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# IDCR: Infectious Diseases in Corrections Report, Vol. 8 No. 3

Infectious Diseases in Corrections

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# IDCR

INFECTIOUS DISEASES IN CORRECTIONS REPORT

FORMERLY HEPP Report

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## ABOUT IDCR

*IDCR, a forum for correctional problem solving, targets correctional physicians, nurses, administrators, outreach workers, and case managers. Published monthly and distributed by email and fax, IDCR provides up-to-the moment information on HIV/AIDS, hepatitis, and other infectious diseases, as well as efficient ways to administer treatment in the correctional environment. Continuing Medical Education credits are provided by the Brown University Office of Continuing Medical Education. IDCR is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, CorrDocs (www.corrdocs.org).*



## SUPPORTERS

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## IDCR MISSION STATEMENT

We changed our name from HEPP Report to IDCR (Infectious Diseases in Corrections Report) to encompass all infectious diseases that impact the correctional setting. IDCR's goal is to educate correctional health care providers about the appropriate medical management of prisoners infected with HIV, hepatitis, TB, and other infectious diseases; to encourage these providers to improve their networks with correctional, academic or community-based infectious disease experts; and to promote a level of infectious disease care in correctional facilities that is equivalent to the "community standard."

# IMMUNE RECONSTITUTION SYNDROMES

*Edward M. Gardner*, M.D., Denver Public Health and the University of Colorado Health Sciences Center*

Potent combination antiretroviral (ARV) therapies have significantly impacted clinical care and improved the prognosis of HIV-infected individuals. Their use, however, is not without complication. In addition to an array of short- and long-term ARV toxicities, immune reconstitution, or the reversal of HIV-related CD4 cell decline, may trigger an inflammatory reaction in some individuals soon after they begin anti-HIV therapy. Known as immune reconstitution syndrome (IRS), immune restoration disease (IRD), or immune reconstitution inflammatory syndrome (IRIS), this process can involve opportunistic infections (OI), malignancies, or inflammatory disorders. Collectively, these are believed to result from restored immune function in the setting of previously unrecognized antigenic stimuli. Since correctional physicians often have to start or re-start highly active antiretroviral therapy (HAART) for inmates/patients who did not receive or have access to such treatments before incarceration, IRS may occur in correctional settings with increasing frequency. This paper will discuss IRS with an aim to alert correctional practitioners to its implications. Readers may also be interested in several recently published review articles for a more in-depth and fully referenced discussion of IRS [1-3].

It has been suggested that IRS occurs in 20 - 30% of patients initiating HAART. However, the true incidence in an unselected population remains unclear because of the lack of prospective data and uniform IRS definition. Nonetheless, IRS appears relatively common. It seems that many events suspicious of IRS in routine clinical care, such as fevers or other mild complaints, may be self-limited and are never classified as disease specific IRS. The onset of IRS is not uniform, nor is it useful in distinguishing between disease specific IRS. The majority of IRS cases occur within two weeks to six months after HAART initiation, yet cases have occurred from as little as one day after HAART initiation, and up to several years later.

There is good evidence that lower nadir CD4 lymphocyte counts increase the risk of IRS. This is not unexpected in the face of the prevailing hypothesis that the presence of previously unrecognized pathogen or antigen triggers IRS. It should be noted that the relationship between lower nadir CD4 count and IRS is likely stronger for conditions that traditionally present at very low CD4 counts in AIDS patients. To date, no correlation between nadir CD4 count and the severity of IRS has been documented. In contrast to CD4 counts, pre-

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## WHAT'S INSIDE

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therapy HIV viral loads have not been predictive. It has been postulated that quicker decline of the viral load may be associated with an increased risk of IRS and there is evidence to support this. One should keep in mind that neither low baseline CD4 lymphocyte counts nor rapid lowering of HIV viremia is universally seen in patients with evidence of IRS, or that patients with either of these features uniformly experience IRS. Patient-specific demographic factors and mode of HIV transmission have not been associated with IRS, though this has not been well studied.

After initiation of HAART, IRS can arise in persons with or without a known history of prior OI. Although IRS presentation in these two settings may be clinically similar, there are unique questions that arise in the setting of recurrent disease. The first regards the appropriate timing of HAART in persons with pre-existing OI. This concept has been best studied in the setting of *Mycobacterium tuberculosis* (MTB) and HIV co-infection and will be discussed later. The second question regards the possibility of a recurrence due to the development of antimicrobial resistance. To date this has been largely a theoretical concern, however, in *Pneumocystis jiroveci pneumonia* (PCP) IRS some clinicians have opted to modify the existing treatment regimen without direct evidence for the presence of resistance. Based on other case reports, it does not appear that resistance was necessarily present. Finally, it must be remembered that a person with a pre-existing OI may have an IRS that is not related to that OI.

Because of the variability in presentation of particular IRS, the sections below will discuss aspects of individual IRS that are more common. The list is not exhaustive, and will focus on conditions that have classically been associated with advanced HIV disease. Other purported IRS have been reviewed recently [1-3]. Following the disease-specific IRS discussions, there will be a summary of what is known about the management and outcomes of IRS.

**Mycobacterium avium complex (MAC).** Atypical presentations of MAC infections during zidovudine monotherapy were the first evidence of IRS in HIV-infected patients prior to the HAART era. Since that time, MAC has been one of the most commonly described causes of IRS. Approximately 75% of MAC IRS represents new infection; the remainder arise in patients with a known history of MAC. The most widely described clinical presentation includes lymphadenopathy and fever; depending on the lymph nodes involved, focal painful syndromes or other symptoms are also common. Sites of lymphadenitis include cervical, mediastinum, abdomen, and the retroperitonium. Patients without lymphadenitis present with conditions including cutaneous abscess, granulomatous hepatitis, osteomyelitis, pyomyositis, hypercalcemia, and pulmonary infiltrates. Evidence that these cases have represented MAC IRS has commonly been obtained through biopsy and/or culture. In contrast to MAC infection with advanced AIDS, in MAC IRS, granulomatous inflammation is commonly recognized on histological examination. Tissue stains and cultures for acid-fast bacilli (AFB) are frequently positive, however, blood cultures for AFB are usually negative.

> Since correctional physicians often have to start or re-start highly active antiretroviral therapy (HAART) for inmates/patients who did not receive or have access to such treatments before incarceration, IRS may occur in correctional settings with increasing frequency.

**Mycobacterium tuberculosis (MTB).** The majority of MTB IRS cases have arisen after HAART initiation in patients with tuberculosis (TB) disease. Because of the immunosuppressive nature of TB, at times, this clinical syndrome can be seen after the initiation of TB treatment alone in those with or without HIV infection. However, there is evidence that these reactions occur with a higher frequency in HIV-infected patients initiating HAART. Several trials have estimated MTB IRS to occur in 20-35% of HIV/TB co-infected patients and there is mounting evidence that earlier initiation of HAART is associated with a higher incidence of IRS in HIV/TB co-infected patients. In these complex cases, one needs to remember the potential for drug-drug interactions and overlapping drug toxicities as a cause of symptomatic complaints in patients on therapy for both TB and HIV. Whether or not to delay HAART must be individualized; there is little data on the overall risk of this strategy.

MTB IRS appears to be more common in patients with pre-existing disseminated (vs. isolated pulmonary) TB infection. It usually presents with fever and new or worsening lymphadenopathy, but many patients have multiple simultaneous complaints and exam findings. Other presentations may include worsening pulmonary symptoms (including acute respiratory distress syndrome), worsening symptoms from extra-pulmonary disease (abdominal pain, hepatosplenomegaly, headache, scrotal swelling, or cutaneous lesions), weight loss, diaphoresis, and hypercalcemia. Biopsies frequently show granulomatous inflammation but consistent findings regarding AFB stain, AFB culture, or MTB upon PCR have not been noted. Baseline tuberculin skin testing with purified protein derivative would not be expected to assist in predicting who will develop MTB IRS. The tuberculin skin test is frequently negative at baseline in patients who go on to develop MTB IRS, although many of these patients convert to a positive test during the period of immune reconstitution.

**Cryptococcus neoformans.** Cryptococcal IRS has most frequently been reported in the setting of pre-existing cryptococcal meningitis. More than 50% of patients with Cryptococcal IRS present with fever, headache, or both of these, and are found to have recurrent meningitis and/or increased intracranial pressure. Lymphadenopathy (mediastinal, supraclavicular, or cervical) is the second most common presentation followed by pneumonia, cutaneous disease, and hypercalcemia. Cultures of cerebrospinal fluid (CSF) or lymph node are usually negative; however, histology of excised lymph node typically shows yeast forms. There is no information on the utility of serum or CSF cryptococcal antigen titers in the diagnosis of Cryptococcal IRS.

**Pneumocystis Jiroveci Pneumonia (PCP).** There are few published reports of PCP IRS, most of which have been seen in patients undergoing treatment for active PCP. It has been estimated to occur in 5 -19% of patients with PCP initiating HAART. In most reported cases, there

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**IMMUNE RECONSTITUTION…**
***(continued from page 2)***

appears to have been either inadequate length of steroid therapy or initiation of HAART prior to completion of PCP therapy. Clinical trials are ongoing to assess the appropriate timing of initiation of HAART in the setting of active OIs. Currently there are no official recommendations, although many clinicians wait until PCP therapy is complete prior to initiating HAART. Patients typically present with worsening symptoms of pneumonia (including respiratory failure) and fever. Atypical presentations have not been noted. Sputum or bronchoscopic specimen examination may be useful to rule out other pulmonary pathogens, but in most cases, identification of PCP does not help distinguish whether or not it is the cause of the pulmonary symptoms.

**Cytomegalovirus (CMV).** About two-thirds of CMV IRS reported in the literature occurs in the face of pre-existing CMV disease. Of all persons initiating HAART, it has been estimated that new CMV, as an IRS, occurs in about 5%. In contrast, up to 60% of patients with pre-existing CMV ocular disease have developed CMV IRS. Most patients present with visual changes and are diagnosed with ocular inflammatory lesions such as vitreitis. Extra-ocular disease has been reported, including colitis, pneumonitis, lymphadenitis, pancreatitis, parotitis, and febrile syndromes. In general, diagnosis has been achieved via direct ophthalmoscopic examination in patients with ocular disease. Of note, the site of primary CMV disease does not necessarily predict the site of recurrence. There is no data regarding the usefulness of serum PCR examination for CMV-DNA in diagnosing CMV IRS.

**JC Virus (JCV).** Because there are no specific antivirals available for the treatment of progressive multifocal leukoencephalopathy (PML) caused by JCV, HAART is the treatment of choice. In some individuals, however, PML commences or worsens after HAART. The symptoms of PML IRS are varied and typical of PML in untreated patients. These include paresis, dysphagia, visual changes, seizures, and ataxia. Most cases are diagnosed by magnetic resonance imaging (MRI) with or without biopsy or CSF-PCR analysis for JCV-DNA. In contrast to the pre-HAART era, when brain MRI rarely had inflammatory changes, in PML IRS, MRI commonly shows contrast enhancement consistent with inflammation. The inflammatory nature of these lesions has been verified in biopsy specimens showing peri-vascular inflammatory infiltrates, which were also very uncommon in the pre-HAART era. MRI, however, may not be helpful in predicting who will have a worsening course of PML after HAART initiation. There is evidence that most patients with a follow-up MRI have inflammatory changes while less than half of these patients have clinical worsening.

**Hepatitis B Virus (HBV) & Hepatitis C Virus (HCV).** It has been difficult to understand the contribution of Hepatitis IRS to abnormal liver function tests (LFTs) after HAART initiation in patients with HBV and/or HCV co-infections. Five to 10% of HAART responders have transaminase levels that reach five times the upper limit of normal and these changes have been more common in patients with chronic HBV or HCV infection. Although not definitive, liver biopsy changes in these patients have frequently been consistent with worsening viral hepatitis as opposed to drug toxicity. In general, LFT abnormalities return to baseline over several months but studies that have looked at this were not limited to patients with Hepatitis IRS as the cause of the LFT abnormality. 'Acute hepatitis', fulminant hepatic failure, and new onset porphyria cutanea tarda in an HCV-infected patient after HAART have been reported. Because of uncertainty in the cause of abnormal LFTs after HAART initiation, IRS and non-IRS causes need to be considered in this population.

**Kaposi's sarcoma (KS).** There has been a remarkable decrease in the incidence of KS in the post-HAART era. Like JCV, the virus associated with KS (human herpes virus 8, HHV-8), does not have effective antiviral options. Thus, HAART has become the treatment of choice and has been quite effective in many KS patients, although some still require chemo- or radiation-therapy. There have been reports of worsening of existing KS lesions, an increase in the number of KS lesions, or new onset KS in patients initiating HAART and these have frequently been associated with lymphadenopathy. One report showed a decrease in HHV-8 DNA by PCR analysis during the KS flare, which suggests that HHV-8-specific immune responses were reconstituted during this interval.

**Management**

There are no guidelines or evidence-based recommendations for IRS management. Several important issues need to be addressed. The first issue regards the continuation of HAART. Because IRS usually occur in the setting of effective therapy, it has generally been recommended to continue HAART except in extreme situations (CNS edema, tracheal or vascular compression, severe hepatitis, etc). Patients need to be counseled prior to HAART initiation and during IRS in order to make the best treatment decisions. In cases where HAART has been discontinued, IRS can recur during re-initiation of therapy, even in the face of specific anti-infective therapy. For these reasons, when possible, HAART should be continued.

A second issue regards the use of specific anti-infective agents (when available). In many cases, there is evidence of IRS resolution with continued HAART with or without anti-infective agents, making the decision of whether or not to initiate anti-infective therapy unclear. In selected circumstances, when a patient has partially completed treatment for a specific infection (e.g., TB infection), the prescribed course of therapy should be completed. The use of chemotherapy and radiation therapy may be required for KS IRS. It should also be noted that the occurrence of an OI after initiation of HAART does not always represent IRS. In patients with poor adherence and/or poor response to HAART, an OI may develop that is not an IRS and would need specific anti-microbial therapy when available. In IRS cases, individualized decisions need to be made based on the potential benefits and risks of specific anti-infective therapies. Prudence is warranted until more information is available.

A third and important issue is the use of anti-inflammatory agents. In many specific IRS there are reports of patients being treated with steroids or non-steroidal anti-inflammatory agents (NSAIDS). At this time it is unknown if either of these treatments should be employed in IRS. In several situations, the use of anti-inflammatory agents may be warranted. In severe or life threatening situations, particularly with pronounced inflammation, steroid use is likely appropriate. In patients with moderate to severe, non-life threatening events, consideration of either steroids or NSAIDS is reasonable, particularly if it can help patients continue their effective HAART.

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# Access to HIV/AIDS Testing and Treatment: Bamako, Mali

*By Courtney E. Colton*, IDCR Managing Editor*

HIV/AIDS is rapidly emerging as one of the worst epidemics Africa has ever faced. At year-end of 2004, an estimated 26 million people in Africa were living with HIV, comprising 66.5% of the total HIV infections worldwide. The disease claimed the lives of an estimated 2.3 million and 3.1 million new infections occurred in sub-Saharan Africa during 2004. Women, particularly between ages 15-25, and children are disproportionately affected by HIV/AIDS. Nearly 60%, or 13.3 million infected adults are women and of those, 76% are between ages 15-25. Approximately three million children under age 15 are living with HIV/AIDS and more than 12 million have been orphaned.

Even though Mali continues to rank among the few sub-Saharan African countries with a low prevalence of HIV/AIDS in the general population, it is estimated that over 120,000 adults and children in Mali are infected. Estimated HIV prevalence in females and males is 2.0% and 1.3%, respectively. Malian women ages 25-29 have the highest prevalence of HIV infection, at 3.2%, and the nation's capital, Bamako, has a higher prevalence of HIV/AIDS, compared to other Malian cities.

**Prisons**

Of the more than 45 jails and prisons in Mali, the largest men's prison is located in downtown Bamako. The facility incarcerates 1,400 inmates, including domestic prisoners and individuals from France, Senegal, Nigeria, Liberia, Benin, and Togo.

The prison's medical facility is centrally located within the compound and consists of one outbuilding containing two small rooms. The first room is used for patient examinations, is approximately 80 square feet, and is furnished with one bed and one desk. The second room contains a single metal cabinet with minimal medical supplies; a few rolls of gauze, scissors, tape, and Aspirin.

The prison's clinic is staffed by one technician from the Institut National de la Recherche en Santé Publique, who is charged with the medical care of all 1,400 inmates. He is available to examine patients twice per week and during times when the technician is unavailable, five inmates who serve as medical nurses staff the clinic. These staff members are not trained in counseling, diagnosis, or treatment of HIV or other diseases. As a result, while minor illnesses are treated within the prison walls, more severe infirmities are referred to Hospital Gabriel Touré. HIV-infected patients who present with severe illnesses are referred to Centre de Soins, d'Animation et de Consei (CESAC) for treatment. Unfortunately, most patients are not transferred until they are extremely sick, and many do not survive.

While HIV, TB, and other infectious disease prevalence rates are unknown in the prison, the technician employed by the prison has estimated that HIV prevalence may be as high as 5%.

Sick inmates obtain medications only if they have the financial resources to pay for them. In such cases, the technician travels to the pharmacy and retrieves the prescription. Most inmates lack sufficient funds to pay for medications and as a result, they are forced to rely on the limited charity of others. Typically, such charity comes from relatives and medical students who visit the prison facility to conduct thesis research and patient visits. Hama Diallo, a medical student at the University of Bamako Medical School, commented, "The medical students have no money because they spend it all on supplies for their patients. If the patient has no money, they die."

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## IMMUNE RECONSTITUTION... *(continued from page 3)*

Finally, in situations where steroids have previously been proven beneficial, such as in moderate to severe PCP, use of these agents is likely warranted. Furthermore, depending on the IRS event, topical or intra-ocular anti-inflammatory agents may be useful. Many other situations may arise in which a decision regarding anti-inflammatory agents will need to be addressed and clinical judgment remains most important.

**Outcomes**

Although IRS can be severe or life threatening, in most instances, patients recover without major morbidity or mortality. However, because of the potential for severe complications, these events must be addressed quickly and appropriately. There have been reports of occasional severe ocular morbidity with CMV IRS, including blindness. At least one-third of patients with PML IRS have expired secondary to PML and most survivors have significant residual neurological deficits. Deaths have also been reported with MTB IRS and Hepatitis IRS. In all of these conditions, we await prospective clinical data to not only assist with finding effective and appropriate IRS management strategies, but also for IRS prevention strategies.

**Conclusions**

It is hopeful that some of these principles will be useful in helping clinicians understand, recognize, and manage IRS. There are many unanswered questions and research continues to help us address the many uncertainties. Recognition and management of IRS remains complicated and clinicians need to consider the many possible causes of symptoms that may or may not be related to HAART initiation. While it is comforting that IRS usually resolves with conservative management, the possibility of severe or life threatening reactions urges vigilance. Over the next several years there will likely be more and better information regarding IRS. Until then we will continue to rely on clinical acumen and the data synthesized from the published experience of many other clinicians.

***Disclosures:***

**Grant/Research Support: Bristol Myers Squibb*

***References:***

*1. Gardner EM, Connick E. Illness of Immune Reconstitution: Recognition and Management. Curr Infect Dis Rep 2004;6:483-493.*

*2. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004;18(12):1615-1627.*

*3. Shelburne SA, 3rd, Hamill RJ. The immune reconstitution inflammatory syndrome. AIDS Rev 2003;5:67-79.*

## ACCESS TO HIV/AIDS TESTING... *(continued from page 4)*

**Hospitals**
Point G Hospital, which is affiliated with Hospital Gabriel Touré, offers free antiretroviral therapy (ART) to HIV-infected patients. The hospital currently monitors 747 HIV/AIDS patients, and of these, 489 patients are receiving ART. While Mali is making great strides in offering free ART, standard therapy provided is not equivalent to the recommended treatments in the United States. The Malian Ministry of Health does, however, base its' guidelines for HIV/AIDS treatment on the current guidelines recommended by the World Health Organization (WHO) for resource-constrained settings. Triple drug therapy is prescribed for HIV-infected adults and infants and nevirapine is the standard for prevention of mother-to-child-transmission (MTCT).

The hospital's lack of resources, including medications, beds for patients, soap, and doctors, plays a large role in diminishing the quality of care patients receive. In addition to this lack of resources, there are several other differences between Point G Hospital and its American counterparts. Hospital rooms are small, dark, unventilated, and house two patients per room on thin mattresses. Patients must rely on family members to provide food and pay for medical treatment, including syringes and intravenous fluids. Additionally, patient confidentiality is often difficult to maintain due to the over-crowding that exists within many hospitals and clinics.

**HIV Testing**
The Malian national policy on HIV testing is based on the World Health Organization's HIV testing recommendations for resource-constrained settings. After pre-test education and counseling, an HIV rapid test, used as a screening test, is performed. When a positive test result occurs, a second HIV rapid test, used as a confirmatory test, is performed. If the first and second test results are contradictory, a third and different HIV rapid test is utilized. Since availability and access to HIV rapid tests is limited, especially in areas outside of the nation's capital, HIV testing often consists of one rapid test. Many HIV-infected patients remain undetected despite the high (>99%) specificity and sensitivity of HIV rapid tests. Non-detection of these patients is most likely attributed to non-testing due to a lack of tests, and reluctance to get tested.

**Access**
Social stigma, limited financial resources, lack of education, pharmaceutical shortages, and lack of transportation are the realities for Malians attempting to access HIV testing and treatment resources. HIV remains extremely taboo throughout Mali, particularly in segments of society where religion plays a large role in cultural beliefs. Accordingly, many Malians do not seek testing or treatment.

The stigmatization associated with HIV/AIDS is so great that many individuals do not want to learn their HIV status, for fear of likely negative reactions of family members and the community. While ART is free, financial resources still play a dominating role in limiting access to HIV care. The average Malian's monthly income is US $30, which is not enough money to support the financial responsibility that accompanies transportation to and from the hospital and/or pharmacy, HIV testing, and medical care costs, excluding antiretroviral (ARV) medications. For many Malians, the final decision to seek HIV care is based on having enough money available for both food and HIV care. Lack of education also contributes to many Malians hesitation when it comes to HIV testing; understanding of the importance of HIV testing is lacking in large portions of the population and common misconceptions concerning HIV include that the virus is acquired from bad food, and that HIV-infected men can be cured by having sex with a virgin. Additionally, Malian pharmacies often accidentally stock counterfeit ARVs, and dosing and quality in these counterfeit medications are often compromised. Transportation difficulties can hinder scheduled deliveries of ARV medications, leading to inadequate stock and the development of resistance in those who have time lapses in their treatment regimen. Additional factors which hinder the fight against the HIV/AIDS epidemic in Africa include inadequate nutrition, infrastructure of the health care system, and diagnostic capability.

When access to treatment is possible, tests that measure if treatment is working, including viral load and T-cell count tests, are unavailable in the majority of Mali. Furthermore, access to opportunistic infection (OI) prevention and treatment is limited. Unlike ARV medications, drugs to combat OIs, excluding anti-tuberculosis drugs, are not free. OIs that are common in Mali include *Cryptococcus neoformans*, *Candidia*, and *Isospora belli* infections, and also Toxoplasmosis and Cytomegaolvirus.

**Recommendations: Accelerating Access to Treatment in Mali**
ART is free to all HIV-infected Malians who receive prescriptions from medical doctors. However, the social situations, financial resources, limited number and locations of pharmacies, and unreliable ARV stock discussed above, combine to create enormous barriers for patients when accessing ARV medications.

Recommendations on how to best address these problems and how to accelerate access to HIV testing and treatment were discussed at the 2nd Annual Conference of HIV/AIDS Specialists held in Bamako, Mali, on January 11-13, 2005.

Recommendations included the establishment of a location that houses both hospital and pharmacy facilities, which would decrease patients' travel time and costs associated with transportation and increase access to pharmacies. Other recommendations included the implementation of a quality control system for ARVs, the development of an MTCT prevention program that includes counseling, and education programs tailored to different risk groups that discuss responsible sexual behavior. It was further recommended that a national reference center for TB and other OIs prevalent in Mali, be developed, and that human resources be mobilized and techniques for supplementary finances be explored. Lastly, conference participants were in agreement that collaboration between the public, private, and political sectors, clinicians and pharmacies, non-government organizations, universities, and laboratories needs to improve for greater efficiency, increased pace, and improved coordination of our efforts. The American, French, and Malian collaborators who attended the conference are currently assessing ways in which these recommendations can be implemented.

***Disclosures:*** **Nothing to disclose.*

# Letter from the Editor

Ever since use of highly active antiretroviral therapy (HAART) became more common, HIV practitioners have reported on cases of HIV-infected patients who developed exacerbations of opportunistic infections in conjunction with rising T-cell counts. These reactions typically occurred within a few months after the initiation of HAART, and usually resolved within a few weeks following the treatment of the opportunistic infection. Today, this presentation of exacerbating opportunistic infection in the context of HAART induction is known as immune reconstitution syndrome (IRS).

Effective HAART suppresses HIV replication, and hence, viral load, resulting in increases in absolute CD4 T-cell counts. Typically, there are two phases in which T-cell counts rise: first, there is a rapid initial rise following effective HAART, followed by a slow, steady increase that may continue for years. Additionally, the loss of functional lymphocyte responses to many pathogen antigens can be reversed by HAART, although HIV-specific T-cell responses are not always reconstituted.[1]

The thymus is the source of new T-cells. It was long believed that the thymus was damaged by HIV infection. However, a number of more recent studies have demonstrated that patients with untreated HIV infection do have active thymic tissue and the amount of thymic tissue that is present at the initiation of HAART correlates with the extent of the subsequent increase in CD4+ T-cells. Thus, the severity of IRS may be linked to the presence of functional thymic tissue at the initiation of therapy.

This month, Dr. Edward Gardner presents an overview of IRS for our readers and Courtney Colton presents a different perspective, reflecting on the difficulties that most patients (incarcerated or not) would have accessing HIV care in Mali. At the conclusion of this issue, readers should be more familiar with the epidemiology, diagnosis, and treatment of IRS, and should know when it is appropriate to initiate therapy in asymptomatic HIV-infected individuals. Lastly, readers should realize which treatment regimens are preferred and alternative.

Sincerely,

David Thomas, MD

*1. Autran, Bridgette et al. Immune Reconstitution after highly active antiretroviral treatment of HIV infection. Adv Exp Med Biol 2001;495:205-12.*

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In accordance with the Accreditation Council for Continuing Medical Education Standards for Commercial Support, the faculty for this activity have been asked to complete Conflict of Interest Disclosure forms. Disclosures are listed at the end of articles. All of the individual medications discussed in this newsletter are approved for treatment of HIV and hepatitis unless otherwise indicated. For the treatment of HIV and hepatitis infection, many physicians opt to use combination antiretroviral therapy which is not addressed by the FDA.

HIV 101

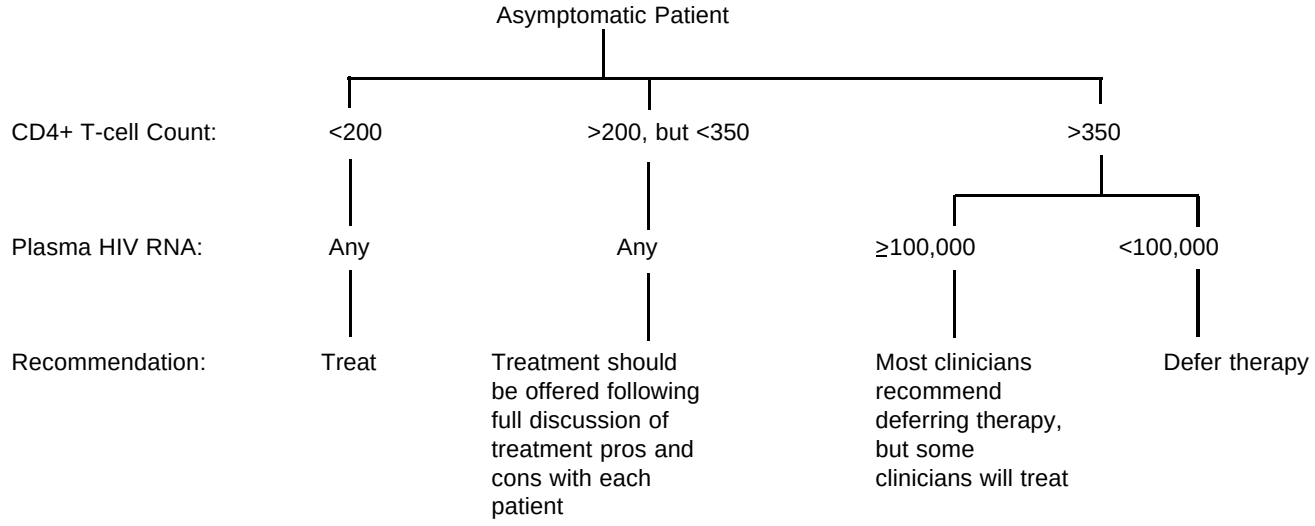
## Preferred and Alternative ARV Therapy

| | | |
|---|---|---|
| **PREFERRED TREATMENTS** | | |
| NNRTI | EFV* | + (3TC or FTC) + (AZT or TDF) |
| PI | LPV/r | + (3TC or FTC) + AZT |
| **ALTERNATIVE REGIMENS** | | |
| NNRTI | EFV* | + (3TC or FTC) + (ABC, ddI or d4T) |
| | NVP** | + (3TC or FTC) + (AZT, ddI, d4T, ABC, or TDF) |
| PI | ATV | + (3TC or FTC) + (AZT, d4T, ABC or ddI) or+ (TDF + RTV 100mg/d) |
| | FPV | + (3TC or FTC) + (AZT, d4T, ABC, TDF or ddI) |
| | FPV/r^ | + (3TC or FTC) + (AZT, d4T, ABC, TDF or ddI) |
| | IDV/r^ | + (3TC or FTC) + (AZT, d4T, ABC, TDF or ddI) |
| | LPV/r | + (3TC or FTC) + (d4T, ABC, TDF or ddI) |
| | NFV | + (3TC or FTC) + (AZT, d4T, ABC, TDF or ddI) |
| | SQV/r | + (3TC or FTC) + (AZT, d4T, ABC, TDF or ddI) |
| 3-NRTI | | ABC + AZT + 3TC^^ |

*Efavirenz is not recommended for use in 1st trimester of pregnancy or in women with high pregnancy potential, including those women who want to conceive or are not using effective contraception.
** Note: High incidence (11%) of symptomatic hepatic events observed in women with pre-nevirapine CD4+ T cell count >250 cells/mm3 and men with CD4 >400 cells/mm$^3$. Use with caution in these patients, with close clinical and laboratory monitoring, especially during the first 18 weeks of therapy.
^Low dose (100-400 mg) ritonavir per day.
^^Only when a preferred or an alternative NNRTI- or PI-based regimen cannot or should not be used.

*Adapted from the Panel on Clinical Practices for Treatment of HIV Infection and Department of Health and Human Services (DHHS). (October 29, 2004). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Retrieved February 22, 2005 from http://www.aidsinfo.nih.gov/guidelines/adult/AA_102904.html*

## IDCR-O-GRAM: When to Initiate Therapy in Asymptomatic HIV-Infected Patients




HIV-infected persons who present with an AIDS-defining illness or severe symptoms, regardless of CD4+ T-cell count and plasma HIV RNA, should have treatment initiated.

Adapted from the Panel on Clinical Practices for Treatment of HIV Infection and Department of Health and Human Services (DHHS). (October 29, 2004). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Retrieved February 22, 2005 from http://www.aidsinfo.nih.gov/guidelines/adult/AA_102904.html

**FEBRUARY IDCR CORRECTION:**
Our apologies to David Ashkin, MD and the Florida Department of Health for accidently excluding the following authors in the IDCR February issue: Tanira Ferreira, Ellen Murray, and Boubker Naouri.

# CROI UPDATE: Details of the New York Case

On February 11, 2005, the New York City (NYC) Department of Health and Mental Hygiene (DOHMH) issued a press release, igniting a flurry of questions and alarm, regarding a NYC resident with a rare strain of 3-drug-class-resistant HIV-1 (3-DCR HIV-1) and rapid progression to AIDS. The patient, a man who has sex with men (MSM), reported crystal methamphetamine use and unprotected anal intercourse with multiple partners.

Twelve days after the initial press release, the 12th Annual Conference on Retroviruses and Opportunistic Infections (CROI), held in Boston, and attended by over 3,000 scientists, included data which revealed the details surrounding the recent New York City case of a, supposedly, "aggressive and untreatable" strain of HIV.

David Ho, of the Aaron Diamond AIDS Research Center, summarized the case and the results of the medical tests the Diamond Center performed. Dr. Ho commented that this isolated case does not indicate that the HIV strain found in this patient is aggressive, as was previously reported, because disease progression is determined not only by the virus, but also by the host's genetic makeup. Dr. Ho confirmed that the patient tested negative for HIV-1 in May 2003. In November 2004, the patient had symptoms of acute retroviral syndrome, including fever and fatigue, and tested positive for HIV-1 by serology on December 16, 2004. The patient was diagnosed with 3-DCR HIV-1 when he presented with a weight loss of 4 kg, continued fatigue, and malaise, in early January 2005. At that time, the patient's CD4 cell count was 80 cells/$mm^3$, which decreased to 28 cells/$mm^3$ in mid-January, and his viral load was 280,000 copies/mL. Although the exact date of the patient's HIV infection is unknown, his progression from HIV-negative in May 2003 to HIV-positive in December 2004 indicates that the maximum amount of time since infection is 20 months. While this relatively short time period of 20 months does indicate an unusually rapid disease progression, similar rapid progressions have been observed before. The Multicenter AIDS Cohort Study (MACS) and the Womens' Interagency Health Study (WIHS) have tracked thousands of HIV-positive and HIV-negative individuals, and have reported cases of rapid progression from HIV to AIDS previously.

The PhenoSense assay was utilized to measure the replicative capacity of this patient's virus, which was found to be 1.38 times greater than wild-type virus. This patient's virus is dual-tropic (can use both CCR5 and CXCR4 co-receptors). Additionally, the diversity within the patient's virus is less than 2% and the patient was found not to possess any genes known to be associated with more rapid HIV disease progression or HLA homozygosity.

Genotypic testing revealed that the patient's virus contained multiple resistance mutations. These mutations were predicted to cause resistance to thymidine analogues, lamivudine (3TC) and emtricitabine (FTC) and reduced susceptibility to abacavir and tenofovir. Most NRTI regimens will likely prove ineffective due to these resistance mutations. Resistance to NNRTIs was also predicted from the presence of mutations Y101E and Y191I, and several protease mutations conferred resistance to PIs. However, a phenotypic analysis of the virus revealed that it is fully susceptible to efavirenz and the fusion inhibitor, enfuvirtide. The patient has started a treatment regimen containing these two antiretrovirals.

Dr. Harold Jaffe, of the University of Oxford, commented "that while this case does highlight the failure of existing HIV prevention strategies for gay men, the case should not be used to scare people. It should be used to remind them of the risks of HIV."
*www.nytimes.com*
*www.natap.org*

# RESOURCES

http://aidsinfo.nih.gov

**60 Minute Audio Program Summarizing the 12th Conference on Retroviruses and Opportunistic Infections (CROI)** convened in Boston, MA. February 22-25, 2005.
www.cchiv.com

# SAVE THE DATES

**Institute of Medicine: "Committee on Ethical Considerations for Protection of Prisoners Involved in Research"**
*March 16, 2005*
*Washington, DC*
Visit: www.iom.edu/events.asp

**Improving the Management of HIV Disease Regional CME Courses**
New York, NY: March 17, 2005;
Los Angeles, CA: April 16, 2005;
Chicago, IL: May 2, 2005;
Washington, DC: May 2005;
San Francisco: May or June 2005:
Registration for this course will open soon.
Visit: www.iasusa.org/registration/index.html

**World TB Day**
*March 24, 2005*
Visit: www.cdcnpin.org/scripts/spotlight/spot_wtd05.asp for World TB Day activities

**ACHSA Diminishing Resources: The New Reality**
*March 31-April 3, 2005*
*Oakland, CA*
Visit: www.achsa.org

**NCCHC Updates in Correctional Health Care**
*April 9-12, 2005*
*Las Vegas, Nevada*
Visit: www.ncchc.org

**AMFAR National HIV/AIDS Update Conference**
*April 10-13, 2005*
*Oakland, CA*
Visit: www.amfar.org

**ICAAC Meeting**
*September 21-24, 2005*
*New Orleans, LA*
Visit: www.icaac.org

**United States Conference on AIDS**
*September 28-October 2, 2005*
*Houston, Texas*
Visit: www.nmac.org

**IDSA Conference**
*October 6-9, 2005*
*San Francisco, CA*
Visit: www.idsociety.org

**National Conference on Correctional Health Care**
*October 8-12, 2005*
*Denver, Colorado*
Visit: www.ncchc.org

# IN THE NEWS

**Number of Reported AIDS Cases Increases in South Florida**
For years, South Florida has had a high prevalence of HIV/AIDS. In 2003 (the latest year for which data are available), Florida had the fourth highest rate of AIDS cases per capita compared to all other states and Miami-Dade County had the second highest rate in the nation, behind New York City. Broward and Palm Beach Counties had the fourth and sixth highest rates, respectively. In 2004, new AIDS cases in Florida increased by 24%. Health officials have speculated that this increase is fueled largely by an increase in the number of patients who are unaware that they are HIV-infected until they get sick. AIDS cases in Broward and Miami-Dade counties increased 49% and 33%, respectively, in 2004, as compared to 2003. The only county in Florida in which AIDS cases did not increase in 2004 was Palm Beach County. Despite the significant increase in reported AIDS cases throughout South Florida, health officials hope that the AIDS spike is only a temporary phenomenon, caused by a statewide campaign that has encouraged HIV testing. The campaign that has tested nearly one million people since 2001 has found thousands of people who did not know they were positive, some with AIDS. Encouragingly, new HIV (not AIDS) cases in Florida dropped by 3% in 2004, as compared to 2003.
*www.natap.org*

**HIV Researchers Urge Routine HIV Testing**
Of the estimated 950,000 people in the United States infected with HIV, approximately 280,000 are unaware of their HIV status. Current HIV screening methods are inadequate and people are often diagnosed late in their disease. Two studies have independently determined, through the development of computer models, that routine screening for HIV in health care settings is cost effective and may offer survival and CD4 benefits, defined as an increased CD4 cell count at detection, by providing highly active antiretroviral therapy (HAART) to people identified earlier through routine testing. Additionally, routine screening would assist in preventing transmission of HIV. Researchers suggest repeated routine testing every three to five years. The Centers for Disease Control and Prevention (CDC) guidelines currently recommend routine HIV testing wherever the prevalence of HIV infection exceeds 1%, typically in large urban areas and high-risk groups. When assessing the cost effectiveness of screening and incorporating costs and benefits to partners, computer models estimated that one-time screening would cost $194 more than the cost of current practice, while increasing life expectancy by 4.70 quality-adjusted days, for an incremental cost-effectiveness of $15,078 per quality-adjusted life-year. Furthermore, testing when the prevalence of unidentified HIV is as low as 0.5% can still result in a cost effective ratio of less than $50,000 per quality-adjusted life-year, excluding the benefits to partners. A one-time screening was also associated with earlier diagnosis of HIV, and the mean CD4 cell count at detection was 210/$mm^3$ compared to 154/$mm^3$ in the absence of screening. From the models, it was estimated that HIV transmission would drop by 20% and survival would increase by one and a half years with the use of widespread screening. Robert Jansen, director of the Division of HIV/AIDS Prevention at CDC said that, "as a result of these findings, CDC will be reevaluating its HIV screening guidelines over the next two years."
*www.natap.org*

**Hepatitis C Virus (HCV) Associated with Faster HIV Disease Progression**
One hundred twenty-six HIV/HCV co-infected injection drug users (IDUs), not receiving treatment for HCV, were assessed to study the effects of HCV genotype on HIV disease progression. HCV genotype was determined using a reverse transcriptase polymerase chain reaction for 104 of the 126 IDUs, and for the remaining 22 subjects, HCV genotype was determined using a line probe assay. Clinical progression was defined as progression to AIDS or pre-AIDS death and immunological progression was defined as a drop in the CD4+ count to 200 x 106 cells/l. The median duration of follow-up was 7.3 years. The distribution of HCV genotypes among the study cohort was as follows: HCV type 1: 48%, HCV type 3: 34%, HCV type 4: 13%, multiple HCV types: 5%. In the pre highly active antiretroviral therapy (HAART) era, IDUs infected with concurrent multiple HCV genotypes showed a significantly elevated risk of clinical progression, compared to IDUs infected with HCV genotype 3 (adjusted hazard ratio [HR] 6.54). When data from the HAART era was included, the risk of clinical progression had an adjusted HR of 3.36 and was not significant. In the pre-HAART era, IDUs infected with multiple HCV genotypes also showed a significantly elevated risk of immunologic progression, compared to IDUs infected with HCV genotype 3 (adjusted HR 4.38). When data from the HAART era was included, the risk of immunologic progression had an adjusted HR of 2.74. Additionally, IDUs infected with genotype 1 had an increased risk of immunologic progression, compared to IDUs infected with HCV genotype 3 (adjusted HR 3.92). Subtype 1a was associated with a higher risk of progression than subtype 1b, when compared to genotype 3, with adjusted HRs of 2.10 and 0.86, respectively. This data suggest that HIV disease progression differs by HCV genotype, and is faster among individuals whose HCV infection involves more than one HCV genotype. The effect of HCV genotype on HIV progression was greater in the pre-HAART era, suggesting that the effectiveness of HAART may diminish the effect of HCV genotype on HIV disease progression.
*www.natap.org*

## Self-Assessment Test for Continuing Medical Education Credit

Brown Medical School designates this educational activity for one hour in category one credit toward the AMA Physician's Recognition Award. To be eligible for CME credit, answer the questions below by circling the letter next to the correct answer to each of the questions. A minimum of 70% of the questions must be answered correctly. This activity is eligible for CME credit through August 31, 2005. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. Which answer below is closest in representing the percentage of patients in which IRS is thought to occur after initiation of HAART?
   a. 5-10%
   b. 15-25%
   c. 30-40%
   d. 55-60%

2. The following regarding IRS are all true, except:
   a. Lymphadenopathy is a common presentation in MAC IRS, MTB IRS, Cryptococcal IRS, and JC Virus IRS.
   b. There have been reports of severe ocular morbidity with both CMV IRS and PML IRS.
   c. Fever is a common presentation in MAC IRS, MTB IRS, Cryptococcal IRS, and PCP IRS.
   d. Symptoms of PML IRS may include visual changes, seizures, and ataxia.

3. There are no guidelines for IRS management. True or False?
   a. True
   b. False

4. A triple NRTI regimen should be used only when an alternative NNRTI- or PI-based regimen cannot or should not be used. True or False?
   a. True
   b. False

5. Treatment should be initiated in the following situations:
   a. When CD4 cell count is <200.
   b. When CD4 cell count is between 350 and 500.
   c. When a person presents with an AIDS-defining illness and the CD4 cell count is >350.
   d. A and B
   e. A and C

## IDCR Evaluation

*5 Excellent 4 Very Good 3 Fair 2 Poor 1 Very Poor*

1. Please evaluate the following sections with respect to:

| | educational value | clarity |
|---|---|---|
| Main Article | 5 4 3 2 1 | 5 4 3 2 1 |
| In the News | 5 4 3 2 1 | 5 4 3 2 1 |
| Save the Dates | 5 4 3 2 1 | 5 4 3 2 1 |

2. Do you feel that IDCR helps you in your work?
   Why or why not?

3. What future topics should IDCR address?

4. How can IDCR be made more useful to you?

5. Do you have specific comments on this issue?

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