
34. MADRUGA JV, CAHN P, GRINSZTEJN B *et al*.: Efficacy and safety of TMC125 (etravirine)

in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; 370: 29-38.
35. SCHÜRMANN D, FÄTKENHEUER G, REYNES J *et al*.: Antiviral activity, pharmacokinetics and safety of vicriviroc, an oral CCR5 antagonist, during 14-day monotherapy in HIV-infected adults. *AIDS* 2007; 21: 1293-9.
36. GULICK RM, SU Z, FLEXNER C *et al*.: Phase 2 study of the safety and efficacy of vicriviroc, a CCR5 inhibitor, in HIV-1-Infected, treatmentexperienced patients: AIDS clinical trials group 5211. *J Infect Dis* 2007; 196: 304-12.
37. SMITH P, FORREST A, BEATTY G *et al*.: Pharmacokinetics/Pharmacodynamics of PA-457 in a 10-day Multiple Dose Monotherapy Trial in HIV-infected Patients. 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 52.
38. ESSER S, HELBIG D, HILLEN U, DISSEMOND J, GRABBE S: Side effects of HIV therapy. *J Dtsch Dermatol Ges* 2007; 5: 745-54.
39. PALELLA FJ, BAKER RK, MOORMAN AC *et al*.: HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006; 43: 27-34.
40. WILLIAM FM, COHEN PR, JUMSHYD J, REVEILLE JD: Prevalence of the diffuse infiltrative lymphocytosis syndrome among human immunodeficiency virus type I-positive patients. *Arthritis Rheum* 1998; 41: 863-8.
41. FRENCH MA, PRICE P, STONE SF: Immune restoration disease after antiretroviral therapy. *AIDS* 2004; 18: 1615-27.
42. GLEESON PA, TOH BH, VAN DRIEL IR: Organ-specific autoimmunity induced by lymphopenia *Immunol Rev* 1996; 149: 97-125.
43. KING C, ILIC A, KOELSCH K, SARVETNICK N: Homeostasis expansion of T cells during immune insufficiency generates autoimmunity. *Cell* 2004; 117: 265-77.
44. POWRIE F, LEACH MW, MAUZE S, CADDLE LB, COFFMAN RL: Phenotypically distinct subsets of $CD4^+$ T cells induce or protect from chronic intestinal inflammation in B-17 scid mice. *Int Immunol* 1993; 5: 1461-71.
45. SAKAGUCHI S, SAKAGUCHI N, ASANO M, ITOH M, TODA M: Immunologic self-tolerance maintained by activated T cells ex-