Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution.

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Immune reconstitution resulting from use of highly active antiretroviral therapy in patients infected with human immunodeficiency virus type 1 (HIV-1) has been associated with a significant decrease in infectious morbidity and with improved survival. Occasionally, patients with quiescent disease due to human cytomegalovirus or nontuberculous mycobacteria may experience paradoxical worsening due to "dysregulated" restitution of the immune system (that is, immune restoration disease [IRD]). Acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy (PML) is uncommon and often improves with immune recovery. We describe 2 HIV-1-infected patients with PML that presented with paradoxical worsening after the patients had commenced active antiretroviral therapy. After they had a transient response to high-dose corticosteroid therapy, both patients died of progressive neurological deterioration. IRD in these patients with PML was unexpected and occurred soon after they had started receiving active antiretroviral therapy, during the period of improved antigen-specific T-helper cell function. Predictors of patients' proclivity for these adverse events are uncertain. Evaluation of targeted immunomodulatory therapy directed towards disease-specific IRD is critical and may play an important role in improved survival for patients who are at risk.

Intramedullary abscess resulting from disseminated cryptococcosis despite immune restoration in a patient with AIDS.

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We report on a case of cryptococcal intramedullary abscess, which occurred three years after a disseminated cryptococcosis and two years after a lymph node cryptococcal recurrence in a HIV-infected patient who exhibited a long-standing immune restoration. At the time of diagnosis, CD4(+) lymphocyte-count was 640x10(6)/l and HIV viral load was undetectable. Spinal involvement is rare during cryptococcosis of the central nervous system. As far as we are aware, there is only one case of proven intramedullary cryptococcal abscess reported in the literature and this case is then the second one. The significant and sustained increase in CD4 count following effective antiretroviral therapy was probably associated with only a partial immune restitution that did not allow to avoid the occurrence of the cryptococcal medullar abscess. Finally, this case raises the question of when to stop secondary prophylaxis of cryptococcal disease after increase in CD4 cell count under antiretroviral therapy.

Uveitis due to Leishmania major as part of HAART-induced immune restitution syndrome in a patient with AIDS.

Blanche P, Gombert B, Rivoal O, Abad S, Salmon D, Brezin A.

HIV combination therapy: immune restitution causing cryptococcal lymphadenitis dramatically improved by anti-inflammatory therapy.

Blanche P, Gombert B, Ginsburg C, Passeron A, Stubei I, Rigolet A, Salmon D, Sicard D.

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Two patients with AIDS developed microscopically verified focal cryptococcal lymphadenitis while treated with highly active anti-retroviral therapy for 8 and 15 months. Both were treated with fluconazole as a secondary prophylaxis for prior cryptococcal meningitis. Cryptococcus neoformans did not grow. Amphotericin was ineffective. Anti-inflammatory drugs had a dramatic effect.

Sarcoid-like lesions associated with the immune restoration inflammatory syndrome in AIDS: absence of polymerase chain reaction detection of Mycobacterium tuberculosis in granulomas isolated by laser capture microdissection.

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Highly active antiretroviral therapy (HAART)-treated human immunodeficiency virus (HIV)-positive patients can develop granulomatous lesions within the first few weeks of initiating therapy. This immune syndrome, called immune restoration inflammatory syndrome (IRIS), can induce sarcoid-like lesions in tissues. The pathogenesis of these granulomas is currently unknown because no pathogen has been identified to date in the lesions using morphological and/or microbiological approaches. However, the role of certain microbes, such as Mycobacterium tuberculosis, is still debated. The aim of this study was to look for the presence of M. tuberculosis in sarcoid-like lesions occurring in 14 AIDS patients treated with HAART. We used the PCR DNA amplification method in granulomas microdissected from sections stained by hematoxylin-eosin from formalin-fixed, paraffin-embedded specimens. Results were compared to those obtained from microdissected tuberculosis (TB) granulomas (15 patients) and from microdissected sarcoidosis granulomas (12 patients). M. tuberculosis DNA was undetectable from the microdissected sarcoid-like granulomas, whereas DNA from M. tuberculosis was isolated in all the microdissected TB granulomas and was absent in the microdissected sarcoidosis granulomas. Taken together, these data showed that M. tuberculosis DNA is not associated with the presence of sarcoid-like lesions occurring in HIV-positive patients treated with HAART.

Acute renal failure associated with immune restoration inflammatory syndrome.

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BACKGROUND: A 30-year-old HIV-infected woman presented with fever and abdominal pain 4 days after initiation of highly active antiretroviral therapy (HAART), and 1 month after initiation of antimicrobial therapy for Mycobacterium tuberculosis infection. A diagnosis of immune restoration inflammatory syndrome (IRIS) was considered, and corticosteroids were started. Steroid therapy doses were progressively tapered, during which time the patient developed renal failure with enlarged kidneys. A renal biopsy showed acute interstitial nephritis. Extensive investigations failed to detect active infection. The efficacy of HAART was attested by increased CD4+ cell counts and undetectable viral replication. INVESTIGATIONS: Physical examination, plasma viral load and CD4+ cell count, abdominal and renal ultrasound, renal and peritoneal biopsies, renal and liver function, chest X-ray, and bronchoalveolar lavage culture. DIAGNOSIS: Acute renal failure secondary to IRIS. MANAGEMENT: Prednisone therapy.

Dissemination of Strongyloides stercoralis as an immune restoration phenomenon in an HIV-1-infected man on antiretroviral therapy.

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We present a case of Strongyloides stercoralis infection in an HIV-infected man, resulting in Escherichia coli meningitis after initiation of antiretroviral therapy. Recent evidence from studies of strongyloides development supports the concept that strongyloides dissemination in this case is an example of an immune reconstitution inflammatory syndrome.

Lung cancer as an immune reconstitution disease in an HIV-1 positive man receiving HAART.

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A case of small-cell lung cancer with prompt worsening of the clinical course was observed in a patient with significant immune restoration after receiving effective highly active antiretroviral therapy (HAART) for seven months. Rapid and enormous enlargement of metastatic liver was the main symptom. Chest x-ray showed an enlargement of the left hilus. The patient died 22 days after the onset of the fulminant disease. We suggest that the occurrence and aggressive course of the lung cancer resulted from the development of immune reconstitution syndrome.

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Neurological complications in AIDS patients receiving HAART: a 2-year retrospective study.

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The positive role of highly active anti-retroviral therapy (HAART) in reducing opportunistic infections in acquired immunodeficiency syndrome (AIDS) patients is well known. However, case reports from around the world have demonstrated that some patients seem to suffer a paradoxical deterioration of health as their immune function improves with treatment. This phenomenon has been called immune restoration inflammatory syndrome (IRIS). In northern Thailand, GPO-vir (Stavudine-D4T + Lamivudine-3TC + Nevirapine-NVP) has been promoted for the treatment of AIDS patients since April 2002, in accordance with the Government Pharmaceutical Organization's guidelines. However, the incidence rates of IRIS affecting nervous system (NIRIS) and non-NIRIS in comparison with the previous incidence of AIDS-defining disease have not been reported. We conducted a retrospective study to review the incidence of NIRIS and non-NIRIS in AIDS patients treated with GPO-vir in Chiang Mai University Hospital, Thailand, between May 2002 and April 2004. We compare these incidence rates with the incidence rates of neurological complications in the pre-HAART era. Altogether 506 AIDS patients were treated with GPO-vir during the specified period. The overall incidence of NIRIS, including progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis and cytomegalovirus (CMV) retinitis, was lower than the previous incidence of AIDS-defining disease in the pre-HAART era. However, the incidence of ischemic stroke, hemorrhagic stroke and primary central nervous system (CNS) lymphoma had increased.

Immune reconstitution inflammatory syndromes: what's new?

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The immune reconstitution inflammatory syndrome (IRIS) is characterized by worsening clinical, laboratory, or radiologic findings despite improvements in the HIV RNA level and CD4 count after the introduction of antiretroviral therapy and is due to the restoration of pathogen-specific immune responses. IRIS may occur during or shortly after the treatment of an opportunistic infection or as a "new" clinical syndrome resulting from a previously unrecognized occult infection. Risk factors for IRIS include a low CD4 count, the presence of latent infection(s), and a robust virologic and immunologic response to HAART. In addition to infectious pathogens, IRIS is associated with autoimmune or malignancy-related conditions. Given the increasing availability of HAART, the number and types of IRIS encountered by HIV care providers will also increase. The prognosis for most IRIS cases is favorable because a robust inflammatory response may predict an excellent response to HAART in terms of immune reconstitution and, perhaps, improved survival. This article summarizes the various clinical presentations of IRIS and discusses the diagnosis and treatment of these immune-related syndromes.

Graves' disease as an immune reconstitution syndrome in an HIV-1-positive patient commencing effective antiretroviral therapy: case report and literature review.

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Combination antiretroviral therapy (cART) reduces morbidity and mortality in human immunodeficiency virus (HIV) infection, but it may also alter the clinical course of subclinical opportunistic infections and can even induce autoimmune disease. These atypical presentations are known as immune restoration disease (IRD), immune reconstitution syndrome/immune recovery syndrome (IRS), or immune restoration inflammatory syndrome (IRIS). We report the case of a 27-year-old, HIV-1-positive woman who developed hyperthyroidism attributable to Graves' disease (GD) after commencing potent cART. At the initiation of cART, her CD4 T cell count was 15 cells/microL and plasma HIV RNA 35 000 copies/mL. Her commencement of cART resulted in complete viral suppression and subsequent improvement of the CD4 T-cell count. Three years later, the diagnosis of GD was established based on a typical clinical picture and the results of hormonal and immunological analyses. It coincided with a 58-fold rise of the CD4 T cells. Retrospective analysis of serum samples revealed normal thyroid function and lack of anti-thyroid peroxidase (anti-TPO), anti- thyroid-stimulating hormone receptor (anti-TSHR), and anti-thyroglobulin (anti-TG) autoantibodies at the beginning of cART. HLA class II gene examination did not reveal susceptibility for the GD development in this patient. We suggest that GD in our patient was an IRD, and advise this as a possible differential diagnosis in patients presenting with hyperthyroidism on cART. To provide further details relevant to this case, we also review the literature concerning IRD-GD.

Central nervous system immune reconstitution disease in acquired immunodeficiency syndrome patients receiving highly active antiretroviral treatment.

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Highly active antiretroviral therapy (HAART)-induced immune restoration has been very beneficial for acquired immunodeficiency syndrome (AIDS) patients. In rare instances, HAART may induce a paradoxical clinical deterioration due to an immune reconstitution inflammatory syndrome (IRIS). This syndrome has been described with a wide variety of systemic infections and, in the central nervous system, with Cryptococcus neoformans infection, cytomegalovirus retinitis, and progressive multifocal leukoencephalopathy (PML). The authors have examined brain tissue in eight cases of IRIS: two autopsy cases and three biopsy cases of HIV encephalitis with IRIS and one autopsy case and two biopsy cases of PML with IRIS. All the patients presented with clinical deterioration following initiation of HAART and imaging showed contrast enhancement of the lesions. The symptoms regressed in four patients whereas the other four patients died. Neuropathological examination revealed severe inflammatory and demyelinating lesions with marked intraparenchymal and perivascular infiltration by macrophages and T lymphocytes. In some cases abundant viral proliferation was identified by immunocytochemistry or in situ hybridization, but in others the infectious agent could only be detected using PCR. T lymphocytes were predominantly CD8(+). In those cases with the more favorable course, inflammation was less severe with marked macrophage activation and a number of CD4(+) lymphocytes; in contrast, in the lethal cases inflammation was severe and mostly composed of CD8(+) cytotoxic lymphocytes. We conclude that HAART-induced paradoxical aggravation of HIV encephalitis or AIDS-related PML due to IRIS is reversible in most cases but may be lethal in others. In fatal cases, fulminant viral infection and/or acute perivenous leukoencephalitis may result from a dysregulation of the CD8(+)/CD4(+) T-cell balance.

Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients.

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OBJECTIVES: To test the hypothesis that an acute exacerbation of mycobacteria-specific Th1 response after HIV infection control by HAART causes immune restoration syndrome (IRS) in HIV-tuberculosis (TB) coinfected patients. DESIGN: Prospective, multicenter study of 19 consecutive untreated HIV-TB coinfected 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- if no IRS occurred within 3 months after HAART initiation. METHODS: Mycobacteria-specific [purified protein derivative (PPD), ESAT-6, 85B] Th1 cells producing interferon (IFN)-gamma quantified by ELISpot, in vitro production of 25 cytokines/chemokines in antigen-stimulated peripheral blood mononuclear cell (PBMC) supernatants quantified by chemiluminescence. RESULTS: Seven patients (37%) experienced IRS (IRS+). Mycobacteria-specific (PPD) Th1 IFN-gamma-producing cells increased sharply during IRS (median, 2970 spot forming cells/10 PBMC), but not the cytomegalovirus-specific responses tested as control. Only three IRS+ patients had low ESAT-6- but no 85B-

specific responses. IRS- 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 [interleukin (IL)-2, IL-12, IFN-gamma, IP10 and monokine-induced by IFN-gamma] without Th2 cytokines, and a peak of non-specific inflammatory cytokines/chemokines (TNF-alpha, IL-6, IL-1beta, IL-10, RANTES and MCP-1) occurred. These findings were independent from CD4 cell count, viral loads or time of HAART initiation. CONCLUSION: An acute exacerbation of Th1 responses against mycobacterial antigens 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.

[Muscular complications of human immunodeficiency virus (HIV) infection in the era of effective anti-retroviral therapy]

[Article in French]

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Introduction of highly active antiretroviral therapy (HAART) has dramatically modified the natural history of HIV disease, but lengthening the survival of HIV-infected individuals has been associated with an increasing prevalence of iatrogenic conditions. Muscular complications of HIV infection are classified as follows: (1) HIV-associated myopathies and related conditions including polymyositis, inclusion-body myositis, nemaline myopathy, diffuse infiltrative lymphocytosis syndrome (DILS), HIV-wasting syndrome, vasculitis, myasthenic syndromes, and chronic fatigue; (2) iatrogenic conditions including mitochondrial myopathies, HIV-associated lipodystrophy syndrome, and immune restoration syndrome; (3) opportunistic infections and tumor infiltrations of skeletal muscle; and (4) rhabdomyolysis. These features are described in the present review.

Gastrointestinal infections in immunocompromised hosts.

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PURPOSE OF REVIEW: Gastrointestinal infections in the immunocompromised host continue to have significant morbidity and mortality throughout the world. They all have similar exposures to viruses, bacteria and parasites and respond to these infections in a similar way. This review will summarize the latest reports on the epidemiology, diagnosis and treatment of known and emerging infections over the last 12 months. RECENT FINDINGS: Highly active antiretroviral therapy has reduced esophageal opportunistic infections in HIV patients compared to patients who are not taking this therapy. Esophageal candidiasis responds to escalating doses of micafungin as effectively as fluconazole. HIV-infected patients with untreated Mycobacterium avium-complex diarrhea are associated with a wasting syndrome that disrupts the somatostatin axis. Polymerase chain reaction testing has improved diagnosis of microsporidial infections. Cytomegalovirus polymerase chain reaction of tissue may improve the diagnosis of cytomegalovirus disease of the gastrointestinal tract in organ-transplant recipients. The treatment of hypogammaglobulinemia in transplant recipients with recurrent

cytomegalovirus gastrointestinal disease may resolve their symptoms. Community viruses are an emerging threat to transplant recipients and may affect drug levels. Lastly, anti-tumor necrosis factor alpha therapy in the treatment of inflammatory conditions may cause Listeria monocytogenes to disseminate. SUMMARY: Immunocompromised hosts remain at risk for severe gastrointestinal and even disseminated infections. Management includes an early rapid diagnosis with rapid restoration of the immune system and appropriate anti-infective therapy. With the immunocompromised population rapidly increasing, prevention of these infections remains the greatest challenge.

Invasive pulmonary aspergillosis transformed into fatal mucous impaction by immune reconstitution in an AIDS patient.

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Reported here is the case of a newly diagnosed AIDS patient with end-stage HIV infection and biopsy-proven invasive pulmonary aspergillosis who responded to antifungal therapy but developed severe mucous impaction in association with rapid immune restoration that was ultimately fatal. Invasive pulmonary aspergillosis complicates about 4% of AIDS infections. A search of the medical literature revealed no previous report of this organism's involvement in immune restoration syndrome.

Immune restoration inflammatory syndromes: apparently paradoxical clinical events after the initiation of HAART.

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Immune reconstitution occurs after initiation of highly active antiretroviral therapy in immunodeficient HIV-positive individuals. Unexpected deterioration of inflammatory disease and atypical clinical features resembling symptoms of autoimmune disease may arise. These atypical inflammatory disorders, synonymously summarized as immune reconstitution syndrome, immune restoration disease, and immune restoration inflammatory syndrome (IRIS), are caused by augmentation of inflammation during immune reconstitution in an immunocompromised host. These disorders have to be distinguished from intercurrent infection and rheumatic disease, respectively. Treatment of IRIS consists of elements for both potential differential diagnoses (ie, anti-inflammatory and immunosuppressive drugs, such as in autoimmune disorders and antimicrobial chemotherapy, to decrease the burden of pathogen, such as in infectious disease). Therefore, awareness for IRIS is of increasing importance from a clinical point of view. However, diagnostic criteria and standards of treatment are still preliminary.

AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy.

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Human immunodeficiency virus (HIV)-infected patients are at increased risk of developing cancer, particularly in the later stages of acquired immune deficiency syndrome (AIDS). Despite the advent of highly active anti-retroviral therapy (HAART), malignancy in this population is a leading cause of morbidity and mortality. Kaposi's sarcoma (KS) and AIDS-related non-Hodgkin's lymphoma (ARL) are the most common AIDS-defining malignancies. AIDS-related KS varies from minimal to fulminant disease. Treatment decisions for AIDS-related KS are guided largely by the presence and extent of symptomatic disease. In addition to HAART, excellent treatments exist for both localized disease (topical gel, radiotherapy, and intralesional therapy) and advanced disease (liposomal anthracyclines, paclitaxel). Novel therapies that have become available to treat AIDS-related KS include angiogenesis inhibitors and antiviral agents. ARL comprises a heterogeneous group of malignancies. With the immune restoration afforded by HAART, standard-dose chemotherapies now can be safely administered to treat ARL with curative intent. The role of analogous treatments used in HIV-negative patients, including monoclonal antibodies and autologous stem cell transplantation, requires further clarification in HIV-positive patients. HIV-infected patients also appear to be at increased risk for developing certain non-AIDS-defining cancers, such as Hodgkin's lymphoma and multiple myeloma. Although the optimal treatment of these neoplasms is at present uncertain, recent advances in chemotherapy, antiretroviral drugs, and supportive care protocols are allowing for more aggressive management of many of the AIDS-related cancers. This article provides an up-to-date review of the epidemiology, pathogenesis, clinical features, and treatment of various AIDS-related malignancies that are likely to be encountered by an oncologist practicing in the current HAART era.

[Immune reconstitution syndromes secondary to effective antiretroviral therapy]

[Article in Polish]

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Highly active antiretroviral therapy (HAART) can improve immune system function through suppression of HIV-1 replication. In some cases, a vigorous paradoxical immune response may develop. Individuals treated effectively can, because of low immune reactivity, suffer from diseases which run subclinically until HAART is introduced. These symptoms are termed IRS (immune reconstitution syndrome/immune recovery syndrome), IRD (immune restoration disease), and IRIS (immune restoration inflammatory syndrome). There are some predisposing factors, such as long-lasting HIV-1 infection, severe immunodeficiency, rapid immune restoration, immune dysregulation during immune reconstitution, subclinical infection, and genetic susceptibility. A common feature of IRS is clinical symptoms different from those observed usually in HIV-1-infected patients. Sarcoidosis and some autoimmune diseases are less common. They are present for the first time or as an exacerbation of established diseases. Diagnosis is difficult. It is very often impossible to identify the pathogen. The clinical symptoms in patients receiving

HAART should be differentiated into IRS, ineffective HAART leading to the development of opportunistic infection, and drug toxicity.

Skeletal muscle involvement in human immunodeficiency virus (HIV)-infected patients in the era of highly active antiretroviral therapy (HAART).

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Skeletal muscle involvement can occur at all stages of human immunodeficiency virus (HIV) infection, and may represent the first manifestation of the disease. Myopathies in HIV-infected patients are classified as follows: (1) HIV-associated myopathies and related conditions, including HIV polymyositis, inclusion-body myositis, nemaline myopathy, diffuse infiltrative lymphocytosis syndrome (DILS), HIV-wasting syndrome, vasculitic processes, myasthenic syndromes, and chronic fatigue; (2) muscle complications of antiretroviral therapy, including zidovudine and toxic mitochondrial myopathies related to other nucleoside-analogue reverse-transcriptase inhibitors (NRTIs), HIV-associated lipodystrophy syndrome, and immune restoration syndrome related to highly active antiretroviral therapy (HAART); (3) opportunistic infections and tumor infiltrations of skeletal muscle; and (4) rhabdomyolysis. Introduction of HAART has dramatically modified the natural history of HIV disease by controlling viral replication, but, in turn, lengthening of the survival of HIV-infected individuals has been associated with an increasing prevalence of iatrogenic conditions.

Docetaxel in anthracycline-pretreated AIDS-related Kaposi's sarcoma: a retrospective study.

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BACKGROUND: Kaposi's sarcoma (KS) is a potentially life-threatening multifocal neoplasm. Despite the significant decline in the incidence of acquired immune deficiency syndrome (AIDS)-related KS with the use of highly active antiretroviral therapy (HAART), some patients, even those with a good immune restoration, still have aggressive disease. Liposomal anthracyclines or combination chemotherapy are widely used but adverse effects limit their utilization. OBJECTIVES: We studied the efficacy and tolerance of docetaxel in the treatment of AIDS-related KS after pretreatment with anthracycline. PATIENTS/METHODS AND MAIN OUTCOME MEASURE: A retrospective cohort study was done. Nine human immunodeficiency virus (HIV)-infected patients were treated from 1997 to 2002 with docetaxel. Tumour response was evaluated using the AIDS Clinical Trial Group (ACTG) staging criteria. Clinical and biological toxicity was evaluated. AIDS status with HIV viral load and CD4 T-cell count were measured at the beginning and at the end of the treatment. RESULTS: A major (complete or partial) response and a stabilization of the disease were demonstrated in seven and two patients, respectively. Grade 4 neutropenia and thrombocytopenia were observed in four of nine and one of nine

patients, respectively. One patient died after sepsis. CONCLUSIONS: Docetaxel has a good and rapid efficacy in anthracycline-pretreated patients with severe AIDS-related KS. Phase II/III trials should be done to compare docetaxel with liposomal anthracyclines as a first-line treatment.

Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy.

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HAART-induced immune restoration is beneficial for patients with AIDS-related progressive multifocal leukoencephalopathy (PML). However, in rare instances, an immune-reconstitution inflammatory syndrome (IRIS) may cause paradoxical clinical deterioration. We report the neuropathological study of an AIDS patient who presented with progressive cognitive deterioration; CD4(+) count was 117 and the HIV viral load >10(4); imaging showed non-enhancing lesions consistent with PML. Following initiation of HAART, CD4(+) was 300 and HIV viral load <10(3), but his neurological symptoms continued to deteriorate. Imaging revealed an increase in the size and number of lesions and enhancement of all the lesions. A stereotactic biopsy showed severe inflammatory and demyelinating lesions with marked infiltration by macrophages and T lymphocytes in the absence of a detectable infectious agent. Despite high doses of steroids, the patient died 3 months after admission. Autopsy showed two types of lesions: (1) active inflammatory PML changes with abundant JC virus, and intraparenchymal and perivascular infiltration by T lymphocytes, and (2) acute perivenous leukoencephalitis devoid of JC virus. Most lymphocytes were CD8(+) lymphocytes; CD4(+) lymphocytes were virtually absent. Two pathological reactions were associated with the paradoxical clinical deterioration related to dysregulation of the immune response characteristic of IRIS in PML: (1) an accentuation of JCV infection, and (2) a nonspecific acute perivenous leukoencephalitis. We suggest that both these types of lesions are due to an imbalance of CD8(+)/CD4(+) T cells, with massive infiltration of the cerebral parenchyma by CD8(+) cytotoxic T lymphocytes in the absence of sufficient CD4(+) response. Better understanding of the mechanisms of the IRIS may enable prevention or cure of this severe, sometimes fatal complication of HAART.

Tumid lupus erythematosus occurring following highly active antiretroviral therapy for HIV infection: a manifestation of immune restoration.

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Tumid lupus erythematosus (LE) is a relatively rare and only recently recognized subset of chronic cutaneous lupus. We report a case occurring in a male with HIV infection whereby his rash was only unmasked by immune restoration following highly active antiretroviral

therapy (HAART). The phenomenon of latent inflammatory or autoimmune disease appearing following HAART is now recognized as the "immune restoration syndrome" and tumid LE has not been reported in this setting previously. Fortunately this variant of lupus does not result in scarring and is responsive to anti-malarials, allowing continuation of HAART in this patient.

Human immunodeficiency virus type 1 (HIV-1) and Mycobacterium leprae co-infection: HIV-1 subtypes and clinical, immunologic, and histopathologic profiles in a Brazilian cohort.

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Co-infections with human immunodeficiency virus (HIV) and Mycobacterium leprae represent unique opportunities to investigate the interaction of both pathogens. We determined the immunologic, virologic, and histopathologic characteristics of 22 co-infected Brazilian patients (median age = 38 years, 81.8% males, 72.2% with paucibacillary leprosy, and 95.4% with acquired immunodeficiency syndrome). The HIV-1 subtypes B and BF predominated in envelope and gag heteroduplex mobility analysis. Borderline tuberculoid (BT), tuberculoid, lepromatous, and indeterminate morphology with CD3+, CD8+, and CD68+ cell distributions compatible with leprosy patients not infected with HIV were observed. Histologic evidence of nerve damage was observed in BT lesions. IgM antibody to M. leprae-specific phenolic glycolipid I was not detected. Two of six co-infected patients monitored during highly active antiretroviral therapy (HAART) developed a leprosy type 1 reaction after an increase in CD4+ cells, suggesting an immune restoration phenomenon. Clinical, immunologic, histopathologic, and virologic features among these HIV-leprosy co-infected patients indicate that each disease progressed as in single infection. However, HAART immune reconstitution may trigger potential adverse effects, such as leprosy acute inflammatory episodes.

Adverse events of desirable gain in immunocompetence: the Immune Restoration Inflammatory Syndromes.

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Augmentation of inflammation may occur during immune reconstitution in a immunocompromised host. This phenomenon is able to cause atypical inflammatory disorders, synonymously summarized as 'Immune Reconstitution Syndrome', 'Immune Restoration Disease' and 'Immune Restoration Inflammatory Syndrome' (IRIS). Immune reconstitution occurs, if temporarily use of immunosuppressive agents was terminated or if highly active antiretroviral therapy in human immunodeficiency virus positive individuals with secondary immunodeficiency was initiated. Unexpected deterioration of inflammatory disease and atypical clinical features, resembling symptoms of autoimmune disease may arise. They have to be distinguished from intercurrent infection and rheumatic disease,

respectively. Treatment of IRIS would consist of both potential differential diagnoses: use of anti-inflammatory and immunosuppressive drugs like in autoimmune disorders as well as antimicrobial chemotherapy to decrease the burden of pathogen like in infectious disease. Therefore, awareness for IRIS is of increasing importance from a clinical point of view. However, diagnostic criteria and standards of treatment still have to be defined.

[Immune restoration inflammatory syndromes]

[Article in German]
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Increase of prevalence of certain immunodeficiencies is caused by more frequent use of immunosuppresive treatment, by advances in supportive care of immunodeficient individuals and by the pandemic spread of HIV-infection respectively. Highly active antiretroviral treatment (HAART) is able to reconstitute the impaired immunity in the HIV-infected individual and therefore to reduce morbidity and mortality. On the other hand paradoxical exacerbation of inflammatory or opportunistic diseases may develop during immunoreconstitution. By their distinct pathophysiological, clinical and therapeutic particularities these disease have been summarized as Immune Restoration Inflammatory Syndromes (IRIS). This review summarizes the variety of immunoreconstitution disorders and describes possible diagnostic pitfalls. Potential therapeutic options and an algorithm for the classification of the syndrome are proposed.

Efavirenz-associated gynecomastia: report of five cases and review of the literature.

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The prognosis of HIV infection has improved dramatically since the introduction of highly active antiretroviral therapy (HAART). However, numerous adverse effects and limitations regarding tolerability remain a concern. Lipomastia (pseudogynecomastia), a breast enlargement due to central adiposity, may occur as part of a fat redistribution syndrome which has been associated with HAART regimens and several pathogenic mechanisms have been advocated in its development. Here we report an observational longitudinal study of five patients diagnosed of gynecomastia associated with efavirenz-based HAART regimens. All cases reached successful immunologic and virologic responses to HAART. The delay of appearance of gynecomastia from the beginning of HAART ranged between 4 to 15 months. In all five cases, gynecomastia regressed after efavirenz withdrawal (mean period of 5 months). In summary, we think that HAART induced gynecomastia should be suspected in HIV patients receiving efavirenz-containing regimens. Although pathogenesis is unclear, this study and a review of the English literature implicates two possible

mechanisms: (a) immune restoration processes and (b) efavirenz mediated estradiol-like effects.

Cerebral CD8+ lymphocytosis in HIV-1 infected patients with immune restoration induced by HAART.

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In HIV infected persons, highly active antiretroviral therapy (HAART) has reduced both the morbidity and incidence of several disorders. Its effects on direct HIV-induced damage to the CNS remain controversial. In addition, HAART may provoke an "immune reconstitution inflammatory syndrome" (IRIS). Herein we report two patients who, despite HAART, developed a diffuse encephalopathy. Their clinical, radiological and neuropathological features are described. Immunohistochemical and PCR analyses were used to detect HIV and to exclude other viruses in brain tissue. The unusual inflammatory reaction in the brain tissue was defined by immunohistochemistry. Both patients had advanced HIV disease with low CD4 counts and high HIV "viral loads" before starting HAART. In both, HAART induced an increase in CD4 count and a marked reduction in HIV viral load, which was accompanied, in patient one, by worsening of pre-existing, and, in patient two, by development of, acute encephalopathy. At post-mortem examination, the brain of patient one showed HIV encephalitis. In addition, the brains of both patients revealed HIV-DNA by PCR, diffuse microglial hyperplasia and massive and diffuse perivascular and intraparenchymal infiltration by CD8+/CD4- lymphocytes. We suggest that the rapid immune reconstitution induced by HAART in these two patients led to a redistribution of lymphocytes into peripheral blood. This was followed by recruitment of CD8+ lymphocytes into the brain, which resulted in the diffuse infiltration described. The appearances in patient two further suggest that HIV brain infection, even without encephalitis, is sufficient to trigger this response.

The immune reconstitution inflammatory syndrome.

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The use of highly active antiretroviral therapy (HAART) has led to a substantial decrease in the frequency of opportunistic infections among HIV-infected individuals, along with a significant reduction in their mortality rate. However, a subgroup of HAART-treated patients will exhibit paradoxical deterioration in their clinical status, despite satisfactory control of viral replication and improvements in CD4 lymphocyte counts. This clinical deterioration, known as the immune restoration syndrome or immune reconstitution inflammatory syndrome (IRIS), is a result of an exuberant inflammatory response towards previously diagnosed or incubating opportunistic pathogens, as well as responses towards other as yet undefined antigens. A variety of manifestations of IRIS have been

described, most prominently including Mycobacterium avium complex lymphadenitis, paradoxical exacerbations of pulmonary and CNS Mycobacterium tuberculosis infection, paradoxical exacerbations of Cryptococcus neoformans meningitis and cytomegalovirus uveitis. Treatment for this disorder includes continuation of primary therapy against the offending pathogen in order to decrease the antigenic load, continuation of effective HAART, and judicious use of anti-inflammatory agents. Although the clinical manifestations of IRIS are sometimes dramatic, and result in substantial morbidity, the fact that these patients are capable of generating an inflammatory response allows many of them to ultimately discontinue secondary prophylaxis for the offending pathogen.

HIV and autoimmunity.

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The association of immune dysfunction in patients with human immunodeficiency virus (HIV) infection and AIDS and the development of autoimmune diseases is intriguing. Yet, the spectrum of reported autoimmune phenomena in these patients is increasing. An infectious trigger for immune activation is one of the postulated mechanisms and derives from molecular mimicry. During frank loss of immunocompetence, autoimmune diseases that are predominantly T cell subtype CD8 driven predominate. There is evidence for B cell stimulation and many autoantibodies are reported in HIV patients. We propose a staging of autoimmune manifestations related to HIV/AIDS manifestations and the total CD4 count and viral load that may be beneficial in identifying the type of autoimmune disease and establishing the proper therapy. In stage I there is the acute HIV infection, and the immune system is intact. In this stage, autoimmune diseases may develop. Stage II describes the quiescent period without overt manifestations of AIDS. However, there is a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found. During stage III there is immunosuppression with a low CD4 count and the development of AIDS. CD8 T cells predominant and diseases such as psoriasis and diffuse immune lymphocytic syndrome (similar to Sjogren's syndrome) may present or even be the initial manifestation of AIDS. Also during this stage no autoimmune diseases are found. In stage IV there is restoration of immune competence following highly active anti-retroviral therapy (HAART). In this setting, there is a resurgence of autoimmune diseases. The frequency of reported rheumatological syndromes in HIV-infected patients ranges from 1 to 60%. The list of reported autoimmune diseases in HIV/AIDS include systemic lupus erythematosus, anti-phospholipid syndrome, vasculitis, primary biliary cirrhosis, polymyosits, Graves' disease, and idiopathic thrombocytopenic purpura. Also, there is an array of autoantibodies reported in HIV/AIDS patients which include anti-cardiolipin, anti-beta2 GPI, anti-DNA, anti-small nuclear ribonucleoproteins (snRNP), anti-thyroglobulin, anti-thyroid peroxidase, anti-myosin, and anti-erythropoietin antibodies. The association of autoantibodies in HIV-infected patients to clinical autoimmune disease is yet to be established. With the upsurge of HAART, the incidence of autoimmune diseases in HIV-infected patients is increasing. In this review, we describe the various autoimmune diseases that develop in HIV/AIDS patients through possible mechanisms related to immune activation.

Immune restoration disorders following HAART.

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Highly active antiretroviral therapy (HAART) leads to a profound and sustained suppression of viral replication, along with a rise in CD4+ cells in most HIV-infected patients. However, reports are accumulating of growing numbers of patients suffering from opportunistic infections despite recovery of CD4+ cells and plummeting viral loads as part of a new syndrome called immune restoration disease. We describe this syndrome in two patients and review the current literature.

Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy.

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OBJECTIVE: Little prospective data are published on the natural history of HIV-associated lipodystrophy (HIVLD) in individuals beginning their first antiretroviral regimen. To investigate this a study was designed to explore changes in body composition occurring with antiretroviral therapy. STUDY DESIGN: A non-randomized, prospective, exploratory study of 40, HIV-infected men, naive to treatment, beginning antiretroviral therapy. Regular assessments of body composition, and metabolic and immunological parameters were performed. RESULTS: Mean follow-up was 96 (SD 45) weeks of therapy. There were increases in limb fat, central abdominal fat and lean mass over the initial 24 weeks of therapy followed by a selective, progressive loss of limb fat from week 24. There was a median 13.6% [interquartile range (IQR), 0.9-26.3] loss of limb fat per year from week 24 onwards. Treatment with stavudine, higher baseline HIV RNA, higher baseline 'T' score and lower week 24 lean mass were associated with higher rate of limb fat loss from week 24. In multivariate analysis, treatment with stavudine was the strongest independent factor associated with rate of limb fat loss (P = 0.05). Hypercholesterolaemia developed early in treatment, whereas hypertriglyceridaemia, hyperinsulinaemia and decreased bone mineral density developed later. The largest changes in CD4 cell counts and HIV viral load, seen early into treatment, were associated with gain rather than loss of fat. CONCLUSIONS: This is the first prospective study demonstrating that treatment with antiretrovirals results in progressive, selective loss of limb fat. Loss of limb fat occurred after the period of most intense immune restoration, making an immune aetiology unlikely.

Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy.

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Five of 10 patients who commenced successful highly active antiretroviral therapy (HAART) for infection with human immunodeficiency virus type 1 (HIV-1) concurrent with or soon after a diagnosis of cryptococcal infection experienced clinical events characterized by sterile inflammation. Two patients developed aseptic meningitis with elevated intracranial pressure, 1 developed intrathoracic lyphadenopathy with hypercalcemia, 1 developed cavitary pneumonia at the site of a cryptococcal nodule, and 1 developed a supraclavicular abscess. These events occurred 2-11 months after initiation of HAART. For 3 patients, biopsy demonstrated findings atypical for acquired immunodeficiency syndrome-associated cryptococcosis. Results of fungal cultures were negative for all 5 patients, and cryptococcal antigen levels had declined markedly in 4 patients. The timing and clinical features of and biopsy findings for these cases of cryptococcosis suggest the existence of a paradoxical reaction to Cryptococcus infection that occurs in the context of HIV immune restoration.

Foreign body granuloma: a new manifestation of immune restoration syndrome.

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BACKGROUND: People with human immunodeficiency virus may experience an immune restoration syndrome during the lymphocyte recovery period following effective highly active antiretroviral therapy. In this syndrome, antigens that previously were ignored by the immune system now induce an exaggerated response with obvious clinical effects. Most cases have been associated with infectious agents such as cytomegalovirus or mycobacterium avium intracellulare. However, the sudden onset of sarcoidal granulomatous reactions have also been described in this setting. OBJECTIVE: We report a 66-year-old HIV-positive man who presented with exacerbation of multiple foreign body granulomas decades after the original injuries. The presentation coincided with a significant rise in CD4 count after beginning highly active antiretroviral therapy. CONCLUSION: We propose that this case demonstrates another manifestation of the immune restoration syndrome and postulate that an uncontrolled Th1 response is the causative mechanism.

[Skin manifestations of immune restoration syndrome in treated tuberculosis]

[Article in French]
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INTRODUCTION: Immune restoration syndrome was first described in 1998 and involved mycobacterium avium complex. We report the case of a patient with acquired immunodeficiency syndrome who had disseminated cutaneous lesions due to

Mycobacterium tuberculosis, following initiation of highly active antiretroviral therapy. CASE REPORT: A 42 year-old HIV-infected man, was admitted for fever, cough, nocturnal sweat and impaired of general condition. He had a viral load of 127,200 copies/ml and 199/ml CD4 T-cells. He was treated with triple tuberculosis combination therapy according to tuberculous contagium, positivity of the tuberculin intradermoreaction (15 mm) and right upper lung nodule on thoracic scan. M. tuberculosis was not found. Fever improved at day 3. Highly active antiretroviral therapy with zidovudine, lamivudine, indinavir, was started at day 11 and 33 days after, fever and dermohypodermal nodules with necrotising evolution appeared. Skin biopsy specimen showed tuberculoid granuloma. The levels of viral load and CD4 T-cells were less than 200 copies/ml and 497/ml respectively. Fever and cutaneous lesions spontaneously resolved without changing therapy. DISCUSSION: Immune restoration syndrome appears after initiation of antiretroviral therapy, in patients with advanced HIV infection and without prophylactic treatment versus MAC. This case report probably involves mycobacterium tuberculosis. Bacterial lysis and immune restoration take part in cutaneous pathogenesis. Subclinical mycobacterial infection should be monitored during initiation of antiretroviral therapy in patients with advanced HIV infection.

Mycobacterium xenopi pulmonary infection in an HIV infected patient under highly active antiretroviral treatment.

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Highly active antiretroviral therapy (HAART) is responsible for a striking reduction in AIDS related morbidity and mortality by partly restoring immune function. However, HAART can also precipitate the development of clinically apparent opportunistic infections in patients with latent infections. We report a case of an HIV infected patient who developed granulomatous nodular and cavitatory lesions of the lungs due to Mycobacterium xenopi as a manifestation of the immune restoration syndro

Case report. Toxoplasma encephalitis after initiation of HAART.

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HIV therapy has advanced greatly in the past couple of decades. Along with advances in treatment have come new adverse effects associated with therapy. We present a case of Toxoplasma encephalitis following initiation of HAART consistent with the emerging syndrome known as immune restoration disease.

Dermatological immune restoration syndrome: does it exist?

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Dermatological conditions are often an early clue to HIV infection and are common. As the disease progresses patients develop a dominant Th-2 immunological response that may facilitate the development of a number of skin conditions. With antiretroviral therapy the Th-1 response is restored and some skin problems regress. But, paradoxically, some cutaneous conditions may worsen, such as herpes zoster, mucocutaneous herpes, eosinophilic folliculitis and mycobacterial infections. This may be because immune restoration of a host's immunity causes recognition of silent or latent infection and results in development of the condition.

Is acute appendicitis another inflammatory condition associated with highly active antiretroviral therapy (HAART)?

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OBJECTIVE: To report the occurrence of acute appendicitis as a possible manifestation of the immune restoration inflammatory syndrome (IRIS) following the commencement of highly active antiretroviral therapy (HAART) in HIV patients. DESIGN: Case-note review of HIV patients on HAART with acute appendicitis. METHODS: Review of HIV markers, antiretroviral therapy and abdominal ultrasound results of four HIV patients with acute appendicitis and the histopathology reports on the appendix in two of the patients. RESULTS: From a population of approximately 350 HIV patients on HAART, we found four patients who developed acute appendicitis within 6 months of commencing or changing HAART. CONCLUSION: Acute appendicitis occurring in HIV patients on HAART may represent a variant of IRIS. Further immunohistopathological and epidemiological evaluation will be needed to define this relationship fully.

Chronic erosive herpes simplex virus infection of the penis, a possible immune reconstitution disease.

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OBJECTIVE: To report a novel clinical presentation: a chronic erosive herpes simplex virus (HSV) infection of the penis which developed in AIDS patients following the commencement of highly active antiretroviral therapy (HAART). The lesions were unresponsive to antiviral treatments which had previously been effective, and this could not be accounted for in terms of increased antiviral resistance. DESIGN: Detailed case-note review and investigation of three cases which presented at two large HIV units in London. METHODS: Review of all histology with immunohistochemistry for HSV, HSV drug susceptibility assays, tissue typing and measurement of in vitro lymphocyte functional activity against HSV. RESULTS: The histology of the lesions was the same in each case,

with the presence of HSV on immunohistochemistry and an unusual prominence of plasma cell and eosinophils in the inflammatory infiltrate. HSV-specific lymphoproliferative responses were normal in two cases, but subnormal in a third case. All individuals shared the HLA class I molecules B72 and Cw0202 and the class II allele DRB4. CONCLUSION: We believe this to be a previously unreported adverse consequence of HAART, the result of partial immune restoration, reminiscent of the the recently described syndrome of immune recovery vitritis.

Sequential occurrence of thyroid autoantibodies and Graves' disease after immune restoration in severely immunocompromised human immunodeficiency virus-1-infected patients.

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We analyzed the kinetics of CD4 cells, human immunodeficiency virus (HIV) viral load, and autoantibodies in acquired immune deficiency syndrome patients with Graves' disease (GD) after immune restoration on highly active antiretroviral therapy (HAART; retrospective study). Five patients (median age, 41 yr) were diagnosed with GD after 20 (range, 14-22) months on HAART on the basis of clinical and biological hyperthyroidism, diffuse hyperfixation of thyroid scan, and the presence of anti-TSH receptor (anti-TSHR) antibodies (Ab). GD was diagnosed several months after the plasma HIV ribonucleic acid load became undetectable, when the CD4+ cell count had risen from 14 (range, 0-62) to 340 (range, 163-460) x 10(6) cells/L. Antithyroid peroxidase (anti-TPO) and anti-TSHRAb appeared 14 (range, 9-18) and 14 (range, 11-20) months after starting HAART and 12 (range, 6-15) and 11 (range, 9-17) months after the increase in CD4+ cells. In 3 patients, TPOAb preceded TSHRAb by 3-10 months. No other autoantibodies were detected. Thyroid antibodies were absent in a group of 55 HIV-1-positive patients with comparable response to HAART and no symptoms of hyperthyroidism (cross-sectional study). Thyroid-specific autoimmunity can occur upon immune restoration with HAART. Our observations suggest a relationship between thymus-dependent immune reconstitution after immunosuppression and autoimmunity and may provide insight into the pathophysiology of GD.

Opportunistic infections shortly after beginning highly active antiretroviral therapy.

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The clinical benefit of highly active antiretroviral therapy (HAART) has been attributed to its suppression of viral replication and improvement in the CD4 lymphocyte count. However, the development of clinical symptoms secondary to previously silent opportunistic pathogens shortly after beginning HAART has been reported as a distinct

clinical syndrome and seems to be associated with inflammatory phenomena surrounding a rapid restoration of the immune system in previously immunosuppressed patients. Herein, we report nine (3.6%) episodes of opportunistic infections (OI) in 247 human immunodeficiency virus (HIV)-infected patients undergoing HAART in a reference HIV/AIDS institution located in Madrid, Spain. In all instances, OI clustered within the first 3 months after beginning HAART. Episodes of cerebral toxoplasmosis (three cases), Pneumocystis carinii pneumonia (two cases), and herpes zoster (two cases) occurred in persons without a previous AIDS-defining illness, in addition a relapse of cytomegalovirus retinitis and a rebound in Kaposi's sarcoma were seen, respectively, in another two patients. Four of the nine subjects had a CD4 count above 200 cells/mm3 before HAART began. Of these, one developed Pneumocystis pneumonia and one other cerebral toxoplasmosis. In conclusion, prophylaxis and close clinical monitoring of HIV-infected patients should be considered for the first 3 months after beginning HAART, even for subjects without severe immunosuppression.

Mycobacterium avium complex causing endobronchial disease in AIDS patients after partial immune restoration.

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OBJECTIVE: To report the development of an unusual manifestation of pulmonary Mycobacterium avium complex (MAC) infection in two patients with the acquired immune-deficiency syndrome (AIDS) after the commencement of combination antiretroviral chemotherapy. PATIENTS: Two Caucasian males with human immunodeficiency virus (HIV) infection and CD4 lymphocyte counts <0.05 x 10x9/1 and with plasma HIV polymerase chain reaction (PCR) >100,000 copies/ml who were commenced on combination antiretroviral chemotherapy including a protease inhibitor. RESULTS: Both patients developed endobronchial polypoid tumours within two months of commencing antiretroviral chemotherapy. Histology demonstrated granuloma formation and acid-fast bacilli. Tissue from both patients grew M. avium. Both patients achieved significant suppression of viral replication and had significantly improved CD4 lymphocyte counts. Both required antimycobacterial therapy. CONCLUSIONS: Endobronchial polypoid tumours due to MAC infection have only been described in HIV-infected patients receiving antiretroviral chemotherapy. A degree of restored immunity is implicated in the pathogenesis of this unusual disease.

Mycobacterial cutaneous manifestations: a new sign of immune restoration syndrome in patients with acquired immunodeficiency syndrome.

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Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome.

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Sarcoidosis has been rarely reported in the presence of HIV infection. Helper T-lymphocyte depletion may attenuate granuloma formation. We present a patient who developed active sarcoidosis after being started on highly active antiretroviral therapy (HAART), which increased his CD4 count and decreased his viral load. There have been reports of exaggerated responses to mycobacteria and viruses with the restoration of T-cell function after HAART in HIV-infected patients. We propose that active sarcoidosis seen in this patient is also a manifestation of this newly observed "immune restoration disease."