



Clinicians who use the system have found that the eight-minute PointCare NOW results and onboard access to all previous test data provide increased options for improved diagnosis and treatment of their HIV patients.

Technical Factors Affecting CD4 Counts: Uses of CD4%

If both CD4 counts and CD4% values change in parallel, the changes are probably HIV-related. If CD4 counts and CD4% values do not change in parallel, the changes are probably not HIV-related.

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For many years, CD4 counts have been recognized as important parameters for tracking progress of HIV infection. CD4 counts have been used as indicators for both initiation and management of antiretroviral therapy in HIV patients. However, many studies have shown that common conditions, including infection with TB and/or other opportunistic infections, stress factors, and circumstances of sample collection, affect CD4 counts. In addition, CD4 counts exhibit day-to-day variability approaching 40 percent. Variability in CD4 counts can mislead clinicians responsible for delivery of antiretroviral therapy. A clinically useful addition to CD4 counts is the ratio of CD4 lymphocytes to total lymphocytes in peripheral blood, or "CD4%." Many factors that impact CD4 counts do not affect CD4% values. Patient management can be improved by simultaneous monitoring of both CD4 count and CD4%.

Cells bearing CD4-antigen are a sub-population of all T-lymphocytes. Estimates are that only about two percent of CD4-bearing lymphocytes are circulating in blood. The remaining 98 percent of these cells are sequestered in tissue compartments. Two important tissue compartments where lymphocytes are found in abundance are connective tissue and lymphatic tissue.

Laboratory procedures for CD4 testing are designed and optimized for blood samples. This means that CD4 lympho-

cyte counts are based on the relatively small fraction of CD4 cells found in circulating or peripheral blood at the moment of sample collection. Consequently, values associated with CD4 lymphocyte counting are subject to problems common to all "small-sample" counting situations, namely, high variability. Several factors, in addition to HIV-infection, can alter CD4 counts in peripheral blood. Understanding these factors will enhance interpretation of CD4 counts. Failure to understand these factors and how to compensate for them, may lead to poor management of HIV patients.

Numerous studies conducted using samples of peripheral blood from patient populations in the industrialized world provided the evidence-base for current guidelines for HIV patient management.¹ In general, these patients presented with relatively uncomplicated HIV disease; they had few if any opportunistic infections, and conditions under which their blood samples were collected were well-controlled.

Today, worldwide focus on HIV-patient management has shifted to resource-poor environments where opportunistic infections, including TB, anemia, and neutropenia, are common, and conditions under which blood samples are collected cannot be well-controlled. This means that it is difficult to obtain reliable CD4 results.

In patients where HIV-infection is the only disease condition, numbers of circulating CD4 lymphocytes decrease during the progression of HIV disease and increase with successful delivery of antiretroviral therapy. In resource-poor settings, it is rare to find patients where HIV is the only disease condition. Thus, in these settings, interpretation of CD4 counts is more complex than in the original studies. In the global epidemic, clinicians regularly see HIV patients who present with opportunistic infections that dramatically affect lymphocyte counts, and hence CD4-lymphocyte counts. In these patients, changes in CD4 counts may have nothing to do with HIV-infection, and clinicians often welcome additional information before making treatment decisions.

Fortunately, many difficulties associated with CD4 counts can be resolved by cross-checking CD4 counts with parallel measurement of CD4% values to help rule out non-HIV-related causes that could affect CD4 counts. In many situations, when CD4 counts change, CD4% values do not change. In these cases, CD4% can be used to exclude non-HIV-related sources of variability. Cross-checking CD4 counts in parallel with CD4% allows clinicians to normalize CD4 testing for some factors. Examples are described below.

Tuberculosis

As the global burden of TB increases, evidence accumulates that TB-status alters CD4 counts. In 2006, a study in South Africa² followed progression of pulmonary TB in 21 newly smear-positive patients, none of whom were HIV-positive. Participants were monitored closely for several parameters, including CD4 counts, as they progressed into early stages of acute disease. The authors observed that numbers of total lymphocytes decreased from 2,300 cells/ μL to 1,300 cells/ μL as patients entered early stages of acute disease. Because TB affects all lymphocytes, CD4 lymphocytes are also affected. In this study, CD4 counts dropped from a mean of 1,100 cells/ μL to 600 cells/ μL as patients entered early stages of acute disease. Although both lymphocyte counts and CD4 counts climbed during 26 weeks of successful treatment, neither count reached "healthy control" levels. Thus, CD4 counts are affected by both progression and treatment of TB infection.

HIV-infection is a significant risk factor for TB.³ Cross-checking CD4 counts with CD4% values can normalize effects of non-HIV factors influencing CD4 counts, including progression of TB. In the example above, "healthy controls" displayed mean CD4% values of 48 percent (1,100/ 2,300), whereas patients in early stages of acute disease displayed mean CD4% values of 46 percent (600/ 1,300). After 26 weeks of successful treatment, the mean CD4% was 44 percent. Even though CD4 counts showed significant changes during treatment, CD4% values did not change. There was almost no difference between CD4% values for healthy controls versus patients in early stages of acute disease and at the end of successful treatment.

Changes in CD4 counts in patients where TB may be present should be confirmed by changes in CD4% values. If CD4% values

do not change, then clinicians may assume there have been no HIV-induced changes in CD4 counts.

Diurnal Variation

Another commonly cited source of lymphocyte (and thus CD4 count) variability is diurnal (time-of-day) variation. In 1990, Malone and coworkers⁴ performed what continues to be the most comprehensive study of diurnal variation in lymphocytes and lymphocyte subsets. Comparing diurnal variation in lymphocyte and CD4 counts between HIV-infected and uninfected patients, they found:

- In uninfected patients, lymphocyte counts increased from 1,902 cells/ μL to 2,242 cells/ μL , between the hours of 8 a.m. and 4 p.m. During the same interval, CD4 counts increased from 818 cells/ μL to 970 cells/ μL . CD4% values remained constant at 43 percent.
- In HIV-infected patients, all of whom had CD4 counts below 500 cells/ μL , lymphocyte counts increased from 1,452 cells/ μL to 1,698 cells/ μL between the hours of 8 a.m. and 4 p.m. During the same interval, CD4 counts increased from 384 cells/ μL to 447 cells/ μL . CD4% values remained constant at 26 percent.

This study is often cited to show that CD4 counts change less during the day in more-advanced-stage HIV patients than in early-stage patients (change of +63/ μL compared to +152/ μL). Perhaps more interesting is that CD4% values did not change at all during the day, providing additional support for cross-checking CD4 counts with CD4% values in HIV-patient monitoring. This study shows that CD4% values can normalize time-of-day variations in sample collection. In many resource-poor settings, time-of-day for sample collection using typical testing procedures is either unknown or uncontrolled.

Closer review of Malone's data reveals that CD4% values can also be used to normalize "between-day" monitoring of CD4 counts. Patient samples were collected at 8 a.m. on three consecutive days. The authors compared between-day variability in testing for total lymphocytes, CD4 counts, and CD4% values. In patients with AIDS (Stage IV HIV-infection), lymphocyte counts showed between-day coefficients of variation (CVs) of 40 percent, and CD4 counts showed between-day CVs of 35 percent. In contrast, CD4% values showed a between-day CV of just 10 percent. Thus, in addition to being useful parameters for during-the-day monitoring, CD4% values are also useful for between-day monitoring.

Pediatric HIV Care

Measurement of CD4% values is essential for optimal care and treatment of pediatric HIV patients. Lymphocyte counts are very high in children, and thus CD4 counts are also very high. In 2010, the World Health Organization released recommendations for initiation and monitoring of pediatric HIV.⁵ Changes from previous recommendations include earlier initiation of antiretroviral therapy in children between the ages of two and five with CD4% values \leq 25 percent, or CD4 counts of \leq 750 cells/ μL .

A final observation about use of CD4 counts and CD4% is warranted. In 2006, Hulgán et al.⁶ studied a large, multi-center HIV patient cohort to find relative prognostic values of CD4% versus CD4 counts for decisions to initiate antiretroviral therapy. The study not only showed considerable ranges of CD4% associated with specific CD4 counts – but also that CD4% correlated well with probabilities that patients would have an AIDS Defining Event (ADE) within six years. For example, patients in the group defined by CD4 counts of 200 cells/μL had CD4% values ranging from five to 40 percent. Patients near the CD4% range of five percent in this group had 60-percent probabilities of six-years-free of an ADE, while patients near the CD4% range of 40 percent in this group had 85-percent probabilities of six-years free of an ADE. Even more interesting were patients in the group defined by higher CD4 counts (300 cells/μL). These patients also had CD4% values ranging from five to 45 percent. While these patients had similar CD4% values to those in the lower CD4 count group, they showed increased probabilities of six-years-

free of an ADE. Patients near the CD4% range of five percent in this group had 75-percent probabilities of six-years-free of an ADE; patients near the CD4% range of 45 percent in this group had 90 percent probabilities of six-years-free of an ADE. Hulgán and coworkers concluded that CD4% at initiation of antiretroviral therapy can predict disease progression independently of CD4 counts. They proposed that CD4% values be used to determine timing of therapy. Studies like these indicate expanded uses for CD4% beyond the current cross-check functions are on the horizon.

In summary, although CD4 counts are used routinely to monitor HIV patients, when used alone, CD4 counts can be misleading. This is because many common conditions interfere with routine CD4 counts and can present difficulties for clinician interpretation of the values. Variability in CD4 counts can be cross-checked by parallel measurements of CD4% values, which can help rule-out non-HIV-related influences in situations where CD4 counts change and CD4% values do not.

Direct Effects of HIV on the Hematology Profile

Highlights

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Routine tracking of hemoglobin values and neutrophil counts in HIV clinics allows clinicians to detect onset and progression of anemia and/or neutropenia. In patients in advanced stages of HIV disease, bacterial infection is a serious and often life-threatening complication. By “trending” neutrophil counts in HIV patients, clinicians will better understand patient risk for bacterial infection.

Hematology Profiles for TB Infection in HIV Patients

Highlights

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Approximately one-third of the world's population (or two billion people) is infected with Mycobacterium tuberculosis the bacterium that causes TB. In patients who develop pulmonary TB, disease progression is characterized by pulmonary clinical symptoms such as severe coughing, often with sputum or blood, and chest pain. TB is termed "inactive" or "latent" when patients' immune systems can control the bacterium and clinical symptoms are unapparent. Although latent TB is not contagious, people with latent tuberculosis are frequently termed "carriers." TB is termed "active" when patients' immune systems are unable to suppress the bacterium. Diagnosis of TB infection usually begins with skin tests and chest X-rays. TB skin tests are simple to administer and react positively for both active and latent disease. Patients who are TB-skin-test positive are referred for chest X-rays. Sites of local inflammation are visible in chest X-rays of patients with active TB.

TB is a leading cause of death of HIV patients, according to the World Health Organization.¹⁶ TB Infection usually occurs before HIV-infection or early in progression of HIV. In HIV patients, latent TB disease can become active disease as HIV progresses and patients' immune systems are impaired. Although knowledge of TB infection-status is especially important for treatment of HIV patients, obtaining information about TB infection-status is extremely difficult, particularly in patients in resource-poor settings.¹⁷

Until recently, undiluted-sputum-smear microscopy has been the primary diagnostic method for TB in resource-poor settings. However, the method is recognized as having high false-negative rates for all TB diagnoses and these high false-negative rates are exacerbated in HIV patients.¹⁸ Many methods for screening and diagnosing pulmonary TB work even less well in HIV patients, who often have extra-pulmonary TB. Indeed, clinicians

have found both TB skin tests and chest X-rays to be notoriously misleading in HIV patients. Weakened patient immune systems are unable to mount inflammatory responses to infection. Recently, Cain et al.¹⁷ presented evidence for an algorithm of interview questions for screening and diagnosing TB in HIV patients.

The definitive method for diagnosis of active TB in HIV patients is culture of sputum. Unfortunately, access to this method is very limited in resource-poor settings. Even in places where access is possible, logistics for this method are formidable. In places where most HIV patients live, establishing facilities to culture TB is a daunting task and locating patients after culture results are available is time-consuming. Under such limitations, patients with clinical symptoms of TB are frequently assigned to therapy presumptively.

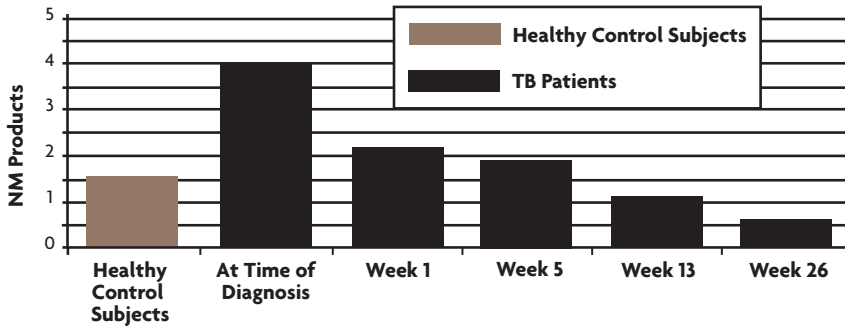
A simple hematology method may buttress presumptive diagnoses of TB. This method arises from work conducted in the 1920s and 1930s,¹⁹ when Florence Sabin studied TB in rabbit models and observed that monocyte counts in blood rose from "normal" levels of eight percent to 15 percent a few days after rabbits were infected with TB. In 2006, Veenstra et al.² confirmed Sabin's work using human subjects in a study of healthy subjects and those in successful treatment for active TB.

The graph on the following page shows trends in NM products (neutrophil counts multiplied by monocyte counts) of TB patients during 26 weeks of treatment for TB, as derived from Veenstra et al.² data. The first bar shows NM products for healthy controls. The second bar shows NM products at the time of diagnosis of pulmonary TB. NM products at the time of diagnosis are 25-fold higher than those of healthy controls. During the 26-week treatment, NM products trend downward (bars three through five).

Upon completion of therapy, values for all NM products of TB patients were below those of healthy-control levels. Total white cell counts and other white cell subsets, including total T cells, B cells, and NK cells, were also at reduced levels

upon completion of therapy. Simple automated white cell differential counts were all that was needed to monitor these events

Trends of NM Products in TB Patients During 26 Weeks of Treatment for TB



Using Eosinophil Monitoring to Manage Helminth Infection in HIV Patients

Highlights

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Eosinophil counts coupled with fecal diagnosis of helminth infection may be a useful tool to help improve management of helminth infections. High eosinophil counts can be used as prompts to obtain and examine stool samples for helminth infection. If stool samples are positive or presumptive for worms, anti-helminth therapy can be initiated and success of therapy can be monitored using eosinophil counts.

Estimates are that one-third to one-half the people who live in poverty are chronically infected with helminths. School-age children are disproportionately affected because helminth infection causes cognitive impairment, poor memory, physical weakness, and stunts growth. Helminth infection commonly accompanies HIV-infection. A recent study by Modjarrad et al.²⁰ in Lusaka, Zambia, showed that 25 percent of HIV patients were co-infected with helminths. These authors suggested that helminth diagnosis and treatment should become a routine part of HIV care.

Borkow et al.²¹ have reviewed relationships between progression of HIV and helminth infection. These authors concluded that well-documented effects of helminth infection on immunity should raise concerns about management of HIV patients. The authors demonstrated correlations between helminth infection and HIV viral loads, showing that when helminths were eradicated in HIV patients, viral loads for these patients decreased significantly. (Their attempts to find correlations between CD4 counts and helminth infection were not successful.)

In a separate study, in Nigeria, Uwah et al.²² demonstrated further correlations between helminth infections and HIV viral loads. In this study, when helminth infections were eradicated in HIV patients, viral loads for these patients decreased and the patients displayed improvement in clinical symptoms associated with HIV.

The most common method for diagnosis of helminth infection is microscopic examination of feces. A World Health Organization publication by P.C. Beaver²³ contains a definitive statistical analysis of the direct-smear method and concentration techniques for diagnosis of helminth infection. Beaver concluded that although the direct-smear technique should be sufficient to detect helminths, it is not capable of providing quantitative estimates of helminth load. This means that current techniques for detection of helminths are not sufficiently quantitative to track success or failure of therapy.

In endemic areas, helminth infections are the most typical reason for elevated eosinophil counts or eosinophilia.²⁴ Although elevated eosinophil counts are not in themselves diagnostic for helminth infections, they can be very useful when coupled with diagnosis by fecal examination. After diagnosis, regular monitoring of eosinophil counts is a powerful tool for monitoring success of anti-helminth therapy. Eosinophil counts are simple to obtain from peripheral blood samples. Loutfy et al.²⁵ demonstrated utility of this tool for monitoring treatment of strongyloidiasis. Harries et al.²⁶ reported on a group of 119 travelers who returned to England with eosinophilia. Even though only 39 percent of the group had definitive fecal sample diagnosis for parasite infections, all were presumptively treated for parasite infections and all experienced decreased eosinophil counts.

SUMMARY AND CONCLUSIONS

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POINTCARE NOW PARAMETERS FOR BETTER DISEASE MANAGEMENT

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