Human Immunodeficiency Virus Hematology

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The advent of potent antiretroviral therapy has altered the expected natural history of human immunodeficiency virus (HIV) infection and of many previously associated opportunistic complications, including malignancies. At the same time, HIV suppression hasn't affected all of these complications equally and the longer expected survival of infected patients may allow the development of newer complications. Additionally, the use of potent antiretroviral combination therapy may itself lead to hematological toxicities. Together these changes affect the consultation role of the hematology-oncology specialist in comprehensive HIV care and demand ongoing education.

In Section I, Dr. Paul Volberding reviews the biology of antiretroviral drug development and the progression in discovering new agents as the viral life cycle is further elucidated. He briefly summarizes the process of combining agents to achieve the degree of viral suppression required for long-term clinical benefit.

In Section II, Dr. Kelty Baker reviews the effects of HIV and its therapy on hematologic dyscrasia and clotting disorders. She summarizes how therapy may decrease certain previously common manifestations of HIV disease while adding new problems likely to result in referral to the hematologist. In addition, she addresses the role of secondary infections, such as parvovirus, in this spectrum of disorders.

In Section III, Dr. Alexandra Levine discusses the still challenging aspects of HIV associated non-Hodgkin's lymphoma and the association between HIV infection and Hodgkin's disease. She addresses current controversies in the pathogenesis of HIV related lymphomas and summarizes a number of recent trials of combination chemotherapy, with or without monoclonal antibodies, in their management. Additionally, she reviews the complex relationship of HIV disease with multicentric Castleman's disease and recent attempts to manage this disorder.

I. The Pathophysiology of HIV Therapy

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The HIV epidemic, the worst epidemic in human history, has already taught us much. It is a convincing illustration of the balance between the power of science and the humanism of modern medicine, a relationship that further integrates behavioral medicine with clinical care. The epidemic has also given birth to an invaluable and informed patient advocacy community—one with clear implications for other diseases.

Antiretroviral therapy, remarkable in its clinical benefits, is itself a paradigm of the dramatic pace of molecular medicine. In only a very few years, HIV therapy moved from limited to striking potency, an advance based on rapid discovery of the structures and functions of the HIV virion and life cycle. As the same tools that elucidate HIV biology are applied more broadly in medicine, it is possible to be optimistic that other diseases will be similarly deciphered and controlled. Drug discovery based on fundamental molecular pathogenesis is rapidly reshaping our concepts of medicine from those based on organ-specific diseases to those recognizing common disease mechanisms. Within a given area, research in one disease illuminates others. For example, advances from HIV research are being applied to new challenges. Emerging infectious diseases such as West Nile Virus[1] and now severe acute respiratory syndrome (SARS)[2] have been quickly characterized and drug discovery is moving forward using approaches in many cases developed in response to HIV/AIDS.

This review will address the biology of HIV as it relates to antiretroviral treatment. It will summarize current questions and approaches in HIV management focusing primarily on the virology of HIV infection. Intentionally, it will not address the immunology of HIV infection in any detail, not because it is less important, but because, to date, it has fewer therapeutic agents of

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established efficacy. The review will also pay only passing attention to the behavioral components of HIV therapy, such as medication adherence. These are critically important—uniquely so in HIV medicine because of rapid selection of drug resistance mutations—but are beyond the scope of this review. This review will refer liberally to several excellent reviews of HIV virology[3,4] and attempt to summarize the clinical application of this new knowledge.

The Origins of the HIV Epidemic

The virus responsible for essentially all AIDS cases in the Western world, HIV-1, represents human infection by a virus originating in another species, in this case, the chimpanzee[5] (which may, in turn, have been infected by another primate species). Based on mathematical modeling of HIV sequence variations, it is estimated that the initial human infections occurred near 1930 in sub-Saharan Africa.[6] The HIV epidemic was probably accelerated by urban population concentration in postcolonial Africa. It was spread worldwide by rapid transportation. Such zoonotic transmission events are now appreciated as quite common. Recent examples include outbreaks of HIV-2,[7] SARS, and monkeypox.[8] HIV-1, hereafter more simply termed HIV, collectively includes a series of similar but unique and relatively stable sequence variations called clades. Each clade is thought to represent an original animal to human transmission event. The biologic variation between clades is an area of very active investigation and may prove clinically relevant, affecting pathways of resistance selection. HIV clades are useful as "fingerprints" in tracking the worldwide HIV spread and local prevalence of one clade is quite characteristic and distinctly different than another region. For example, while clade B is almost universal in infected persons in the United States, clade C is similarly dominant in southern Africa. Regions at the interface of two dominant clade prevalences may also contain a substantial population infected with recombinants of the two clades.[9] It is not clear to what degree this represents simultaneous dual infection or later superinfection of a new clade in a patient already chronically infected with a first clade. True superinfection, if common, could suggest difficulties in vaccine development as it would indicate the failure of host response even when ideally primed.

HIV infection as a disease

Initial cases of advanced immune deficiency (almost immediately associated with CD4 T-lymphocyte depletion), often with striking opportunistic infections or malignancies, led to the recognition of the AIDS epidemic. The identification of HIV as the causative agent offered insight into the epidemiology and pathogenesis of AIDS. Tests for HIV-induced antibodies found a large epidemic, mostly of those not yet ill but with signs of progressing immune depletion. Clinical attention thus appropriately shifted from AIDS to HIV and the recognition that HIV infection is a disease in its own right and one, moreover, appropriate for treatment.[10]

HIV infects CD4 cells and can be directly cytotoxic.[11] Other complex mechanisms, however, appear important in explaining the progressive depletion of this key cellular element of immunity.[12] Immune-mediated cytotoxicity is probably involved, as T-cell regeneration in the thymus is also limited by HIV infection.[13,14] Along with CD4 T cells, macrophage/monocytes are also infected. These cells may be key to maintaining and spreading HIV within the body and are probably not directly killed by infection. Along with $CD4^+$ cell depletion, which is the easiest measure to stage HIV disease, infection damages many components of normal immunity. T-cell proliferative response, especially to HIV antigens, is quickly lost and the repertoire of antigen recognition diminishes with time.

HIV structure

HIV is a small virus containing 2 single RNA strands in a core structure bound by a gag-derived protein, p24. The viral core also packages key enzymes needed for replication, including reverse transcriptase, integrase, and an HIV-specific protease. These will be described in more detail below.

The HIV core is contained within a lipid bilayer, a portion of the infected cell membrane taken during viral budding. The viral envelope contains specific structures, several key to infectivity. One, a glycoprotein of 120,000 molecular weight, gp120, was quickly recognized as the main viral structure interacting with the CD4 protein on the surface of cells susceptible to infection. Most early attempts to create an HIV vaccine used recombinant gp120 as an antigen in the hope that antibodies to this protein would effectively neutralize HIV, a strategy unsuccessful to date. Although neutralizing antibodies are found in some cases, their low titer and narrow specificity made these antibodies incapable of providing protection against the variable viruses in actual infection.

The glycoprotein gp120 is bound to the HIV envelope by a second glycoprotein, gp41. gp41 has an envelope spanning region, but also a complex triple-helical region projecting from the outer aspect of the envelope. This, along with gp120, appears to be essential for cellular infectivity.

As infection necessarily involves interactions between the virus and the target cell, cellular membrane

structures are also involved. These include the CD4 antigen and, as will be described below, chemokine receptors, particularly CCR5 and CXCR4.

The HIV life cycle and antiretroviral drug development

Many elements of the HIV life cycle have been elucidated, at least sufficiently to provide a basis for antiviral drug development. Major steps in this life cycle will be reviewed, followed by a brief discussion of antivirals available or in development targeting that biology. The lifecycle is depicted in **Figure 1** (see Appendix, page 613).

1. Binding of gp120 to CD4

One of the domains of CD4 binds to a structurally protected pocket of the gp120 viral glycoprotein. Even simple mutations in this gp120 site affect binding significantly. The CD4/gp120 interaction is necessary, but not itself sufficient for cellular infection. As a key step in infection, however, numerous attempts have targeted this for antiretroviral therapy. In early and unsuccessful approaches, the small, water soluble, gp120 binding domain of CD4 was cloned, expressed, and injected in HIV-infected subjects. This soluble CD4 was designed to occupy the gp120 of HIV and was active in vitro. It was inactive, however, against the more variable HIV of actual primary isolates.[15] Recently, one company announced early development of a small molecule inhibitor of gp120/CD4 binding, a promising approach that could potentially avoid the toxicities seen with drugs acting within the cell.

2. CD4 undergoes structural transformation following gp120 binding

This "melting" of CD4 allows a subsequent interaction between gp120 and the chemokine receptors physically close to CD4 at the cell surface. One company has developed a humanized murine anti-CD4 monoclonal antibody that binds to the pretransformed CD4, stabilizing it. This prevents HIV infection of the cell, presumably by preventing gp120/chemokine receptor interaction. This antibody was effective in vitro and in an early Phase I trial in human HIV-infected subjects. Individuals were given a single intravenous dose of the monoclonal antibody. Higher doses resulted in a 1–1.5 log viral suppression lasting for as long as 3 weeks with no reported toxicity or antibody production.[16] Multidose trials are currently in process.

3. The gp120 interacts with the chemokine receptor

This step in the viral life cycle is another target of active drug development. Almost all patients are initially infected with a virus that uses the CCR5 chemokine receptor, often termed R5 HIV. Some cases of advanced HIV disease show evolution of the virus (through mutations affecting the gp120 binding site) to enable use of the CXCR4 chemokine receptor, termed X4 HIV. There is some evidence that the X4 virus is more rapidly cytopathic than R5[17] and thus concern that blocking interactions with the CCR5 chemokine receptor may favor evolution to this more virulent form. To date, however, this has not been observed in drug development. Various strategies of blocking the gp120/chemokine receptor are being explored, and this approach does appear amenable to small molecule drug development. In at least 1 case, a promising compound was found to prolong the Q-Tc interval, a potentially serious toxicity.[18,19] Other related compounds that do not share this problem are in development. One question in chemokine blocking is whether this will cause impairment of one component of innate immunity, the natural function of these structures. To date, this has not been observed. Perhaps speaking to this issue is the observation that individuals with a homozygous deletion of the gene coding for the CCR5 chemokine receptor show no evidence of immune deficiency, although they are naturally resistant to infection with R5 HIV.[20]

4. The gp120–chemokine receptor interaction triggers uncoiling of the triple-helical external domain of HIV gp41, which is then inserted into the cell membrane leading to fusion of the viral and cell membranes

This step, an elegant biologic process, has been resolved through careful structural biologic investigation. Understanding this process has already resulted in successful drug development with the approval of enfuvirtide.[21] In a manner comparable to that of a harpoon, following the uncoiling of gp41, the triple-helical structure extends and inserts its tip containing the fusion domain directly into the cell membrane. This tethers the virus to the cell. Fusion and actual infection require a subsequent recoiling of the gp41, an active process that approximates the 2 membranes. This recoiling is prevented by enfuvirtide (formerly T-20), a 36-mer polypeptide that binds to the uncoiled, triple-helical region of gp41, stabilizing it in that conformation.

Because of its novel mechanism, enfuvirtide is fully active, despite high-level resistance to all other antiretroviral drugs. The drug must be given as a twice daily subcutaneous injection. If not combined with other active antiretrovirals, resistance develops quickly. Other fusion inhibitors are also being developed. One, T-1249, acts in HIV that has developed enfuvirtide resistance and can be given as a single daily subcutaneous injection.

5. Reverse transcription of the viral single-strand RNA eventuating in a dual strand DNA copy occurs in the cytoplasm following viral entry

Reverse transcriptase, the enzyme needed for this process, is contained within the viral core and coded by the HIV genome, *pol*. Reverse transcription, relatively unique to the lentiviruses, including HIV, was an obvious and quickly successful target of drug development (**Table 1**). Already, 2 classes of reverse transcriptor inhibitors are in use: 8 nucleoside-analog inhibitors and 3 with other structures (thus termed non-nucleoside reverse transcriptase inhibitors). In both categories, new agents are in advanced development stage. In common parlance, the reverse transcriptase inhibitors structurally related to nucleosides or, in one case, nucleotides, are collectively called the nucleoside reverse transcriptase inhibitors (nRTIs). The nRTIs are often considered the "backbone" of HIV therapy and, very typically, 2 of these drugs are included in multidrug regimens. Appreciating that full medication adherence is essential to durable clinical benefits, several coformulations of these drugs are either available or in development, thus reducing daily pill burden. The nRTIs have few class-specific toxicities, but each agent has a unique and important toxicity profile. Side effects range from mild to life threatening.

Drug resistance is key to regimen design. While certain drugs select quickly for a single mutation conferring high-level phenotypic resistance,[22-24] others require multiple mutations over prolonged time for similar consequences.[24] Furthermore, it is believed that certain resistance mutations may compromise the capacity of the virus to replicate compared to wild-type HIV and that such mutations may allow some continued clinical benefit, even in the face of high-level resistance.[26] This observation is leading to very interesting treatment strategy trials in advanced HIV virologic failure. This is, again, beyond the scope of this review.

6. Reverse transcriptase inhibitors not structurally related to nucleosides are termed non-nucleoside reverse transcriptase inhibitors (nnRTIs)

The nnRTIs are more alike in terms of toxicity and resistances than their nRTI relatives. These agents bind to a very specific site on the reverse transcriptase (**Table 1**). They are inactive against the otherwise closely related virus HIV-2, and a single genotypic mutation is able to bestow complete viral resistance. This resistance is essentially complete across the group of currently approved nnRTIs. Thus, in contrast to the nRTIs—where continued activity is possible with selective, sequential replacement of drugs within the class—with the nnRTIs, only a single failed attempt is possible. For this reason, these drugs require careful selection of supporting agents, careful patient selection, and scrupulous adherence.

Despite seeming limitations, the nnRTIs are crucial components, especially in early treatment regimens. Two nnRTIs, nevirapine and efavirenz, are in common use. A third, delavirdine, is less convenient, less potent, and is rarely chosen. The nnRTIs, as a class, are potent and the most widely used are convenient with compact formulations and prolonged half-lives enabling once- or twice-daily administration. Toxicities of nnRTIs tend to be most common during initial weeks of use. Rash and hepatic effects are seen with both commonly used agents. Central nervous system side effects are common with efavirenz, while hepatotoxicity is more common with nevirapine, especially in patients coinfected with HIV and either hepatitis B or C.[26,27] Newer agents are in development in this class, some appearing to have unique resistance pathways.

7. The DNA copy of the HIV genome is integrated into the host cell DNA in the nucleus through the action of the HIV integrase enzyme

This process is quite complex but substantial advances in our understanding of it are leading to early drug development. Among the steps in the integration process are the interactions in the cytoplasm (again, integrase is carried into the cell within the viral core) where the enzyme is attached to each end of the newly copied viral DNA, forming a complex that is then taken into the nucleus through pores in the nuclear membranes. The integrase then breaks the host DNA—probably in selected sites—and transfers the viral DNA strand to the opened end of host DNA. Integrase then repairs the

Table 1. Human immunodeficiency virus (HIV) drugs.

nRTIs	nnRTIs	PIs	Fusion Inhibitors
Zidovudine: ZDV	Efavirenz: EFV	Indivavir: IDV	Enfuvirtide: T-20
Stavudine: d4T	Nevirapine: NVP	Ritonavir: RTV	
Lamivudine: 3TC	Delavirdine: DLV	Nelfinavir: NFV	
Didanosine: ddI		Amprenavir: APV	
Abacavir: ABC		Lopinavir: LPV	
Zalcitabine: ddC		Atazanavir: ATV	
Tenofovir: TDF			
Entricitabine: FTC			

Abbreviations: nRTIs, nucleoside reverse transcriptase inhibitors; nnRTIs,non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors

breaks, leaving the proviral DNA inserted into the host genome. Because the active site of integrase involves DNA, the structure has been difficult to resolve. But it is now relatively well characterized and is the basis of active drug development. Several compounds have shown in vitro activity and at least one is in early human trials.[28]

8. The proviral DNA is activated and transcribed into RNA, which is then translated to form viral-coded proteins

Viral activation typically occurs early after infection, but in some cells does not occur even after prolonged periods. These latently infected cells are thought to form a reservoir of infection, making viral eradication or cure highly improbable, as most antiretroviral drugs target active steps of replication. The activation and transcription of HIV, and the transport of gene products from the nucleus to the cytoplasm, involves regulatory genes *tat* and *rev*. To date, drug development of agents targeting these genes or their gene products have been unsuccessful; but they represent attractive areas of investigation as interfering with them may prove useful in decreasing the production of viral particles from already infected cells.

HIV viral components assemble at the inner aspect of the cell membrane, bud from the cell, and finish maturation into an infectious virion after release.

A very active area of HIV research and drug development addresses the later steps in infection. While some aspects such as the selective proteotic cleavage of precursor HIV proteins is well understood and has led to important approved agents, earlier steps in viral assembly are only now being elucidated. It is clear that viral assembly is carefully targeted. Certain regions of the cell membrane are favored for viral assembly and budding,[29] and cells contain endogenous materials that inhibit retrovirus production. Still under active investigation, lentiviruses including HIV have a gene, *vif*, that appears to inactivate this "natural" protective cellular mechanism through an interaction with the product of the *APOBEC3G/CEM 15* gene.[30] An intriguing potential target for drug development, this system is being explored by several HIV laboratories.

Once the assembly of the virus inside the cell membrane is advanced, the budding begins to pinch off the forming viral core within a pocket of the cell membrane. The immature viral particle is at first attached to the cell by a thin stalk of cell membrane, which then breaks to release the virion into the external environment. The process of budding and release is still rather poorly understood, but is a likely target of drug development.

As the virion buds and is released, HIV-specific protease begins to cleave viral proteins into active truncated forms needed for full viral maturity and infectivity. Specific inhibitors of HIV protease are in wide use[31] (**Table 1**). Their potency has revolutionized HIV therapy and the continued development of new compounds is addressing problems seen with the first generation of this drug class. Very broadly speaking, early protease inhibitors (PIs) were inconvenient, with high pill burden, large pill size, and restrictions on use with food and water. As a class, these agents were often associated with gastrointestinal disturbance and dyslipidemias. Specific protease inhibitors had other toxicities limiting use in some patients. Resistance to this drug class resembles the nRTIs more than the nnRTIs, typically requiring multiple mutations for full resistance and usually occurring only after prolonged viremia in the presence of the drug. The cytochrome p450 induced metabolism of most members of the class is significantly blocked in the presence of even low concentrations of ritonavir, one of the earliest of these drugs to be developed. This effect has enabled more convenient dosing of this class.[32]

Ritonavir, while poorly tolerated in full doses, and thus seldom used as a protease inhibitor in its own right, is often used in conjunction with a second protease inhibitor to boost that drug's pharmacologic profile. An interaction seen with all drugs in the class except nelfinavir, low-dose ritonavir raises peak and trough concentrations of protease inhibitors as well as their integrated concentration over time, the area under the curve (AUC). Ritonavir enhancement or boosting makes it possible to use indinavir twice daily instead of 3 times daily and enables other protease inhibitors to be used once daily. Ritonavir enhancement is necessary for the investigational protease inhibitor, tipranavir, to be used at all, given otherwise limited serum levels.

Protease inhibitor resistance is a complex problem and the subject of much research. Mutations conferring resistance may well impair viral fitness similar to that observed with the nRTIs. Protease resistance patterns may have implications for the choice of initial and salvage protease inhibitor–containing regimens. One recent observation suggests that certain resistance mutations may even confer increased susceptibility to other members of this drug class.

Protease toxicity is quite drug specific and beyond the scope of this review. But it is clear that some agents in this class may interfere with both carbohydrate and lipid metabolism.[33] Highly controversial and still being clarified in prospective cohort studies, protease inhibitor use may contribute to visible and characteristic morphologic alterations in lipid deposition, although recently some nRTIs have been even more implicated, especially in the loss of subcutaneous fat.[34] Hyperlipidemias including LDL

cholesterol and triglycerides are seen with some protease inhibitors and have raised concerns in the field about accelerated cardiovascular complications.[35,36] Carbohydrate metabolism effects cause relative insulin resistance and in some cases, frank diabetes.

Newer protease inhibitors are showing promise in many respects. New drugs or reformulations of existing ones allow similar and fewer pills and less frequent administration. One recently approved drug, atazanavir, can be used once daily, soon as a single daily tablet, and furthermore, does not cause hyperlipidemia.[37]

General Approaches to HIV Therapy

Successful antiretroviral therapy allows durable suppression of viremia below the quantitation limits of sensitive viral assays. Treatment is best started before very advanced disease stages, but even when begun later can often substantially reverse the immune deficiency of HIV infection. The optimum timing of therapy and choice of drugs is well described in published treatment guidelines.[38,39] In general, treatment should be initiated before a CD4 cell count of 200/mm^3, as the risk of complications, infections, and cancer increase below that level. Therapy can safely be deferred in most cases until the CD4 cell count is 350/mm^3, as the risk of symptomatic disease is small in that region and given the cost and adverse consequences—toxicity and resistance—of more prolonged therapy. An absolutely key issue is the patient's motivation to be treated and his or her ability to adhere fully to the prescribed regimen. Any delay in initiating HIV therapy should be used to prepare patients to comply once it has begun.

The choice of drugs in the initial regimens, given the almost limitless number of permutations of existing agents, is also complex, but recent guidelines from the Department of Health and Human Services (DHHS) have selected certain combinations as preferred. A combination of 3 or more drugs of combined potency able to suppress viral replication is key (**Table 2**).

Table 2. Human immunodeficiency virus (HIV) drug regimens.

Always combine multiple agents

Usually two nRTIs along with:

- A single PI
- A PI enhanced with a low dose of a second PI, RTV
- An nnRTI
- One or 2 nRTIs

Abbreviations: nRTIs, nucleoside reverse transcriptase inhibitors; nnRTIs,non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; RTV, ritonavir

But nearly as important is the individualization of regimen choice in terms of convenience and side effects to improve the durability of clinical benefits and forestall nonadherence leading to drug resistance selection.[40,41]

The field of HIV medicine continues to evolve rapidly. Vigorous fundamental research is constantly opening new possibilities for effective drug development and new insights into drug resistance and toxicity. Lessons learned from this investment in HIV biology are increasingly applicable to other fields of medicine and the tools of this science are immediately applicable to even newer pathogens introduced into the human population.

II. The Hematologic Complications of HIV Infection

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Hematologic abnormalities are among the most common complications of infection with HIV.[1]

Anemia

Depending on the study setting, anemia can be found in 63%–95% of those with HIV infection at some point during the course of their disease.[2] Sullivan and colleagues in the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project reviewed the records of 32,867 HIV-infected individuals and reported that the incidence of anemia increased with the clinical stages of disease.[2] Three percent of those with HIV infection alone developed anemia at 1 year of follow-up, compared with 12% of those with immunologic AIDS (CD4 count less than 200/μL or CD4 percentage less than 14%) and 37% of those with clinical AIDS.[2] The presence of anemia in an HIV-infected patient is significantly associated with an increased risk of death, and this is independent of the CD4 count or viral load.[2,3] Conversely, recovery from anemia is associated with a decreased risk of death.[2]

A wide range of etiologic factors may cause anemia, but for the sake of this review, only those causes specific to HIV infection will be considered in detail. A more complete list of diagnostic possibilities is in **Table 3**. The most frequent cause of anemia in HIV-infected patients is anemia of chronic disease. CD34$^+$ stem cells express low levels of CD4 and CD11a, making them relatively resistant to direct infection by HIV. However, mononuclear-macrophage cells can develop

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productive HIV infection and the resultant release of cytokines, such as transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1), contribute to the suppression of hematopoiesis.[1] Although serum erythropoietin levels can be high in these patients, the elevation is blunted compared to patients with uncomplicated iron-deficiency anemia of comparable severity.[1,4]

Drug therapy for HIV infection or its subsequent complications is also a common cause of anemia. Zidovudine (AZT), the most notorious culprit, inhibits in vitro erythroid colony formation in a dose-dependent manner.[5] Severe anemia, defined either as a hemoglobin level of less than 7.5–8.0 grams per deciliter or anemia that requires transfusion, can be seen in 24% of those who receive AZT 1500 mg daily.[6] Although macrocytosis develops within weeks in most patients taking AZT and is a useful marker of compliance,[1] neither vitamin B_{12} or folinic acid are helpful in preventing AZT-induced myelotoxicity.[7] In fact, serum vitamin B12 levels are often low in HIV-infected patients, but only a few patients have true vitamin B_{12} deficiency, as indicated by elevated homocysteine and methylmalonic acid levels.[8]

Other drugs that cause anemia in AIDS patients include ganciclovir, which can induce marrow suppression and pancytopenia.[1] Amphotericin B may cause anemia by suppressing erythropoietin production,[9] but this is controversial.[10] Trimethoprim interferes with folate metabolism in erythroid cells, while sulfamethoxazole, dapsone, and primaquine can cause hemolysis in glucose-6-phosphate dehydrogenase (G6PD)–deficient individuals. Survival in G6PD-deficient patients is, however, not compromised despite putative oxidative stress on red cells produced by HIV infection.[11]

Human parvovirus B19, a small single-stranded DNA virus, can cause severe, chronic anemia in AIDS patients. The virus, usually acquired via the respiratory tract, invades erythroid progenitor cells via the blood group P antigen, and then replicates extensively, ultimately lysing the infected cell. Because of incompetent humoral immunity during advanced stages of HIV infection, patients are unable to generate neutralizing immunoglobulin (Ig) M or IgG antibodies; consequently, viremia persists unchecked. The result is pure red cell aplasia, with a block in erythroid maturation and characteristic giant pronormoblasts found in the bone marrow.[12] These findings are not universal,[13] however, so bone marrow aspiration should not be the cornerstone of diagnosis. Instead, the patient's serum should be assayed for parvovirus B19 DNA using dot blot hybridization or polymerase chain reaction (PCR) assays. According to data from the University of Washington, evidence of parvovirus B19 infection is found by dot blot hybridization in 17% of HIV-infected patients who have severe anemia.[13] Treatment consists of one or more courses of intravenous immunoglobulin therapy (400 mg/kg/day for 5 days)[12] in an attempt to provide the antibodies necessary to clear the infection, but this is not efficacious in all individuals.[14] Multiple recent case reports suggest that institution of highly active antiretroviral therapy (HAART), with subsequent recon-

Table 3. Anemia.

Decreased Production

- Drugs
  - Zidovudine
  - Trimethoprim-sulfamethoxazole
  - Amphotericin B
  - Ganciclovir
  - Dapsone
  - Delavirdine
- Deficiencies
  - Erythropoietin
  - Iron
  - Folate
  - Vitamin B12
  - Infection
    - HIV
    - Parvovirus B19
    - *Mycobacterium avium* complex (MAC)
    - *Mycobacterium tuberculosis*
    - *Histoplasma capsulatum*
- Neoplasia
  - Non-Hodgkin's lymphoma
  - Multiple myeloma
  - Castleman's disease
  - Hodgkin's disease
- Miscellaneous
  - Anemia of chronic disease
  - Preexisting condition (sickle cell disease, thalassemia, etc.)

Increased Loss

- Hemolysis
  - Thrombotic thrombocytopenic purpura
  - Glucose-6-phosphate dehydrogenase deficiency (trimethoprim-sulfamethoxazole [TMP-SMX], dapsone, primaquine)
  - Autoimmune hemolytic anemia
- Idiopathic
- Drugs (ceftriaxone, indinavir, "Ecstasy")
- Infection (cytomegalovirus [CMV])
- Gastrointestinal bleeding
  - Kaposi's sarcoma
  - Non-Hodgkin's lymphoma
  - Infection (CMV, *Candida*)
- Hypersplenism
  - Infection
  - Lymphoma
  - Hemophagocytosis
  - Cirrhosis (hepatitis B virus [HBV], hepatitis C virus [HCV])

stitution of the patient's humoral immunity, results in spontaneous clearance of parvovirus B19 infection.[15]

Mycobacterium avium complex (MAC), *Mycobacterium tuberculosis* (MTB), and *Histoplasma capsulatum* cause anemia in AIDS patients by infiltrating the marrow. Patients from the Mediterranean may also develop anemia as a result of infection with *Leishmania donovani*, whereas those from Southeast Asia and southern China are susceptible to *Penicillium marneffei* infection.[16] Bone marrow aspiration and biopsy provide evidence of infection in 25%–42% of patients tested.[16,17] Frequently, however, the diagnosis can be made equally rapidly and accurately using less-invasive modalities[18] such as lysis-centrifugation blood culture, serology, or nucleic acid hybridization. This is especially true for mycobacterial infections.[17,19] Bone marrow provides a unique diagnosis in only 10% of the procedures performed, and is more likely to be useful in patients with low CD4 counts or a hematocrit less than 25%.[16]

Surprisingly, autoimmune hemolytic anemia (AIHA) is not common in patients with HIV infection. Although the prevalence of a positive direct antiglobulin test (DAT) is high in this population, ranging from 18% to 43%,[20] only a few cases of HIV-associated AIHA have been reported.[21] DAT-positive patients generally have lower hemoglobin levels than DAT-negative patients.[20] This is, however, most likely because both the prevalence of DAT-positivity[20] and the severity of anemia[2] increase with more advanced stages of HIV infection. In the few cases of symptomatic autoimmune hemolytic anemia reported in HIV-positive patients, both warm and cold antibodies have been found, sometimes simultaneously.[22] Reticulocytopenia is sufficiently frequent in those with HIV infection that its presence cannot be used to exclude hemolysis. However, the patient's haptoglobin level is usually decreased, the lactate dehydrogenase level elevated, and the bone marrow normocellular with erythroid hyperplasia. Successful treatments have included corticosteroids, intravenous immunoglobulin, withdrawal of any offending drugs, and splenectomy.[22] Aggressive transfusion therapy should be undertaken with caution in HIV-associated AIHA, as fatal pulmonary embolization due to augmented hemolysis and disseminated intravascular coagulation has been reported.[23-25] Indinavir,[26] ceftriaxone,[27] and "Ecstasy"[28] have been reported to cause hemolytic anemia in HIV-infected patients. Rarely, cytomegalovirus (CMV) infection can also cause hemolysis.[29]

Fatigue, the cardinal symptom of anemia, is also the most common symptom of HIV infection and is responsible for impaired physical function and poor quality of life.[30] Numerous open-label and randomized, double-blind, placebo-controlled trials using a variety of regimens have found that the use of recombinant human erythropoietin in HIV-associated anemia frequently results in higher hemoglobin levels, fewer transfusions, and a better quality of life.[31,32] In an observational study at the Johns Hopkins HIV Clinic,[33] treatment of anemic patients with erythropoietin also resulted in a significantly reduced risk of death. In contrast, several studies have suggested that transfusion therapy, even early in the course of HIV infection, is associated with increased mortality.[33-35] Explanations for this include the following: transfusion-associated infection with agents such as CMV, hepatitis B and C, human T-cell lymphotropic virus (HTLV I/II), or parvovirus B19; transient activation of HIV expression; and transfusion-associated immunosuppression mediated by inflammatory cytokines that cause decreased lymphocyte, natural killer cell, and monocyte function.[1,36] However, a randomized, double-blind trial comparing the use of leukoreduced versus unmodified red blood cells in patients with advanced HIV infection found no evidence of HIV, CMV, or cytokine activation following transfusion. Furthermore, leukoreduction provided no clinical benefit and may have even worsened survival.[37] Excessive transfusion can cause iron overload, which may provoke HIV progression and increase susceptibility to infection with *Candida* species, *Pneumocystis carinii*, and *Mycobacterium* species by impairing macrophage function.[38]

Thrombocytopenia

An association between HIV and thrombocytopenia was first described in 1982.[39] A list of possible etiologies can be found in **Table 4**. The most common cause of this complication is now known to be immune thrombocytopenic purpura (ITP), which occurs in 30% or more of patients with AIDS.[40] While slightly more prevalent in those with advanced disease, ITP typically arises early in the course of HIV infection and can be seen before other manifestations of AIDS.[1] Unlike the usual form of ITP, HIV-associated ITP is more frequently seen in men than women, and is commonly associated with elevated levels of platelet-associated IgG, IgM, C3C4, and circulating immune complexes. These polyethylene glycol (PEG)-precipitable serum immune complexes contain high-affinity IgG directed against an 18 amino acid peptide sequence in platelet glycoprotein IIIa known as GPIIIa-(49-66).[41] This antibody may be induced by HIV glycoprotein 120 and then cross-react with platelet GPIIIa,[42] and can be found even in patients who are not thrombocytopenic.[40] In addition, patients with HIV have relatively increased numbers of $CD5^+$ B cells, which produce IgM rheumatoid factor directed against the Fc portion of IgG,[43] as well as IgM

Table 4. Thrombocytopenia.

Decreased Production

- Drugs
  - Trimethoprim-sulfamethoxazole
  - Pentamidine
  - Pyrimethamine
  - Ganciclovir
  - Fluconazole
  - Alpha-interferon
  - Rifabutin
  - Clarithromycin
  - Didanosine
  - Amphotericin B
  - Indinavir
  - Ritonavir
  - Delavirdine
  - Nelfinavir
- Deficiencies
  - Folate
  - Vitamin B_{12}
- Infection
  - HIV
  - Parvovirus B19
  - *Mycobacterium avium* complex (MAC)
  - *Mycobacterium tuberculosis*
  - *Histoplasma capsulatum*
  - *Bartonella henselae* (bacillary angiomatosis)
- Neoplasia
  - Non-Hodgkin's lymphoma
- Miscellaneous
  - Preexisting condition

Increased Loss

- Immune thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Hypersplenism
  - Infection
  - Hemophagocytosis
  - Cirrhosis
- Drugs
  - Saquinavir
  - Interferon

against the $F(ab')_2$ fragments of anti-GPIIIa-(49-66) antibodies.[44] The presence of this latter anti-idiotypic antibody has been correlated with higher platelet counts, suggesting that ITP arises in those whose dysfunctional immune systems can no longer generate sufficient antiidiotype antibody to neutralize circulating anti-GPIIIa-(49-66).[44]

Dominguez and coworkers[45] studied platelet kinetics in 41 HIV-infected thrombocytopenic patients and found that platelet survival was lower in those with CD4 counts above 200 cells/mL than in those with counts below this level, implying that platelet destruction is more important in patients with high CD4 counts, and decreased platelet production is more important in those with lower CD4 counts. Similar kinetic studies performed by Cole et al[46] concluded that HIV-infected patients have ineffective delivery of viable platelets to the peripheral circulation, despite a 6-fold elevation in thrombopoietin levels and a 3-fold expansion of megakaryocyte mass compared to normal controls. This finding suggests the possibility of HIV-induced apoptosis of megakaryocytes[47] and is compatible with the results of kinetic experiments, which found increased platelet turnover but no change in platelet survival following the initiation of zidovudine (AZT) therapy, indicating that platelet production had increased during treatment.[44] Megakaryocyte infection by HIV is supported by the following: denuded nuclei and ballooning of the peripheral zone of megakaryocyte cytoplasm have been observed by electron microscopy; internalization of HIV particles has been seen in coculture studies; the presence of the HIV p24 antigen has been shown by immunohistochemical techniques; and expression of HIV RNA has been found using in situ hybridization.[1] Marrow infiltration by infectious organisms or neoplasms, as well as adverse drug effects, can also cause impaired platelet production and thrombocytopenia.

Although 8% of patients with HIV-associated thrombocytopenia will have a hemorrhagic event,[48] treatment is usually not necessary unless the platelet count is below 30,000/μL or the patient is symptomatic. Patients with hemophilia or other coagulopathies should probably receive therapy when their platelet counts are below 50,000/μL because of their higher risk of bleeding.[1] As many as 18% of patients who have HIV-associated thrombocytopenia will undergo spontaneous remission.[49] In those who do not, therapy historically has consisted of institution of AZT.[1] Recent studies indicate that HAART is equally effective.[50-51]

Other treatment modalities specifically for HIV-associated ITP include glucocorticoids, intravenous IgG (IVIG), intravenous anti-D therapy, splenectomy, danazol, interferon, and vincristine. Glucocorticoids, typically prednisone 1 mg/kg daily, increase the platelet count in many patients; however, long-term use can result in Cushing's syndrome, an increased risk of fungal infection, and acceleration of the course of Kaposi's sarcoma.[1] Infusion of IVIG induces rapid but unsustained remissions in 71%–100% of HIV-infected patients,[52] but is costly and cumbersome to administer. Intravenous anti-D therapy is less expensive, but increases the platelet count above 50,000/μL in only 34% of patients treated.[53] Although the response to anti-D is longer than that seen with IVIG,[53] the extent of hemolysis in D^+ (Rh^+) patients is unpredictable. Patients with baseline hemoglobin levels above 12 g/dL are more likely to have a clinically important elevation of their platelet counts than those with anemia.[53] Splenectomy can also be successful and, despite early concerns, does

not obviously increase the risk of progression of HIV infection to symptomatic AIDS.[1] In fact, a long-term cohort study of 45 patients (17 had splenectomies and 28 did not) demonstrated a significant reduction in the risk of developing full-blown AIDS and a trend toward reduced mortality in splenectomized patients.[54] This may be due in part to a temporary reduction in plasma viremia and an increase in absolute CD4 and CD8 counts.[55] Splenic irradiation is of minimal benefit, resulting only in small increases in platelet counts for brief periods of time.[56]

Thrombotic microangiopathy (TMA) is also a well-recognized complication of HIV disease, seen in 1.4% of affected patients before the introduction of HAART.[57] Both hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) have been described. When compared to TTP, HUS is more likely to present at later stages of HIV disease, to be refractory to therapy, and to result in death. It is not known if HIV-associated TMA is provoked or potentiated by endothelial cell perturbation or damage, as by HIV itself, cytomegalovirus (CMV), inflammatory cytokines, or toxins produced by *Shigella dysenteriae* and *Escherichia coli* O157:H7.[58] In 2 cases of HIV-associated TTP studied thus far,[59,60] persistence of high-molecular-weight von Willebrand factor multimers (vWF) and complete deficiency of vWF-cleaving protease (ADAMTS-13) were found, but in only 1 case[59] was this due to a demonstrable IgG_1 inhibitor of ADAMTS-13. Therapy consists of plasma exchange. The response may be better in patients who have previously been splenectomized.[58] It is unclear currently whether HAART decreases the incidence of TTP or improves the response to therapy.

Neutropenia

Causes of low absolute neutrophil counts in HIV patients include inhibition of granulopoiesis by the virus itself, marrow infiltration by infectious organisms or neoplasia, adverse drug effects, autoimmune neutropenia, and hypersplenism.[1] A list of drugs most likely to cause neutropenia is in **Table 5**. Treatment of neutropenia includes initiation of antibiotic therapy for fever or other overt evidence of infection; antiretroviral therapy for individuals who have untreated HIV infection; withdrawal of potential offending drugs; and stimulation of myelopoiesis using either granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF).[1]

Thrombosis

Thrombosis reportedly occurs in up to 2% of HIV-infected patients. Factors associated with venous thromboembolic complications include age over 45 years, advanced stage of HIV infection, the presence of CMV or other AIDS-defining opportunistic infections, hospitalization, and therapy with indinavir or megestrol acetate.[61] The association between opportunistic infections and thrombosis may simply reflect immobility due to illness.[62] Alternatively, CMV may promote adhesion of neutrophils and platelets to the endothelium, induce production of antiphospholipid antibodies, enhance synthesis, and increase secretion and survival of factor VIII and von Willebrand factor.[63] Why indinavir would predispose to thrombosis is unclear,[61] but megestrol, like other progestational agents, may cause acquired resistance to activated protein C.[64]

In addition, individuals with HIV infection may be at increased risk for thrombosis because of decreased levels of antithrombin, free protein S, protein C, or heparin cofactor II; the presence of anticardiolipin antibodies; coexistence of malignant, inflammatory, or autoimmune disorders; or vascular damage due to injection drug use, placement of intravenous catheters, or CMV infection.[62] Antithrombin deficiency can occur in association with HIV nephropathy as a result of losses in the urine. The nephrotic syndrome seen in HIV neph-

Table 5. Neutropenia.

Decreased Production

- Drugs
  - Ganciclovir
  - Zidovudine
  - Trimethoprim-sulfamethoxazole
  - Pentamidine
  - Rifabutin
  - Antineoplastic chemotherapy
  - Dapsone
  - Amphotericin B
  - Ritonavir
  - Delavirdine
  - Nelfinavir
- Deficiencies
  - Folate
  - Vitamin B_{12}
- Infection
  - Human immunodeficiency virus (HIV)
  - *Mycobacterium avium* complex (MAC)
  - *Mycobacterium tuberculosis*
  - *Histoplasma capsulatum*
- Neoplasia
  - Non-Hodgkin's lymphoma
  - Multiple myeloma

Increased Loss

- Autoimmune neutropenia
- Hypersplenism
  - Infection
  - Hemophagocytosis
  - Cirrhosis

ropathy may also result in compensatory hepatic synthesis of factors V, VIII, and X induced by hypoalbuminemia, and increased platelet adhesion and aggregation.[65] Acquired protein S deficiency can be found in up to 75% of HIV-infected children and adults, especially in patients with CD4 counts below 200/μL or AIDS, resulting in thrombotic complications in as many as 12%.[66] Acquired free protein S deficiency in HIV is not caused by changes in levels or function of C4b-binding protein but rather by the appearance in some patients of antibodies against protein S.[67] The levels of free protein S antigen in HIV patients can appear artificially low when assayed by the PEG precipitation technique, so that the prevalence of protein S deficiency in HIV-positive patients may actually be lower than previously thought (about 10%).[68]

The lupus anticoagulant is found in 0%–70% of patients with HIV infection, depending on the sensitivity of the assay and the characteristics of the patients examined. Anticardiolipin antibodies are detected in 46%-90% of these patients.[69] Neither is strongly associated with an increased risk of venous thromboembolic complications in HIV,[1] but events such as multiple transient ischemic attacks and stroke, avascular necrosis of bone, skin necrosis, and brachial artery thrombosis have occasionally been described in patients with anticardiolipin antibodies.[69]

Hemophagocytic Syndrome

The hemophagocytic syndrome is an uncommon complication of HIV infection that is characterized by proliferation of histiocytes and phagocytosis of marrow blood cell precursors. It typically presents with fever, pancytopenia, lymphadenopathy, and splenomegaly. The syndrome may be the result of infection with HIV itself or may occur in association with Epstein-Barr virus (EBV), CMV, *Herpes simplex* virus, tuberculosis, human herpesvirus 8 (HHV-8), or parvovirus B19 infections. Hemophagocytosis may also complicate malignancies like T cell non-Hodgkin's lymphoma or Kaposi's sarcoma.[70]

III. AIDS-Related Lymphoma and Hodgkin's Disease

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Epidemiology of AIDS-Related Lymphoma

Lymphoma is a late manifestation of HIV infection, more likely to occur in the setting of significant immune suppression,[1] with CD4 cells below 200/mm^3, and prior history of an AIDS-defining illness. Following an earlier diagnosis of AIDS, the relative risk of immunoblastic lymphoma is increased approximately 627-fold, whereas that of diffuse large cell lymphoma is 145-fold higher than that expected in the general population.[2,3] Of interest, when linking cancer and AIDS registries, even low grade lymphoma was found to be increased 14-fold,[2,3] while the incidence of T-cell lymphoma is also increased among patients with AIDS.[4]

Highly active antiretroviral therapy (HAART) has resulted in a highly significant decline in mortality, and in development of new opportunistic infections, Kaposi's sarcoma, and primary central nervous system lymphoma among patients with AIDS.[5-7] While significant decreases in systemic AIDS-related lymphoma have also occurred, the decline is not as profound as that seen in other AIDS-defining conditions,[6,7] and lymphoma has now become one of the more common of the initial AIDS-defining illnesses.[7]

Genetic epidemiology of AIDS-related lymphoma

AIDS-related lymphoma, similar to lymphoma occurring in immunocompetent hosts, is more common in men than in women.[8] Although major environmental factors have not been associated with an increased risk for AIDS lymphoma,[9] genetic factors in the host may be operative. Heterozygotes for the Δ32 deletion of the CCR5 coreceptor gene are statistically less likely to develop lymphoma,[10] while those with SDF-1 mutations (3´A) are statistically more likely to develop lymphoma.[11]

Cytokine profile associated with AIDS lymphoma

The Multi-Center AIDS Cohort Study (MACS) evaluated the cytokine profile in serum of homosexual/bisexual men who went on to develop lymphoma within the next 6-month period.[12] Markers of activation, including soluble CD27, CD30, and CD44 were elevated when compared with HIV-positive controls who did not develop lymphoma. In addition, markers of isotype switching, including soluble CD23 and IgE, were elevated, as was serum interleukin (IL)-10, a marker of B-cell stimulation. Serum levels of immunoglobulin (Ig) M and IgG were decreased when compared with controls. In multivariate analysis, serum CD23, CD27, IgM, IgG, IgE, and IL10 were independently associated with lymphoma. While it is highly likely that lymphoma had already developed in these patients, who were formally diagnosed within 1 to 6 months after serum collection, it is of interest that a particular pattern of markers, related to B-cell activation, stimulation and isotype switching were consistently expressed. These markers may provide

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the ability to predict which HIV-infected patients are at increased risk for development of B-cell lymphoma.[12]

Prognostic factors in patients with systemic AIDS-related lymphoma

The factors associated with shorter survival in patients with AIDS-lymphoma include CD4 cells < 100/mm^3, stage III or IV disease, age > 35 years, history of injection drug use, and elevated LDH.[13] The International Prognostic Index (IPI) for aggressive lymphoma has also been validated in patients with AIDS-related lymphoma.[14]

Therapy of Patients with Systemic AIDS-Related Lymphoma

Standard versus low-dose chemotherapy

Prior to the development of HAART, phase II and III clinical trials demonstrated that low-dose chemotherapeutic regimens, such as mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), were as efficacious as standard dose regimens, but had the advantage of statistically decreased rates of hematologic and other toxicity.[15,16] With the addition of HAART to chemotherapy, standard dose therapy has become feasible and advantageous.

Use of concomitant HAART plus chemotherapy

The use of HAART, along with dose-reduced and standard-dose CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) was evaluated by the National Cancer Institute (NCI)-sponsored AIDS Malignancy Consortium in a group of 65 patients with newly diagnosed AIDS-lymphoma.[17] HAART therapy consisted of indinavir, stavudine, and lamivudine, the former of which is a protease inhibitor, while the latter 2 are nucleoside reverse transciptase inhibitors. Grade 3 or 4 neutropenia was more common among patients receiving full-dose CHOP (25% vs 12%), but there were similar numbers of patients with other toxicities. Doxorubicin clearance and indinavir concentration curves were similar in patients on this study when compared to historical controls. Cyclophosphamide clearance was decreased 1.5-fold when compared to controls, although there was no apparent clinical consequence of this change. The authors concluded that HAART could be administered safely with concomitant low-dose or standard-dose CHOP chemotherapy.[17] Caution should be used when using chemotherapy together with zidovudine, since this antiretroviral agent may cause significant bone marrow compromise in itself.[18]

Infusional cyclophosphamide, doxorubicin and etoposide

The 96-hour continuous infusion cyclophosphamide, doxorubicin, etoposide (CDE) regimen[19,20] has been tested in a large, multi-institutional ECOG trial of 107 patients, including 48 who were also given antiretroviral therapy with didanosine (ddI), and 59 who received HAART regimens.[19,20] For the group as a whole, the rate of complete remission was 44%, similar in patients who received either HAART or single agent didanosine. However, as has been described in the setting of other AIDS conditions, the median overall survival was significantly longer in AIDS lymphoma patients who received combination antiretroviral therapy. Thus, response rates to infusional CDE appear similar to those achieved with either low-dose or standard-dose m-BACOD, although survival is certainly superior in those patients who receive concomitant HAART.

Infusional, risk-adjusted EPOCH regimen

Wilson and his group at the NCI developed the dose-adjusted EPOCH regimen (**Table 6**), consisting of a 4-day infusion of etoposide, vincristine, and doxorubicin, with risk-adjusted bolus dosing of cyclophosphamide on day 5, and prednisone given orally on days 1 through 5 of each 22 day cycle.[21] Granulocyte colony-stimulating factor (G-CSF) was used uniformly, beginning at day 6, and intrathecal methotrexate was given at a dose of 12 mg on days 1 and 5 of cycles 3 through 6. Of interest, all antiretroviral therapy was withheld until day 6 of the last dose and last cycle of chemotherapy. A total of 39 patients was accrued, including 41% with CD4 cells < 101/mm^3, and 59% who had IPI scores of 2 or 3, indicating high-risk disease. A complete remission rate of 74% was achieved, including 56% in those with CD4 lymphocyte counts < 100/mm^3 and 87% among patients with CD4 lymphocyte counts > 100/mm^3. With a median follow up of 56 months, there have been only 2 relapses, and the disease-free survival is 92%. Overall survival at 56 months is 60%,

Table 6. EPOCH regimen of infusional chemotherapy.

- Etoposide 50 mg/m^2/day x 4 days
- Vincristine 0.4 mg/m^2/day x 4 days
- Doxorubicin 10 mg/m^2/day x 4 days
- Cyclophosphamide 187 mg/m^2 IV on day 5 for CD4$^+$ < 100 cells/mm^3 or 375 mg/m^2 IV on day 5 for CD4$^+$ >/= 100 cells/mm^3
- Prednisone 60 mg/m^2 orally, days 1-5
- Granulocyte colony-stimulating factor (G-CSF): start on day 6
- Repeat on day 22 times 6 cycles

while the overall survival of patients with CD4 cells > 100/mm^3 at entry is 87%. One controversial aspect of this regimen is the discontinuation of antiretroviral therapy until completion of all chemotherapy. In this regard, the median HIV viral load rose by 0.5 to 1 log over the first month of chemotherapy, but fell promptly to pre-EPOCH levels very quickly after reinstitution of HAART. Likewise, although CD4 lymphocyte counts fell by a median of 189 cells/mm^3 by the completion of cycle 6, the CD4s had returned to baseline levels by 12 to 18 months following completion of EPOCH. No new opportunistic infections (OIs) occurred during chemotherapy, although 3 patients developed OIs within the first 3 months of completion of EPOCH. During EPOCH, neutropenia (< 500 cells/mm^3) was evident in 30% of cycles, febrile neutropenia was seen in 13% of cycles, and 21% of cycles were associated with a platelet count < 50,000/mm^3.

Several biologic markers associated with prognosis in lymphoma were studied as part of this trial, and their impact upon prognosis was assessed. High MIB-1 activity (> 80%), associated with greater proliferative rate and poor prognosis in HIV-negative patients, was present in 85% of these HIV-positive individuals, but did not correlate with response or survival after EPOCH. Similarly, p53 expression, associated with poor prognosis in HIV-negative cases, was of no significance in terms of predicting survival in these EPOCH-treated patients. Bcl 2 expression, however, was predictive of shorter survival.

Most recent studies have demonstrated the advantage of combination antiretroviral and chemotherapy for AIDS-lymphoma, and there is no question that HAART has been associated with a remarkable prolongation in survival of these patients.[22,23] Thus, Antinori and colleagues demonstrated that virologic response to HAART was the only factor associated with improved rates of complete remission to CHOP or CHOP-like chemotherapy.[23] These data are in contrast to the NCI's results with EPOCH, in which outstanding rates of complete remission and long-term, disease-free survival were achieved, while purposely omitting HAART during chemotherapy.[21] The immediate reinstitution of HAART at the completion of chemotherapy is clearly an important aspect of this approach.

Value of Rituximab when Combined with CHOP Chemotherapy in AIDS-Lymphoma

The addition of rituximab to the CHOP regimen has been associated with statistically significant improvements in response and survival among elderly patients with de novo diffuse large B-cell lymphoma.[24] With these facts in mind, NCI sponsored the AIDS-Malignancy Consortium (NCI/AMC), which conducted a Phase III randomized trial of the standard CHOP regimen versus CHOP plus rituximab in a group of 151 patients with newly diagnosed AIDS-lymphoma.[25]

The regimens employed included cyclophosphamide (750 mg/m^2, IV on day 1); doxorubicin (50 mg/m^2, IV on day 1), vincristine (1.4 mg/m^2 IV on day 1, capped at 2.0 mg total), and prednisone, 100 mg orally from days 1 through 5. In patients randomized to R-CHOP, rituximab was given at a dose of 375 mg/m^2 on day 1 of each cycle, while the same doses of CHOP were begun on day 3 of each 21-day cycle. After attainment of CR, the R-CHOP patients also received 3 monthly doses of the antibody. Thus, a maximum of 9 to 11 doses of rituximab were given to R-CHOP treated patients. All patients were treated until achievement of complete remission, plus 2 additional cycles, or a minimum of 6 cycles of therapy. Antiretroviral therapy, filgrastim, and prophylaxis for *Pneumocystis* pneumonia were mandated. Meningeal prophylaxis was not routinely given.

The median CD4 cell count in the R-CHOP group was 128/mm^3, versus 154/mm^3 in the CHOP patients. Approximately half of the patients on each arm had received prior antiretroviral therapy including a protease inhibitor. Diffuse large B-cell lymphoma was present in 82% of the R-CHOP and 74% of the CHOP treated patients. Approximately 80% of both groups had stage III or IV disease.

Complete remission rates (including CR unconfirmed) were statistically similar, achieved in 57% of the R-CHOP patients and in 49% of those who received CHOP alone. Progression of lymphoma occurred in 7% of R-CHOP and 19% of CHOP patients.

Nineteen percent of R-CHOP patients were considered unevaluable, versus 5% of those who received CHOP, with unevaluable status primarily due to adverse events. Absolute neutrophil counts < 500/mm^3 occurred in 61% of R-CHOP versus 45% of CHOP patients (P = .07), and in 20% of R-CHOP cycles versus 15% of CHOP cycles (P = .11). Rates of febrile neutropenia were also similar, occurring in 30% of R-CHOP cycles and 21% of CHOP cycles (P = .86). Nonetheless, there was a significant increase in death due to infection in the R-CHOP group, occurring in 10% of R-CHOP patients versus 2% of the CHOP group (P = .027). Thus, 14 of the 15 patients who died of infection had been randomized to R-CHOP. Of note, the CD4 cell count was available on 13 of these individuals, and 8 (61%) had CD4 cells < 50/mm^3. Six (40%) of the 15 fatal infections occurred during the maintenance phase of rituximab, after completion of all chemotherapy. In contrast, death due to lymphoma occurred in 10% of the R-CHOP group versus 19.5% of CHOP treated patients.

The results of this study are somewhat difficult to interpret, especially in terms of the reported increase in infectious deaths in the patients treated with R-CHOP. The fact that over 60% of these deaths occurred in patients with CD4 cells < 50/mm^3 would indicate the possibility that this fatal complication was more related to the severe underlying immune deficiency[26] than to the use of rituximab per se. The fact that there was no statistically significant difference in the incidence of infection, or in the occurrence of neutropenic sepsis would also mandate a consideration of the myriad factors that may predict whether a neutropenic patient with sepsis actually dies. Nonetheless, it may be important to note that a maximum of 9 to 11 doses of Rituximab were given to R-CHOP treated patients. This is substantially greater than that given in other settings of R-CHOP,[24] and may have contributed to the findings.

The finding that R-CHOP was no more efficacious than CHOP alone in the AMC/NCI trial is also noteworthy. The R+ CHOP treated patients tended to have a higher CR rate than those treated with CHOP alone. Further, 19.5% of CHOP treated patients died of progressive lymphoma, versus 10% of those who received CHOP with rituximab. A recent Phase II French study of R-CHOP in patients with AIDS-lymphoma[27] reported a higher complete remission rate (77%) than that reported by the AMC/NCI (59%). Nonetheless, the majority (54%) of the French patients had low-risk IPI scores (0 or 1), and the study was therefore "driven" by the inclusion of these individuals. Further, the median CD4 cell count was relatively high (180/mm^3), and the median HIV viral load was relatively low (9236 copies/cc) in the French study. It is possible that the excellent results in the French R+ CHOP trial were due to the addition of rituximab to CHOP. Alternatively, these results may also be due to the fact that a relatively low-risk group of patients was enrolled. The French study was also smaller than that of the NCI/AMC, and was not randomized.[27]

It is clearly possible that rituximab does *not* improve the response rate of patients with AIDS-lymphoma, when added to the standard CHOP regimen. In this regard, Bcl-2 has been associated with poor prognosis in patients with aggressive B-cell lymphoma.[28] Bcl-2 expression is also important in determining response to R-CHOP in elderly HIV negative patients, with Bcl-2 positive cases more likely to benefit from addition of rituximab.[29] It is certainly possible that AIDS related aggressive lymphomas may be less likely to express Bcl-2, and thus less likely to benefit from the addition of rituximab. In this regard, Little and colleagues from the NCI have compared Bcl-2 expression in 25 HIV infected and 33 HIV negative patients with diffuse large B-cell lymphoma.[21] Bcl-2 was expressed in 16% of the AIDS related cases, and 41% of the *de novo* lymphomas. If these data hold true in larger series, one might expect that addition of rituximab would be less beneficial in the setting of AIDS-lymphoma, simply because Bcl-2 is less frequently expressed.

A full understanding of the results of the current AMC/NCI trial will require further elucidation of Bcl-2 status of these patients, and further detailed analysis of the factors associated with infectious death among the R-CHOP treated patients.

Use of CNS prophylaxis in patients with systemic AIDS-lymphoma

No prospective, randomized study has yet addressed the issue of CNS prophylaxis in patients with AIDS-lymphoma. However, the risk of leptomeningeal (cerebrospinal [CSF]) relapse is a real one in this setting, reported in approximately 15-20% of patients, and more likely to occur in patients with bone marrow involvement. The majority of trials in the US have included intrathecal chemotherapy (methotrexate or cytosine arabinoside), given a total of 4 to 6 times during induction chemotherapy.[15,16,21] In the recent NCI trial of dose adjusted infusional EPOCH, CNS prophylaxis was added to the last 17 patients, after late CSF relapse occurred in earlier patients who did not receive such therapy.[21] Involvement of the CNS is an independent predictor of poor prognosis in patients with systemic AIDS-lymphoma.[21]

Therapy of patients with relapsed or primary resistant AIDS-lymphoma

Treatment options for patients with relapsed or refractory AIDS-lymphoma are limited. The infusional CDE regimen has been associated with a complete remission rate of 4% in a group of 24 patients with relapsed/refractory disease, and a median survival of 2 months.[30] A regimen consisting of etoposide, prednimustine, and mitoxantrone resulted in complete response in 8 (38%) of 21 patients but a median survival of only 2 months.[31] While associated with uniform grade 4 neutropenia, the ESHAP regimen, when given to 13 patients with relapsed or refractory AIDS-lymphoma, led to complete remission in 31%, overall response in 54%, and median survival of 7.1 months from the time of ESHAP.[32] High-dose chemotherapy, followed by autologous stem cell rescue has been efficacious in patients with relapsed/refractory AIDS-lymphoma, with complete remission rates and toxicity profiles similar to that seen in HIV negative patients, provided that effective antiretroviral therapy is also employed.[33]

Primary effusion lymphomas

Primary effusion lymphoma (PEL) is an aggressive B-cell lymphoma, usually confined to body cavities, which occurs primarily, but not exclusively, in HIV-infected patients.[34,35] Patients with HIV-associated PEL tend to be homosexual/bisexual males, with severe immunosuppression. PEL is caused by a gamma 2 herpesvirus termed Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8).[34] HHV-8 is also the cause of Kaposi sarcoma, from which it was first isolated.[36]

The malignant cells in PEL are large and pleomorphic, and may resemble Reed Sternberg cells, although they are CD15 negative. Phenotypically, the cells stain for leukocyte common antigen CD45 and various activation antigens (HLA-DR, EMA, CD30, CD38, CD77), but are usually negative for other B- and T-cell markers including CD20 and CD19. The B-cell nature can be demonstrated by the presence of immunoglobulin gene rearrangements by Southern blot or PCR. The malignant cells in PEL are derived from postfollicular B cells, which harbor somatic hypermutations of the immunoglobulin genes. The pathogenesis of PEL is of interest, since HHV-8 carries a number of oncogenic sequences including a Bcl-2 like sequence, a G-coupled receptor, and a type D cyclin similar to PRAD1.[37] The virus also produces cytokines such as viral IL-6, capable of contributing to angiogenesis and tumor cell growth.[38]

Patients with PEL classically present with symptoms and signs of an effusion (pleural, pericardial, or ascitic) in the absence of a tumor mass. Extension to adjacent structures such as the chest wall, pleura, or peritoneum may also occur. Rarely, PEL may be diagnosed in the absence of an effusion, either at diagnosis or during the course of disease. With standard CHOP chemotherapy, median survival has been in the range of only 60 days.[34] Several case reports have documented the successful use of HAART, either with[39] or without[40] antiherpetic therapy. While the PEL cells do not classically express CD20, a case of pathologically confirmed complete remission of PEL after HAART and rituxan has also been described.[41]

Castleman's disease in the setting of HIV infection

Multicentric Castleman's disease (MCD) is a polyclonal lymphoproliferative disorder characterized by recurrent fevers, lymphadenopathy, hepatosplenomegaly, and autoimmune phenomena, which often progresses to malignant lymphoma. The plasma cell variant of MCD has been described in the setting of underlying HIV infection, and appears to be associated with HHV-8 infection, with a high degree of HHV-8 lytic gene activity and high-titer viremia.[42] While cidofovir and ganciclovir have been effective against HHV-8 in vitro, cidofovir was shown to be ineffective when used in patients with AIDS-KS.[43] Nonetheless, AIDS patients receiving ganciclovir for cytomegalovirus retinitis had a 40% reduction in the risk of developing KS over time, suggesting that antiherpetic therapy may be of some clinical value in HHV8 related diseases.[44] The optimal therapy of HIV associated MCD is unknown. Recently, Casper and colleagues demonstrated the efficacy of ganciclovir (5 mg/kg twice daily for 1 week, and then once daily) given to 3 HIV infected patients with MCD.[45] Rituximab has also shown activity in this setting, with complete remission attained in 4 of 6 such patients.[46] Of interest, splenectomy has also been efficacious in HIV-infected patients with MCD, associated with resolution of fevers, and improvement in anemia.[47] Long-lasting remission was described in 8 of 10 such patients, after receipt of both splenectomy and HAART.[47]

Hodgkin's disease in the setting of HIV infection

While not considered an AIDS-defining illness, the incidence of Hodgkin's disease (HD) is clearly increased among HIV-infected individuals.[48] Unusual clinical and pathologic characteristics of HD have been described in this setting. Thus, systemic "B" symptoms are almost always present, mixed cellularity HD is the predominant pathologic subtype of disease, and advanced, extranodal disease is expected in the majority.[48] Bone marrow involvement has been documented in 40% to 60% of patients at initial diagnosis, and patients often undergo the initial diagnostic bone marrow examination for the evaluation of fever of unknown origin in the setting of HIV infection and pancytopenia. While standard multiagent chemotherapy may be curative in most HIV negative patients with stage III or IV HD, the median survival for HIV infected patients has been in the range of 1 to 2 years.[48] Standard-dose ABVD with hematopoietic growth factor support was evaluated in a multi-institutional trial of 21 HIV infected patients.[49] Antiretroviral therapy was not used. Neutropenia (< 500 cells/mm^3) developed in almost 50%, and median survival for the group was only 18 months. It is possible that results would have improved with concomitant use of highly active antiretroviral therapy (HAART), as was demonstrated with the Stanford V regimen, employed in 59 HIV infected patients from Italy.[50] In this study, complete remission was attained in 81%, and 56% of these (i.e., 45% of all patients treated) are estimated to remain disease-free at a median follow-up interval of 33 months.[50] Grade 3 or 4 neutropenia occurred in 78%, despite use of G-CSF. Further work will be required to define the optimal therapy for such patients.

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