A PUBLICATION OF THE INTERNATIONAL AIDS SOCIETY–USA

IMPROVING THE MANAGEMENT OF HIV DISEASE®

VOLUME 6 ISSUE 2 JUNE 1998

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Recent Advances In

Drug-Drug Interactions in the HIV-infected Patient

HIV Resistance to Antiretroviral Drugs

Plus

Reprint: Clinical Guidelines for the Treatment of CMV Infection

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ABOUT THIS ISSUE...

This issue of *Improving the Management of HIV Disease*, the first developed from the International AIDS Society-USA antiretroviral therapy CME courses this year, highlights talks on two topics of increasing importance in HIV disease management: drug-drug interactions and the development and evaluation of viral resistance to antiretroviral drugs.

The review of various interactions among drugs taken by people with HIV infection summarizes data presented by Dr Charles W. Flexner at the course in Atlanta on February 13. The summary covers basic pharmacology of HIV therapies as well as strategies for how to avoid or capitalize on drug-drug interactions. The second article summarizes a discussion of the various issues raised by the emergence of resistance to antiretroviral drugs, based on Dr Victoria A. Johnson's lecture in Atlanta. Concerns regarding the evaluation of resistance and its impact on therapeutic options are addressed.

In addition, included in this issue is a reprint of clinical recommendations for the treatment of CMV infection, developed by an International AIDS Society-USA-appointed panel and originally published in *Archives of Internal Medicine* in May. The 17-member panel, representing international expertise in the management and biology of HIV-related CMV diseases, was convened to address the shifting realities of CMV manifestations in the era of potent antiretroviral therapy. The recommendations cover a wide range of issues from initial treatment options to tailoring specific patient regimens.

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Reprint

Guidelines for the Treatment of Cytomegalovirus Diseases in Patients With AIDS in the Era of Potent Antiretroviral Therapy . . . . . **Insert**
Recommendations of an International Panel.
Richard J. Whitley, MD; Mark A. Jacobson, MD; Dorothy N. Friedberg, MD, PhD; Gary N. Holland, MD; Douglas A. Jabs, MD; Douglas T. Dieterich, MD; W. David Hardy, MD; Michael A. Polis, MD, MPH; Thomas A. Deutsch, MD; Judith Feinberg, MD; Stephen A. Spector, MD; Sharon Walmsley, MD, FRCPC; W. Lawrence Drew, MD, PhD; William G. Powderly, MD; Paul D. Griffiths, MD; Constance A. Benson, MD; Harold A. Kessler, MD; for the International AIDS Society-USA
Arch Intern Med. *1998; 158: 957-969.*

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Drug-Drug Interactions in the HIV-Infected Patient

The issue of potential drug-drug interactions in HIV disease management was addressed at the Atlanta course by Charles W. Flexner, MD, from The Johns Hopkins University, in Baltimore, Maryland. Dr Flexner reviewed the definitions and mechanisms of inhibitors and inducers, discussed selected specific metabolic drug interactions, highlighted new information, and described some strategies in which some drug-drug interactions can be exploited to benefit HIV disease management.

Polypharmacy is a growing complication in HIV disease management. As the number of available drugs continues to increase, patients and physicians must deal with increasingly complex regimens and the increased risk of adverse drug interactions. The approved HIV protease inhibitors (saquinavir, ritonavir, indinavir, and nelfinavir) and the nonnucleoside reverse transcriptase inhibitors (NNRTIs; nevirapine and delavirdine) are especially susceptible to pharmacokinetic drug-drug interactions.

All of the protease inhibitors and NNRTIs are substrates for cytochrome P450 drug metabolizing enzymes, and primarily the 3A4 isoform. The four approved protease inhibitors are also inhibitors of cytochrome P450 3A4. Ritonavir is by far the most potent inhibitor; nelfinavir and indinavir have intermediate potency; and saquinavir is the least potent inhibitor. The new soft gel capsule formulation of saquinavir results in higher drug concentrations, with additional potential for drug interactions. Delavirdine is a modest competitive inhibitor of the metabolism of some P450 substrates. Nelfinavir, nevirapine, and ritonavir are modest hepatic enzyme inducers.

Basic Pharmacology

A P450 substrate is any drug whose metabolism or biotransformation (chemical oxidation or reduction) is catalyzed by enzymes (isoforms) in the cytochrome P450 family. These enzymes are called cytochromes because they contain a reactive metal ion (in this case iron) that serves as the ultimate electronic acceptor or donor in these chemical reactions.

There are at least 25 different cytochrome P450 isozymes in humans, but only a few of these enzymes are involved in drug metabolism. The 3A4 cytochrome is the major isoform in HIV drug metabolism to date.

Inhibition

A P450 inhibitor is any drug that inhibits the metabolism or biotransformation of another drug catalyzed by enzymes in the cytochrome P450 family. Like most enzyme inhibition, P450 inhibition is competitive and reversible; once the inhibitor is withdrawn, the inhibition stops.

Ritonavir and delavirdine are P450 inhibitors that have very different effects on other drugs that are metabolized by these same enzymes. The inhibitory effects on selected drugs used in HIV infection are listed in Table 1. Delavirdine does not significantly affect ritonavir pharmacokinetics, but a dose adjustment of ritonavir may be required when it is combined with indinavir or saquinavir.

Unfortunately, it is not possible to precisely predict the magnitude of effect of one P450 inhibitor on another P450 substrate. It will be necessary to assess the individual effects in clinical studies.

There has been controversy about the role of grapefruit juice as an inhibitor of drug metabolism. Grapefruit juice contains a flavonoid, the complex

Table 1. Selected P450 Enzyme Inhibitors

Ritonavir	*increases*	rifabutin AUC by 350% 25-desacetyl rifabutin AUC by 3500% clarithromycin AUC by 77% trimethoprim AUC by 20%
Delavirdine	*increases*	indinavir AUC by 50% saquinavir trough (C_{min}) by 560%
Amprenavir	*increases*	rifabutin trough, (C_{min}) by 3- to 6-fold erythromycin AUC by the same amount as ketoconazole (270% increase in unmetabolized erythromycin)
Efavirenz	*increases*	nelfinavir AUC by 20%

AUC indicates area under the curve.

Table 2. Selected Agents Involved in Potentially Serious Drug-Drug Interactions With Protease Inhibitors

- Terfenadine, astemizole, cisapride
- Ergot alkaloids
- Midazolam, triazolam
- 3,4-methylenedioxymethamphetamine* (MDMA; also known as Ecstasy)

*Anecdotal evidence

molecule naringenin, which is a potent cytochrome P450 inhibitor. Grapefruit juice increases the saquinavir area under the curve (AUC) by approximately 2-fold to 3-fold, similar to the magnitude of effect of ketoconazole or erythromycin on saquinavir, but not nearly the magnitude of effect that ritonavir has on saquinavir.

Grapefruit juice increases the saquinavir AUC by 2-fold to 3-fold, similar to the magnitude of effect of ketoconazole or erythromycin on the drug

The interaction is likely to involve the intestinal and hepatic cytochrome P450 3A4 systems; drugs can be metabolized by cytochrome P450 in the intestinal tract before they reach the liver.

There is one case of death reported in the literature that is possibly linked with this effect. After taking terfenadine and drinking large quantities of grapefruit juice, a man died suddenly and without explanation while mowing his lawn. However, the patient was also alcohol dependent and had a cardiomyopathy. Staggering the grapefruit juice and the drug is being considered as a way to reduce this interaction. According to Dr Flexner, it is conceivable that having patients who drink grapefruit juice wait for some period of time (eg, 2 hours) before taking saquinavir or indinavir might avoid this interaction, but the issue requires further study.

There are several agents that are involved in potentially serious metabolic drug interactions (Table 2). The use of these drugs should be avoided by patients taking P450 inhibitors, including HIV protease inhibitors and delavirdine.

Induction

A P450 inducer is a drug that causes increased production of enzymes responsible for the metabolism or biotransformation of another drug. In contrast to inhibition, induction reduces rather than increases drug concentrations. The inducer acts directly as a transcriptional transactivator, binding directly to regulatory regions in the DNA upstream from the genes that encode the drug-metabolizing enzymes and increasing transcription of those genes. Because the process of induction has a functional half-life of approximately 3 days, the effect is not immediately reversible when the drug is withdrawn. It takes approximately 2 weeks before enzyme levels return to pre-drug administration levels after stopping an inducer.

Table 3 lists the induction effects associated with selected drugs. Ethinyl estradiol, a synthetic estrogen component in most oral contraceptives, and zidovudine are metabolized by different pathways. Ethinyl estradiol is metabolized via cytochrome P450, and zidovudine is metabolized through hepatic glucuronyl transferase. Because ritonavir is a more ubiquitous molecular promoter/inducer, it has about the same effect on both drugs. Ritonavir increases P450 drug metabolism and increases other drug metabolizing enzymes in the liver.

While the inhibitors have a broad variety of effects on other drugs, the inducers have a predictable and consistent magnitude of effect for any given enzyme. Also, an inducer may exert an effect on more than one class of enzymes, such as P450 enzymes and glucuronyl transferases affected by ritonavir.

Dr Flexner and colleagues studied the relative effect of rifampin and rifabutin on the pharmacokinetics of oral contraceptives containing ethinyl estradiol and norethindrone. As P450 inducers, rifampin and rifabutin can accelerate clearance of both components.

Table 3. Selected P450 Enzyme Inducers

Ritonavir	*reduces*	ethinyl estradiol AUC by 40% zidovudine AUC by 25% theophylline AUC by 43%
Nevirapine	*reduces*	indinavir AUC by 28% saquinavir-HGC AUC by 27%
Efavirenz	*reduces*	amprenavir AUC by 26% saquinavir-SGC AUC by 60%

AUC indicates area under the curve; HGC indicates hard gel capsule.

There have been anecdotal reports of unplanned pregnancies in oral contraceptive users who were taking rifampin. In a randomized, double-blind, placebo-controlled, cross-over trial with 12 women, administration of rifampin decreased the ethinyl estradiol AUC by 64%, compared with 34% for rifabutin. Administration of rifampin decreased the norethindrone AUC by 49% compared with a reduction of 12% for rifabutin. Despite this substantial pharmacokinetic effect, ovulation was still fully suppressed in all 12 women taking either drug in combination with their oral contraceptives. Thus, a statistically significant pharmacokinetic interaction may not always result in clinically significant consequences.

New Issues in Drug Interactions

Recently presented data indicate that efavirenz (DMP 266), an investigational NNRTI, and amprenavir (VX-478), an investigational protease inhibitor, have the potential to be involved in some clinically significant drug interactions. Efavirenz appears to be both a modest P450 inhibitor and inducer, and amprenavir is a modest P450 inhibitor (Tables 1 and 3).

Strategies for Avoiding or Capitalizing On Drug Interactions

In the future, based on a better understanding of pharmacology, new drugs that avoid interactions will likely be developed, and new combinations that take advantage of drug interactions, or that circumvent interactions, may be utilized.

Combined drug administration may take advantage of beneficial pharmacokinetic drug interactions, improving bioavailability and allowing less frequent drug administration

For example, fexofenadine is a nonsedating antihistamine that was developed to avoid drug interactions. A dose of terfenadine is almost immediately converted in the liver to fexofenadine. Giving fexofenadine directly avoids the cardiac arrhythmias associated with terfenadine, the parent compound. If terfenadine is combined with a P450 inhibitor, conversion to fexofenadine is blocked and terfenadine concentrations increase, in some cases causing sudden death. Fexofenadine is the active metabolite of terfenadine. This metabolite is orally bioavailable and is not cardiotoxic. It is also clinically effective, and it is not apparently susceptible to adverse drug interactions.

Combined drug administration may take advantage of beneficial pharmacokinetic drug interactions. Benefits include improving bioavailability through inhibition of first-pass metabolism, reducing clearance to allow less frequent drug administration, increasing concentrations of active drug metabolites, and displacing highly protein-bound drugs from plasma protein binding sites. Treatment regimens employing dual protease inhibitor combinations may take advantage of such interactions and are currently under investigation.

The figure illustrates the pharmacokinetic enhancement of the indinavir

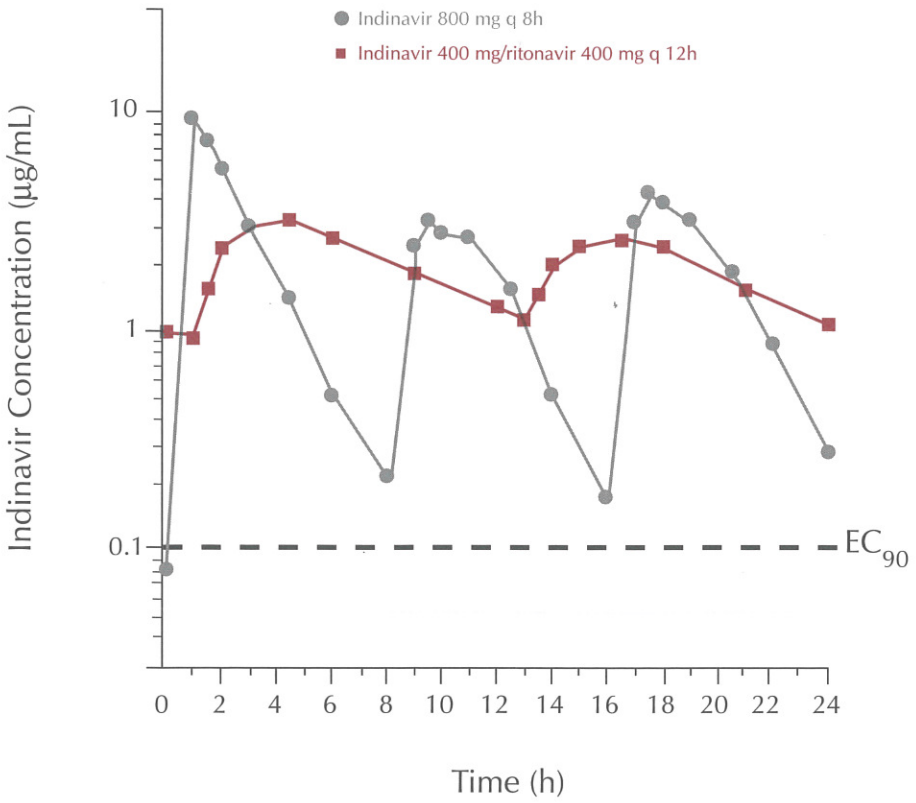

Figure. *Steady-state indinavir plasma profile.* ***Gray*** *line indicates administration of indinavir 800 mg every 8 hours under fasting conditions.* ***Red*** *line indicates administration of indinavir 400 mg/ritonavir 400 mg every 12 hours taken with regular meals. Adapted and used with permission from Abbott Laboratories.*

800 mg every-8-hours concentration time profile by combining it with ritonavir. A reduced dose of indinavir (400 mg every 12 hours) combined with ritonavir 400 mg every 12 hours results in a 10-fold increase in the trough concentration of indinavir during a 24-hour dosing interval. A reduction in the indinavir peak concentration may be advantageous with respect to the formation of kidney stones, although further study is required. This combination may have the advantages of improved convenience and relative cost-effectiveness.

The combination ritonavir/saquinavir is currently the most well-studied dual protease inhibitor regimen, and it has been suggested that the combination has two-dimensional synergy. Dr Flexner presented information on nelfinavir/ritonavir, which he noted to have the potential for three-dimensional synergy. The drugs select nonoverlapping primary resistance mutations and have a beneficial pharmacokinetic interaction. Nelfinavir, unlike the other protease inhibitors, makes an active metabolite, M-8, which in vitro appears to have antiretroviral activity similar to nelfinavir. Ritonavir may inhibit M-8 clearance to a greater extent than it does nelfinavir clearance. Finally, both drugs are highly protein-bound, especially to alpha-1 acid glycoprotein; one drug may displace the other from its protein binding sites and transiently increase free-drug concentrations.

Preliminary data from studies with ritonavir 400 mg twice daily/nelfinavir 500 or 750 mg twice daily in patients who are protease inhibitor-naive show an approximate 100- to 1000-fold drop in plasma HIV RNA levels. Most patients had added nucleoside reverse transcriptase inhibitors (nRTIs) to their regimens at 16 weeks of therapy in order to achieve plasma HIV RNA levels below the 20 copies/mL threshold. In contrast, fewer patients taking ritonavir/saquinavir added nRTIs to achieve plasma HIV RNA levels below the 50 copies/mL limit.

Summary

Clearly, the potential for dangerous drug interactions exists in patients taking anti-HIV medications. However, as noted by Dr Flexner, the chemical and pharmacologic principles involved are simple, only a few pharmacokinetic drug interactions are clinically significant, and some of these interactions may be clinically advantageous.

Charles W. Flexner, MD, is Associate Professor of Medicine and Pharmacology at The Johns Hopkins University in Baltimore, Maryland.

Suggested Reading

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HIV Resistance to Antiretroviral Drugs

Eleven antiretroviral drugs, representing 3 drug classes, are presently commercially available in the US for the treatment of HIV infection. Viral resistance to the drugs was quickly recognized as these compounds became widely used. HIV resistance now constitutes a major challenge to any drug's or regimen's ability to produce durable suppression of viral replication. Knowledge of the issues regarding the prevention and recognition of viral resistance is therefore central to the clinician's decisions about antiretroviral therapy. At the Atlanta Meeting in February, Victoria A. Johnson, MD, summarized the current understanding of viral resistance to antiretroviral drugs.

Cause of Antiretroviral Failures

Dr Johnson began with a simple clinical question: Why do drugs used to treat HIV fail? Many of the available antiretroviral drugs have potent activity in vitro and are capable of suppressing HIV replication in simple systems, but treatment failure can occur in vivo for a number of reasons (Table 1). First, drug treatment may not completely suppress viral replication in all tissues and cells. Even with optimal drug administration and pharmacokinetics, protected cellular microenvironments exist in certain sites such as macrophages, follicular dendritic cells, and cells in the central nervous system. Antiretroviral drugs do not have an optimal effect in all tissues, and although the total body viral burden may decrease with treatment by 3 or 4 log (eg, from 10^{12} to 10^{8} copies/mL). HIV replication may continue in selected microenvironments. Secondly, drug failure can be associated with poor adherence to a regimen. Less than strict adherence can allow ongoing viral replication, which can result in the evolution of drug-resistant virus. The complicated, multi-drug regimens now in use make strict adherence difficult. Two other reasons for drug treatment failure include emergence of more virulent, rapidly replicating forms of viruses, and perturbations or defects in host cell metabolism (and activation) of antiretroviral drugs. Lastly, mutant viruses can emerge that have a lower susceptibility to the antiretroviral effect of a particular drug or drug class. Dr Johnson focused her presentation on this latter issue.

Table 1. Reasons for Drug Failure

- Incomplete suppression of HIV replication
- Patient nonadherence to antiretroviral therapy
- Emergence of virulent HIV sub-types
- Altered host cell drug metabolism
- Viral resistance to antiretroviral drugs

Mechanisms of Viral Resistance

Landmark studies of the kinetics of HIV replication during the chronic, steady-state phase of HIV infection showed that although plasma HIV RNA levels and CD4+ cell numbers appear to be quite stable and constant, there is in fact a very high rate of viral replication and lymphocyte turnover. This high rate of replication results in a higher frequency of mutations, some of which can affect the susceptibility to antiretroviral drugs. Because of the high replication rate of HIV and the relatively high error (mutation) rate associated with the HIV reverse transcriptase (RT), single and sometimes double mutations that encode for viral resistance frequently preexist in a large population of virions (eg, exist prior to exposure to that drug). The use of an antiretroviral drug that only partially suppresses viral replication results in inhibition of only the HIV that is susceptible to the drug; drug-resistant variants continue to emerge and

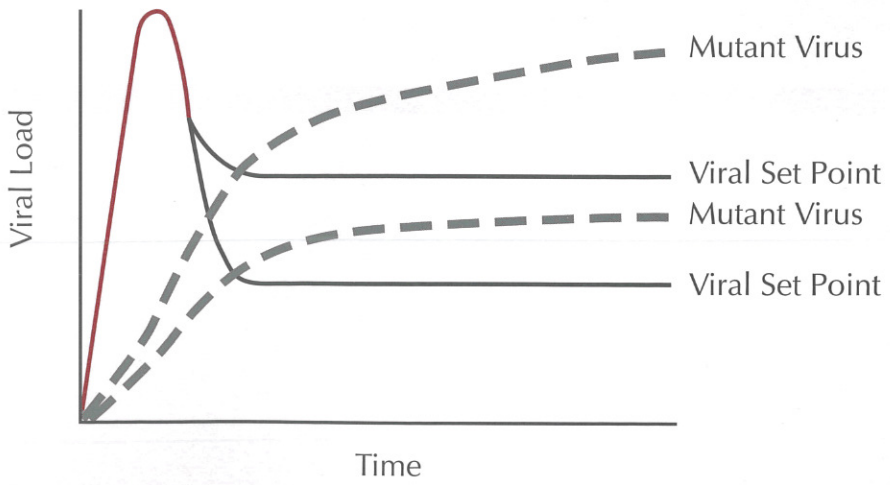

Figure 1. *Relationship between rate of viral replication and prevalence of resistance mutations. Those patients with a higher set point have a higher rate of replication and more mutant virus. Adapted in part from Ho DD.* Science. *1996;272:1124; and Coffin JM.* Science. *1995;267:483.*

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SPECIAL ARTICLE

Guidelines for the Treatment of Cytomegalovirus Diseases in Patients With AIDS in the Era of Potent Antiretroviral Therapy

Recommendations of an International Panel

Richard J. Whitley, MD; Mark A. Jacobson, MD; Dorothy N. Friedberg, MD, PhD; Gary N. Holland, MD; Douglas A. Jabs, MD; Douglas T. Dieterich, MD; W. David Hardy, MD; Michael A. Polis, MD, MPH; Thomas A. Deutsch, MD; Judith Feinberg, MD; Stephen A. Spector, MD; Sharon Walmsley, MD, FRCPC; W. Lawrence Drew, MD, PhD; William G. Powderly, MD; Paul D. Griffiths, MD; Constance A. Benson, MD; Harold A. Kessler, MD; for the International AIDS Society–USA

Objective: To provide recommendations for the treatment of acquired immunodeficiency syndrome–related cytomegalovirus (CMV) end-organ diseases, including retinitis, colitis, pneumonitis, and neurologic diseases.

Participants: A 17-member panel of physicians with expertise in clinical and virological research and inpatient care in the field of CMV diseases.

Evidence: Available clinical and virological study results. Recommendations are rated according to the quality and strength of available evidence. Recommendations were limited to the treatment of CMV diseases; prophylaxis recommendations are not included.

Process: The panel was convened in February 1997 and met regularly through November 1997. Subgroups of the panel summarized and presented available information on specific topics to the full panel; recommendations and ratings were determined by group consensus.

Conclusions: Although the epidemiological features of CMV diseases are changing in the setting of potent, combination antiretroviral therapy, continued attention must be paid to CMV diseases in patients infected with the human immunodeficiency virus to prevent irreversible end-organ dysfunction. The initial and maintenance treatment of CMV retinitis must be individualized based on the characteristics of the lesions, including location and extent, specific patient factors, and characteristics of available therapies among others. Management of relapse or refractory retinitis must be likewise individualized. Ophthalmologic screening for patients at high risk for retinitis or who have a prior diagnosis of extraretinal disease is recommended. Recommendations for gastrointestinal, pulmonary, and neurologic manifestations are included.

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CYTOMEGALOVIRUS (CMV) is a common opportunistic pathogen among individuals infected with the human immunodeficiency virus (HIV) and often results in end-organ diseases such as retinitis, colitis, and encephalitis. The recent availability of several new modalities of therapy for CMV disease provides a number of appropriate treatment options.

Recent data have documented the profound impact of the increased use of potent, combination antiretroviral therapy on the natural history of HIV infection. In addition to suppressing plasma HIV viral load and increasing $CD4^+$ lymphocyte counts ($CD4^+$ cells), use of the newer therapies has been associated with decreased hospitalizations, decreased incidence of associated opportunistic infections, and increased survival. While the short-term clinical impact of potent antiretroviral therapies on HIV infection and the incidence of associated established opportunistic diseases is clear, the impact of modulating established opportunistic infections, including CMV diseases, is less clear. Preliminary data challenging the tenet that CMV retinitis requires active therapy for the life of the patient have recently been reported in the context of potent antiretroviral therapy.[1-4]

A panel of physicians with expertise in clinical investigation, virological research, and patient care in the field of HIV-related CMV diseases was convened by the International AIDS Society–USA, San Francisco, Calif. The panel reviewed available data and developed recommendations for the treatment of CMV disease in patients

Authors' affiliations are listed in the Acknowledgment section on page 967.

This article is also available on our Web site: www.ama-assn.org/internal.

Table 1. Levels of the Strength and Quality of Evidence Considered*

Categories of the Strength of a Recommendation
(A) Strong evidence of efficacy and substantial clinical benefit support recommendation for use; should always be offered
(B) Moderate evidence of efficacy or strong evidence of efficacy, but only limited clinical benefit supports recommendation for use; should generally be offered
(C) Evidence of efficacy is insufficient to support a recommendation for or against use or evidence of efficacy may not outweigh adverse consequences, such as toxic effects, drug interactions, or cost of the chemoprophylaxis or alternative approaches; optional
(D) Moderate evidence of lack of efficacy or of adverse outcome supports a recommendation against use; should generally not be offered
(E) Good evidence of lack of efficacy or of adverse outcome supports a recommendation against use; should never be offered
Categories Reflecting Quality of Evidence
(I) Evidence from at least 1 properly randomized controlled trial
(II) Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, or from multiple time-series studies, or dramatic results from uncontrolled experiments
(III) Evidence from opinions of the panel

**Recommendations were rated according to the strength and quality of available evidence. The categories have been adapted from Gross et al.[6]*

with the acquired immunodeficiency syndrome (AIDS). The recommendations of the panel focus on the diagnosis and treatment of CMV manifestations. Detailed recommendations for primary prevention of CMV diseases appear elsewhere.[5] The recommendations are rated according to the strength and quality of supporting evidence presented herein, using a system similar to that developed by the US Public Health Service/Infectious Diseases Society of America[6] (**Table 1**). The goal of this report is to assist clinicians in choosing the most appropriate treatment of HIV-related CMV diseases.

Cytomegalovirus end-organ disease has been shown to occur in approximately 20% to 40% of patients with AIDS. People who are HIV-infected and CMV-seropositive who have $CD4^+$ cell counts below 0.05×10^9/L (50/μL) are at highest risk for CMV disease.[7] Preliminary virological data suggest that a high copy number of plasma CMV DNA or CMV antigen is also a significant risk factor for the development of end-organ disease.[8-10]

CMV RETINITIS

Retinitis is the most common manifestation of CMV infection in patients with AIDS, accounting for 75% to 85% of CMV disease.[11,12] The diagnosis of CMV retinitis is clinical. Typically, the disease appears as a yellow to white area of retinal necrosis and edema that follows a vascular distribution and is sometimes hemorrhagic. An ophthalmologist can establish the diagnosis with a dilated retinal examination and indirect ophthalmoscopy. In cases in which the disease is unusual in presentation or is unresponsive to therapy, vitreous or aqueous humor sampling with analysis for CMV DNA[13] or an endoretinal biopsy[14] may be helpful to establish a diagnosis, but such biopsy may be associated with a substantial risk of visual loss from associated complications, such as retinal detachment.

Cytomegalovirus lesions may be located in 3 arbitrarily defined anatomical zones (**Figure**).[15] The location of the retinal lesions and the patient's visual function are important considerations in developing a treatment plan.

Most of the knowledge of the natural history of CMV retinitis is from the era prior to the availability of effective anti-CMV and anti-HIV therapies. Patients presented with relentlessly progressive, necrotizing retinitis that often resulted in blindness.[16] This generally occurred over a period of months and was characterized by slow enlargement of disease foci to involve the entire retina, occasionally with new foci of disease, and eventually with involvement of the other eye; retinal detachment commonly occurred.

Symptoms of CMV retinitis are nonspecific but may include light flashes, floaters, loss of central or peripheral visual field, and blurred or distorted vision. Patients may be asymptomatic initially or may have poorly defined visual complaints about their vision. Patients with CMV retinitis do not present with a red eye, photophobia, or pain. Asymptomatic retinitis can be detected by ophthalmologic screening of HIV-infected persons at high risk.[17] The value of early detection and treatment of asymptomatic retinitis on survival and relapse has not been evaluated. However, because extensive peripheral disease is a risk factor for retinal detachment,[18] it is hoped that early detection and therapy of asymptomatic cases will result in better long-term visual results.

The cumulative risk of retinal detachment within 6 months after the diagnosis of retinitis in patients treated with intravenous (IV) ganciclovir or foscarnet sodium therapy is 25% to 30% and may be as high as 50% to 60% at 1 year.[19,20] Retinal detachments are the cause of substantial visual morbidity, despite surgical repair with techniques such as vitrectomy and silicone oil tamponade. After a detachment has been repaired, cataracts that may require additional surgery often develop.[21]

Most patients with CMV retinitis have good vision at presentation, with 70% to 80% having a visual acuity of 20/40 or better.[19,20] Despite systemic ganciclovir or foscarnet therapy, progressive visual loss occurs over time. In a series of 287 patients with CMV retinitis, the median time to vision of 20/200 or worse in an eye with retinitis was 13.4 months and to bilateral vision of 20/200 or worse was 21.1 months.[19]

Recommendations

- Patients with HIV infection should be educated about the symptoms of CMV retinitis and advised to seek care in a timely manner after the onset of visual symptoms. The importance of regular ophthalmologic and medical follow-up should be stressed (B III).
- Many experts recommend that patients at high risk should have ophthalmologic screening (including indirect ophthalmoscopy) every 3 to 6 months. Before the widespread availability of potent antiretroviral therapy, patients at high risk included those who were CMV-seropositive and had $CD4^+$ cell counts be-

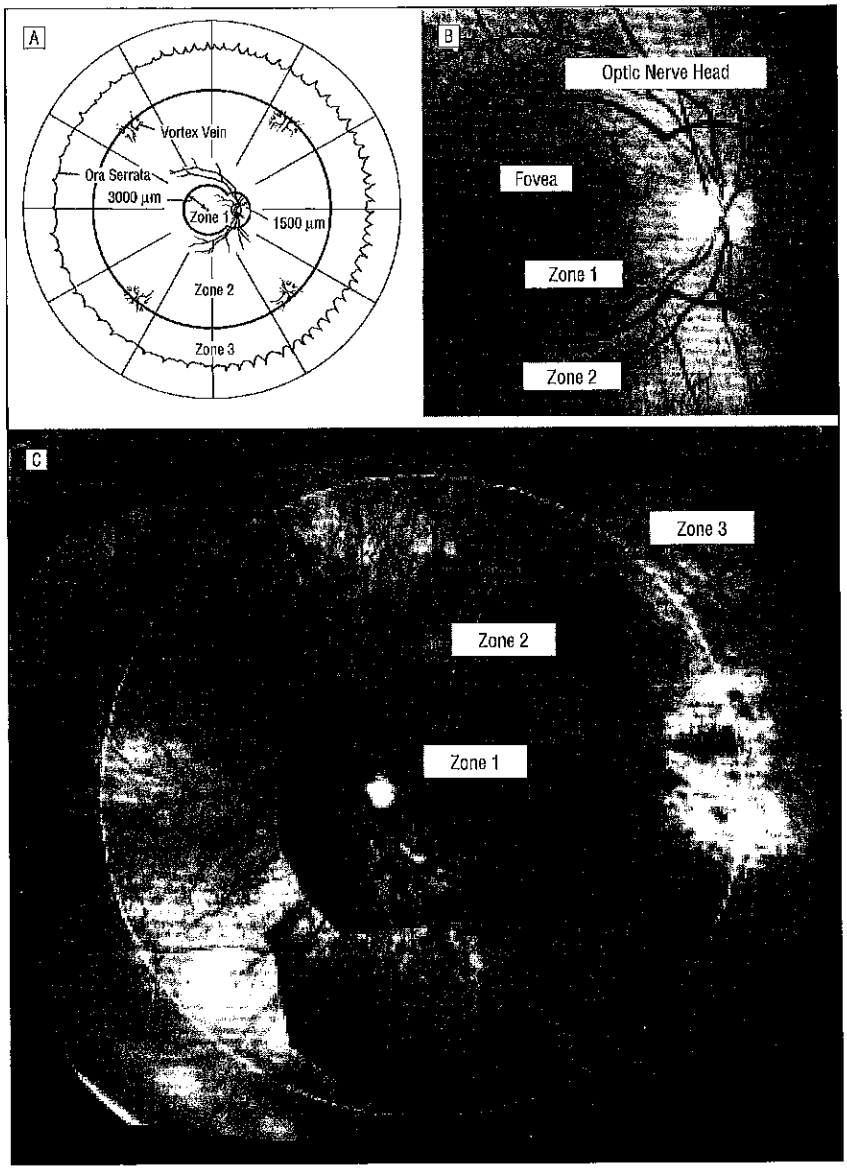
low 0.05×10^9/L. Some experts screen patients with $CD4^+$ cell counts below 0.10×10^9/L. Patients with any diagnosis of extraocular CMV disease should also be examined regularly (B III).

- The diagnosis of CMV retinitis should trigger a thorough examination for extraocular CMV disease. Likewise, patients with extraocular CMV disease should undergo an ophthalmologic examination. Regular ophthalmologic and medical examinations should continue for life (B III).
- Successful management of CMV retinitis requires close collaboration between the ophthalmologist and the treating physician (A III).

Ophthalmologic Examinations in Patients With CMV Retinitis

Ophthalmologic examinations should include visual acuity determinations, slitlamp examination, measurement of intraocular pressure (when appropriate), and the examination of both fundi by indirect ophthalmoscopy after pupillary dilation. Indirect ophthalmoscopy allows visualization of the entire retina; in contrast, the direct ophthalmoscope, which is the only instrument that is available to most nonophthalmologists, can provide a view of only the posterior portion of the retina (Figure). Examination of the retina is essential in assessing the response to treatment.

Photographs of the retina at every examination are considered the optimal means of monitoring the efficacy of therapy. Photographs enable the detection of retinal changes, such as new lesions or increased activity of the border, earlier than is possible with notes or drawings alone.[22,23] Some authorities are comfortable not ordering photographs at every visit in certain cases. In these situations, periodic photographs of the fundus (eg, every 3 months) may allow identification of small changes in lesion size or other subtle evidence of low-grade activity. In settings in which retinal photography is not available, careful drawings should record the presence of border activity; the number and anatomical location of lesions; and the position of the lesion borders in relation to specific fundus landmarks, such as blood vessels.



A, The anatomical zones of the retina. Zone 1 encompasses less than 10% of the total retina and includes the area surrounding the optic disc and fovea; lesions here are considered to be immediately threatening to sight. Zone 2 is the midperipheral retina; zone 3, the far peripheral retina. Zone 3 includes the area of attachment of the vitreous base, and necrotic holes that develop here have the highest risk of leading to retinal detachments. B, The posterior portion of the fundus, with the border separating zones 1 and 2 indicated. The photograph corresponds to the approximate area that can be examined with the handheld, monocular direct ophthalmoscope. C, A photographic montage of a fundus, showing a peripheral lesion in the anterior portion of zone 2 and in zone 3. This lesion could only be visualized with an indirect ophthalmoscope. Panels A and B reprinted from Holland et al[6] with permission, copyright 1989. Panel C was reprinted courtesy of the Studies of the Ocular Complications of AIDS Research Group.

In general, ophthalmologic examinations should be performed immediately before therapy is initiated, at the end of the induction (or reinduction) therapy, and monthly thereafter. The goal of the examination after the induction (or reinduction) therapy is to assess the therapeutic response and provide a reference for subsequent evaluations. The precise schedule of examinations must be individualized on the basis of several factors, including the ease with which retinal disease is controlled. Regular examinations should be continued even if patients with unilateral disease eventually lose the vision in that eye despite therapy; examinations may make early detection of new disease in the other eye possible.

Recommendations

- Ophthalmologic examinations should be performed immediately before treatment is begun, af-

ter induction (or reinduction) therapy is completed, and monthly thereafter (A II).

- Examination schedules should be individualized for patients on the basis of ophthalmologic factors and response to treatment (A II).
- Patients should return immediately for follow-up examinations if new ocular symptoms develop (A II).
- Use of retinal photographs in conjunction with regular clinical examinations is the optimal means for monitoring patient status (A III).

Available Treatments for CMV Retinitis

In most clinical situations, more than one treatment option could be appropriate. Choosing among the different treatment options now available involves considerations of the relative efficacies, the risk of specific toxic effects and adverse outcomes, and quality-of-life issues.

General Considerations. Standard therapy with ganciclovir or foscarnet requires lifelong daily IV infusions. The cost and inconvenience of these infusions and the risk of serious infections in conjunction with central venous catheters[24,25] are problematic. Cidofovir, oral ganciclovir, and the intraocular implant are options that eliminate the need for central venous catheter access. The limited bioavailability of oral ganciclovir reduces its efficacy, but higher doses (eg, 4500 or 6000 mg/d) are more efficacious,[26] and certain adverse effects occur less frequently with the oral formulation. The sustained high intravitreous concentrations of drug achieved with the ganciclovir intraocular implant have resulted in longer maintenance of CMV retinitis inactivity than with any other treatment to date. However, there is a risk of vision-threatening surgical complications with the implantation procedure. Furthermore, because CMV retinitis is part of a systemic disease and hematogenous dissemination of CMV is thought to be central in its pathogenesis,[27] the use of local intravitreous therapy without systemic anti-CMV therapy is associated with an increased risk of extraocular CMV disease and contralateral retinitis.[28] A summary of the characteristics of the currently available treatment options is presented in **Table 2** and in the rest of the article.

IV Ganciclovir Induction and Maintenance. In randomized studies that have used masked reading-center analyses of retinal photographs, the median time to the first progression (ie, enlargement of existing lesions or development of new lesions) of retinitis with IV ganciclovir has ranged from 47 to 104 days.[20,29-33] Higher doses may be more effective than standard doses,[34] but have not been compared in randomized trials. Rates of severe neutropenia (absolute neutrophil count, $<0.5 \times 10^9$/L) and thrombocytopenia (platelet count, $<20 \times 10^9$/L) after 6 months of treatment have been 34% and 4%, respectively.[35] Dose-limiting ganciclovir-induced neutropenia can be reversed with the use of adjuvant granulocyte colony-stimulating factor, starting at a dose of 300 µg 3 times per week and then titrating the dose over time.[24,36]

IV Foscarnet Induction and Maintenance. In a randomized trial, IV infusion of foscarnet was shown to be as efficacious as IV infusion of ganciclovir.[20] Maintenance dosages of foscarnet sodium of 120 mg/kg per day may be more efficacious, but may also have more adverse effects.[22,37] Dose-limiting toxic effects occur in approximately 30% of patients and include reversible increases in serum creatinine levels, nausea, malaise, genital ulcers, and neurologic symptoms.[35] Infusion-related malaise and neurotoxic effects may be ameliorated by slowing the infusion rate. Foscarnet is the least convenient systemic therapy to administer; the duration of the IV infusion is 2 hours (that of ganciclovir is 1 hour), and an infusion pump and concomitant hydration are required to prevent nephrotoxic effects.

IV Ganciclovir Induction and Oral Ganciclovir Maintenance. Ganciclovir has poor oral bioavailability. In early published reports maintenance therapy with IV ganciclovir was favored over oral ganciclovir, 3000 mg/d, in controlling retinitis in patients who had already responded to IV ganciclovir induction, although there was no statistical difference between the 2 treatments.[30,31] Subsequent data have confirmed that oral ganciclovir, 3000 mg/d, is less effective than the IV form as a maintenance regimen but higher doses (4500 or 6000 mg/d) are approximately as effective as IV therapy.[26,32] Although randomized trials that have compared oral and IV ganciclovir maintenance strategies have lacked long-term outcome data, oral ganciclovir has been associated with fewer serious IV catheter complications and less marked neutropenia.

Ganciclovir Intraocular Implant. The time to first progression associated with the ganciclovir intraocular implant when used for initial treatment of newly diagnosed CMV retinitis has been substantially longer than that of any other current treatment (virtually equal to the duration that the device continues to release the drug).[29,38] However, implantation requires intraocular surgery and is subject to surgical complications. Many patients have immediate transient blurred vision with their current glasses that resolves within a few weeks. In randomized trials, a vision-compromising event occurred in approximately 10% of the patients who received implants. The majority of adverse events were retinal detachments; major intravitreous bleeding and endophthalmitis rarely occurred. Retinal detachment is a complication of CMV retinitis itself, and whether implantation causes an increased short-term risk of retinal detachment or a long-term decreased risk of retinal detachments (because of better retinitis control) is unknown. Patients with extensive lesions in the anterior retina may be at higher risk for retinal detachment after implant placement. The implant is depleted of the drug after 5 to 8 months, which necessitates replacement with the attendant risk of additional complications. The outcome of undergoing several reimplantation procedures is not known.[29]

For a median of 7 months of follow-up in patients who received the implant as the sole therapy, gastrointestinal, neurologic, or pulmonary CMV disease occurred in 15%

to 31%, and retinitis in the contralateral eye occurred in 40% to 67%.[29,38] For a median follow-up of 3 months, no extraocular CMV disease was reported in patients assigned to receive IV ganciclovir, and contralateral retinitis occurred in only 15%.[29] In a recent randomized trial, the incidence of extraocular disease and contralateral retinitis was significantly lower and the time to retinitis progression was longer among patients assigned to receive the implant and oral ganciclovir, 4500 mg/d, compared with patients who received the implant plus placebo.[28]

IV Cidofovir Induction and Maintenance. The efficacy of cidofovir appears similar to that of IV ganciclovir or foscarnet, but, to our knowledge, no studies have directly compared cidofovir with other therapies.[39,40] Because of cidofovir's prolonged antiviral activity, IV infusion every 2 weeks is possible, which obviates the need for an indwelling central venous catheter.

Nephrotoxic effects are the most serious adverse events of cidofovir therapy and can be prolonged and potentially irreversible in some patients. Concomitant use of probenecid and hydration with IV saline solution are required to reduce this risk. The concurrent administration of other potentially nephrotoxic drugs (including nonsteroidal anti-inflammatory drugs) should be avoided and regimens should be discontinued at least 1 week before cidofovir therapy is initiated. Cidofovir use should be discontinued or the dosage reduced at the earliest signs of renal damage (including ≥2+ proteinuria). Uveitis and hypotony[41] also can occur, and regular measurement of intraocular pressure and slitlamp examination of the anterior chamber of the retina are necessary.

Intraocular Injections of Ganciclovir or Foscarnet. Weekly or twice-weekly intravitreous injections of ganciclovir or foscarnet through a small-gauge needle have appeared to slow the progression of retinitis in uncontrolled case series conducted primarily in patients who cannot tolerate systemic therapy or in whom retinitis had progressed despite attempts at systemic therapy.[42-46] As with the implant device, the risk of contralateral eye or extraocular CMV disease is high in the absence of concomitant systemic therapy.[47]

Recommendations

- The treatment of CMV retinitis should be individualized on the basis of the unique characteristics of the ophthalmologic disease, underlying medical condition (including concomitant medications), living conditions, and the patient's lifestyle preferences (A III).
- Daily IV infusions of ganciclovir, daily IV infusions of foscarnet, or weekly then biweekly IV infusions of cidofovir are each appropriate initial choices for induction and maintenance therapy for CMV retinitis (A I).
- The ganciclovir intraocular implant is an appropriate choice for initial therapy for CMV retinitis (A I).
- Many experts consider the implant to be the preferred choice for patients with immediately sight-threatening disease (B III).
- Oral ganciclovir should not be used as the sole form of induction therapy for any patient (E III) and should not be the sole form of maintenance therapy in patients with an immediately sight-threatening disease (D III).
- It may be an appropriate maintenance treatment choice for patients whose retinitis does not immediately threaten their vision (B I).
- In certain circumstances, intermittent intravitreous injections of ganciclovir or foscarnet may be an appropriate choice for induction and maintenance therapy for CMV retinitis. Concomitant systemic anti-CMV therapy (eg, oral ganciclovir) is recommended with any local intraocular therapy (Table 1).

Relapsed and Refractory CMV Retinitis

Relapse of CMV retinitis (ie, recurrence of clinically apparent viral activity) occurs in nearly 100% of patients despite treatment, at least with current systemically administered drugs.[19,20] Relapse may be due to one or more factors, including limited delivery of drug into the eye, a decline in the patient's immune function, and viral resistance to the drug. Most cases of simple relapse during systemically administered treatment are probably due to the limited intraocular penetration of these drugs.[48,49] The ganciclovir intraocular implant produces sustained intraocular levels of the drug that are approximately 4 times greater than can be obtained with systemically administered drugs.[38]

Refractory disease must be distinguished from simple relapse. Refractory disease occurs when therapy is ineffective in controlling the disease in 2 clinical situations. In the first clinical situation there is little evidence of a response to the induction therapy and the disease remains persistently active without any period of inactive borders after 6 to 8 weeks of therapy. In the second, relapses occur often enough that it appears as though the current treatment is inadequately effective for long-term control. Clinical trials have defined refractory disease as 2 relapses within a 10-week period despite 2 induction and maintenance cycles.[50]

Most simple relapses following systemically administered therapy can be treated by reinduction with the same drug followed by maintenance therapy. However, the ability to control the retinitis progressively declines, as evidenced by a shortening interval between successive relapses.[20] The reasons for this declining control are unclear but may be associated with worsening of the factors noted earlier, including further decline in immune function or further decrease of virus susceptibility to the therapy. Ganciclovir-resistant CMV emerges slowly after exposure. Before drug exposure, nearly 100% of clinical CMV strains are susceptible to ganciclovir at 50% inhibitory concentrations of less than 6 μm.[51,52] After 3 months of ganciclovir therapy, approximately 8% of patients shed resistant virus (ie, strains with 50% inhibitory concentration of >12 μm).[51] However, there appears to be a decreasing sensitivity even in those patients who do

Table 2. Available Treatments for CMV Retinitis*

	IV Ganciclovir	IV Foscarnet Sodium	Combination IV Ganciclovir and IV Foscarnet Sodium
Median time to first retinitis progression, d (by retinal photography where available)†	47-104	53-93	129
Dosing regimen	Standard Induction: 5 mg/kg every 12 h for 14-21 d Maintenance: 5 mg/kg every day High-dose/intensive for refractory disease Induction: 7.5 mg/kg every 12 h for 14-21 d Maintenance: 10 mg/kg every day (Note: dosage should be adjusted for creatinine clearance <1.16 mL/s [<70 mL/min] according to algorithm in package insert)	Induction: 90 mg/kg every 12 h for 14-21 d Maintenance: 90-120 mg/kg every day (Note: dosage should be recalculated according to dose-reduction algorithm in package insert based on most current serum creatinine); 500-100 mL of 0.9% saline solution with each dose	Prior ganciclovir: Induction: both IV foscarnet 90 mg/kg every 12 h and IV ganciclovir 5 mg/kg every day for 14-21 d Maintenance: both IV foscarnet 90-120 mg/kg, and IV ganciclovir 5 mg/kg, every day Prior foscarnet sodium: Induction: both IV ganciclovir 5 mg/kg every 12 h and IV foscarnet 90-120 mg/kg every day for 14-21 d Maintenance: IV ganciclovir 5 mg/kg and IV foscarnet 90-120 mg/kg every day Reinduction: IV ganciclovir 5 mg/kg and IV foscarnet 90 mg/kg every 12 h for 14-21 days Maintenance: same as above
Select adverse effects	Neutropenia; thrombocytopenia; catheter sepsis	Nephrotoxicity; electrolyte abnormalities; anemia; catheter sepsis; nausea/irritability; genital ulceration	Same as IV ganciclovir and IV foscarnet
Important drug interactions	↑ Neutropenia with zidovudine, cancer chemotherapy ↑ Didanosine levels	↑ Nephrotoxicity with other nephrotoxic drugs, eg, amphotericin B, aminoglycosides, IV pentamidine	Same as IV ganciclovir and IV foscarnet
Adjunctive therapy	G-CSF/GM-CSF effective for neutropenia	IV or oral hydration essential; potassium, calcium/magnesium supplements, antiemetics may be required	Same as IV ganciclovir and IV foscarnet
Advantages	Systemic therapy; anti-HSV activity	Systemic therapy; anti-HSV (acyclovir-resistant) activity; anti-HIV activity	Increased efficacy compared with either IV ganciclovir or IV foscarnet alone; improved response for relapsed disease
Disadvantages	Hematologic toxicity; requires daily infusions; indwelling catheter	Nephrotoxicity; requires daily infusions/indwelling catheter; supplemental hydration required; prolonged infusion time; requires infusion pump or controlled rate infusion device	Same as IV ganciclovir and IV foscarnet; prolonged daily infusion time and impact on quality of life
Monitoring requirements	Induction therapy: (a) CBC with WBC differential, platelet count weekly (twice weekly if baseline ANC $<1.0 \times 10^6$/L [<1000/μL] or platelet count $<50 \times 10^9$/L [<50 000/μL]); (b) serum creatinine weekly Maintenance therapy: (a) CBC with WBC differential, platelet count weekly; (b) serum creatinine every 2-4 wk	Induction therapy: (a) serum creatinine twice weekly; must be used to recalculate dosage if change in creatinine level occurs; (b) serum Ca^{++}, albumin Mg^{++}, phosphates, and K^+ twice weekly; (c) hemoglobin and hematocrit weekly Maintenance therapy: (a) serum creatinine weekly; (b) serum Ca^{++}, albumin Mg^{++}, phosphates, and K^+ weekly; (c) hemoglobin and hematocrit every 2-4 wk	Same as both IV ganciclovir and IV foscarnet
Precautions and contraindications	Moderate to severe thrombocytopenia (platelet counts $<25 \times 10^9$/L)	Concomitant use with other nephrotoxic drugs (eg, amphotericin B, aminoglycosides, or IV pentamidine) or in patients with preexisting moderate to severe renal insufficiency (serum creatinine >168 μmol/L [>1.9 mg/dL]) or creatinine clearance <0.83 mL/s (<50 mL/min)	Same as IV ganciclovir and IV foscarnet

**CMV indicates cytomegalovirus; IV, intravenous; ↑, increased; NSAID, nonsteroidal anti-inflammatory drugs; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; HIV, human immunodeficiency virus; CBC, complete blood cell count; WBC, white blood cell count; and ANC, absolute neutrophil count.*

†Times to progression of CMV retinitis are from the start of induction treatment for IV ganciclovir, IV foscarnet, combination IV ganciclovir and IV foscarnet, intraocular ganciclovir insert, and IV cidofovir, and from start of maintenance treatment for IV then oral ganciclovir.

‡Zidovudine dose should be reduced by 50% or withheld on the day of infusion only. Rifampin, ketoprofen, chlorpropamide, dapsone, methotrexate, trimethoprim-sulfamethoxazole, zalcitabine, and NSAID should be withheld on the day of dosing only.

§Some experts recommend monitoring intraocular pressure and slitlamp examination prior to each IV cidofovir infusion.

IV Then Oral Ganciclovir	Intraocular Ganciclovir Implant	IV Cidofovir
29-53	216-226	64-120
Induction: same as IV ganciclovir Maintenance: 3000-6000 mg/d in 3 divided doses with food (Note: dose reduction recommended for creatinine clearance <1.16 mL/s [<70 mL/min], follow algorithm in package insert)	Surgical: intraocular implantation via pars plana of ganciclovir (4.5 mg) implant releasing 1 µg/h (duration: 6-8 mo; then replacement required every 5-8 mo) Concomitant systemic anti-CMV therapy recommended; oral ganciclovir maintenance dosing of 4500 mg/kg in 3 divided doses	Induction: 5 mg/kg every week for 2 wk Maintenance: 5 mg/kg every 2 wk (Note: dose reduction to 3 mg/kg for ↑ serum creatinine by 26-35 µmol/L [0.3-0.4 mg/dL] above baseline [see below]; all doses given with probenecid and IV fluid)
Neutropenia; diarrhea/nausea	Surgical complications: transient blurred vision; infection; hemorrhage	Nephrotoxicity; neutropenia; probenecid adverse effects (rash, fever, nausea, fatigue); uveitis; alopecia; hypotonia
Same as IV ganciclovir		↑ Nephrotoxicity with other nephrotoxic drugs, eg, amphotericin B, aminoglycosides, IV pentamidine, NSAID Probenecid: ↑ Level of most proximal tubular-excreted drugs‡
Same as IV ganciclovir	Systemic anti-CMV therapy recommended (oral ganciclovir, 4500 mg/d)	Probenecid and IV hydration essential; antiemetic, antihistamine, acetaminophen premedication commonly used for probenecid toxicity
Systemic therapy; oral administration; less catheter/sepsis complications	Longest time to retinitis progression in treated eye; no IV dosing or catheter required	Systemic therapy; no indwelling catheter required; infrequent dosing
Faster time to retinitis progression; high pill count; poor oral bioavailability (6%)	↑ Fellow eye and extraocular disease; requires surgery; postintraocular surgical complications	Requires probenecid and IV hydration; probenecid toxicity; nephrotoxicity (may be prolonged)
Induction therapy: IV ganciclovir Maintenance therapy: oral ganciclovir (a) CBC with WBC differential, platelet count every 2 wk; (b) serum creatinine every 2-4 wk	No specific laboratory monitoring required for implant; if oral ganciclovir therapy is added, follow monitoring guidelines as outlined	Within 48 h prior to each induction and maintenance dose (a) serum creatinine quantitative proteinuria; (b) WBC with differential cell count; monitor intraocular pressure and slitlamp examination at least monthly§
Use with caution in patients with immediately sight-threatening (zone 1) retinitis	External ocular or nasolacrimal infection; patients with ↑ risk of postoperative intraocular infection	Same as IV foscarnet except parameters are baseline serum creatinine level >133 µmol/L (>1.5 mg/dL) or creatinine clearance <0.91 mL/s (<55 mL/min), or 2+ proteinuria (after IV fluid) Discontinue therapy for 3+ proteinuria, if serum creatinine level increases by 44 µmol/L (0.5 mg/dL) above baseline, or if intraocular pressure decreases by 50% of baseline value

not have overt resistance, defined as a specific cutoff of 50% inhibitory concentration,[53] suggesting that the progressive shortening of the intervals between relapses may be due to decreasing CMV sensitivity. The proportion of cases of refractory disease (rapidly relapsing disease) that is due to overt resistance is unknown.

Altering Monotherapy. Relapse may prompt a change to an alternative drug. The CMV Retinitis Retreatment Trial[54] showed that for simple relapse, switching monotherapy had

no additional benefit compared with continuing with the same drug. However, there have been case reports of patients with documented virological resistance and uncontrolled retinitis who have responded to a change in their monotherapy.[55] A study of relapsed retinitis suggests that cidofovir may be of value in patients who have had relapses while taking ganciclovir or foscarnet.[56]

Combination Therapy. In a study of relapsed CMV retinitis, the median time to disease progression was approximately 1 to 2 months in patients who received foscarnet or ganciclovir monotherapy and 4.3 months in patients treated with the combination of the 2 drugs.[54] The occurrence of adverse effects and the overall measures of quality of life (such as general health and mental health) were no different between combination therapy and monotherapy. However, combination therapy required greater daily infusion time than monotherapy and was associated with a significant negative treatment impact. In vitro additive or synergistic effects of ganciclovir and foscarnet[57,58] suggest that combination approaches may be of value in refractory disease. Alternative approaches, such as the implant and IV foscarnet, IV foscarnet and oral ganciclovir, and IV monotherapy (eg, cidofovir) and intravitreous injections, may have merit but have not been tested in clinical trials.

Ganciclovir Intraocular Implant. The ganciclovir intraocular implant appears to be effective in nearly all patients with newly diagnosed retinitis and to control the retinitis until the implant is depleted of the drug (typically within 5-8 months).[54] The implant is an acceptable option for relapsed retinitis but it is somewhat less effective (ie, 75% of patients have been described as responding to the implant in uncontrolled studies).[59] In patients who do respond, relapses tend not to occur until the implant is depleted of the drug. The addition of a second drug, in an effort to take advantage of the additive or synergistic effects, may be a reasonable approach in patients with relapsed retinitis who do not respond to the implant alone. For refractory disease, some experts recommend one or more intravitreous injections of high-dose (2-mg) ganciclovir to assess therapeutic response before subjecting patients to a surgical procedure.

The treatment of relapse for patients who began therapy with the ganciclovir intraocular implant depends on the nature and timing of the relapse. If relapse occurs more than 6 months after implantation, the implant is likely to be depleted of the drug, and simple replacement is appropriate. Earlier relapse may be due to the implant's being depleted of the drug or to viral drug resistance. A replacement may be tried but alternative approaches may be necessary. Some experts recommend routine replacement of the implant (eg, every 6-7 months) rather than waiting until relapse occurs. As noted, the cumulative risks of adverse visual outcomes resulting from surgical complications in patients undergoing more than 2 consecutive implant replacement procedures in the same eye is unknown.

Intravitreous Therapy. Intravitreous injection of ganciclovir or foscarnet is often used in clinical practice in patients who appear to have refractory disease. Ganciclovir doses generally range from 0.2 to 2 mg and foscarnet sodium from 1.2 to 2.4 mg; the higher doses are now routinely used. Induction therapy consists of 2 to 3 injections per week for 2 to 3 weeks until an adequate response is noted, followed by weekly injections for maintenance. Higher intraocular levels of the drug may provide benefit in patients whose disease is refractory, particularly those patients who cannot tolerate systemic administration of the drug. Since the availability of the implant, the routine use of intravitreous injections has become uncommon. However, if the implant is not readily available, intravitreous injections may have a role in the treatment of refractory disease. Although case series have suggested efficacy for intravitreous cidofovir,[60,61] the current formulation of cidofovir is not recommended for intravitreous use.

Recommendations

- The treatment of relapsed retinitis and refractory disease should be individualized and depends on several factors, including other health measures (eg, renal function), previous therapy, and the retinitis disease history (A III).
- For simple relapsed retinitis, reinduction with any available induction treatment (including the same drug that the patient initially received) is acceptable (A III).
- For refractory disease, reinduction with combination therapies with a different induction drug or with local therapy is recommended (A II).

CMV GASTROINTESTINAL TRACT DISEASE

The clinical presentation of CMV disease in the gastrointestinal tract is largely dependent on the site of infection. Patients with esophageal disease usually present with odynophagia or dysphagia that fails to respond to a 1-week empirical course with an antifungal azole for presumptive candidal esophagitis. Endoscopy with biopsy is required to confirm the diagnosis.[62] Cytomegalovirus most commonly causes ulcers at the lower esophageal sphincter, but can cause diffuse esophagitis, ulcers higher in the esophagus, gastritis, gastric ulcers, duodenitis, duodenal ulcers, and enteritis.[63] To confirm a diagnosis of CMV gastrointestinal tract disease, a mucosal biopsy must be performed and show evidence of inflammation and of CMV inclusion bodies.

Cytomegalovirus in the lower gastrointestinal tract most often affects the colon (67% in 1 series),[64] but can also cause perforations in the ileum and rectal ulcers.[65,66] The diagnosis is most often made using colonoscopic biopsy when stool studies have not shown a cause for the diarrhea. Cytomegalovirus causes a spectrum of diseases, ranging from no visibly apparent colitis to deep ulcers, with the most common finding being a mild, patchy colitis. The diarrhea is usually accompanied by low-grade fever and abdominal pain.[67] Occasionally, rebound tenderness is found.[68] Diar-

rhea is common, but it is not always present or can be sporadic. The diagnosis must be made with the use of biopsy, even if mucosa appear normal on endoscopy.

Treatment

Treatment of CMV disease in the gastrointestinal tract is similar to that for disease of the retina, with some notable exceptions. Most clinicians use induction therapy for 3 to 6 weeks (compared with 2 weeks for retinitis). An early report suggested that some patients benefit from a 14-day course of therapy.[69] More recent data indicate the disappearance of CMV inclusion bodies after 3 weeks and complete healing after 6 weeks of therapy.[70]

There are more data to support the use of ganciclovir than foscarnet for CMV colitis,[64,69,71,72] but the latter can be used initially[73] or when ganciclovir therapy has failed.[74] The drugs can be combined after the failure of either.[75] In previous studies,[64,71] the time to relapse of CMV gastrointestinal tract disease after induction treatment was 9 weeks (compared with approximately 3 weeks for retinitis without maintenance therapy), although it was as long as 1 year in some patients. There is no universal agreement about the use of maintenance therapy in CMV gastrointestinal tract disease. The retina should be closely monitored, and maintenance therapy following reinduction should be considered if CMV gastrointestinal tract disease relapses. To our knowledge, there are no available data on the use of cidofovir for CMV gastrointestinal tract disease.

Recommendations

- Induction therapy with IV ganciclovir or IV foscarnet for symptomatic CMV gastrointestinal tract disease should be given for 3 to 6 weeks depending on the clinical circumstances (B I).
- Maintenance therapy should be considered, particularly after reinduction for a relapse. The role of oral ganciclovir has yet to be established, but it may be a reasonable option (C III).
- Combination IV ganciclovir and IV foscarnet therapy may be effective after monotherapy has failed (B III).
- Patients with CMV gastrointestinal tract disease should undergo regular ophthalmologic screening for CMV retinitis (A III).

CMV NEUROLOGIC DISEASE

Two major CMV neurologic syndromes are associated with AIDS: CMV polyradiculopathy and CMV ventriculoencephalitis.[76] The former is characterized by urinary retention and progressive bilateral leg weakness.[77] The symptoms may progress rapidly over several weeks to include loss of bowel and bladder control and flaccid paraplegia. A spastic myelopathy has been reported, and sacral paresthesia may occur. The cerebrospinal fluid findings are unusual for a viral infection, evidenced by high protein and low glucose levels and a pleocytosis, in which 50% or more of the cells are polymorphonuclear leukocytes.[78,79] Isolation of CMV in the cerebrospinal fluid by cell culture has been demonstrated, but CMV antigen and DNA assays are more sensitive measures.

Ventriculoencephalitis usually occurs in the setting of diagnosis of CMV disease elsewhere.[80-82] Typically, patients present with lethargy, confusion, and fever. Nystagmus, ataxia, and unilateral or bilateral cranial nerve palsies are the most characteristic neurologic signs. Cerebrospinal fluid analysis shows few white blood cells, normal glucose levels, and variable protein concentrations, but CMV DNA may be detected in the cerebrospinal fluid using polymerase chain reaction assays.[83,84]

Treatment

Therapy with IV ganciclovir, IV foscarnet, or the combination of the 2 drugs has been used in patients with CMV neurologic disease. Initiating therapy promptly is essential for an optimal clinical response, but there is no evidence that treatment with ganciclovir or foscarnet for CMV neurologic disease extends survival,[85] and there are no data on the use of cidofovir in this setting, to our knowledge. Many patients with CMV neurologic disease have received therapy for CMV before the diagnosis of CMV neurologic disease and may have a drug-resistant virus.[86-88] Some experts recommend therapy with a combination of ganciclovir and foscarnet, but there are no supportive data from clinical trials. In many cases, treatment is initiated after irreversible damage has occurred. Thus, emphasis must be placed on maintaining a high index of suspicion for and on diagnosing CMV neurologic disease early.

Recommendations

- A high index of suspicion for CMV neurologic disease must be maintained and therapy should be initiated as soon as possible (B III).
- Therapy with IV ganciclovir or IV foscarnet or a combination of the 2 drugs is recommended (B III); combination therapy should be considered for patients who have received prior anti-CMV therapy (A III).
- Patients with CMV neurologic disease should undergo regular ophthalmologic screening for retinitis (A III).

CMV PULMONARY DISEASE

Because of the high incidence of prior CMV infection, asymptomatic viral shedding, and the frequent presence of other pulmonary pathogens, CMV pneumonia in patients with HIV infection is difficult to diagnose definitively.[89] The isolation of CMV from bronchoalveolar lavage fluid or lung tissue does not differentiate asymptomatic infection from true pneumonitis.[90-98] Cytomegalovirus can be isolated from pulmonary secretions or lung tissue in approximately 50% of HIV-infected patients who undergo bronchoscopic examination. There are no clinical findings specific to CMV pneumonitis.[90-93,98] The incidence of CMV pneumonitis is approximately 3% to 4% in patients who have had diagnostic bronchoscopy for evaluation of pulmonary infiltrates of unknown origin.[98,99] Whether other pulmonary pathogens should be absent before a diagnosis of CMV pneumonitis is made has been controversial. Of 17 patients in whom lung biopsy aided in their being diagnosed as having CMV pneumonitis, no distin-

guishing clinical, radiographic, or histological findings were evident between patients with CMV as the sole pulmonary pathogen and those with CMV and other pulmonary pathogens.[98] In another study of patients with histologically diagnosed CMV pneumonitis, the clinical outcome was no different whether CMV was present as the sole pulmonary pathogen or was a copathogen with *Pneumocystis carinii*.[90] The minimal diagnostic criteria to establish a diagnosis of CMV pneumonitis should include pulmonary infiltrates on a chest radiograph; detection of CMV using viral culture, antigen, or nucleic acid studies of pulmonary secretions or lung tissue; the presence of characteristic intracellular inclusions in lung tissue or bronchoalveolar macrophages; and the absence of other pulmonary pathogens (or confidence that other pulmonary pathogens have been effectively treated).

Treatment

Therapy with standard induction doses of IV ganciclovir or IV foscarnet should be used for pulmonary CMV infection. The duration of therapy has not been established, but should probably be at least 21 days. The response rates with ganciclovir or foscarnet have been 60% to 70%.[98,100,101] Available data do not support the use of concomitant high-dose immunoglobulin. Relapses of pneumonia or the development of other CMV end-organ diseases after induction therapy have been reported, but to our knowledge data to support maintenance or suppressive therapy for CMV pneumonitis are not available. In the absence of retinitis or other active CMV disease, patients can be observed for evidence of relapse. If the patient has recurrent CMV pneumonitis, reinduction therapy followed by long-term suppressive therapy is recommended. To date, efficacy data for the use of oral ganciclovir for suppression of CMV pneumonitis are not available.

Recommendations

- Cytomegalovirus should be considered the cause of pneumonitis in an HIV-infected patient who meets the diagnostic criteria presented earlier, and treatment is recommended (B III).
- Therapy for CMV pneumonitis should be considered in a patient with coinfection with another pulmonary pathogen(s) who does not respond to therapy against the copathogen(s) (B III).
- Therapy with IV ganciclovir or IV foscarnet for at least 21 days is recommended for patients with CMV pneumonitis (B III).
- Long-term suppressive therapy after treatment for CMV pneumonitis is not recommended unless there is a documented relapse or evidence of extrapulmonary end-organ disease (D III).

OTHER CMV DISEASES

Autopsy study findings indicate that CMV infection can often occur in several organs, such as the adrenal glands, liver, biliary tract, and pancreas, that were not noted to be associated with clinically apparent disease before death.[102-106] For example, CMV is often detected in the adrenal glands at autopsy. Cytomegalovirus adrenalitis is a cause of mortality in mouse models of CMV infection, and there may be inadequate response to corticotropin stimulation tests in patients with CMV viremia.[107] The mortality rate is increased in patients with high CMV loads in the blood.[108,109]

Treatment

Patients with constitutional signs, such as fever, malaise, and weight loss, should be thoroughly examined for opportunistic infections and tumors, several of which are potentially treatable. The usefulness of treating CMV viremia under these circumstances is not supported by data from clinical trials, but in the absence of other causes for persistent constitutional symptoms, many physicians will elect to treat CMV viremia and monitor patients for evidence of clinical response. Since drugs that eliminate the virus from the blood are indicated, ganciclovir or foscarnet is preferred to cidofovir.[110] Induction doses for 2 or 3 weeks are generally used, and the need for continued therapy is determined empirically.

Recommendation

- Cytomegalovirus viremia may be associated with subclinical involvement of other organ systems. In the symptomatic patient with CMV viremia without other treatable pathogens identified after a thorough evaluation, a therapeutic trial of ganciclovir or foscarnet may be warranted (C III).

CMV RETINITIS IN PATIENTS WHO RESPOND TO POTENT ANTIRETROVIRAL THERAPY

The recent availability of potent, combination antiretroviral regimens for HIV may be changing the incidence, clinical presentation, and course of CMV disease, at least temporarily. Many large HIV care centers and associated ophthalmologists have recently observed a decrease in the number of new cases of CMV retinitis.[111] In addition, CMV disease has been diagnosed in some HIV-infected patients at higher $CD4^+$ cell counts than previously reported, including some greater than 0.20×10^9/L, shortly after potent antiretroviral regimens were initiated. Furthermore, there has been an increasing number of anecdotal reports documenting stabilization of established but inactive CMV retinitis among patients who discontinued their anti-CMV maintenance therapy after initiating potent antiretroviral therapy.[1-4] The period of follow-up, however, has been short (only several months). Although such reports could represent ascertainment bias, they suggest that there may be selected patients in whom anti-CMV therapy can be safely discontinued for an indeterminate period of time. However, neither the long-term implications on morbidity and mortality nor the precise identification of the patients who are the best candidates for such discontinuation of therapy have been determined. These issues need to be addressed in controlled studies.

RECOMMENDATIONS

- All HIV-infected patients with CMV disease should receive potent, combination antiretroviral

therapy as tolerated and according to recommended guidelines[112] (A I).

- Generally, patients in whom CMV disease has been diagnosed should be advised to continue their anti-CMV maintenance therapy as indicated because the effect of potent antiretroviral therapy on the course of CMV disease is still poorly understood (B III).

CONCLUSIONS

The challenges presented by CMV disease in persons with HIV infection require the coordination of care between primary care physicians and specialists (eg, ophthalmologist, infectious disease specialist, gastroenterologist, and neurologist) to manage end-organ disease appropriately. The selection of antiviral therapy must be made with the knowledge of the advantages and limitations of each approach. Treatment decisions must be individualized depending on the specific circumstances of each patient.

The effectiveness of potent antiretroviral therapy for HIV infection should not lull the medical community into the perception that CMV end-organ disease will disappear. Although the incidence of CMV retinitis appears to be decreasing, patients may develop CMV disease prior to initiating antiretroviral therapy or before its full benefit is achieved. Furthermore, CMV disease may develop or relapse in patients in whom antiretroviral therapy has failed. Thus, potent antiretroviral therapies may only delay the appearance of CMV end-organ disease until HIV becomes resistant to the newer combination treatments. Attention to the epidemiological features of CMV disease and the vigilant evaluation and care of individuals at risk remains of paramount importance.

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replicate and may eventually dominate the population of infecting virus.

The same mechanism operates during acute HIV infection (Figure 1). At this point, the HIV viral load will typically decline to a particular "set point" in an individual patient. If the set point is relatively high, there is greater opportunity for emergence of viral resistance because there is a higher rate of viral replication. If the set point is low, there is less replication and, subsequently, a lower rate of development of resistance mutations. This is the rationale for the current focus on selecting an initial antiretroviral regimen that produces maximal suppression of HIV replication.

Mathematical Basis for Combination Drug Therapy

Given that the development of viral resistance is related to the rate of viral replication, one means of slowing the development of resistance is the simultaneous use of drugs of different classes early in HIV infection. The goal is to maximally suppress early viral replication and prevent expansion of resistant subpopulations. The use of a combination of drugs may also provide a mathematical advantage. For example, the frequency at which a specific, single base mutation occurs in HIV is typically about 10^{-5}, (ie, one virus with a specific mutation will occur per 100,000 virions). Therefore, in a patient with a viral load of 10^8 virions, there may be approximately 1000 viral mutants of that type ($10^8 \times 10^{-5} = 10^3$), and the odds of resistance developing during monotherapy are very high. However, the frequency at which 2 specific mutations occur in the same virion is greatly reduced. From our knowledge of genetics, if they are independent mutations, the frequency can be calculated by multiplying the individual mutation frequencies, as in the example above: $10^{-5} \times 10^{-5}$, or 10^{-10}. If the viral load is 10^8, the odds of carrying a specific mutation to both drugs are $10^{-10} \times 10^8$, or 10^{-2} (1 in 100). Adding an effective third drug to the combination further increases the mathematical advantage and theoretically, at least, should make drug resistance rare.

Continued Presence of Mutant Viruses

According to Dr Johnson, if the antiretroviral drug pressure is removed by stopping therapy, the predominant HIV population will revert to wild-type virus (susceptible to the drug) over a period of months. However, a subpopulation of mutant variants with resistance to that particular drug will remain at a frequency that is much higher than before treatment was introduced. This mutant population may replicate slowly, but it will persist in lymph nodes or other sequestered sites. When treatment with the same drug or a drug of the same class that is associated with cross-resistance to that drug is initiated, these mutants quickly reemerge and again predominate in the viral population. This resistant virus will reemerge more rapidly than it did initially. The clinical result is that the drug will be less effective when used a second time. For this reason, the patient's first treatment with antiretroviral drugs is currently considered to be the one with the best chance to succeed. For previously treated patients, knowing the complete drug treatment history can be essential to planning changes in the therapy.

Viral Susceptibility and Resistance Testing

Laboratory testing of the susceptibility of an HIV isolate to different drugs in vitro, and for detecting and quantifying resistance mutations, are beginning to become available. These assays can be broadly subdivided into 2 types: (1) phenotyping, and (2) genotyping (See sidebar definitions).

Phenotyping: Direct Measurement of Viral Susceptibility

HIV phenotyping can be considered analogous to determining the minimum inhibitory concentration of a streptococcal isolate to penicillin in vitro. The viral isolate to be tested is exposed to varying concentrations of the antiretroviral drug in cell culture, and the drug concentration that has a specific inhibitory effect is determined. Phenotyping requires the use of infectious virus, requires days to perform, is expensive, and lacks standardization. Furthermore, it is not yet clear what the measurements precisely mean, nor where the cut-off should be made between "susceptible" and "resistant" virus. In addition, the viral population being tested may consist of a mixture of subtypes with varying responses to the drug being evaluated. Nonetheless, this assay method has a relatively long history, and research into making this test faster and simpler is progressing.

Genotyping: Measurement of the Genetic Potential for Resistance

Genotyping assays are used to detect the presence of viral nucleic acid sequences

Table 2. Clinical Application of Viral Resistance Testing

- Viral resistance is only one possible cause of treatment failure; possible other causes should be evaluated, as well.
- The susceptibility of virus found in the plasma may not reflect the susceptibility of virus in sequestered sites.
- Serial quantification of plasma HIV RNA level and CD4+ cell count (the clinical response) should remain the primary guide for evaluating the response to antiretroviral therapy.
- Knowledge of a patient's complete drug history is essential for the clinical management of drug failure.
- Viral susceptibility and resistance assays are not yet standardized or validated, and their clinical utility has not yet been established.
- Interpretation of viral resistance data must consider the patient's complete drug history, plasma HIV RNA level, response to therapy, and patient adherence to dosing regimens.

known to be associated with phenotypic or clinical resistance. The assay does not require live, infectious virus and can use a small amount of plasma, tissue, or other body fluid. However, the specimen must contain a sufficient number of copies of the viral genome (about 1000) to allow adequate amplification of the target HIV nucleic acid. Genotyping can be completed in hours and may be less expensive than phenotyping, but the interpretation of the results is much more complex than are the results from phenotyping methods. Genotyping can detect resistance subtypes of virus in the tested population. However, genotyping detects single mutations that may not be relevant, and may miss important resistance mutations that are rarer. This latter problem can be overcome by complete sequencing of portions of the viral genome; but sequencing is time-consuming and impractical for large numbers of isolates.

Dr Johnson stressed that neither phenotyping nor genotyping alone is optimal at present, and probably both are needed, along with plasma HIV RNA, CD4+ count, and complete drug history data, for the proper clinical use of resistance information.

Specific Viral Resistance Mutations

HIV Reverse Transcriptase Mutations

Figure 2 shows the common viral mutations in the HIV-1 RT gene associated with phenotypic resistance to RT inhibitor drugs. Didanosine, zalcitabine, and stavudine commonly select for resistance mutations between positions 69 and 74, along with lamivudine in the 184 position. There is expectedly some cross-resistance among these compounds, although Dr Johnson indicated that this was sometimes a low-level resistance, as occurs between didanosine and zalcitabine. This moderate degree of resistance may be overcome by using higher doses of a drug to raise tissue concentrations to near the increased 50% inhibitory concentration (IC_{50}) value. For the lamivudine 184 position mutation, and for the nonnucleoside RT inhibitor (NNRTI) nevirapine, only 1 mutation is usually required to cause high-level resistance (eg, a 100- to 1000-fold increase in the IC_{50}). For zidovudine, a step-wise accumulation of 2 mutations must occur for high-level resistance to develop (ie, mutations at positions 41 and 215). Because 2 rather than 1 mutations are required, resistance will appear more slowly than that associated with a single point mutation.

Theoretically, knowledge of the existing genotypes prevalent in a heavily pretreated patient in whom therapy has failed may be useful in determining which new drug regimen is most likely to be virologically effective. For example, a patient with the 184 position mutation may not achieve a satisfactory clinical response by retreatment with lamivudine or didanosine. Dr Johnson noted that although this type of application of genotypic information is being studied, there are not yet enough data to use it in routine practice.

DEFINITIONS

Genotype The genetic make-up of a virus, determined by the sequence of nucleotide bases in the viral genome. Changes (or mutations) in the sequence change the genotype and may encode viral proteins that respond differently to an antiretroviral drug. If the mutation causes decreased susceptibility, the change is termed a mutant genotype. Based on prior laboratory analysis, specific genotypes are known to be associated with resistance to specific drugs. Genotyping requires only detectable viral genome, not live virus.

Phenotype The ability of a virus to grow in cell culture in the presence of various concentrations of an antiviral drug. Usually a virus is tested in comparison with a control, wild-type virus known to be drug-susceptible. Infectious (live) virus is required to measure phenotype.

Mutations to HIV Protease Inhibitors

There are a significant number of common or overlapping resistance mutations among saquinavir, ritonavir, and indinavir (Figure 3). Cross-resistance

Amino Acid	41M	65K	67D	69T	70K	74L	75V	103K	106V	108V	181Y	184M	188Y	190G	210L	215T	219K	236P
Zidovudine	L		N		R										W	Y,F	Q	
Didanosine		R				V						V						
Zalcitabine		R		D		V						V						
Lamivudine												V						
Stavudine							T*											
Nevirapine								N	A	I	C, I		C	A				
Delavirdine								N			C, I							L*

Figure 2. *Known HIV-1 reverse transcriptase (RT) mutations associated with resistance to RT inhibitor drugs.*
**Mutations selected in vitro, but not often found in patients in whom the drug has failed.*

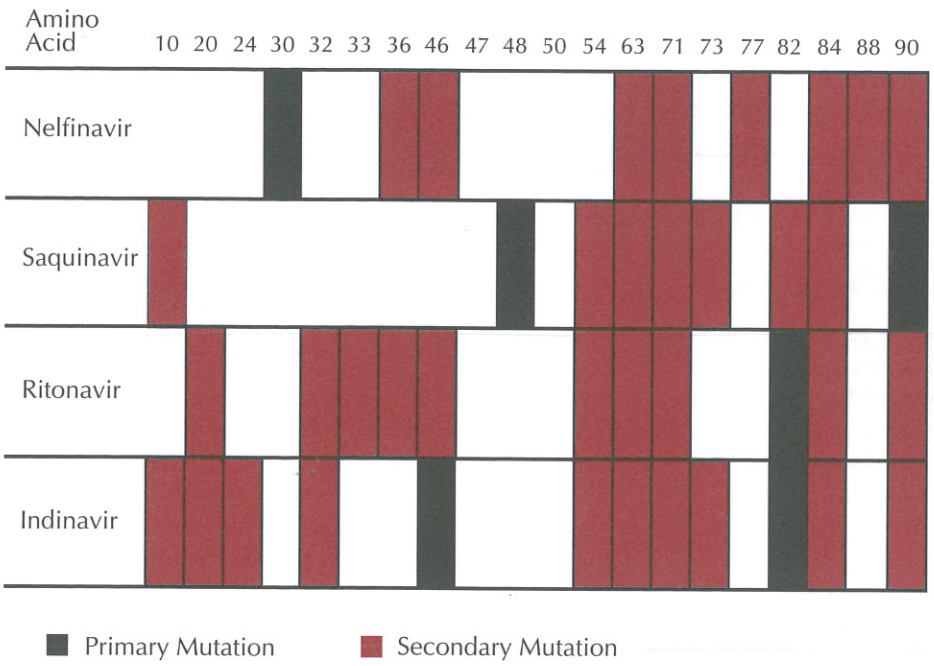

Figure 3. *Known HIV-1 protease mutations that are associated with resistance to protease inhibitor drugs. Primary mutations are generally selected early in mutation accumulation and are relatively inhibitor specific. Secondary mutations accumulate in viral genomes already containing one or more primary mutations and may be selected because they improve viral fitness.*

among the protease inhibitors was first noted when patients who had participated in early studies of saquinavir were later found to have reduced susceptibility to indinavir, even though they had never taken indinavir. As a drug class, protease inhibitors have the greatest degree of cross-resistance, and clinicians usually do not switch from indinavir to ritonavir, or vice versa, in the setting of treatment failures (except when the ritonavir/saquinavir combination is used to increase serum levels of saquinavir). For this reason, it is important that the protease inhibitor in an initial regimen be used at the optimum dose, consistently with strict adherence to the dosing schedule, and in a regimen as one in a combination of drugs.

There is now crystal structure information on the HIV protease molecule revealing the positions in the protein where the various resistance mutations occur. Protease inhibitor molecules fit into the active site pocket of the enzyme. Three common mutations sites for indinavir and ritonavir resistance are at positions 82, 84, and 90 of the protease gene. Saquinavir has a different mutation site, which explains the lower level of cross-resistance between saquinavir and indinavir or ritonavir than between the latter two drugs. An important resistance mutation for nelfinavir is at position 30 on the protease gene. As this drug becomes more widely used, additional resistance mutation sites will most likely be identified.

Multiple mutations are required for HIV to develop high-level phenotypic resistance to indinavir or ritonavir. For example, the IC_{50} of HIV to indinavir may not change with only 1 or 2 active site mutations. The IC_{50} will be increased with the third, fourth, and fifth mutation, by approximately 2.5-fold, 4-fold, and 8-fold, respectively. At the point where there are 4 or 5 mutations, it will be difficult to achieve a high enough drug concentration in vivo to inhibit replication.

Experience in the Clinic

Dr Johnson discussed the application of HIV drug susceptibility and resistance testing in the clinical setting, as summarized in Table 2. The development of HIV viral resistance testing as a clinical tool is very new; there are no standardized kits or accepted and validated test conventions on which to base clinical decisions.

Available resistance data suggest that HIV carrying resistance mutations for RT inhibitors or protease inhibitors can be transmitted from person to person. Furthermore, in certain regions of the country, 5% to 10% of the HIV-infected patients have broad, multiple drug resistance. In this regard, viral resistance testing may become useful in those regions to assist in the design of initial treatment regimens for HIV-infected pregnant women, occupationally exposed health care workers, and in patients with primary HIV infection.

Over the next few years we can expect that the methodology for HIV resistance testing will become simpler, less expensive, and faster. This, along with clinical studies, will facilitate advances in the understanding of the clinical relevance of resistance data and may lead to more rational, less empirical, antiretroviral therapy.

Victoria A. Johnson, MD, is Associate Professor of Medicine and Microbiology at the University of Alabama at Birmingham.

Suggested Reading

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Hertogs K, DeBethune MP, Miller V, et al. A rapid method for simultaneous detection of phenotypic resistance to inhibitors of protease and reverse transcriptase in recombinant human immunodeficiency virus type 1 isolates from patients treated with antiretroviral drugs. *Antimicrob Agents Chemother.* 1998;42:269-276.

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Electronic Media

http://hiv-web.lanl.gov/

http://www.viral-resistance.com

Upcoming IAS-USA Activities

International AIDS Society-USA Symposium at the12th International Conference on AIDS in Geneva, Switzerland

Wednesday, July 1, 1998 3:00 PM - 5:00 PM

Antiretroviral Therapy and HIV Drug Resistance Testing in 1998: Issues and Applications

The International AIDS Society-USA will convene its International Panels on Antiretroviral Therapy and Resistance Testing to present and discuss the recent recommendations developed by the two groups. The following Panel members will be in attendance to discuss the respective recommendations:

Co-Chairs

Scott M. Hammer, MD
Boston, Massachusetts

Martin S. Hirsch, MD
Boston, Massachusetts

Patrick G. Yeni, MD
Paris, France

Welcome, Introductions, and Closing Remarks

Charles C. J. Carpenter, MD
Providence, Rhode Island

John G. Bartlett, MD
Baltimore, Maryland

Anthony S. Fauci, MD
Bethesda, Maryland

Paul A. Volberding, MD
San Francisco, California

Topics

- HIV Pathogenesis
- Clinical Aspects of Resistance Testing
- Antiretroviral Therapy: When to Start/What to Start With
- Antiretroviral Therapy: When to Change/What to Change to

Panelists

Françoise Brun-Vézinet, MD
Paris, France

Bonaventura Clotet, MD, PhD
Barcelona, Spain

Brian Conway, MD, FRCPC
Vancouver, British Columbia

Richard T. D'Aquila, MD
Boston, Massachusetts

Margaret A. Fischl, MD
Miami, Florida

Victoria A. Johnson, MD
Birmingham, Alabama

David A. Katzenstein, MD
Stanford, California

Daniel R. Kuritzkes, MD
Denver, Colorado

Clive Loveday, MD, PhD
London, England

John W. Mellors, MD
Pittsburgh, Pennsylvania

Julio S. G. Montaner, MD
Vancouver, British Columbia

Douglas D. Richman, MD
San Diego, California

Michael S. Saag, MD
Birmingham, Alabama

Robert T. Schooley, MD
Denver, Colorado

Melanie A. Thompson, MD
Atlanta, Georgia

Stefano Vella, MD
Rome, Italy

For information about the symposia, contact the IAS-USA at the address in the next column.

Current Challenges in HIV Disease: A Cased-based Advanced Course in Clinical HIV Management

The annual fall CME courses are under development. New data will be presented in didactic formats as well as within the context of clinical case presentations, blending advanced-level understanding of HIV treatment with the realities of patient care. Faculty will include experts from the various disciplines in the field of HIV medicine. The following sites and dates have been scheduled for these upcoming courses, and brochures and registration materials will be available shortly.

New York, October 9, 1998
Chair: Douglas T. Dieterich, MD
Vice Chair: Michael L. Tapper, MD

Chicago, October 15, 1998
Chair: John P. Phair, MD

San Francisco, October, 1998
(Date to be determined)
Chair: Molly Cooke, MD
Vice Chair: Kathryn Kocurek, MD

Atlanta, October/November, 1998
(Date to be determined)
Chair: Michael S. Saag, MD

For further information about these and other IAS-USA activities, contact:

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fax 415-561-6740;
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Invitational brochures and complete symposia information will be available shortly.

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