The most important message that could be delivered is the need for identification of persons at risk, so that PCP prophylaxis can be administered. The marked reduction in morbidity with this simple intervention is still one of the major advances in the care of HIV infected patients, and the continued high incidence of PCP in patients not previously known to be HIV infected tell us that we are not effectively reaching this group.

-- Peter Frame, M.D.

We are just one short step, whether by drug toxicity or microbial mutation, away from a much less satisfactory situation... In too many cases, our successes are dependent on just one medication, the loss of which may be catastrophic.

-- William Powderly, M.D.

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FOREWORD

by William G. Powderly, M.D.

Opportunistic infections (OIs) remain the most important complications of HIV infection, resulting in profound morbidity and mortality. They clearly will remain a major issue as long as immunodeficiency is the inevitable result of long-standing HIV infection. As data from natural history studies show, while PCP prophylaxis has increased survival and delayed the onset of AIDS-defining illnesses, the inevitable is merely postponed. The advent of newer, more effective antiretroviral therapeutic regimens has clearly altered the equation in favor of the patient, but for many the question will be for how long? Furthermore, it is clear that even for patients who experience effective antiviral responses to therapy, important questions regarding their immunocompetence and vulnerability to OIs remain.

The last ten years have elevated many once obscure pathogens to new prominence, and significant advances have been made. Just ten years ago, in 1987, OI research was in its infancy. *Pneumocystis carinii* pneumonia was by far the most common OI, with an associated mortality of 20-40%. Two drugs were available for therapy, trimethoprim-sulfamethoxazole Bactrim (TMP/SMX), and pentamidine, and they were associated with dose-limiting toxicity in up to half of patients. Prophylaxis was used sparingly, only in certain parts of the country, and was not widely accepted. For the fungal infections, amphotericin B was the only available therapy, although phase I studies of the triazole antifungal agents fluconazole and itraconazole had been completed. For *Toxoplasma* encephalitis, pyrimethamine/sulfadiazine was effective, but it shared the same tolerability problems as TMP/SMX. Effective therapies for cytomegalovirus (CMV) retinitis, *Mycobacterium avium* complex (MAC) or acyclovir-resistant herpes simplex were not available or were not standardized, and treatment was based on anecdotal information at best. The co-epidemic of tuberculosis was yet to be recognized.

We now have very effective therapies for many of the common OIs, such as PCP, tuberculosis, cryptococcosis and histoplasmosis; effective but toxic therapies for toxoplasmosis and moderately effective treatment regimens for disseminated MAC and CMV infections. Only the enteric parasitic diseases such as cryptosporidiosis and microsporidiosis and the viral brain disease PML elude us in terms of at least modestly active treatment.

Yet these advances give us no reason for complacency. In some cases, we are just one short step, whether by drug toxicity or microbial mutation, away from a much less satisfactory situation. Clinicians well recognize the problems posed by sulfa-drug allergies in the management of PCP and toxoplasmosis, and by fluconazole- resistant fungal organisms such as *Candida*. Microbial resistance is increasingly an issue for mycobacterial and CMV infections as well. In too many cases, our successes are dependent on just one therapeutic agent, the loss of which may be catastrophic in terms of care.

The last ten years have also seen an increasing recognition that many OIs can be prevented. The use of prophylaxis for PCP has increased survival and delayed the onset of an AIDS-defining illness. The counterpart of this increased survival, however, is that patients using effective PCP prophylaxis have an increased risk of developing disseminated *Mycobacterium avium* complex (MAC), CMV disease, wasting syndrome and esophageal candidiasis -- as well as the opportunistic neoplasms such as Kaposi's sarcoma and lymphoma. Prevention of MAC has also proved to extend survival, and data also demonstrate that some fungal and viral infections are preventable. However, this knowledge is tempered by the fact that multiple drug therapy for prevention of OIs is complicated by issues of toxicity, resistance, drug interactions, and cost. Thus, no consensus on how to best use multiple agents has yet been reached.

More effective antiretroviral therapy has provided new hope for many, and may be changing the course of OIs. Indeed, it could be argued that the most effective preventive therapy for all of the opportunistic infections will be more complete control of retroviral replication and with it preservation of better immunocompetence. It is clear that there are fewer OIs with the protease inhibitors -- both in clinical trials and in clinical practice. What is not

clear is the extent or durability of the immunologic protection. Thus, the answer to a critical question for patients and doctors alike -- Can I stop the prophylaxis? -- is unknown. Clearly this question needs to be addressed by clinical researchers.

We are all glad to be in an era of optimism about the prospects for treating AIDS and HIV disease, and hope it will continue. Nonetheless, we must recognize that our current foundations are shallow, and must strive to improve our chances of overcoming these opportunistic pathogens. In many cases, while we have improved diagnosis, treatment and prophylaxis, our understanding of the microbial pathogenesis of these opportunistic organisms has not kept pace with our clinical advances. Yet only by developing a fuller understanding of the complex stages of the life cycles of these parasites, and their interactions with the human host immune defenses will we be able to keep up with their alarming ability to mutate away from antimicrobial control. Only increased research on the pathogenesis of the OI organisms will provide us with success. An important goal, therefore, is to define better predictors of certain OIs and thus identify subsets among patients with advanced HIV disease who are at increased risk for these infections. One approach is to attempt to use clinical parameters. Patients who have experienced one OI are at greater risk of developing a second, at any given CD4 count -- this is particularly true for MAC and CMV. Unfortunately, thus far these indicators merely identify relative rather than absolute risks and are not discriminatory enough to suggest strategies for prevention.

A more promising avenue is the use of microbiologic and immunologic markers, especially for CMV infection and MAC. As an example, the pathogenesis of CMV in patients with AIDS is far from clear. A majority of HIV-positive individuals have been exposed to CMV, yet only a minority develop overt CMV disease. A high proportion of individuals with advanced HIV disease are CMV viremic and/or viruric, yet many of these never develop overt CMV disease. Several reports have suggested that CMV virologic measures might be predictive of invasive CMV disease, especially retinitis . If confirmed, it might be possible to identify patients at high risk of developing CMV disease. In that case, regular screening for early evidence of viral replication by polymerase chain reaction (PCR) might be useful in targeting early intervention, rather than true prophylaxis. Additionally, certain OI-specific immune response (or perhaps loss of specific OI responses) may be critical in the development of certain infections. These too could be used to better target prevention or early treatment. What is clear is that there should be a high priority for clinical and basic research in this arena.

The series of articles that you will read in this report provides a thorough review of the state of the art for these tremendously varied infections and provides a more detailed analysis of some of the questions that I have alluded to. It is to be hoped that all of you who read this will be provoked into recognizing that there are many more questions to be answered and will be stimulated into providing support and encouragement to help produce some of the answers. We should be unstinting in our thanks to Michael Marco and his colleagues from the Treatment Action Group for producing this document.

*

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INTRODUCTION

by Michael Marco

February 1998

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Six years ago, at the Amsterdam AIDS Conference, I joined a group of activists to zap the Astra booth in protest at the obscene price of Foscavir™ brand foscarnet and accompanied them to a canal into which they scattered the ashes of Michael Wright, an AIDS treatment activist from San Francisco who died that January of hepatitis, and whose ashes they had brought to the Astra zap. Right then and there I realized that people with AIDS needed a lot more than zaps to save their lives, and that dedicated treatment activists were dying a lot faster than they were being replaced. So I decided to become an AIDS treatment activist. I had never met Michael Wright, but I knew that he'd worked wonders in a brief, brilliant activist career which began after watching Peter Staley's inspirational opening address at the 1990 San Francisco AIDS Conference. Soon after, I started working with Andy Zysman, also of San Francisco, who educated me about the ins and outs of AIDS malignancy research, until he too died suddenly during mid-1993.

Treatment activists are still being lost faster than they're being replaced, and one of the great pleasures of creating this report has been working with a group of committed TAG volunteers to develop a new understanding of the challenges facing AIDS research as we approach the next millennium. AIDS-related opportunistic infections (OIs) will be with us for the foreseeable future, because — contrary to the assertions of naively-optimistic commentators in *The New York Times* and *The Wall Street Journal* — AIDS is not over. Indeed, on a global scale, the killing has just begun. HIV disease is still chronic, but it is not yet manageable, and what limited tools we have to extend health and life largely began with the explosion of AIDS OI research — an explosion instigated by AIDS treatment activists — in the late 1980s. "More OI Research!" was one of ACT UP's demands at "Storm the NIH" in 1990, and this report documents the major progress made in preventing and treating AIDS-related OIs in response to activist pressure. Special mention here should be made of the Countdown 18 Months Project of ACT UP/New York's Treatment + Data Committee (T+D), which included Garance Franke-Ruta, Derek Link, Rich Lynn, Kim Powers, Jerry Jontz and Scott Slutsky, the last two of whom did not live to see the fruit of their labors. Scott Slutsky in particularly continued to work on expediting development of MAC treatment and prophylaxis even as he contended with CNS lymphoma; the major advances in this field documented below are a testament to his work.

It has been exciting to work with the researchers (and some veteran treatment activists) who cut their teeth in the early days by forcing the government to pay attention to the "S" in AIDS — the syndrome of opportunistic complications -- not just the underlying HIV infection. For the first part of the past decade, it is safe to say, advances in OI research saved more lives than antiretrovirals. While this is changing with potent protease inhibitor combination therapy (PPICT), we have only short-term data on PPICT, and the likelihood is that all many people will eventually progress, as before, only over a longer period of time. This report is dedicated to all the treatment activists who have struggled before, and to those who will follow.

It is seldom recognized how great the benefit is for people with other life-threatening diseases because of AIDS treatment activism. Every year hundreds of thousands of people *without* HIV will take drugs which were tested and approved faster because of AIDS activists. Eventually, everyone will develop a disease — be it cancer, iatrogenic infection or autoimmune disorder — whose treatment outlook may be better because of research done on people with HIV.

OIs in people with AIDS *are* the acquired immunodeficiency syndrome(s) caused by HIV-inflicted immune damage. As an HIV-positive person becomes increasingly immune deficient, he or she becomes increasingly

vulnerable to a myriad of viral, bacterial, fungal and protozoal infections. Many OIs can be treated, yet a person remains at risk for relapse or a cascade of different OIs, which may cause suffering or death. No HIV-positive person is immune from any OIs, nor will he or she be able to tell which will strike first. Thus, the clinical spectrum of OI research – manifestations, diagnosis, treatment, and prevention – should be of concern to all HIV-positive individuals, their physicians and care partners.

Many of the common OIs, *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV) retinitis, *Mycobacterium avium* complex (MAC), and candidiasis, are not new to AIDS; they have often affected individuals with primary immunodeficiency syndromes, organ transplant patients and those immunosuppressed due to cytotoxic chemotherapy regimens used to treat cancer. Research on treatment for many of these OIs began in the 1960s and 1970s with the advent of many new antibiotics. For example, it was Walter Hughes who discovered that TMP/SMX could treat and prevent PCP in childhood leukemia. Likewise, fluconazole was originally developed and tested in cancer patients to treat their various fungal infections.

Nonetheless, this OI report is AIDS-specific, and attempts to detail what we know and what we don't know about the epidemiology, pathogenesis, diagnosis, treatment and prevention of approximately sixteen viral, bacterial, fungal and protozoal infections. *The OI Report*, version 2.0, is the work of eight dedicated members of TAG's OI Committee who have spent over two years researching, writing and editing articles on their respective pathogens. All of us were gifted to have prominent AIDS researchers -- many of whom conducted major OI studies detailed in the report -- as our advisors and editors.

This new version includes chapters on bacterial Infections and AIDS-related tuberculosis as well as a preface which details the current epidemiology and clinical course of the major OIs since the advent of protease inhibitors. We have attempted to write this report for multiple audiences, including people with HIV, primary care physicians, researchers, industry representatives, and government officials. Herein lies a detailed history of, and unanswered questions about, our most commonly used drugs (i.e, Bactrim, ganciclovir, clarithromycin, fluconazole), as well as practical information ("the basics") for people living with HIV, which may help them understand their infection and give them the tools they need to stay healthy and live longer by making informed treatment decisions. Broader use of PCP and MAC prophylaxis alone will save tens of thousands of lives.

A majority of data discussed in this report are from studies completed before the advent of the protease inhibitors. As PPICT became the standard of care over the last 18 months -- at least for those with access -- we know that the incidence of OIs has markedly decreased. Nonetheless, OIs are not simply "going away." For many, protease inhibitors may not rebuild a devastated immune system. We still need basic and clinical research on a majority of OIs so that we might better understand their pathogenesis and treat or prevent them successfully with less toxic agents, as well as manage emerging drug-resistant organisms. This will take a concentrated effort on the part of industry, physicians, government and the HIV community alike if we are to challenge and ultimately overcome the syndrome of AIDS.

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OPPORTUNISTIC INFECTIONS IN THE ERA OF PPICT[1]

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by Michael Marco

1 January 1998

INTRODUCTION

Two years ago marked the dawn of the protease inhibitor era, one of dramatic breakthrough in our ability to treat HIV infection. Two years ago, on February 1, 1996, during the "late breakers" session at the Third Conference on Retroviruses and Opportunistic Infections in Washington DC. In front of a standing-room-only crowd of over a thousand, Bill Cameron presented preliminary results of Abbott's pivotal study 247, demonstrating that the protease inhibitor ritonavir, when added to an underlying regimen of reverse transcriptase inhibitors in severely immune-compromised patients (CD4 below 100) significantly decreased the occurrence of AIDS-related opportunistic infections (OIs) and death (Cameron 1996). The emotional impact of these data, indicating that, "For outcomes after one month on study, AIDS-or-death occurred in 69 [patients](12.7%) versus 149 [patients] (27.3%, $p < 0.001$, HR 0.44, 95% CI 0.33 - 0.58)" is still difficult to put into words. It was the first antiretroviral licensing study to show a survival benefit since BW-02 did so with AZT in 1987.

OI Endpoints in Abbott Study 247

Endpoint (OI)	*Ritonavir (N=543)*	*Placebo (N=547)*	*p-value*
Cytomegalovirus (CMV), all sites	16	30	<.05
Retinitis	13	17	
Other	3	13	
Esophageal Candidiasis	16	38	<.05
***Mycobacterium Avium* complex (MAC)**	6	9	
***Pneumocystis carinii* pneumonia (PCP)**	6	16	<.05
Wasting	2	8	<.05
Kaposi's Sarcoma	8	22	<.05
Non-Hodgkin's Lymphoma	3	7	
Others	10	26	<.05

(Cameron 1996)

Later in 1996, at the Eleventh International AIDS Conference in Vancouver, British Columbia, additional data indicated the possibility of attaining profound, and hopefully prolonged antiretroviral suppression by simultaneously initiating therapy with one potent protease inhibitor and one or two new nucleoside reverse

[1] THE ACRONYM HAART (HIGHLY ACTIVE ANTIRETROVIRAL THERAPY) HAS BEEN USED TO DISCUSS PROTEASE INHIBITORS IN COMBINATION WITH REVERSE TRANSCRIPTASE INHIBITORS. HOWEVER, IT HAS BEEN USED TO DESCRIBE MANY REGIMENS IN WHICH A PROTEASE INHIBITOR WAS SIMPLY ADDED TO AN UNDERLYING NUCLEOSIDE REGIMEN, SUCH AS IN ABBOTT 247, OR WHEN THAT PROTEASE INHIBITOR LACKED SUFFICIENT POTENCY, SUCH AS ROCHE'S INVIRASE™ BRAND SAQUINAVIR. HENCE WE USE THE TERM HAART WHEN UNSURE WHETHER THE REGIMEN USED WAS MAXIMALLY SUPPRESSIVE, AND THE TERM PPICT (POTENT PROTEASE INHIBITOR COMBINATION THERAPY) WHEN DATA REFER TO REGIMENS LIKELY TO LEAD TO MAXIMAL VIRAL SUPPRESSION, AS RECOMMENDED IN THE HIV TREATMENT GUIDELINES RECENTLY PUBLISHED BY THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) (BARTLETT 1997).

transcriptase inhibitors (RTIs). Before Vancouver, many simply added protease inhibitors to an underlying RTI regimen, as in Abbott 247. After Vancouver, and particularly after the release of the HHS Guidelines one year later, the standard of care evolved to improve the chances for maximal suppression with the simultaneous initiation of at least two new antiretrovirals at a time. Thus, the two-nucleoside era was succeeded by the era of HAART and, after Vancouver, by that of potent protease inhibitor combination therapy (PPICT).

Because all these changes occurred so rapidly, the full impact of PPICT on the incidence and prevalence of AIDS-related OIs did not begin to become clear until early 1997 at the Fourth Retrovirus Conference, later that spring with the release of the results of ACTG 320, and then more fully in fall 1997 at the 35th annual meeting of the Infectious Diseases Society of America (IDSA) and the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Three substantive themes in OI research and treatment emerged in 1997:

- The incidence of OIs in people with AIDS (PWAs) on HAART or PPICT markedly decreased;
- PPICT has changed the natural history of OIs and, in some cases, appears capable of treating OIs for which specific antimicrobial therapy does not yet exist;
- OIs affect the natural history of HIV infection and vice versa

Incidence Rates of OIs in PWAs on HAART or PPICT

Michaels and colleagues, in conjunction with the Adult Spectrum of Disease Cohort (ASDC), conducted a retrospective cohort study of HIV-positive individuals (CD4s <200) attending an HIV outpatient clinic in New Orleans from 1 December 1994 to 1 January 1998 (Michaels 1998). Baseline characteristics grouped 1,181 patients before 1996 and 1,248 patients after 1996. The most common OIs, including PCP, CMV, MAC, KS, and wasting, were markedly lower in 1996 and 1997.

OI Incidence Rates from the Tulane/Adult Spectrum of Disease Cohort, 1994-1998			
	Jan 94 to Dec 96 (N=1,181)	***Jan 96 to Jan 98 (N=1,284)***	***p-value***
PCP	18.0%	11.7%	<0.01
Wasting	9.5%	4.8%	<0.01
MAC	8.5%	6.1%	<0.05
CMV	4.6%	3.0%	<0.05
Kaposi's sarcoma	4.3%	2.5%	<0.05
Toxoplasmosis	2.9%	1.9%	<0.15
Dementia	3.8%	2.8%	<0.20
Esophageal candidiasis	9.5%	8.0%	<0.20
Cryptococcal meningitis	3.3%	2.7%	<0.35
Cryptosporidiosis	3.8%	3.2%	<0.45

(Michaels 1998)

The decreases are at least in part a testament to HAART/PPICT's direct antiretroviral effect and ensuing improvements in cell-mediated immunity, yet the decrease is also likely to be in part due the use of a macrolide (azithromycin, clarithromycin) for MAC prophylaxis, and behavioral modifications such as better dietary habits to prevent wasting, or a change in gay male sexual practices to avoid human herpes virus-8 (HHV-8).

At ICAAC 1997, Palella and colleagues presented data from the HIV Outpatient Study (HOPS) Group, a three-year study of PWAs with CD4 counts below 100. These data convincingly document the recent decline in OIs and death in patients on PPICT.

Decline in Deaths and OIs in 2,957 PWAs from the HOPS Group, 1994-1996			
	Died	***OI Rate***	***Rx Included PI***
1994	6.1%	18.5%	20% (4th quarter)
1995	6.9%	18.0%	
1996 overall	3.9%	10.5%	
1996 3rd quarter	2.8%	8.3%	
1996 4th quarter	2.0%	3.2%	75%

PI = protease inhibitor *(Palella 1997)*

The clearest demonstration of the PPICT on PWAs is documented in the preliminary data analysis of OI events in ACTG 320, the indinavir clinical endpoint study that randomized 1,156 patients with CD4 counts below 200 and at least three six months of prior AZT therapy to either AZT/3TC/indinavir (n=577) or AZT/3TC (n=579). The study was stopped early because of statistically significant differences in deaths and AIDS events favoring the triple therapy group (Hammer 1997).

At the 23rd ACTG Meeting in Washington, DC, Judith Currier presented Paige Williams' preliminary data analysis of the OI events in ACTG 320. Ninety-one OI events occurred in ACTG 320: 60 in the AZT/3TC arm and 31 in the AZT/3TC/indinavir arm. Below is a breakdown of the eight most common OIs:

320: Preliminary Analysis				
	N cases	***75)***	***vir (N=579)***	***p-value***
	23			<0.05
	18 (16 first event)			0.55
	15 (12 first event)			NS
	4			NS
didiasis	4			NS
sis	4			NS
	2			NS

320: Preliminary Analysis				
na	3			NS

(Currier 1997)

320 Patients with <50 CD4 cells at Baseline (Preliminary Analysis)			
			vir

(Currier 1997)

e (IR) of OIs in ACTG 320 per 100 Patient Years of Follow-up: Preliminary Analysis			
			vir

(Currier 1997)

More detailed analyses of ACTG 320 are underway but the incidence of OIs in the triple therapy arm of ACTG 320 may be among the lowest ever documented in a study this size with this patient population. It will be interesting to see if any of these OIs developed in individuals on prophylaxis, and at what CD4 count. For example, did patients with CD4 counts above 100 develop CMV or MAC?

This significant decrease in OIs, especially MAC and CMV, was also documented outside the United States. Two oral abstracts at the 37th ICAAC from the Hôpital de la Pitié-Salpêtrière in Paris reported a dramatic decrease in the rates of MAC and CMV after the initiation of PPICT.

Hôpital de la Pitié-Salpêtrière Cohort's Incidence Rates of MAC & CMV before and after PPICT				
OI	***1/95 - 9/96***	***After 9/96***	***p-value***	***ref.***
MAC	~14%	1.8%	<0.001	(Jouen 1997)
CMV	18.7%	5.0%	<0.01	(Baril 1997)

The Changing Natural History of OIs in the PPICT Era

While the incidence rate of OIs is decreasing since the advent of PPICT, the natural history of many OIs is changing as well. CMV for example, may now occur at higher CD4 counts, if those counts have recently risen. Some OIs, such as microsporidiosis, cryptosporidiosis, and progressive multifocal leukoencephalopathy (PML) are

being successfully treated with PPICT alone. While most of the reports that follow are small case series from various institutions around world, their findings are being consecutively confirmed by other institutions.

Cryptosporidiosis, Microsporidiosis & PML

At the Fourth Retrovirus Conference, two posters reported on case series of patients with microsporidiosis and cryptosporidiosis who started PPICT. In the first case series, all five patients with cryptosporidiosis and seven patients with microsporidiosis had a remission of diarrhea within 12 weeks of starting PPICT. Only in one patient were parasites still observed in the stools, and only one patient relapsed (Carr 1997). In the second, 27 patients with chronic cryptosporidiosis and microsporidiosis began PPICT. After treatment, all but two patients with microsporidiosis cleared parasites from the stools (Benhamou 1997). Yet another group reported on the disappearance of microsporidiosis and absence of *E. bienusi* organisms in the stools of 15 patients who initiated PPICT in ARNS trials 034 and 054 (Goguel 1997). Since no curative therapy exists for cryptosporidiosis and microsporidiosis, these data are inspiring, yet in one sense they are not new. In 1992, Flanigan and colleague documented that patients whose CD4 counts rose above 180 cells while receiving AZT monotherapy (the old days) overcame cryptosporidiosis within a month (Flanigan 1992). This proves that the improved immune function that a decrease in viral load and an increase in CD4 cells reflect can overcome and kill these parasites.

A handful of abstracts have also documented the resolution of PML after the initiation of PPICT.

The most dramatic effect of HAART on PML is reported in (Albrecht 1997; Hoffmann 1997). A retrospective natural history study of 29 patients (median CD4 count of 40) with polymerase chain reaction (PCR) or histologically confirmed PML analyzed patient survival according to antiviral usage. In group "A", 14 patients never received or stopped antiviral therapy; 10 patients in group "B" were treated with nucleoside analogues alone; and five patients in group "C" were administered HAART.

Median Survival After PML Diagnosis According to Antiviral Usage		
Antiviral Usage	***N***	***Survival (days)***
Group A: never started, or stopped	14	123
Group B: nucleoside analogue(s)	10	127
Group C: HAART	5	>500

(Albrecht 1997; Hoffman 1997)

At the time of presentation, four of five PPICT patients were still alive. They were progressing more slowly or had experienced resolution of their PML symptoms. Of interest, median CD4 count, prior AIDS diagnosis, or treatments, including Ara-C, foscarnet, or alpha interferon did not affect the survival of these patients.

CMV

PPICT might not benefit certain PWAs in preventing CMV retinitis. Jacobson and colleagues have reported on 5 patients with CD4 counts over 195 who developed CMV retinitis just 4 to 7 weeks after initiating PPICT (Jacobson 1997). Five to 24 weeks before initiating HAART, all five had CD4 counts below 85.

To demonstrate how the common CD4 threshold has changed after PPICT, Jacobson conducted a retrospective analysis of 76 patients from an ACTG study 266 who developed CMV retinitis between 7/95 and 8/96. The data below document the change:

CD4 Counts of Newly Diagnosed CMV Retinitis Cases Before and After PPICT		
	Cases with CD4 >50	***Cases with CD4 >100***
7/95 - 2/96	1/27 (4%)	0
3/96 - 8/96	14/49 (29%)	7/49 (14%)

(Jacobson 1997)

Similar results from a prospective cohort study were recently reported by a group from Spain. Mallolas and colleagues documented 21 cases of CMV end-organ disease (nine initial episodes and 12 relapses) in patients on PPICT (Mallolas 1997). Nineteen (90%) of 21 cases occurred within two months of initiating PPICT, and none occurred during the three month median follow-up period (range: 0 - 8 months). The median CD4 count of the 21 cases was 30 (range: 2 to 225), however, 25% of the patients had more than 50 CD4 cells at diagnosis.

Thus, CMV retinitis will develop or progress in some patients despite a rise in CD4 count, from PPICT, to levels previously perceived as safe. It is possible that these patients had asymptomatic CMV retinitis or were CMV DNA PCR positive (viremic) and that the CMV virus had already seeded the eye before they started PPICT. Once the CMV is in the sanctuary of the eye, PPICT might not effectively halt the clinical progression to retinitis.

MAC

The incidence of disseminated MAC disease (dMAC) has decreased since the advent of PPICT, but the decrease may not be as large as for CMV and PCP. At the Fourth Retrovirus Conference, two teams reported on eight persons who developed MAC disease shortly after starting PPICT (Race 1997; Phillips 1997). All cases noted focal, inflammatory lymphadenitis (FIL) and fever. In fact, the three patients from Race and colleagues had CD4 counts below 50, FIL and developed MAC six to 21 days after initiating PPICT. According to Race, "The development of fever, leukocytosis, and FIL in patients with unrecognized MAC infection following initiation of PRI [PPICT] may be stimulating antigen-specific T-cell mediated inflammatory reactions."

These same findings were documented in Abbott's 247 ritonavir study. Ten of the 15 cases of MAC disease that occurred in the ritonavir arm were reported in the first 28 days of therapy, and several cases of lymphadenitis were identified (Judith Currier's personal communication with M. Heath-Chiozzi, ACTG 362 protocol).

THE EFFECT OF HIV ON THE NATURAL HISTORY OF OIs AND VICE VERSA

HIV Viral Load Predicts OIs

For many years we have known that a patient's CD4 count is a predictor of the development of certain OIs (e.g., before PPICT almost all CMV cases occurred in patients with CD4 counts below 50). Now, however, HIV load -- and its changes after initiating antiretroviral therapy -- might further help us in identify those at risk for some OIs.

Swindells, Currier and Williams conducted a retrospective data analysis (DACS 071) on 813 patients from four pre-PPICT ACTG antiviral studies which documented the predictive value of plasma HIV RNA and CD4 cells on the development of CMV, PCP and MAC (Swindells 1997). DACS 071 documented that both baseline and post-treatment HIV RNA levels -- as well as CD4 cell count -- were strong predictors of these three OIs. Patients with baseline HIV RNA over 100,000 copies/mL had twice the risk of PCP and five to six times the risk of CMV and MAC as those with less than 100,000 copies/mL. The relative risk (RR) for PCP, CMV and MAC was, 2.29, 5.64, and 4.74, respectively. Likewise, patients with CD4 counts below 75 had four to six times the risk of PCP, CMV and MAC. Alarmingly, patients with over 100,000 copies/mL of virus and CD4 counts below 75 had approximately 28 times the risk of MAC.

After the initiation of antiretroviral treatment, a one-log rise in HIV RNA doubled the risk of PCP and tripled the risk of CMV and MAC. An increase in CD4 count of just 50 reduced the risk of developing each OI by 30-35%. At eight weeks, a 0.5 log decrease in HIV RNA significantly reduced the risks of CMV and PCP, by approximately 70%. Any decrease in HIV RNA was shown to reduce the risk of MAC significantly. After 24 weeks on antiretroviral therapy, a sustained 0.5 log decrease in HIV RNA further reduced the risks -- for CMV and MAC by approximately 85%, and for PCP by 57%. After controlling for HIV RNA level, CD4 increases at week eight or 24 provided no extra benefit.

These viral load data -- albeit from older, pre-protease inhibitor studies -- will help identify specific "thresholds" or cutoff values for targeting prophylaxis regimens in patients at highest risk for OIs. For these three OIs, which cause significant morbidity and mortality, this study proves that lowering the HIV RNA level with potent antiretroviral therapy is necessary for proper prevention. Approved OI prophylaxis medications [e.g., TMP/SMX (Bactrim) for PCP and a macrolide for MAC] might not be effective prevention if a patient's HIV viral load is skyrocketing.

OIs Increase Risk of Death

Chaisson and colleagues presented data from a retrospective analysis of 2,081 HIV-positive patients from Johns Hopkins (mean follow-up period of 30 months). The development of PCP, CMV, MAC, esophageal candidiasis, Kaposi's sarcoma, non-Hodgkin's lymphoma, PML, dementia, wasting syndrome, toxoplasmosis and cryptosporidiosis was found to be independently associated with death while cryptococcal meningitis and herpes zoster were not. Moreover, the development of PCP, CMV, MAC and toxoplasmosis was associated with an increased risk of death and shorter survival regardless of CD4 count (Chaisson 1997).

Increased Risk of Death After Developing an OI			
OI	***Relative Hazard***	***95% Confidence Interval***	***p value***
MAC	2.56	2.1 - 3.1	0.0001
Toxoplasmosis	1.85	1.3 - 2.6	0.0003
CMV	1.63	1.3 - 2.1	0.0001
PCP	1.29	1.1 - 1.5	0.005

(*Chaisson 1997*)

The fact that these OIs increase the risk of death independently of CD4 count tells us that the development of an OI probably increases HIV expression and immune damage by causing immune activation. Thus, an OI is not just an annoying infection that warrants treatment, it is affecting the natural history of HIV with significant shorter survival. This alone warrants initiating effective OI prophylaxis regimens in patients at risk.

OIs Increase HIV Load

Bush and colleagues conducted a retrospective analysis of ten patients whose viral load was monitored before, at time of diagnosis, and after the resolution of PCP. Seven of the patients were antiretroviral naive and three continued antiretroviral monotherapy during their course of PCP. The medium serum HIV RNA prior to diagnosis of PCP (median time before onset = 81 days) was 113,850 copies per mL, as compared with 231,450 copies per mL at the time of PCP diagnosis (p=0.03). Nine of these ten patients had marked elevations of their HIV RNA upon developing PCP -- five of whom had three-times baseline or more. Seven of ten patients showed a decrease of their HIV RNA upon resolution of PCP (median HIV RNA = 198,500 copies/mL) (Bush 1997).

Similar results have been reported by Cooper and colleagues on a group of five children with dMAC who had elevated HIV RNA at the time of diagnosis. Four of the five children had an approximate one log drop in their HIV RNA within two months of initiating three or four-drug anti-MAC therapy (Cooper 1997).

The most convincing evidence that OIs increase HIV replication ("with a burst of virus") was recently published in *Science* (Orenstein 1997). Orenstein biopsied lymph nodes of patients to look for co-expression of HIV and OIs. Using in situ hybridization, he found that "unprecedented levels of HIV production were evident in the tissues of patients with OIs." Moreover, Orenstein found that the pathogens -- namely PCP and MAC -- were localized in macrophages and not lymphocytes.

HIV-Expression of Mononuclear Cells in Biopsied Lymph Nodes of PWAs with and without OIs		
	N	***HIV+ cells/10mm³***
AIDS OI		
PCP	1	118.8
MAC	6	58.9
MTB	1	54.6
Histoplasmosis	1	26.3
M. kansasii	2	14.9
HIV+ - no OI		
Follicular hyperplasia	24	2.8
Hyperplasia/Involution	21	1.4
Involution	18	2.0

HIV-Expression of Mononuclear Cells in Biopsied Lymph Nodes of PWAs with and without OIs		
Lymphoid depletion	4	0.5

(Orenstein 1997)

The elevation in HIV RNA seen with the development of PCP and MAC (and possibly other OIs) seriously calls into question the routine discontinuation or interruption of antiretroviral therapy when a patient develops an OI. This has been done to simplify the management of the toxicities that can occur from the combination of many medications. These data, however, suggest that effective antiretroviral therapy during the life-span of the OI may be necessary to prevent or control a burst of HIV expression.

Discontinuing OI Prophylaxis and Maintenance Therapy After PPICT

PPICT has been documented to decrease patients' viral RNA to undetectable levels and to raise CD4 counts. This remarkable antiviral activity is not matched by an equally strong cell-mediated immune recovery (i.e., an increase in broad and diverse CD4 number and function). Nonetheless, many patients with CD4 counts between 50 and 100 are seeing an increase of 100-200 cells. Researchers, clinicians and primary care physicians have been asking three primary questions about this rise in CD4 cells, such as: 1) What is the true significance of this increase? 2) Are these new CD4 cells as functional and competent as ones lost in the course of HIV-associated CD4 depletion? 3) Can OI prophylaxis be stopped in patients whose CD4 counts increase above the threshold of risk after starting PPICT?

Recent data suggest that the new CD4 cells acquired by PPICT *might* be able to function as well as old naive CD4 cells in *some* patients, but only after a certain period of time on PPICT. In May 1997, Connors and colleagues reported that HIV progression is associated with a preferential decline in naive CD4 T cells and that the disruption in one's complete CD4 T cell repertoire was most prevalent in PWAs with very low CD4 counts. After the initiation of PPICT, naive CD4 T cells only increased in number if they were present before initiation of therapy (Connors 1997) Thus, PPICT does not appear to completely restore depleted pathogen-specific immunity, regardless of initial increases in total CD4 lymphocyte count.

In July 1997, Autran and colleagues reported that there were three phases of CD4 T cell reconstitution after PPICT: 1) an early rise of memory CD4 cells; 2) a reduction in T cell activation with improved CD4 T cell reactivity to recall antigen; and 3) a late rise in "naive" CD4+ lymphocytes while CD8+ T cells declined, *yet without complete normalization* (Autran 1997).

According to Bill Powderly at the 35th IDSA Meeting, an absolute recovery of one's complete immunologic functions after PPICT may not be possible and may depend on the degree of damage. But the recovery provided by PPICT may still be sufficient to protect against most OIs (Powderly 1997). A critical question still unanswered is, "How much immunologic recovery (and of what) is necessary for complete protection from OIs?" And will this answer pertain to all OIs or is it pathogen specific? With a complete understanding of the pathogenesis for PCP, MAC and CMV still unclear, Powderly contends:

We still do not know what the critical effector arms of the immune system are that provide protection against invasive disease...and, in most cases, we don't even know what (or how) to measure to determine if patients lack specific immunity." (Powderly 1997)

Discontinuing OI Prophylaxis

In late 1996, many months before these questions were actually addressed and before these data became available, primary care physicians, prison doctors and HMO clinicians were taking patients on PPICT off their MAC and PCP prophylaxis if their CD4 counts increased to above the threshold of risk (50 for MAC and 200 for PCP). This is still continuing even though the USPHS/IDSA OI prophylaxis guidelines panel recommends "continuing prophylaxis based on the nadir [the lowest level ever attained] of a patient's CD4 count." (USPHS 1997).

In order to test whether stopping OI prophylaxis is sound or harmful in patients whose CD4 counts have risen above a certain threshold, Currier and colleagues developed ACTG 362, the first "stop MAC prophylaxis trial." ACTG 362 is a randomized, double-blind, placebo-controlled trial available for enrollment to any PWA who is receiving antiretroviral therapy and has had a documented increase in CD4 cell count from below 50 on one occasion to above 100 on two separate occasions, sequentially, at least four weeks apart. There will be 636 patients enrolled. Participants will be randomized to receive azithromycin 1200 mg once weekly or matching placebo (a look-alike sugar pill) and will be followed closely every eight weeks until study closure or for 72 weeks. Patients whose CD4 count drops below 50 on two occasions at least four weeks apart will be offered open-label azithromycin. Patients will be stratified at baseline for prior use of MAC prophylaxis (ACTG 362).

ACTG 362 also has three important substudies, one looking at stopping PCP prophylaxis in 50 patients and two looking at specific immunologic parameters in patients on PPICT.

- ACTG 888: Impact of discontinuing primary PCP prophylaxis in patients receiving antiretroviral therapies who have had increases in CD4 counts to above 200 cells. Patients whose CD4 cell count has fallen below 200 on two separate occasions and those with symptoms of oral thrush or unexplained fever for over two weeks will restart conventional PCP prophylaxis and be discontinued from the PCP substudy.
- ACTG 889: *In vitro* or *ex vivo* correlates of risk for opportunistic infections: recall or naive antibody responses and recall DTH.
- ACTG 899: *M. avium* skin test reactivity and development of MAC disease.

Preliminary results from a study on discontinuing PCP prophylaxis were presented at the 37th ICAAC. Schneider and colleagues from the Netherlands presented data on 45 patients who discontinued their primary PCP prophylaxis and five who stopped their secondary prophylaxis. At the time of discontinuation, the mean CD4 cell count was 370 and HIV-RNA was undetectable in 40 patients. The remaining ten patients' HIV RNA levels did not exceed 15,000 copies/mL. The mean CD4 cell count nadir of the patients was 77. Eleven of the 50 patients were antiretroviral naive when they started PPICT. After a median follow-up of 3.9 months (range 0.4-30.5 months; median follow-up for the five secondary prophylaxis patients, 1.3 months), no episodes of PCP occurred (Schneider 1997).
It is hard to make much of these results with such short follow-up. Likewise, only having data on five secondary prophylaxis patients tells us nothing about the wisdom of discontinuing maintenance therapy. Some are hopeful that ACTG 362 and 888 will help us answer questions about discontinuing primary OI prophylaxis. Both studies are well thought out, with proper patient management and specific safeguards.

Taking a patient off prophylaxis just because of cost (Bactrim is less than 25 cents a day) or convenience is presently neither recommended nor acceptable patient management. Until we have more answers, all physicians treating PWAs should follow the USPHS/IDSA OI prophylaxis guidelines.

Discontinuing Suppressive/Maintenance OI Therapy

Two small retrospective studies in which patients discontinued CMV maintenance treatment were presented at the 37th ICAAC. Torriani and colleagues from UCSD presented data on 8 patients who had "voluntarily" discontinued CMV maintenance therapy after long periods of non-progressive disease; five were on IV or oral ganciclovir and three were receiving intraocular cidofovir. At time of discontinuation, the median CD4 count of the patients was 172 (range: 63 - 404) and the ***median HIV RNA was 68,000 copies/mL (range: <200 - 508,000 copies/mL)***. None of the eight patients progressed after a median follow-up of 146 days (range: 72-205). *Nevertheless, during this follow-up, six of eight patients had detectable [HIV] viral loads* (Torriani 1997).

This study created some well-deserved controversy. NIAID's Michael Polis was the first up to the microphone asking Torriani how in the world could she discontinue CMV maintenance therapy on a patient with an HIV RNA of 508,000 copies/mL. Another question which occurred to an intelligent observer was, "Why didn't you take that patient over to the virology team of Richman and Havlir to get new antiretroviral therapy instead of monkeying with his/her CMV therapy?" Lastly, some wonder if those three patients on cidofovir intraocular therapy voluntarily went into the study with open arms, or were they just fed up or frightened by that needle poking them in the eye?

The Spanish team of Tural and colleagues conducted a similar, but less risky study. Seven newly diagnosed CMV retinitis patients on ganciclovir or foscarnet induction therapy were followed for observation. All were on antiretroviral therapy without protease inhibitors, were CMV DNA PCR positive, and had a median CD4 count of 56. Within 6.3 months, 5 patients experienced at least one relapse (8 relapses total). When protease inhibitors became available in Spain, all seven patients initiated PPICT. After 3.5 months on PPICT, all patients had at least 150 CD4 cells and undetectable HIV RNA and CMV DNA. Soon after, patients voluntarily discontinued maintenance therapy and had opthalmologic evaluations weekly for three months and subsequently every two weeks. Thus far, no CMV relapses have been documented (Tural 1997).

To confirm the relevance of their findings, Tural and colleagues are planing a prospective study which will use four specific criteria for entry: quiescent CMV, CD4 count over 150, undetectable HIV RNA, and undetectable CMV DNA. Torriani and colleagues from the ACTG and SOCA have also developed a sound, soon to open, 125 patient study, ACTG 379, "The Effects of Stopping CMV Maintenance Therapy."

No data have been generated on stopping patient's suppressive MAC therapy. To address this question, Judith Aberg and Judith Currier have developed a protocol concept sheet for the ACTG, CS 719: "Eradication of Disseminated *Mycobacterium avium* Complex (dMAC) After Twelve Months [of] Anti-Mycobacterial Therapy and Immune Reconstitution with Highly Active Antiretroviral Therapy (HAART)."

CONCLUSION

For PWAs who have access, 1997 was the year of PPICT. Two years ago, it was almost unthinkable that combination antiviral therapy could suppress HIV below the levels of detection. The results from ACTG 320 have proven that PPICT, compared with combination nucleoside analogue therapy, can increase survival and decrease OIs. The marked decrease in OIs is undoubtedly welcome news for PWAs.

Nonetheless, many clinicians and researchers express caution and fear that we are in a "honeymoon phase" over our recent success. Some say that in six to 18 months we may well see a substantial number of patients fail PPICT, either due to antiretroviral drug resistance or patient non-adherence, and then see a substantial increase in OIs. The future is uncertain, especially for those heavily pretreated patients whose viral loads rebound and whose CD4 counts decrease significantly.

Only effective OI prophylactic regimens, such as Bactrim for PCP and a macrolide for MAC, can ensure patients who have failed PPICT proper protection from a cascade of OIs. We still do not have a thoroughly effective, inexpensive and convenient drug to prevent CMV. Luckily, Hoffmann-LaRoche has finally consented to provide its ganciclovir prodrug (valganciclovir) to the ACTG and SOCA for a study of preemptive therapy/targeted prophylaxis among PWAs whose CMV DNA is positive.

Given the uncertainties, answering the many questions about opportunistic infections and developing new drugs with increased activity will have to be a joint effort on the part of clinicians, researchers, primary care physicians, industry, government and people with HIV and treatment advocates.

*

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Viral Infections

HERPES SIMPLEX VIRUS

by Paul Dietz

INTRODUCTION

Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) are members of the human herpesvirus family, which also includes cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), human herpesviruses 6 and 7, and Kaposi's sarcoma-associated herpesvirus, also known as human herpesvirus 8 (KSHV or HHV-8). HSV-1 and 2 are quite similar to each other in nature, though their modes of transmission and clinical manifestations differ.

HSV-1, the cause of the familiar cold sore, produces ulcerative lesions in and around the mouth and nostrils. It is transmitted through direct contact with infectious mucous membranes, usually by kissing or oral-genital contact.

HSV-2 is transmitted through sexual contact, causing lesions on the penis in males, and around the vagina, cervix, vulva, and perineum in females. In both sexes, lesions in the perianal area and buttocks are common. Herpes sores may be accompanied by pain, itching, adenopathy (swelling of the lymph nodes), painful urination or defecation, fever, and fatigue. During primary infection, inflammation of the meninges can occur in 5-10% of patients.

HSV-1 and 2 are common in patients with HIV, often appearing among the earlier infections associated with AIDS. For some people with AIDS (PWAs), HSV remains asymptomatic or causes only occasional outbreaks. For others, HSV lesions may persist or continue to enlarge, exposing the patient to secondary infection and excruciating pain. In very severe cases, HSV may spread through the blood or cerebral spinal system to the esophagus, lung, eye, or brain. HSV lesions presenting for longer than a month, or the occurrence of HSV-related pneumonitis, bronchitis, or esophagitis in a person with HIV (or with no other apparent cause for immunodeficiency) are considered AIDS-defining (McGrath 1994). Though it occurs rarely, HSV-associated encephalitis (an infection of the brain) is a debilitating and life-threatening disease.

There is no cure for HSV, though the frequency and severity of attacks can be reduced through use of antiviral drugs such as acyclovir (Zovirax) or famciclovir (Famvir). However, the emergence of resistance to these drugs in immunocompromised patients may curtail the long-term effectiveness of these treatments. In such cases, alternative therapies include foscarnet or topical trifluridine, depending on the nature and severity of the HSV illness. Both are regarded as fairly safe and effective second-line treatments. Topical cidofovir and topical foscarnet are under investigation for this indication as well.

EPIDEMIOLOGY

HSV-1 is pervasive. In 1989, Johnson and colleagues reported that an estimated 70% of the adult U.S. population was infected with HSV-1 (Johnson 1989). Another study found that 46 of 68 (66%) HIV-infected patients with *Pneumocystis carinii* pneumonia (PCP) had antibodies to HSV-1 (Safrin 1991a). As a sexually transmitted disease, the epidemiology of HSV-2 closely resembles that of HIV, though genital herpes is much more common in women. Data from a San Francisco General Hospital trial in 1986 revealed that 77% of 68 patients with PCP tested positive for HSV-2 antibodies (Safrin 1991a). Without regard to type, herpes lesions are

infectious from shortly before lesions develop to the point of full healing. The risk of transmitting HSV-2 can be reduced, though not prevented, with use of latex condoms. Once infected, patients should use good hygiene to reduce the chance of spreading the infection to other body parts. Topical antiseptic creams may help avoid superinfection of herpes lesions.

A report from the Fourth Conference on Retroviruses and Opportunistic Infections suggested that ulcerative herpes lesions are capable of aiding the sexual transmission of HIV. Schacker and colleagues tested 24 herpes ulcers from twelve HIV-infected men and found that 23 (96%) of the lesions contained large amounts of replication-competent HIV (Schacker 1997). The measured levels of HIV decreased after herpes treatment was initiated. The investigators suggested that these data provide biological evidence for the epidemiological association between HIV infection and genital herpes, and suggested studying the effect of acyclovir on genital HIV shedding.

PATHOGENESIS

Soon after resolution of the primary symptoms, HSV assumes a latent status in the patient's sensory nerve endings and ganglia. In most cases, orolabial HSV establishes latency in the trigeminal root ganglia (face/jaw), while genital herpes establishes latency in the sacral plexus (genital/pelvis/buttocks area). Unlike HIV, HSV assumes both a clinical and cellular latency as the virus is believed to replicate at a lower rate during this period. The immune response appears to play an important role in driving HSV into its initial latent state and in maintaining HSV latency (McGrath 1994). The chronic immunodeficiency brought upon by HIV puts patients at increased risk of HSV reactivation. HSV replication is believed to be stimulated by a number of factors including fever (thus the term *fever blister*), sun exposure, concurrent viral infection, and possibly also localized trauma, hormonal changes, or stress (Erlich 1995).

DIAGNOSIS

The first incidence of HSV can be diagnosed through viral culture or Tzanck smear. Subsequent recurrences are often diagnosed by clinical examination. Serologic testing is not very useful since a large segment of the population has HSV antibodies indicating prior infection (Erlich 1995).

CLINICAL MANIFESTATIONS

HSV Esophagitis

HSV-1 esophagitis is characterized by extremely painful swallowing, sore throat, and retrosternal pain. Diagnosis is made by upper endoscopy with confirmatory biopsy for virus culture. Differential diagnosis should rule out esophageal candidiasis and CMV. HSV esophagitis responds well to oral acyclovir, though intravenous (IV) acyclovir may be used if throat pain impedes oral use (Erlich 1995).

HSV Proctitis

HSV-2 is a common cause of proctitis among sexually active individuals. Symptoms include anorectal pain, perianal lesions, painful urination and defecation, constipation, fever, and inguinal adenopathy (Goodell 1983). Diagnosis can often be made clinically, but should be confirmed with viral culture. Herpes proctitis generally responds well to treatment with oral acyclovir, though IV administration may be used for severe cases or where diarrhea may impede gastrointestinal absorption (Erlich 1995).

Ocular HSV Disease

Herpes simplex infections of the eye include keratitis, keratoconjunctivitis, uveitis, and keratouveitis. Serious cases can result in damage to the cornea. HSV-1 induced keratitis is "the principal infectious cause of blindness in the developed world" (Streilin 1997). Ophthalmic diagnosis requires differentiation from varicella-zoster virus. Herpetic keratitis may be treated with topical antiviral formulations of acyclovir or trifluridine (Klein 1988). Systemic therapy may be required to prevent recurrences.

HSV Encephalitis

Though rare, HSV encephalitis is a catastrophic and potentially fatal condition in PWAs (Fletcher 1992). Symptoms include headache, fever, nausea, lethargy, confusion and seizures possibly leading to coma and death. Some patients present with similar but milder symptoms resembling a benign meningitis. Until recently, HSV encephalitis was diagnosed by brain biopsy or serological testing of the cerebrospinal fluid for differentiation from toxoplasmosis, *Cryptococcus neoformans*, and lymphoma (Erlich 1995). However, the use of HSV DNA polymerase chain reaction (PCR) testing of the cerebrospinal fluid (CSF) is rapidly gaining acceptance and may have replaced brain biopsy as the preferred diagnostic method. In one study, PCR correctly diagnosed 53 of 54 patients with HSV encephalitis (Lakeman 1995). Proven cases of HSV encephalitis should be treated with IV acyclovir at 10 mg/kg every eight hours for at least ten days (Sasadeusz 1993). Foscarnet has not been well studied, but is known to penetrate the CNS (Raffi 1992). Treatment outcome appears to be related to the severity of disease, the person's age, and the state of consciousness at baseline (Whitley 1986). Despite treatment, the six-month mortality is 19%, with one-third of surviving patients suffering residual neurological damage (Sasadeusz 1993).

HSV Pneumonia

Though rare in patients with HIV, HSV-related pneumonia can be serious in immunocompromised patients if not properly diagnosed and treated. HSV pneumonia may result from the contiguous dissemination of HSV from the esophagus or from the visceral spread of HSV through the bloodstream. In 1982, Ramsey and colleagues isolated HSV from lung specimens of 20 patients who had died of respiratory insufficiency, though none of the patients had previously been diagnosed with HSV pneumonia (Ramsey 1982). Mucocutaneous herpes manifestations predated the pneumonia in 17 of 20 patients. Thus, clinicians may wish to consider HSV as a possible pathogen in patients with pneumonia and a history of HSV disease, especially if there is evidence of recent mucocutaneous HSV or visceral dissemination (Ramsey 1982). Diagnostic methods include culture from lung biopsy, histologic examination, and examination for virus antigen by immunofluorescence.

TREATMENTS

Acyclovir (Zovirax™, Glaxo Wellcome)

Acyclovir is a well-established, safe and effective treatment for HSV-1 and 2. It is approved for the treatment and suppression of recurrent HSV. Acyclovir is available in topical, oral, and IV forms. IV acyclovir, however, is reserved for the treatment of HSV encephalitis, severe mucocutaneous disease, and where oral administration is not feasible (Sasadeusz 1993). Topical acyclovir is rarely used due to its limited effectiveness. Acyclovir has a favorable toxicity profile and has been used safely for over five years by a large number of patients. A minority of patients experience rash, nausea and loss of appetite. Reversible renal deterioration has been associated with high doses, and temporary neurotoxic symptoms such as disorientation, tremors, slurred speech, and seizures are

infrequently associated with IV acyclovir (McGrath 1994). Acyclovir's disadvantage is its poor bioavailability (15% to 30%) which necessitates frequent dosing. CSF acyclovir concentrations average 50% of plasma levels.

Acyclovir (ACV) Dosages for HSV Infections in Immunocompromised Patients	
Mild to moderate monocutaneous HSV-1 or 2	Oral ACV 200 mg 5 times daily or 400 mg 3 to 5 times daily
Severe or unrelenting monocutaneous HSV-1 or 2, or if oral absorption is dubious	IV ACV 5 mg/kg every 8 hours
Visceral or disseminated HSV, or HSV encephalitis	IV ACV 10 mg/kg every 8 hours.
Maintenance to suppress reactivation	No uniform standard;400 mg twice or thrice daily is commonly prescribed.

(Fletcher 1992)

In patients with severe immunodeficiency, HSV may recur soon after discontinuation of therapy. In varying doses, acyclovir has been shown to reduce the frequency of recurrences (Straus 1984). Maintenance therapy is indicated for frequent or severe recurrences.

Acyclovir-resistant HSV occurs with significant frequency in HIV-infected and other immunocompromised patients. A retrospective study conducted at the University of Minnesota found acyclovir resistance in 7 of 148 (4.7%) immunocompromised patients with HSV (Englund 1990). A survey conducted at a major metropolitan hospital between 1992 and 1995 noted that 10% of HSV isolates demonstrated decreased susceptibility to acyclovir (Cotarelo 1996).

Most patients with acyclovir resistant HSV have profound immunosuppression (Balfour 1994). In one study, the median CD4 count in 25 HIV-positive patients with acyclovir-resistant HSV infection was 24 (Safrin 1991b). Taking acyclovir intermittently or in suboptimal doses may also encourage drug resistance (Balfour 1994). The FDA turned down Glaxo-Wellcome's application to market over-the-counter acyclovir, partly due to fear of encouraging the emergence of acyclovir-resistant HSV.

To act as an effective agent, acyclovir must first be triphosphorylated through a series of steps involving viral and cellular enzymes. The primary mechanism of acyclovir resistance is selection for virus deficient in thymidine kinase (Chatis 1992). Unfortunately, many other herpes drugs also require thymidine kinase for phosphorylation. As a result, acyclovir-resistant strains tend to be cross-resistant to ganciclovir, valacyclovir (the acyclovir prodrug), and famciclovir (the prodrug of penciclovir). This leaves few alternatives in the face of acyclovir resistance, though both foscarnet, cidofovir and trifluridine have shown activity against acyclovir-resistant HSV (Safrin 1991b; Kessler 1993; Lalezari 1996).

An algorithm for the treatment of acyclovir-resistant HSV was developed at a round-table symposium held in March 1993:

Increase the dosage of oral acyclovir to 800 mg 5 times a day if new lesions continue to form after 3 to 5 days of treatment at the standard dose listed above.

If there is no response after 5 to 7 days, and lesions are accessible, the panel recommended the addition of topical trifluridine every 8 hours until healing is complete. If lesions are not accessible, IV foscarnet at 60 mg/kg twice daily or 40 mg/kg thrice daily until complete healing. *(Balfour 1994)*

Foscarnet (Foscavir™, Astra)

Foscarnet has *in vitro* activity against a number of human herpes viruses, including HSV-1 and 2, CMV, EBV, VZV, and also HIV (Sasadeusz 1993). Foscarnet is approved by the FDA for the treatment of CMV and for acyclovir-resistant herpes simplex in immunocompromised patients. Its side effects include nephrotoxicity (kidney disease), neutropenia, anemia, elevated liver enzymes, penile ulcers, hyperphosphatemia, hypocalcemia, and gastrointestinal intolerance (Safrin 1992).

Foscarnet was tested against vidarabine (ara-A) in ACTG 095, a randomized trial of 14 AIDS patients with acyclovir-resistant HSV. Foscarnet was found to be more effective and was associated with fewer adverse reactions (Safrin 1991b). Lesions healed in all eight patients assigned to receive foscarnet and in none of the six patients receiving vidarabine. Three patients receiving vidarabine had neurological abnormalities while no patient receiving foscarnet experienced any dose-limiting toxicities (Safrin 1991b). Resistance to foscarnet has also been documented (Hardy 1992).

In January 1996, Hardy and colleagues reported results from an open-label pilot study of topical foscarnet cream in 20 patients with acyclovir-resistant HSV. Side effects included skin ulcerations and fever. Of 15 patients reporting pain at baseline, 11 reported complete resolution and 2 reported partial resolution of pain. The median time to complete lesion healing was 44 days (Hardy 1996).

According to Astra Pharmaceuticals, further testing and development of foscarnet cream is under review pending ongoing analysis of trial data.

Foscarnet is available through a compassionate use program for patients with herpes simplex infection that does not respond to standard treatment with acyclovir. The cream formulation is likewise available to patients unable to tolerate IV foscarnet.

Trifluridine (Viroptic™, Glaxo Wellcome)

Trifluridine inhibits HSV by thymidine substitution and has activity against acyclovir-resistant strains. Ophthalmic trifluridine 1% solution is approved for the treatment of HSV keratitis and keratoconjunctivitis and can be used for mild cutaneous HSV that has stopped responding to treatment with acyclovir. In ACTG 172, Kessler and colleagues conducted an open-label study to evaluate the safety and efficacy of topical 1% trifluridine solution for the treatment of chronic acyclovir-resistant mucocutaneous HSV in 26 PWAs. Seven of 24 evaluable patients had complete healing of lesions within a median of seven weeks. An additional seven patients had at least a 50% reduction in lesion size with an estimated median time to 50 percent healing of 2.4 weeks. Seven patients (29%) discontinued treatment for failure to respond to therapy, and eight (33%) patients developed new lesions outside of the treatment area during the study, reflecting the local nature of this therapy. No dose-limiting toxicities were reported, though application of the solution and dressings to genital and perirectal regions three times a day was cumbersome and inefficient. However, given the limited options for the treatment of acyclovir-resistant herpes simplex disease, topical trifluridine may be a useful alternative for some patients (Kessler 1993).

Famciclovir (Famvir™, SmithKline Beecham)

Famciclovir is a nucleoside analogue which is converted to penciclovir in the body. In December 1995, the drug was approved for the treatment of genital herpes in immunocompetent patients. Famciclovir is more bioavailable than acyclovir (77% versus 30%) and has a longer intracellular half-life which allows for a twice daily dosing (Boyd 1988). Since famciclovir relies on viral thymidine kinase for processing, it is generally ineffective against acyclovir-resistant strains. In Europe, Famvir cream is approved for the treatment of herpes cold sores. Loveless and colleagues conducted three studies of 951 HIV-negative patients which compared various doses of famciclovir (250, 500, 750 mg thrice daily) to acyclovir 200 mg 5 times a day. There was no significant difference in the duration of viral shedding, time to healing, or reduction of symptoms in any of the arms. Both

were equally tolerable (Loveless 1995). Schacker and colleagues compared 500 mg famciclovir twice daily with placebo for eight weeks in 48 HIV-infected individuals (45 men, three women) who experienced HSV-2 reactivation. Median CD4 count at entry was 384. By intent-to-treat, HSV-2 was isolated on 122/1114 (11%) placebo days versus 9/1071 (1%) of famciclovir days (relative risk, 0.15, $p<0.001$). "Breakthrough reactivations that occurred while patients were on famciclovir were infrequent, short, and often asymptomatic." Treated patients also experienced a shorter time to lesion healing. Unfortunately, this study made no comparison to acyclovir (Schacker 1996, 1998), as the sponsor apparently plans to promote Famvir's favorable dosing schedule rather than do further studies to establish equivalence or superiority of treatment. SmithKline Beecham plans to file a supplementary new drug application for Famvir for the treatment of acute herpes zoster and recurrent genital herpes in immunocompromised patients soon.

INVESTIGATIONAL HSV TREATMENTS

Cidofovir (HPMPC, Vistide™, Gilead Sciences)

Cidofovir -- a nucleotide analogue -- has broad spectrum of activity against several viruses. Approved in 1996 for the treatment of CMV, cidofovir is phosphorylated by cellular rather than viral enzymes and has shown *in vitro* activity against acyclovir-resistant HSV (DeClerq 1993). *In vitro*, HPMPC is not as effective as trifluridine or foscarnet against acyclovir-resistant strains (Kessler 1993). Moreover, mucocutaneous outbreaks of herpes simplex have been noted in patients receiving intravenous cidofovir for treatment of CMV (Wohl 1997).

In January, 1996 Lalezari and colleagues reported results of a Phase I/II randomized, double-blind, placebo-controlled trial of topical cidofovir gel in PWAs with mucocutaneous herpes simplex unresponsive to acyclovir. A total of 30 patients received either placebo or cidofovir gel at 0.1% or 0.3% concentrations for five days. By day 15, one-half of those treated with the gel had experienced a greater than 50% reduction in the size of lesions. However, complete responses were seen in only 3 of 11 patients receiving the low concentration and in just three of nine (33%) patients receiving the high concentration gel (Lalezari 1996). Based on these data, Gilead applied to the FDA for approval to market cidofovir gel for refractory herpes simplex infection in PWAs. Cidofovir gel, now known under the brand name Forvade™, is currently available from the manufacturer, under a compassionate use program, to patients with mucocutaneous herpes simplex who have failed conventional therapy with acyclovir.

CONTRAINDICATED TREATMENTS

Valacyclovir (Valtrex™, Glaxo Wellcome)

Valacyclovir -- the prodrug of acyclovir -- yields greater bioavailability than its metabolite. Oral administration of 1,000 mg of valacyclovir thrice daily yields plasma concentrations comparable to intravenous acyclovir. Since valacyclovir is converted to acyclovir inside the body, it is not active against thymidine kinase deficient, acyclovir-resistant strains (Easterbrook 1994).

Fife and colleagues compared valacyclovir (100 mg twice daily) against acyclovir (200 mg 5 times a day) in a 643 HIV-negative patient study for the treatment of primary genital HSV. Duration of HSV shedding, pain, and symptoms and time to healing were similar in the two groups (Fife 1995, 1997).

A Phase I trial conducted in HIV-positive patients with CD4 counts less than 150 established a generally favorable safety profile for valacyclovir (Jacobson 1994). Nausea, vomiting, and abdominal pain were reported as well as a few cases of neutropenia. Valacyclovir, however, carries a warning against its use in immunocompromised patients because of its association with hemolytic uremic syndrome / thrombotic

thrombocytopenic purpura (bursting blood vessels in the kidneys) as seen in ACTG 204, a study comparing valacyclovir to acyclovir for CMV prophylaxis HIV-positive patients (FDA Data 1996, Feinberg 1998). Ironically, the ACTG is continuing studies in HIV-positive children (ACTG 253).

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VARICELLA ZOSTER VIRUS

by Paul Dietz

INTRODUCTION

Varicella zoster virus (VZV), a member of the human herpesvirus family, is the cause of both chicken pox (varicella) and shingles (herpes zoster). Like other members of the herpesvirus family, VZV is not eliminated from the body after the acute illness but remains in a latent state for the life of the host. While antibodies generally prevent the recurrence of chickenpox, latent VZV can reactivate to cause herpes zoster, a more localized cutaneous (skin) disease which is commonly referred to as shingles. Zoster is a painful blistering skin rash, usually confined to either the trunk, forehead, or scalp. In a minority of zoster patients -- mostly the elderly -- severe pain may persist after resolution of the zoster skin lesions.

VZV reactivation (zoster) is very common in people with AIDS (PWAs), and it is frequently among the first opportunistic infections (OIs) to emerge. Due to the strong correlation between the reactivation of VZV and immunodeficiency, an episode of zoster in an otherwise healthy person provides grounds to suspect an underlying HIV infection (Melbye 1987).

While most PWAs with zoster suffer only one self-limiting course, up to a quarter of PWAs with zoster experience repeated episodes (Colebunders 1988) which may be more severe and resistant to treatment depending on the extent of immunosuppression. Visceral (internal organ) complications of herpes zoster have been reported to occur in 20% of immunocompromised patients, though treatment is believed to reduce the risk of complications considerably (Whitley 1982). In patients with HIV, such complications most often involve the eye or central nervous system (CNS) (Sharon Safrin, personal communication). Patients developing certain ocular complications of VZV are at risk of permanent vision damage (Cole 1984; Pinnolis 1995). Though rare, CNS involvement (i.e., VZV myelitis and encephalitis) represents a potentially fatal condition (Drew 1995).

EPIDEMIOLOGY

VZV seropositivity exceeds 90% for adults living in the United States (Gershon 1981). VZV is spread through oral-nasal absorption of airborne antigens or by direct physical contact with infectious lesions. Exposure can come from someone with chickenpox or shingles. Patients are thought to be infectious from two days preceding the rash up to the point that all lesions have crusted over (Erlich 1995).

A vaccine for chicken pox has been approved by the FDA for immunocompetent patients and for immunosuppressed children with acute lymphocytic leukemia. The vaccine is not currently given to children with HIV because there is concern that the active, attenuated virus contained in the vaccine may cause disease (Drew 1990). However, a clinical trial to test the vaccine in HIV-positive children, ACTG 265, is underway. The Public Health Service recommends that HIV-infected patients with no history of varicella who have recently been exposed at close contact (within 96 hours) to someone with chickenpox or shingles receive varicella zoster immune globulin prophylaxis.

Zoster is not newly acquired, but represents the reactivation of an existing latent infection. Therefore, contact with an actively infected individual (whether the infection is primary or secondary) is not believed to cause another person's dormant VZV infection to reactivate. The incidence of zoster in the general population is moderate (1.3 episodes per 1,000 person years) (Ragozzino 1982), though it occurs more frequently in people with weakened immune systems such as PWAs and cancer patients who have been exposed to immunosuppressive chemotherapeutic agents (Melbye 1987). A high incidence of zoster is also seen in the elderly, presumably as a result of declining immune status (Waldman 1990).

An observational study of 1,246 HIV-infected patients with CD4 counts of less than 300 found that VZV occurred at rates between 2 and 4 episodes per 100 person-years (Moore 1996). Furthermore, a retrospective review of 300 AIDS patients with Kaposi's sarcoma noted that 8% of those patients had at least one prior attack of zoster (Drew 1990). There is no established prophylaxis for herpes zoster.

PATHOGENESIS

Two weeks or so following initial infection, varicella lesions emerge in the form of small red blemishes on the skin, progressing over one to three days while they become fluid-filled vesicles. Lesions can surface anywhere on the body but tend to concentrate on the face, neck, and trunk. The patient may experience fatigue and flu-like symptoms before and during the outbreak. In the majority of HIV-infected patients receiving treatment, new lesion formation ceases within four days (FDA Data 1996).

In the face of an effective immune response, VZV retreats through cutaneous nerve endings to establish latency in the dorsal root or cranial nerve ganglia. Laboratory studies have discovered latent VZV in the thoracic dermatomes, cervical region, trigeminal nerve, and lumbo-sacral region (Waldman 1990). Multiple ganglia can be infected simultaneously (Mahalingam 1990).

Reactivation of zoster is first characterized by specific symptoms, including pain and hypersensitivity near the affected area. After a few days, a rash emerges in the form of a band or patch of raised, fluid-filled reddish-looking vesicles, often around the head or trunk. New vesicle formation ceases in roughly four to five days, and the rash and pain disappear within three to five weeks for most HIV-positive patients receiving proper treatment (FDA Data 1996).

DIAGNOSIS

Cutaneous varicella or zoster is usually simple to diagnose. Zoster lesions demarcate the distribution of the underlying nerve region, and pain and sensory symptoms characterize nerve involvement. In cases of doubt resulting from disseminated VZV, an atypical lesion pattern, or when scalp lesions are difficult to observe, VZV can be isolated from vesicular fluid by culture or stained with a flourescent monoclonal antibody test kit. This may take up to two weeks. Serological testing is not helpful since much of the population has previously been exposed to chickenpox (Erlich 1995).

OTHER CLINICAL MANIFESTATIONS

Post-Herpetic Neuralgia

One of the most troublesome complications of herpes zoster is post-herpetic neuralgia (PHN), a condition characterized by severe, unremitting pain and hypersensitivity remaining for a significant period beyond the resolution of zoster skin lesions. PHN can be debilitating and may cause psychological trauma and depression in its sufferers (Waldman 1990). The risk of PHN is associated more with advanced age than with immune status (Bruxelle 1995). Nevertheless, some researchers believe that prompt (within 48 hours of the first outbreak of rash), effective treatment of an acute zoster outbreak reduces the duration of zoster-associated pain in the normal host (Boon 1995).

The symptoms of post-herpetic neuralgia are often treated with antidepressants (such as amitriptyline), nerve blockers, narcotic analgesics, and/or topical pain relievers (Waldman 1990; Watson 1995). Though such treatments may bring only partial relief, some patients experience gradual resolution of pain over time (Bruxelle 1995).

VZV Infections of the Eye

Primary varicella and herpes zoster involving the ophthalmic division of the trigeminal nerve can affect the eye. The eye infection may or may not occur in conjunction with a cutaneous outbreak. Symptoms include floating spots, loss of vision, and a high incidence of retinal detachment (Neger 1996). VZV-associated progressive outer retinal necrosis is a sight-threatening condition which is difficult to treat (Pinnolis 1995). Patients may also develop keratitis, anterior uveitis, or corneal scarring, which can lead to permanent visual loss.

Limited treatment options include, intravitreal injections (injecting medication directly into the eye) and/or intravenous (IV) ganciclovir or foscarnet (Cochereau 1995). There has also been at least one reported case of success in treating VZV-associated progressive outer retinal necrosis with a combination of IV ganciclovir and oral sorivudine (see investigational treatments below) in a PWA who had failed standard therapy (Pinnolis 1995). However, sorivudine is no longer under development by its licensee Bristol-Myers Squibb.

VZV Encephalitis and Myelitis

These potentially fatal complications of VZV are very rare. It tends to occur in conjunction with ocular or viscerally disseminated VZV. In an observational study of 626 PWAs with central nervous system manifestations, only four (0.5%) resulted from VZV (Bossi 1996). PWAS have reportedly developed VZV-related neurological disease up to three months after the onset of localized zoster (Ryder 1986). Symptoms include headache, vomiting, lethargy, tremors, and dizziness (Drew 1990). Diagnosis is often aided by the presence of cutaneous zoster. With encephalitis, a brain scan often reveals a multifocal infection of white matter or vasculitis. Gershon and colleagues reported success in serological testing for VZV antibody in the cerebrospinal fluid (Gershon 1980), though this is not a universally accepted practice. More recently, positive results in detecting VZV in cerebrospinal fluid (CSF) with polymerase chain reaction (PCR) have been documented (Burke 1996).

VZV Pneumonia

Though not often seen in patients with HIV, pneumonia may result from primary varicella or secondary zoster, and its severity can range from mild respiratory symptoms to potentially life-threatening hypoxemia (low concentration of oxygen in the blood) (Erlich 1995).

TREATMENTS FOR VZV

Acyclovir (Zovirax™, Glaxo Wellcome)

Acyclovir is considered first-line therapy for primary varicella or herpes zoster (Balfour 1994). It has been used by more than 30 million patients to date and has been shown to reduce the mortality and incidence of serious complications resulting from herpes zoster in both normal and immunocompromised patients (Easterbrook 1994). Acyclovir has poor bioavailability and only modest activity against VZV. High and frequent dosing is required to achieve a therapeutic effect. For immunocompromised patients with severe cases, cautious clinicians favor intravenous administration of 10 milligrams per kilogram (mg/kg) of acyclovir every 8 hours for seven to ten days or until all vesicles are crusted over (Fletcher 1992). Treatment outcome improves when therapy is administered within 24 to 48 hours of an outbreak (Balfour 1996).

Patients not ill enough to require hospitalization are often treated with high doses of oral acyclovir. An oral dose of 800 mg 5 times a day has been approved for the treatment of primary varicella and recurrent zoster in otherwise-healthy patients. Though commonly also used in immunocompromised patients, the 4 grams a day

oral regimen has been inadequately studied in this population and should therefore be accompanied by careful patient monitoring (Fletcher 1992).

Acyclovir has a good safety profile even at the high doses required for the treatment of VZV. Reported side effects include nausea, diarrhea, headaches, dizziness, and rash (Huff 1988; McGrath 1994). There have also been reports of nephrotoxicity (kidney damage) in connection with intravenous administration and when administered in conjunction with other nephrotoxic medications. This may be overcome through adequate hydration (Shepp 1988).

Adult Dosage Compendium for Treatment of Adult VZV	
Primary Varicella	IV 10 mg/kg thrice daily (for children, IV 500 mg/m^2 thrice daily) or 800 mg orally 5 times daily
Localized Zoster	IV 10 mg/kg or 800 mg orally 5 times daily
Severe, recurrent, or when oral absorption dubious; Visceral disseminated VZV	IV 10 mg/kg thrice daily
Acyclovir-resistant VZV	IV Foscarnet 40 mg/kg thrice daily

(Fletcher 1992)

Acyclovir-resistant VZV is rare and appears to be confined to the immunosuppressed patient (Balfour 1994). Resistance usually results from treatment-induced selection for thymidine kinase-deficient VZV strains, which may present distinctly thickened wart-like lesions (Jacobson 1990).

An algorithm for the treatment of acyclovir-resistant VZV was developed by Balfour and colleagues. Practitioners should consider beginning therapy with IV acyclovir (10 mg/kg thrice daily) or foscarnet in the face of *a priori* evidence of acyclovir resistance. Such evidence may include previous episodes of resistant zoster, recurrence in the same location after treatment with acyclovir, recurrence in the face of ongoing administration of acyclovir or ganciclovir, or the appearance of atypical hyperkeratotic lesions. Patients not responding to seven to ten days of IV acyclovir therapy should be switched to foscarnet (40 mg/kg thrice daily) until all lesions are crusted (Balfour 1994).

In a randomized trial of 22 severely immunocompromised non-AIDS patients presenting within 72 hours of onset of zoster, IV acyclovir was found superior to vidarabine (ara-A, the then-current standard of care) in shortening the period of viral shedding (four versus seven days), the period of new lesion formation (three versus six), time to first lessening of pain (four versus seven), time to crusting of all lesions (seven versus 17), and time to full healing of all lesions (17 versus 28 days) (Shepp 1988). Cutaneous dissemination occurred in 50% of patients receiving vidarabine, but in none receiving acyclovir.

For HIV-positive patients with multiple post-treatment zoster recurrences, maintenance therapy with oral acyclovir 400-600 mg three to five times daily may be justified, though lack of proof of efficacy and the potential for selection of acyclovir-resistant VZV add controversy to this practice (Jacobson 1990).

Foscarnet (Foscavir™, Astra Pharmaceuticals)

Foscarnet has demonstrated *in vitro* activity against several human herpes viruses including HSV 1 and 2, VZV, cytomegalovirus, Epstein-Barr virus and also HIV. Foscarnet's side effects include severe kidney toxicities -- such as dangerous reductions in phosphate, calcium and magnesium levels -- as well as seizures, anemia, thrombocytopenia, neutropenia, penile ulcers and gastrointestinal intolerance (Sasadeusz 1993; McGrath 1994).

In a very small study in patients with acyclovir-resistant cutaneous VZV, lesions healed completely in 4 of 5 patients treated with foscarnet (Safrin 1991). Though data regarding foscarnet's efficacy against VZV are scant, for lack of alternatives, it has become the second-line therapy for VZV (Balfour 1994).

Famciclovir (Famvir™, SmithKline Beecham)

Famciclovir is a nucleoside analogue which is converted to penciclovir in the body. It was approved for the treatment of zoster in immunocompetent patients, and it is starting to undergo tests in patients with HIV. Famciclovir is similar in nature to acyclovir but is reportedly more bioavailable (77% versus 30% or less) and has a much longer intracellular half-life (Boyd 1988). It is thus administered only three times rather than five times per day as for acyclovir. Famciclovir relies on viral thymidine kinase for phosphorylation, and so is ineffective against most acyclovir-resistant strains of VZV. A trial comparing various dosages of famciclovir to acyclovir in immunocompetent adults with acute zoster found all regimens equally effective (Gheeraert 1992).

Sullivan and colleagues reported interim results from an open-label study of famciclovir in HIV-infected patients at the Fourth Conference on Retroviruses and Opportunistic Infections. Fifteen HIV-infected patients with uncomplicated herpes zoster were treated with a seven day course of famciclovir (500 mg thrice daily). By day seven, blister formation had ceased in all patients, and complete resolution of pain was reported in 6/11 patients by day 28. One patient required hospitalization for the management of zoster pain (Sullivan 1997). Unfortunately, no comparison was made with acyclovir, as the sponsor apparently plans to rely upon famciclovir's favorable dosing advantage to market the drug. SmithKline Beecham plans to file a supplementary new drug application for Famvir for the treatment of acute herpes zoster and recurrent genital herpes in immunocompromised patients.

INVESTIGATIONAL TREATMENTS

Valacyclovir (Valtrex™, Glaxo Welcome)

Valacyclovir, a drug that is converted to acyclovir *in vivo*, is approved to treat HSV and VZV in immunocompetent patients. An oral dose of 1 gram thrice daily results in roughly the same level of acyclovir in the body as IV acyclovir (Easterbrook 1994). In a Phase II trial comparing 1 gram of valacyclovir per day to the standard acyclovir regimen of 800 mg 5 times daily in immunocompetent adults, the valacyclovir group had a slightly lower median duration of pain (38 for valacyclovir versus 51 days for acyclovir) though no other significant benefits were noted (Beautner 1995).

A Phase I trial conducted in HIV-infected patients with CD4 counts of less than 150 established a generally favorable safety profile for valacyclovir at dosages of 1,000 and 2,000 mg four times a day for 30 days, though a small number of patients developed neutropenia (Jacobson 1994). However, valacyclovir carries a warning against its use in immunocompromised patients because of its association with hemolytic uremic syndrome / thrombotic thrombocytopenic purpura (potentially fatal bleeding in the kidneys) in this population (FDA Data 1996). The warning resulted from the results of ACTG 204, a study comparing valacyclovir to acyclovir for the prevention of CMV retinitis in HIV-positive patients. Ironically, the ACTG has commenced a study, ACTG 253, in HIV-infected children.

Sorivudine (BV-araU/Bravavir™; Bristol Myers Squibb)

Sorivudine is a nucleoside analogue with extremely potent *in vitro* activity against herpes zoster. In a study comparing the *in vitro* sensitivity of over twenty antivirals to VZV (including acyclovir, penciclovir, foscarnet, and others) sorivudine was found to be the most potent among 14 acyclovir-sensitive strains (Andrei 1995). It has a bioavailability of 63% versus 30% for acyclovir. Moreover, sorivudine's longer half-life permits once per day dosing as compared to 5 times per day for acyclovir.

While sorivudine is well tolerated when taken alone (Easterbrook 1994), the drug is extremely dangerous when administered along with certain other drugs including the cancer drug fluorouracil and the anti-fungal drug flucytosine. The latter is often used by PWAs in combination with amphotericin as a treatment for cryptococcal meningitis (Whitley 1995). For a brief period, sorivudine was licensed in Japan for the treatment of herpes zoster. It was, however, quickly taken off the market after its concomitant use with fluorouracil derivatives caused 15 deaths in Japan.

Comparative clinical trials have found sorivudine to be at least as effective as acyclovir (Whitley 1995). As a result, Bristol-Myers Squibb presented the drug for approval to the FDA on June 6, 1996. Unfortunately, the FDA Antiviral Advisory Committee voted 7 to 2 against approval due to its concerns over the fatal drug interaction. We believe this was an over-reaction based on avoidable deaths in Japan where physician education about the drug's toxic interactions was inadequate. After the FDA rejected Bristol-Myers Squibb's new drug application (NDA) for sorivudine, the sponsor stopped all ongoing clinical trials, canceled a planned open-label study in patients with sight-threatening VZV retinitis and a trial in HIV-positive children with herpes zoster or primary varicella, and the drug's development was halted.

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CYTOMEGALOVIRUS (CMV) RETINITIS

by Michael Marco

EPIDEMIOLOGY

Before AIDS, cytomegalovirus (CMV) retinitis was a rare viral disease occurring only among individuals with primary immunodeficiency syndromes or autoimmune disorders, organ transplant patients and immunosuppressed cancer chemotherapy patients (Fiala 1975). In bone marrow transplant patients, there is a greater incidence of CMV pneumonitis than retinitis (Coskuncan 1994).

CMV infection is not the same as CMV disease. CMV infection simply means that CMV organisms live in one's body and that one tests positive for CMV antibodies. Most HIV-positive and HIV-negative people have been exposed to CMV at some time. People may be infected perinatally, in early childhood, or through sexual contact. The initial infection (referred to as primary infection) may present as a mononucleosis-like syndrome which soon resolves; most people then remain latently infected but asymptomatic for life (Jordan 1983). A very high proportion of gay men -- over 90% -- have antibodies to CMV (Drew 1981; Mintz 1983). Primary infection of CMV is thought to be rare in HIV-positive individuals because most have been exposed to CMV prior to their HIV infection (Gallant 1992).

CMV can be transmitted through viral shedding in both oral and genital secretions which allows for primary infection or reinfection (Merigan 1990). Studies conducted at San Francisco's UCSF noted that receptive anal-genital intercourse correlated strongly with acquiring CMV (Mintz 1983) and that condoms -- using an *in vitro* model -- blocked CMV transmission (Katznelson 1984).

CMV disease occurs when a previously latent CMV infection is activated -- usually when a patient is immunosuppressed -- and causes clinical "end-organ" disease, such as CMV retinitis [affecting the eye(s) and causing a loss of vision], pneumonitis (lungs), encephalitis (brain) or colitis (colon).

From the 1980s to 1996, the incidence of CMV end-organ disease among people with AIDS was estimated to range between 10 and 40% (Peters 1991; Gallant 1992; Hoover 1993; Chan 1995). In the new era of potent protease inhibitor combination therapy, the incidence rate of CMV – for those who have access to protease inhibitors -- is down to under 5% (Baril 1997, Currier 1997). CMV retinitis is by far the most common manifestation, accounting for between 77 and 90% of all CMV disease in people with HIV (Peters 1991; Gallant 1992).

CMV end-organ disease occurs late in the course of AIDS and is associated with extremely low CD4 counts. The average CD4 count in patients with newly diagnosed CMV retinitis is below 30 (SOCA/ACTG 1992; Kuppermann 1993). A 132 patient natural history study noted that of the 26 patients who developed CMV retinitis (20%), *none* had a CD4 count above 50 (Kuppermann 1983).

The risk of developing CMV retinitis increases markedly as one becomes more immunocompromised and CD4 cells decrease. In a 1002 patient natural history study, Gallant and colleagues found that the probability of CMV disease (at two years) was 21.4% for patients below 100 CD4 cells as compared to 10.3% for patients with CD4 counts above 100 ($p<0.001$) (Gallant 1992). The incidence of CMV also increased since *Pneumocystis carinii* pneumonia (PCP) prophylaxis became standard of care. Multicenter AIDS Cohort Study (MACS) data reveals that the cumulative incidence of CMV retinitis in AIDS patients rose from 24.8 to 44.9% after the introduction of primary PCP prophylaxis -- presumably because people who previously died of PCP now lived long enough to develop CMV (Hoover 1993).

The advent of potent protease inhibitor combination therapy (PPICT) has dramatically reduced the incidence of CMV disease, as evidence from both randomized, controlled trials and from epidemiological studies testifies:

Decreasing CMV Disease in the Protease Era				
Randomized trials	***Non-PI Regimen***	***PI Regimen***	***p-value***	***ref.***
Abbott 247	**NRTI(s)**	**RTV + NRTI(s)**		Cameron 1996
CMV, all sites	30/547 (5.5%)	16/543 (2.9%)	<0.05	
CMV retinitis	17/547 (3.2%)	13/543 (2.4%)		
CMV other	13/574 (2.3%)	3/543 (0.5%)		
ACTG 320	**AZT/3TC**	**AZT/3TC/IDV**		Currier 1997
CMV – all pts.	11/577 (1.9%)	5/579 (0.9%)	0.055	
CMV – CD4<50	9/220 (4.0%)	5/219 (2.3%)		
Epidemiological studies	***Before PPICT***	***After PPICT***	***p-value***	***ref.***
Tulane/ASDC	1994-1996	1996-1998		Michaels 1998
CMV	4.6%	3.0%	<0.05	
Pitié-Salpêtrière	**1995-9/96**	**After 9/96**		Baril 1997
CMV	18.7%	5.0%	<0.01	

[ASDC = Adult Spectrum of Disease Cohort; IDV = indinavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir]

While before the protease era virtually all CMV cases presented with CD4 counts below 50, there have been several reports of individuals whose CD4 counts rose after starting PPICT but who nonetheless developed CMV disease – usually in the first weeks or months of PPICT, presumably either before the immune system had a chance to recover, or else reflecting a permanent deletion of CMV-specific T-cell immunity. Jacobson and colleagues reported on five patients with CD4 counts over 195 who developed CMV retinitis just four to seven weeks after initiating PPICT (Jacobson 1997). Each of their CD4 counts had been below 85 five to 24 weeks before initiating PPICT.

To demonstrate how the common CD4 threshold for CMV retinitis has changed has changed after PPICT, Jacobson conducted a retrospective analysis of 76 patients who developed CMV retinitis between July 1995 and August 1996. The data below document the change:

CD4 Counts Among Patients with Newly Diagnosed CMV Pre and Post-PPICT		
	CD4 >50	***CD4 >100***
7/95 - 2/96	1/27 (4%)	0
3/96 - 8/96	14/49 (29%)	7/49 (14%)

(Jacobson 1997)

Similar results from a prospective cohort study were recently reported by a group from Spain. Mallolas and colleagues documented 21 cases of CMV end-organ disease (nine initial episodes and 12 relapses) in patients on PPICT (Mallolas 1997). Nineteen of 21 (90%) cases occurred within two months of initiating PPICT, and none occurred during the three month median follow-up period (range: 0 - 8 months). The median CD4 count of the 21 cases was 30 (range: 2 to 225), however, 25% of the patients had CD4 counts above 50 at diagnosis.

Thus, CMV retinitis will develop or progress in some patients despite a rise in CD4 counts to levels previously deemed safe. *It is possible that these patients had asymptomatic CMV disease or were CMV DNA PCR positive (viremic) and that the CMV virus had already seeded the eye before they started PPICT*. Once CMV is in the sanctuary of the eye, PPICT might not effectively halt the clinical progression to retinitis.

PATHOGENESIS

The pathogenesis of CMV retinitis remains incompletely understood. CMV is a herpes virus which infects endothelial cells, monocytes, and granulocytes (Dunn 1996). After 20 years, leading researchers still ask, "What are the key pathogenetic determinants of CMV end-organ disease?" (Jacobson 1995).

CMV DNA PCR

Many clinicians realize that using only a patient's CD4 count to predict the risk of CMV disease is not sensitive or specific enough. Hence, the search for more sensitive markers to predict the development of disease, including polymerase chain reaction (PCR) and antigen testing, is currently in process.

Shinkai and colleagues followed 94 patients in AIDS Clinical Trials Group (ACTG) 181 with quarterly urine and leukocyte (blood) cultures and plasma PCP to determine the risk of developing CMV disease. After a mean follow-up of 12 months, 26 (28%) patients developed CMV end-organ disease. Only two had a negative CMV DNA PCR. Urine cultures, leukocyte cultures and qualitative plasma PCR had a positive predictive value of 31%, 69% and 58%, respectively. However, a CMV DNA PCR copy number of more than 1000/µl (microliter) had a positive predictive value of 100%.

CMV Disease Based on Qualitative & Quantitative CMV DNA PCR			
	CMV disease	***No CMV Disease***	***p-value***
CMV DNA PCR +	24 patients	17 patients	0.006
>1000 copies/µl	9 (100%)	0 (0%)	0.002 (vs. <100)
100-1000 copies/µl	10 (59%)	7 (41%)	NS
<100 copies/µl	5 (33%)	10 (67%)	0.002 (vs. >1,000)
Median CMV DNA PCR	473 copies/µl	35 copies/µl	0.0007

(Shinkai 1997)

Spector and colleagues conducted a virology sub-study within Syntex/Roche 1654, an oral ganciclovir CMV prophylaxis study. Baseline plasma samples were evaluated in 85% of the 725 patients. About 55% of the patients were CMV DNA PCR positive at entry in both treatment groups (ganciclovir and placebo).

Plasma CMV DNA PCR in Syntex/Roche 1654 Oral GCV Prophylaxis Trial			
Baseline Plasma CMV RNA (copies/mL)	***Proportion developing CMV end-organ disease***		
	Ganciclovir	***Placebo***	***N***
<50,000	20%	40%	
50,000-150,000	75%	75%	16
>150,000	100%	100%	10

(Spector 1996c)

Patients Developing CMV End-Organ Disease			
	Ganciclovir	***Placebo***	***p-value***
Plasma PCR- at baseline	1%	14%	<0.01
Plasma PCR+ at baseline	**26%**	**43%**	**0.017**

(Spector 1996c)

This viral load sub-study provided useful natural history data about the relationship between CMV viral load and risk of end-organ disease. In the Roche study, about half the patients were CMV DNA positive at baseline. About 15% of the negatives and 45% of the positives developed CMV end-organ disease. Patients with a high CMV viral load were likelier to develop CMV end-organ disease. Only 40% of the CMV PCR DNA positive placebo patients with less than 50,000 copies developed CMV end-organ disease compared to 100% (all ten) of the oral ganciclovir patients with CMV load over 150,000 (Spector 1996c).

Three prospective natural history CMV studies of 90 to 200 patients, all employing different PCR assays, were published in 1997. Approximately one-third of the patients with an average CD4 count of 50 or less were CMV DNA PCR positive and of that one-third, approximately 58% developed CMV end-organ disease (Shinkai 1997, Dodt 1997, Bowen 1997).

Lastly, ACTG 360, "HIV and CMV Viral Burden and the Development of CMV" will help us identify the approximate HIV and CMV viral load threshold in those who develop CMV. Likewise, this study is attempting to validate five different CMV viral load assays. The study has just completed enrollment with 403 patients.

pp65

Several European studies have tested the diagnostic value of CMV pp65 antigenemia in CMV disease (pp65 is a CMV protein) (Torrus 1996a, 1996b; Reynes 1996). In these small (fewer than 75 patient) studies, over 50% of patients positive for the pp65 antigen developed CMV end-organ disease. While pp65 may be more predictive than CMV culture, data are still too preliminary to recommend its wide-scale use, particularly as direct measurement of CMV viral load in plasma and urine with polymerase chain reaction (PCR) technology is becoming more widespread, though neither are commercially available in the United States (Frances Bowen, personal communication). Larger studies should be conducted to standardize these tests and validate their clinical relevance.

CMV PCR as a Prognostic Tool

Bowen and colleagues used PCR (Roche Amplicor™) to detect CMV viral load in the blood and urine of 45 patients on intravenous (IV) ganciclovir therapy. At baseline, 39 (87%) patients with newly diagnosed CMV retinitis were either blood or urine CMV PCR-positive – 46% in blood only, 23% in urine only, and 31% positive for both. The median pre-therapy viral load in the blood was 4.95 $\log_{10}$ copies/µl (range, 3.6 - 7.05) and in urine was 4.90 $\log_{10}$ copies/µl (range, 4.45 - 6.46). After 21 days of IV ganciclovir induction therapy, 33 (85%) of 39 patients became CMV PCR-negative. Six patients were still detectable for CMV DNA: three from blood, two from urine and one from both. After one month of maintenance therapy, five of these six patients became undetectable, and the other one died. The pretreatment viral loads of blood from these six patients who were detectable after their induction therapy were significantly higher than the other 36 patients (median load 6.18 $\log_{10}$ copy/µl versus 4.79 $\log_{10}$ copies/µl; $p=0.005$). Overall, there were no significant differences in the rate of progression between those patients who were blood or urine PCR-positive or negative at baseline. When

restricting the analysis to blood, a loose trend suggested that patients with elevated blood viral loads (more than 4.95 $\log_{10}$ copies/μl) had a shorter time to first progression ($p=0.16$) and a significantly shorter time to death ($p=0.007$). The median survival difference between the two groups was 3.9 months (125 days). This relatively small study suggests that CMV PCR measurement may be useful in determining the prognosis of patients (Bowen 1996). Nonetheless, Bowen believes that PCR is not particularly helpful in monitoring PCR negative patients on maintenance therapy, since the majority of them will progress without systemic viremia due to inadequate drug levels in the eye (personal communication). By contrast, apparently disregarding PCR's prognostic utility, Douglas Jabs asks, "Why use a lab test when an eye exam by an ophthalmologist gives answers?" (personal communication).

In a presentation at the 35th IDSA meeting in San Francisco during fall 1997, Finkelstein and colleagues presented an analysis of CMV viremia (blood) and viruria (urine) from 177 patients in ACTG 181. CMV DNA was found in urine samples from 68/177 (58%) patients, and in blood from 22/177 (12%). Just 33/177 patients developed end-organ disease. However, CMV viruria increased the risk of end-organ disease by 3.08-fold, and viremia by 9.2-fold. After shedding CMV, disease occurred at three months in 5% and at six months in 16%. The authors proposed screening individuals with CD4 counts below 50 monthly for CMV viruria. If found positive, they would be screened for viremia. If viremic, they suggested administering pre-emptive CMV treatment, since the risk of end-organ disease in the CMV viremic population with CD4 counts below 50 appears to be in the range of 20% (Finkelstein 1997). Further prospective studies are warranted.

CLINICAL MANIFESTATIONS & DIAGNOSIS

The main symptoms of CMV retinitis include floaters, blurred vision, missing portions of vision and flashing light/sparks. Even subtle changes, such as a minor loss of peripheral vision, can indicate the development of CMV retinitis. There is usually no pain involved. It is important for patients to report any and all visual abnormalities to a primary care physician so that a referral to an ophthalmologist can be made. Some patients can have progressive CMV retinitis and be asymptomatic. Fifteen percent of patients in one CMV treatment study were asymptomatic yet had sight threatening CMV disease (Kupperman 1993).

Because CMV retinitis can be asymptomatic, and because many patients might not understand the sight-threatening implications of their symptoms, routine ophthalmological screening is recommended (Kupperman 1993). Patients with CD4 counts above 100 should see an ophthalmologist yearly; patients with counts between 50 and 100, every six months; and those with counts under 50, every three to four months (Dunn 1996).

Diagnosis must be made by an experienced ophthalmologist. Clinical manifestations of progressive CMV retinitis include a dry appearing, granular border with little vitreous inflammation. The edema and necrosis are also known to cause irregular patches of retinal whitening. A "brushfire" pattern can be visualized once a photograph of the lesion is enlarged.

Ocular zones have been established to define the location of lesions in relation to key parts of the visual apparatus such as the optic nerve and the fovea. Zone 1 disease (defined as 1500 microns from the optic nerve or 3000 microns from the fovea) is considered immediately sight-threatening and requires prompt treatment. Zone 2 disease immediately adjacent to zone 1 also necessitates prompt treatment. Outer Zone 2 and Zone 3 disease are sometimes referred to a "peripheral retinitis" since the lesion is further from the fovea. Untreated peripheral retinitis progresses, usually within a median of two to three weeks, but patients may be able to wait a few days to explore treatment options.

Fundus photographs are often taken to document the extent of a patient's disease and the response to therapy. The ophthalmologist will dilate the patient's eye and photograph the fundus (the interior of the eye). These photographs are then made into slides and kept as a permanent record.

TREATMENTS FOR CMV RETINITIS

There was no FDA-approved drug for CMV retinitis until 1989, when ganciclovir (DHPG, Cytovene™, made by Syntex, now a subsidiary of Hoffmann-La Roche) was licensed. The drug was approved in the absence of controlled data because of strong community pressure and widespread consensus among clinicians, based on five years of experience with open-label ganciclovir distributed under a compassionate use program to thousands of patients, that the drug was effective. Subsequently, foscarnet (Foscavir™, made by Astra) and cidofovir (Vistide™, made by Gilead Sciences) have also been approved by the FDA for this indication. Efficacy for all three drugs was demonstrated by studies comparing immediate versus deferred treatment for non-sight-threatening, peripheral CMV retinitis (Spector 1993; Palestine 1991; Lalezari 1997b). Chiron Vision's Vitrasert™ intraocular ganciclovir implant is now also FDA-approved, although it provides only local treatment and does not protect the other eye or the rest of the body from disseminated CMV disease.

SYSTEMIC THERAPY FOR PRIMARY CMV RETINITIS

Ganciclovir (DHPG, Cytovene™, Syntex/Roche)

In ACTG 071, Spector and colleagues randomized 42 HIV-positive patients with peripheral CMV retinitis to receive either immediate therapy with IV ganciclovir (5 mg/kg twice daily for 14 days followed by 5 mg/kg for 14 weeks) of deferred treatment. Those on deferred treatment were offered ganciclovir when their retinitis progressed. Progression, documented by retinal photography, was defined as any new lesion equal to or greater than 750 microns or an existing lesion expanding by 750 microns or more. Thirteen immediate treatment patients and 22 deferred treatment patients were evaluable.

ACTG 071: Immediate versus Deferred Ganciclovir for Peripheral CMV Retinitis

	Immediate GCV	*Deferred GCV*	*p-value*
Progressed	**10/13 (76.6%)**	**20/22 (90.9%)**	**0.001**
Mean time to progression	**66.4 days**	**19.3 days**	**<0.001**
Median time to progression	49.5 days	19.3 days	<0.001
Progressed by 14 days	8.3%	68.2%	<0.0001

(Spector 1993)

About 40% of the ganciclovir patients developed neutropenia and 25% developed thrombocytopenia. There were no differences in the causes of death between the two groups (Spector 1993). The excessively high doses of AZT (1200 mg/day) then recommended may have exacerbated the rate of neutropenia seen in this study, which enrolled between March 1989 and October 1990.

Data from over 300 ganciclovir-treated patients showed that over 90% become urine and blood culture negative within two weeks of starting therapy (Buhles 1988). Maintenance therapy for life is warranted, because relapse is virtually inevitable two to four weeks after discontinuing treatment (Jacobson 1988).

Foscarnet (Foscavir™, Astra Pharmaceuticals)

Foscarnet's efficacy was demonstrated in a similar immediate versus deferred therapy study in which 24 patients with peripheral CMV retinitis were randomized to receive immediate IV foscarnet (60 mg/kg thrice daily for 3 weeks followed by a maintenance regiment of 90 mg/kg once daily) or deferred therapy. The mean time to progression in the 11 evaluable patients on deferred therapy was 3.2 weeks, compared to 13.3 weeks in the 13

foscarnet patients ($p<0.001$). Over 25% of the foscarnet-treated patients experienced nephrotoxicity (an elevation in serum creatinine) and over 75% developed hypomagnesemia and hypocalcemia (Palestine 1991). In a more recent study, approximately 13% of the foscarnet patients experienced nephrotoxicity (SOCA/ACTG 1995). Foscarnet patients should have their serum creatinine levels monitored closely, particularly when they are also receiving other nephrotoxic drugs such as amphotericin B. In addition, penile and genital ulcers have been reported in uncircumcised males and in patients receiving high-dose foscarnet (Moyle 1993, Katlama 1992). A subsequent study found that a once-daily maintenance dose of 120 mg/kg was more effective at preventing relapse than the dosage of 90 mg/kg (Jacobson 1993).

Ganciclovir versus Foscarnet for CMV Retinitis

From January 1990 through October 1991, the Studies of Ocular Complications of AIDS (SOCA) Research Group, in collaboration with the ACTG, compared both drugs in the Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial (FGCRT) (SOCA 1992, 1994, 1995, 1996a, 1996b; Holbrook 1996; Jacobson 1996). No significant difference was noted between either drug with regard to visual outcome (SOCA 1994). The fundus photograph reading center documented that the median time to first progression for the foscarnet patients was 53 days as compared with 47 days for the ganciclovir patients ($p=0.997$). However, patients randomized to receive foscarnet survived approximately

four months longer (12.6 months versus 8.5 months) than those initially assigned to receive ganciclovir ($p=0.007$) (SOCA 1992), possibly due to foscarnet's anti-HIV activity (Jacobson 1991).

Despite this apparent survival advantage for foscarnet, "Most physicians currently initiate therapy for CMV retinitis with ganciclovir and reserve foscarnet for treatment of retinitis recurrence or ganciclovir intolerance" (Spector 1996). Moreover, this survival advantage occurred between 1990 and 1991 while AZT and ddI were the only available antiviral agents; AZT's bone-marrow toxicities may have increased those of ganciclovir. The availability of new, more potent antiretroviral combinations may render foscarnet's anti-HIV activity, when weighed against its inconvenience, cost, and nephrotoxicity, inadequate for it to replace ganciclovir as first-line CMV therapy.

TREATMENT OF CMV RETINITIS FOLLOWING REACTIVATION

Even with maintenance, relapse and continued progression of retinitis are common when, whether due to inadequate tissue penetration or the evolution of drug resistance, CMV reactivation occurs. To optimize therapy for CMV retreatment, SOCA and the ACTG conducted ACTG 228, the CMV Retinitis Retreatment Trial (SOCA 1996c), a Phase III study which compared ganciclovir alone, foscarnet alone, and ganciclovir and foscarnet together for patients relapsing on either one.

ACTG 228: The CMV Retinitis Retreatment Trial				
	Ganciclovir	***Foscarnet***	***GCV/FOS***	***p-value***
N	**89**	**83**	**87**	
Retinitis progression	82.0%	81.9%	58.6%	<0.001
Median time-to-progression	**2.0 months**	**1.3 months**	**4.3 months**	**<0.001**
Rates of visual field loss	**18°/month**	**28°/month**	**16°/month**	**<0.009**
Rates of increased retinal area involved	**1.40%/month**	**2.47%/month**	**1.19%/month**	**0.041**
Median survival	**9.0 months**	**8.4 months**	**8.6 months**	**0.89 (NS)**
Adjusted mortality rate	**0.88/year**	**1.22/year**	**0.89/year**	**0.23 (NS)**

ACTG 228: The CMV Retinitis Retreatment Trial				
Adjusted mean change in quality of life (QOL)	**-1.0**	**-4.0**	**-9.8**	**0.03**

(SOCA 1996c)

While the rate of progression, loss of retinal area and loss of visual field all favored the combination therapy arm, no difference was detected in the rate of loss of visual acuity. Mortality rates were similar among the three treatment groups. For patients originally on monotherapy, switching to the alternate monotherapy was no more effective than staying on the same drug. About 70% of the patients were ganciclovir-experienced and one-third were randomized to receive ganciclovir monotherapy. The initial response and subsequent relapse at a median of 2 months among the ganciclovir monotherapy patients may indicate poor drug penetration to the eye rather than viral resistance.

ACTG 228 was stopped by the SOCA data safety and monitoring board (DSMB) in mid-April 1995, and its results were discussed with the ACTG Executive Committee and all SOCA investigators a few weeks later. These were the only people privy to the treatment results because of SOCA's policy not to publicly present study data until after publication in a peer-reviewed medical journal. Under much pressure from AIDS activists community and some ACTG investigators, SOCA consented to publicly present ACTG 228 in January 1996. In the ten months between study closure and presentation, clinicians were unable to show slides or mention the results of ACTG 228 at lectures or conferences. Many believe that these data were clinically important, and that SOCA's outdated policy hampered the free flow of scientific information. SOCA subsequently changed its ways and has publicly presented data from its most recent studies in a more timely manner.

Cidofovir (HPMPC, Vistide™, Gilead Sciences)

Cidofovir is a nucleoside analogue with broad-spectrum antiviral activity. It has good tissue penetration to the eye and a long half-life, enabling effective anti-CMV activity with once-a-week dosing. However, it is poorly absorbed orally and must be taken intravenously. Moreover, it is highly toxic to the kidneys and requires co-administration of probenecid, which increases the excretion of uric acid and hence improves the kidney's ability to handle cidofovir. However, probenecid increases the elimination rate of other widely-used treatments such as anti-inflammatories and rifamycins, increases concentrations of the cancer chemotherapy drug methotrexate, and has been reported to cause headache, dizziness, liver cell death (hepatic necrosis), vomiting, nausea, anorexia, sore gums, kidney stones, anaphylactic shock, fever, rash, anemia, leukopenia and hair loss. Patients who are sulfa-intolerant should be particularly careful to avoid developing a severe allergic reaction to probenecid (PDR 1996).

Cidofovir was approved by the FDA for the treatment of CMV retinitis in the summer of 1996. Gilead's new drug application (NDA) focused on three studies: 1) a 48 patient Phase II/III immediate versus deferred study of cidofovir treatment for peripheral CMV retinitis; 2) a 100 patient study comparing two maintenance doses (3 mg/kg versus 5 mg/kg) of cidofovir after induction for the treatment of relapsed CMV retinitis (both sponsored by Gilead); 3) a Phase II/III study of immediate versus deferred cidofovir conducted by SOCA and the ACTG. The Gilead 106 study randomized 48 patients with newly diagnosed CMV retinitis to receive either 5 mg/kg of cidofovir immediately or only when progression occurred (Lalezari 1997b).

Gilead 106: Immediate vs. Deferred Cidofovir for Initial Treatment of CMV Retinitis			
	Immediate	*Deferred*	*p-value*
Time to progression, Gilead version	120 days	21.5 days	0.000006
Time to progression, FDA version	**78 days**	**21 days**	**0.001**

(Lalezari 1997b)

Some investigators felt that Gilead skewed its analysis by censoring data on patients who died, progressed, or dropped out, thus exaggerating the treatment effect. These investigators were vindicated on March 15, 1996, when the FDA medical officers presented their analysis, reducing the median time to progression in the immediate cidofovir arm from 120 days to 78 days. Adverse events included a 23% rate of proteinuria (protein in the urine, which may indicate kidney damage), neutropenia (15%), and creatinine increases (an increase in serum creatinine of $\geq$ 0.5 mg/dl from baseline) in 5%.

Gilead's larger 107 study randomized 100 patients to two maintenance regimens of cidofovir (3 versus 5 mg/kg) after induction for the treatment of relapsed CMV retinitis (Lalezari 1996). Fifty-one patients received the 3 mg dose and 49 received the 5 mg dose. These advanced patients had already progressed an average of four times on either ganciclovir or foscarnet.

Gilead 107: Two Doses of Cidofovir for Maintenance of Relapsed CMV Retinitis			
	3 mg/kg	*5 mg/kg*	*p-value*
Time to progression, Gilead version	49 days	115 days	0.0017
Time to progression, FDA version	**33 days**	**55 days**	**0.01**

(Lalezari 1996)

Once again, the FDA's estimate of the drug's efficacy was more conservative than that of the sponsor. Gilead 107 has yet to be published in a peer-reviewed journal, though it has been presented twice at conferences (Lalezari 1995b, 1996c). Each abstract cited the Gilead estimated time to progression rather than the FDA figures. Proteinuria and increased creatinine levels occurred in approximately 16.5% of the patients and 47% experienced mild to moderate reactions (fever, rash, chills) to probenecid, which must be coadministered with cidofovir.

The SOCA cidofovir study had two stages. In stage one, 30 patients were randomized to immediate or deferred induction with 5 mg/kg for two consecutive weekly induction doses, followed by 3 mg/kg every other week for maintenance. In stage two, the remaining patients were randomized to immediate or deferred induction treatment with the same dose, but increased the maintenance dose to 5 mg/kg. Of 64 patients enrolled, 56 were evaluable by the third DSMB interim analysis.

SOCA Cidofovir Study: Immediate vs. Differed Cidofovir Induction Followed by Two Maintenance Doses				
		Immediate Cidofovir followed by maintenance at		
	Deferred Cidofovir	***3 mg/kg***	***5 mg/kg***	***p-value***
N	24	21	11	
Median time to progression	**21 days**	**69 days**	**NA**	**0.03**
Median time on cidofovir	**4 months**	**3 months**	**NA**	

(Meinert 1996)

While full toxicity data are not yet available, four patients had to discontinue cidofovir due to elevated creatinine levels (Curtis L. Meinert, FDA presentation, 15 March 1996).

Clearly, while cidofovir is active against CMV retinitis, and its once-weekly dosing schedule appears convenient, its nephrotoxicity and the requirement to coadminister probenecid to reduce the risk of serious kidney trouble may limit its applicability. In patients who did not receive probenecid during early trials, the dose-limiting cidofovir toxicity was severe kidney damage associated with dose-dependent kidney tubular

cell injury resulting in serious blood abnormalities (Lalezari 1995a). The exact mechanisms of cidofovir-induced injury within the tubule cell remain elusive.

In these three Phase II/III studies – and in the Vistide™ treatment IND program – severe nephrotoxicity was minimal due to intensely close monitoring of concomitant probenecid and prehydration of patients. Guidelines state that probenecid dosing must be "clinic witnessed" and "completed" before cidofovir may be given. Even with probenecid, however, approximately 20% of patients still develop proteinuria and approximately 10% have creatinine increases which mandate discontinuation of cidofovir. Unlike with amphotericin B and IV pentamidine, discontinuation of cidofovir does not ensure a rapid reduction in serum creatinine levels, which often continue rising after discontinuation of cidofovir only to plateau weeks later before returning to near-baseline (Mark Jacobson, personal communication).

Before the drug's approval, AIDS treatment activists and many clinicians voiced their concern that the incidence of cidofovir-associated nephrotoxicity would increase when the drug was approved and in the hands of inexperienced clinicians. Gilead, however, spent most of its time emphasizing the "ease," "freedom," and "convenience" of cidofovir as compared to foscarnet and ganciclovir. They would down-play the seriousness of the nephrotoxicity by explaining that probenecid use and careful monitoring would solve everything.

After a few months of approval, Gilead learned the hard way just how nephrotoxic cidofovir was outside of a closely monitored clinical setting. In September 1996, Gilead sent an "Important Drug Warning" letter to health care professionals that read:

> ***Gilead Sciences. Inc., has become aware of several reports of severe renal impairment associated with the use of VISTIDE (cidofovir injection).... The [package] insert has been revised to emphasize further the importance of appropriate patient selection, treatment administration and monitoring when using VISTIDE.***

Pronounced probenecid reactions are another concomitant of cidofovir therapy; between 40 to 50% of patients in these studies had allergic reactions to probenecid. Probenecid is a toxic, sulfa-based drug. Patients unable to tolerate probenecid should not be given cidofovir.

Other serious toxicities have recently been identified with intravenous cidofovir use. Davis and colleagues reported the development of 11 cases of iritis (inflamation of the iris) in 46 treated patients, and six cases of hypotony (reduced eyeball tension due to muscle stretching) in four patients (Davis 1997). Five of the patients were noted to have a persistent decrease in visual acuity. These same toxicities have also been reported by Dorothy Friedberg (NYU) and Palau and colleagues from New Orleans (Friedberg 1997; Palau 1997).

Another concern with cidofovir is the threat of extra-ocular CMV disease**.** No data on cidofovir's preventive effect on extra-ocular CMV disease have been presented. CMV is not solely an ocular disease. Extra-ocular CMV disease – esophagitis, colitis, gastritis, hepatitis, pneumonitis, and encephalitis – accounts for approximately 20-50% of all cases of HIV-related CMV disease (Gallant 1992; Peters 1991). Unlike foscarnet and ganciclovir, which render 90% of patients culture-negative after two weeks, cidofovir renders only approximately 50% (four of eight evaluable patients) culture negative. Does cidofovir cross the blood-brain barrier in order to prevent CMV encephalitis as do ganciclovir and foscarnet, which are 40% permeable?

For those physicians who still wish to use cidofovir in light of its toxicity profile, many still wonder, "What is the correct maintenance dose for primary therapy?" Gilead study 107 for relapsed patients demonstrated that the 5 mg/kg dose was more effective than the 3 mg/kg dose. The SOCA study, however, was not designed to show which dose was more effective, or less toxic, for maintenance therapy after induction for primary CMV disease.

EXPERIMENTAL SYSTEMIC TREATMENTS FOR PRIMARY CMV RETINITIS

Valganciclovir (RS-790070, Pro-Ganciclovir, Hoffmann-LaRoche, Inc.)

Pro-ganciclovir, a valine ester of ganciclovir, is a pill being studied in for induction therapy of peripheral CMV retinitis. In asymptomatic HIV-positive patients who were CMV seropositive (with no active disease), pro-ganciclovir was compared to IV ganciclovir and oral ganciclovir to test its pharmacokinetics and oral bioavailability. The absolute oral bioavailability of pro-ganciclovir given in a fasted state was 60.9% compared to 5.6% for oral ganciclovir. Plasma concentrations of pro-ganciclovir following the administration of a single oral dose of 360 mg were higher than those obtained with a 1000 mg dose of IV ganciclovir (Jung 1995). A later multiple-dose, dose-ranging study of pro-ganciclovir determined than an approximate dose of 1,800 mg given immediately after food garnered the same systemic exposure as that of a 10 mg/kg daily dose of IV ganciclovir. The 900 mg daily dose of pro-ganciclovir had comparable exposure to that of the standard daily IV maintenance dose of 5mg/kg (Brown 1997).

Hoffmann-La Roche is testing pro-ganciclovir against IV ganciclovir for induction therapy, followed by open-label pro-ganciclovir for maintenance therapy, in patients with peripheral CMV retinitis at trial sites in the US and internationally. This study, WV15376B, will also assess the effects of induction and maintenance level dosing of pro-ganciclovir on CMV viral load, estimated by plasma CMV PCR.

This study, with only 70 patients, is not a true head-to-head comparison. It is only large enough to reliably detect a 30% difference between the two treatment groups. Nonetheless, this is probably one of the most important CMV studies in the past ten years, because it is the first promising an orally-formulated anti-HIV-associated CMV drug to go into a primary induction therapy clinical trial, and it is the first time a drug has been tested against IV ganciclovir for induction since SOCA tested foscarnet vs. ganciclovir (FGCRT) in 1990. If pro-ganciclovir is shown to be safe and effective (comparable to IV ganciclovir) in this study, and if it does well in Hoffmann-La Roche's planned, yet infinitely delayed, immediate versus deferred peripheral CMV retinitis study, it will completely change the standard of care for treating CMV. Likewise, pro-ganciclovir will finally mean the end to Roche's marketing its approved oral ganciclovir for maintenance therapy and prophylaxis. A Roche employee, so excited about the possibility of pro-ganciclovir replacing oral ganciclovir, privately said, "We've all known that it [oral ganciclovir] is shit."

MAINTENANCE THERAPY

Oral Ganciclovir

Oral ganciclovir (GCV) has been studied in many randomized, controlled trials for maintenance therapy of CMV retinitis (Squires 1993; Drew 1995; Oral Ganciclovir European and Australian Cooperative Study Group 1995; Masterson 1996; Lalezari 1996b). The most important and controversial oral GCV maintenance trial was Syntex 1653, which randomized 123 patients with newly-diagnosed and stabilized CMV retinitis to receive either 3 grams daily of oral GCV or 5 mg/kg of IV ganciclovir. CMV progression was monitored by masked fundoscopic photographs and by fundoscopy from a clinical ophthalmologist (Drew 1995).

Syntex 1653: IV vs. Oral Ganciclovir (GCV) for CMV Maintenance			
	IV GCV	***Oral GCV***	***p-value***
Mean time to progression			
by masked fundoscopy	**63 days**	**57 days**	**0.63**
by clinical assessment	**96 days**	**68 days**	**0.03**

Syntex 1653: IV vs. Oral Ganciclovir (GCV) for CMV Maintenance			
Median time to progression			
by masked fundoscopy	**49 days**	**29 days**	**NOT GIVEN**
by clinical assessment	**105 days**	**48 days**	**NOT GIVEN**
New lesions in other eye			
by masked fundoscopy	**9%**	**21%**	**0.21**
by clinical assessment	**6%**	**33%**	**0.005**
Neutropenia	**37%**	**24%**	**0.02**
Catheter infections	**31%**	**10%**	**0.006**

(Drew 1995)

Survival and changes in visual acuity were similar for both groups. What accounted for the discrepancies between readings by clinical ophthalmologists and those at the fundus photography reading center? In an editorial published alongside the peer-reviewed journal article, Gary Holland wrote, "This discrepancy most likely reflects the fact that clinicians can see the entire retina with indirect ophthalmoscopy, whereas only that portion of the retina posterior to the vortex veins (the "equator" of the eye) can be photographed routinely" (Holland 1995). Oral ganciclovir looked worse according to the median time to progression than according to the mean. Indeed, as Gary Holland noted, "Because this median is only slightly longer than the length of time to progression reported for untreated disease, some investigators have questioned the value of maintenance therapy with oral ganciclovir" (Holland 1995).

In a letter to *The New England Journal of Medicine*, SOCA statisticians Mark Van Natta and Janet Holbrook took issue with Drew's conclusion that oral and IV ganciclovir demonstrated relative equivalence in Syntex 1654 and that "oral ganciclovir is safe and effective as maintenance therapy for cytomegalovirus retinitis." They based their disagreement on the inadequate sample size and short duration of follow-up, concluding, "Given the above calculations along with the conflicting results of the fundoscopic and photographic evaluation, with respect to the time to progression and the occurrence of new cytomegalovirus retinitis in the previously uninvolved eye, we believe the authors have overstated their conclusion." (Van Natta 1996)

The unconvincing data from this study – as well as data from Syntex study 1774 (Squires 1993) – have made a majority of clinicians decide either not to use oral ganciclovir alone as maintenance therapy or to limit its use to patients *without* immediately sight-threatening disease (Jabs 1996a; Jacobson 1996a).

Nonetheless, oral ganciclovir at the dose of 3 grams a day is approved and is being used in the community, most often at a patient's request. Syntex/Roche 2226 has now called into question the efficacy of that 3 gram dose (Lalezari 1996b). Syntex 2226 was a randomized, controlled trial comparing three doses of oral ganciclovir (3, 4.5 or 6 grams) with IV ganciclovir (5 mg/kg daily) for maintenance therapy in 281 patients with CMV retinitis. This study, like the earlier studies, enrolled patients whose CMV retinitis was stable after induction therapy, yet, unlike the previous studies, no restriction was placed on the duration of retinitis at entry.

Syntex 2226: Three Doses of Oral vs. IV Ganciclovir for CMV Maintenance				
	Oral Ganciclovir			
	3 gm	***4.5 gm***	***6 gm***	***IV GCV***
Median time to progression	41 days	50 days	57 days	70 days

(Lalezari 1996b)

The difference between the 41 days for the 3 gram arm and the 70 days for the IV arm was significant (p=0.0515). Likewise, there was a trend toward better suppression on retinitis with higher oral doses compared to the 3 gram dose (p=0.09). In this study, patients assigned 3 grams of oral ganciclovir fared more poorly than in previous oral ganciclovir studies in which this dose was used. A sub-group analysis which adjusted for duration of retinitis (less than or more than 100 days of retinitis) showed that, when compared to the IV dose, the 25 patients in the 3 gm arm with more than 100 days of retinitis at entry (median 8 months) did far worse than the 48 patients in the 3 gm arm who had less than 100 days at entry (>100 days, p=0.025; <100 days, p=0.499) (Lalezari 1996a).

These disquieting results have led clinicians such as Jacob Lalezari to advocate using oral ganciclovir maintenance only in patients with stable and early peripheral retinitis (Jacob Lalezari, personal communication). It is unknown if the higher oral doses are equivalent to IV. Taking 6 grams of oral ganciclovir would come to 24 pills a day and cost over $50,000 a year.

Is Stopping CMV Maintenance Treatment Sensible in the Protease Era?

Two small retrospective studies in which patients discontinued CMV maintenance treatment were presented at the 37th ICAAC in fall 1997. Torriani and colleagues from UCSD presented data on eight patients who had "voluntarily" discontinued CMV maintenance therapy after long periods of non-progressive disease; five were on IV or oral ganciclovir and three were receiving intraocular cidofovir. At time of discontinuation, the median CD4 count was 172 (range 63-404) and the *median HIV RNA was 68,000 copies/µl* ***(range: <200-508,000 copies/µl).*** None of eight patients progressed after a median follow-up of 146 days (range: 72- 205). *Nevertheless, during this follow-up, six of eight patients had detectable HIV RNA* (Torriani 1997). This study created some well-deserved controversy. NIAID's Michael Polis was the first up to the microphone asking Torriani how in the world she could discontinue CMV maintenance therapy in a patient with HIV RNA levels of 508,000 copies/µl.

In Spain, Tural and colleagues conducted a similar yet less risky study. Seven patients with newly diagnosed CMV retinitis were given ganciclovir or foscarnet induction and maintenance therapy, and then followed. All were on antiretroviral therapy without protease inhibitors, were CMV DNA PCR positive, and had a median CD4 count of 56. Within 6.3 months, five patients experienced at least one relapse (eight total relapses). When protease inhibitors became available in Spain, all seven patients initiated PPICT. After 3.5 months on PPICT, all patients had CD4 counts of at least 150, and their HIV RNA and CMV DNA levels became undetectable. At this point, patients voluntarily discontinued maintenance therapy and received weekly opthalmologic evaluations for three months, and then every other week. At the time of presentation, no CMV relapses were documented.

To confirm the relevance of their findings, Tural and colleagues planned a prospective study which will use four specific criteria for entry: quiescent CMV, CD4 count over 150, undetectable HIV RNA, and undetectable CMV DNA PCR. Torriani and colleagues from the ACTG and SOCA have also developed a sound, soon to open, 125 patient study, ACTG 379, "The Effects of Stopping CMV Maintenance Therapy."

LOCAL THERAPY

Chiron Vision's Vitrasert™ Intraocular Ganciclovir Implant

Vitrasert is the brand-name of Chiron's intraocular ganciclovir implant. The ganciclovir implant – half the size of a postage stamp, with approximately 7 months' worth of ganciclovir compressed into a pellet – is surgically placed in the eye through an incision at the pars plana. GCVI-606-NEI was the first multi-centered, randomized, controlled study of the ganciclovir implant and used the familiar immediate versus deferred design (Martin 1994). Twenty-six patients (30 eyes) were randomized to receive either immediate treatment with a ganciclovir implant (1 microgram per hour) or deferred treatment with an implant after progression was detected.

GCVI-606-NEI: Immediate vs. Deferred Intraocular GCV Implant			
	Immediate	***Deferred***	***p-value***
Median time to progression	226 days	15 days	<0.0001

(Martin 1994)

Retinal lesion border activity was significantly reduced 4 weeks after surgery in the 76% of the implant group, whereas everyone in the deferred group progressed ($p=0.0001$). Extraocular CMV (visceral disease) was reported in 8 (31%) of the 26 patients. The estimated median time to visceral disease was 248 days. Contralateral involvement (CMV occurring in the other, non-implanted eye) developed in 14 (67%) of 21 patients who entered the study with unilateral CMV retinitis. About 50% developed contralateral disease by 203 days. Retinal detachment occurred in 7 (17%) eyes with implants. A temporary loss of functional visual acuity (blurriness) occurred in almost all patients following the surgery. It took approximately one month for this to resolve (Martin 1994).

GCVI-601-CMV was a randomized, controlled trial which compared 2 doses of the ganciclovir implant (1 or 2 micrograms per hour) with IV ganciclovir. 188 patients with newly-diagnosed, active CMV retinitis were enrolled.

GCVI-601-CMV: Two Doses of Intraocular vs IV Ganciclovir:				
	Vitrasert Ganciclovir Implant			
	1 µg/hour (N=62)	*2 µg/hour (N=55)*	*IV Ganciclovir (N=56)*	*p-value*
Median time to progression	221 days	191 days	71 days	< 0.001
Contralateral disease*	**34.2%**	**45.7%**	**15.6%**	**0.221**
Extraocular disease	10.3% (both doses)		0%	0.04
Median survival	268 days (both doses)		262 days	0.80

* Percentages for contralateral disease are taken from Chiron Vison's Intraocular Implant FDA new drug application (NDA) (Chiron Vison 1995), but were not published in the relevant *New England Journal of Medicine* article (Musch 1997).

There were no statistically significant differences between the implant groups and the IV group in survival (286 implant versus 262 days IV; p=0.80). Complications arising from the implant surgery were pronounced: 21 cases (11.9%) of retinal detachment, 7.8% vitreous hemorrhage and a 1.7% incidence of endophthalmitis (bacterial infection of the eye) in the implant group. Patients with the implant experienced an approximate four-week period of blurry vision (Chiron Vision 1995; Musch 1997).

Hoffmann-La Roche conducted study 2304 in order to determine whether or not adding oral ganciclovir to the ganciclovir intraocular implant would lessen the development of contralateral and extraocular disease. From May 1994 to July of 1996, 377 patients with unilateral CMV retinitis (CMV retinitis in only one eye) were randomized to receive an implant plus oral ganciclovir, implant plus placebo, or IV ganciclovir.

The incidence of biopsy-proven extraocular disease and photographically confirmed contralateral disease at six months was 37.8% for those in the implant plus placebo group, compared to 22.4% for the implant plus oral ganciclovir group (p=0.016) and 17.9% in the IV group (p=0.001) (Martin 1997a). Of interest, there was a protective effect against Kaposi's sarcoma (KS) in those patients receiving oral and IV ganciclovir: eleven percent in the implant plus placebo group developed KS versus 2.7% in the combination group and 1.5% in the IV arm (p=0.008 for both ganciclovir groups). The protective effect seen with ganciclovir may be due to its anti-KSHV/HHV-8 properties.

Martin and colleagues recently reported on the complications arising from multiple exchanges of implants in 22 eyes of 15 patients receiving a second implant and four eyes of four patients who received a third implant. Complications after the second implant procedure included transient vitreous hemorrhage in five eyes, postinterior inflammation in one eye, and retinal detachment in one eye. It took a 42 days for visual acuity to return to 20/20. Three of four eyes had documented dense vitreous hemorrhage after the third procedure. Thus, while multiple implants continue to control long-term CMV, they are also associated with an increased risk of vitreous hemorrhage (Martin 1997). Lastly, it is believed that patients receiving potent protease inhibitor combination therapy (PPICT) will have longer, sustained quiescent disease and thus require few if any implants to be changed (Daniel Martin, personal communication).

While the implants appear effective in protecting the implanted eye, they appear ineffective in protecting the fellow eye and in preventing systemic disseminated CMV disease. Ongoing studies of the implants with oral ganciclovir (or possibly cidofovir) as maintenance might help with these progressions. In addition, ongoing technological developments in implant technology and surgery are warranted in light of the high rate of retinal detachment and the threat of endophthalmitis (inflammation of eye tissue).

Intravitreal Anti-CMV Therapy

Patients failing or intolerant to all IV therapies may be considered for intravitreal injections. Results from single institution, uncontrolled, non-randomized case-series of ganciclovir, foscarnet, and cidofovir intravitreal injections for CMV retinitis have been published (Heinemann 1989; Cochereau-Massin 1991; Diaz-Llopis 1994; Kirsch 1995a, 1995b; Rahhal 1996a, 1996b). These agents are usually injected directly into the vitreous humor using a tuberculin syringe with a 30-gauge needle placed 3 to 4 mm from the corneal limbus. The drug is delivered in a volume of 0.05 to 0.1 milliliter depending on the dose and concentration (Palestine 1996). As with the ganciclovir implant, patients are at increased risk for contralateral and extraocular CMV disease, as well as early retinal detachment, endophthalmitis, vitreous hemorrhaging, and hypotony (reduced eyeball tension due to muscle stretching).

Intravitreal Ganciclovir

Heinemann administered intravitreal ganciclovir injections to 7 patients intolerant of systemic ganciclovir and foscarnet. Five of 7 patients responded to therapy for 14 to 56 weeks (18 to 58 injections). Two patients immediately discontinued therapy, one due to severe thrombocytopenia (platelet reduction), the other due to retinal detachment. One treated patient developed endophthalmitis (Heinemann 1989). Cochereau-Massin and colleagues studied 44 patients (64 eyes) who were intolerant of or refused systemic anti-CMV therapy. Fifty-two of the first 53 injections (98%) led to cicatrization (scarring). The eight-week relapse rate was 53%. Contralateral disease developed in 11% of patients, and 16% developed extraocular disease. Five patients had retinal detachment, and two had intravitreal hemorrhages (Cochereau-Massin 1991).

Intravitreal Foscarnet

Diaz-Llopis and colleagues studied intravitreal foscarnet in 11 patients (15 eyes) who were either refractory or intolerant to systemic anti-CMV therapy. After 3 weeks of induction therapy, complete resolution was noted in 5 of 8 (62.5%) evaluable patients. The 20-week relapse rate was 33%. No local or intraocular toxicities were noted (Diaz-Llopis 1994).

Intravitreal Cidofovir

Four published studies of intravitreal cidofovir treatment have come from William Freeman's group at UCSD (Kirsch 1995a, 1995b; Rahhal 1996a, 1996b). All studies used 20 microgram injections of cidofovir given every 5 to 6 weeks on patients who either refused or were refractory or intolerant to systemic therapy. In one study, 31 cidofovir injections were administered to 24 eyes in 17 patients. The median time to progression was 55 days. Mild to moderate iritis (inflamation of the iris) developed in 4 eyes, and one case of visually significant hypotony (reduced eyeball tension due to muscle stretching) was reported (Kirsch 1995a). Another study (a prospective case series) of 53 eyes in 35 patients documented anti-CMV activity. Of 24 eyes in CMV antiviral-naive patients, none progressed during the study. Four of 29 eyes in the refractory/relapse patients progressed. One patient had retinal detachment and mild inflammation of the iris developed after 14% of the injections. Irreversible visual significant hypotony developed in two eyes (Rahhal 1996b).

In two larger case series looking at the toxicity of intravitreal cidofovir, more cases of hypotony, iritis, and uveitis (an inflammation of the uveal tract of the eye which may lead to blindness) have been documented (Banker 1997; Taskintuna 1997). Taskintuna and colleagues (UCSD) had documented follow-up on 63 patients who had 246 injections in 93 eyes. Three percent of the eyes (1% of injections) experienced permanent visual loss due to chronic hypotony and another 14% with transient hypotony experience mild-to-moderate visual loss. Transient hypotony in the injected eye could predict chronic hypotony in the fellow eye ($p=0.02$). The incidence of iritis was 32% (Taskintuna 1997).

With such an unsettling and dangerous toxicity profile, many wonder why Freeman's group and others around the country continue to administer intravitreal cidofovir to CMV retinitis patients. Let us hope that the magnitude of possible toxicities is explained to patients before they start therapy.

ISIS 2922

Isis 2922 is an experimental antisense oligonucleotide used only in intravitreal form. Twenty-four patients with refractory CMV retinitis were enrolled in an open-label, dose-ranging study of ISIS 2922. Intravitreal doses of 83, 165, 330, and 496 micrograms were given once weekly for 3 weeks of induction followed by weekly maintenance doses, or after biweekly induction doses of 330 micrograms. Time to progression for patients receiving three doses was about 8 weeks (range 3 to 50 weeks) (Hutcherson 1995). The side effects were pronounced. A majority of patients developed anterior and posterior chamber inflammation. Most responded to topical steroid treatments, but others were left with acute decreases in visual acuity. Some patients treated with doses of 330 micrograms or higher developed extensive destruction of the peripheral retina and retinal pigment epithelium, resulting in severe and irreversible peripheral visual field loss (Palestine 1996).

MSL-109

MSL-109, an anti-CMV monoclonal antibody directed against specific proteins was shown to supplement the antiviral activity of both ganciclovir and foscarnet in a small open-label, Phase I CMV retinitis study. When MSL-109 was added to either ganciclovir or foscarnet, the median time to progression was over 200 days (Tolpin 1993). Attempting to duplicate these results, SOCA and the ACTG conducted ACTG 294, a multicenter, Phase II/III, placebo-controlled study which randomized 209 CMV retinitis patients taking any approved anti-CMV therapy to receive MSL-109 (60 mg IV every two weeks) or placebo. The study was stopped early by the Patient Data and Monitoring Board because about twice as many relapse patients in the MSL-109 group died as compared with those receiving placebo ($p=0.016$). Moreover, there was no difference documented in the

median time to progression in either arm for either newly- diagnosed and relapsed patients – 67 days for the MSL-109 group and 65 days for the placebo recipients (p=0.753) (SOCA 1997). Many believe the mortality difference to be a statistical fluke, citing an exceptionally low mortality rate in the relapse placebo patients which is incongruous with other treatment and natural history studies. Nonetheless, MSL-109 appears to add nothing to an existing anti-CMV regimen and could well be harmful.

Are Immediate versus Deferred Studies Ethical?

As noted, all three drugs approved for the treatment of CMV retinitis were licensed on the basis of studies which randomized patients with peripheral, allegedly "non-sight-threatening" CMV retinitis to receive immediate or deferred therapy. Yet even when this study design was piloted with ganciclovir in ACTG 071, many in the activist community questioned the ethics of the scheme, asking whether there really was such a thing as "non-sight-threatening CMV retinitis" (ACT UP/New York 1989). Indeed, ganciclovir was licensed later in 1989 on the basis of open-label data gathered in a several-thousand patient compassionate use program. Both ganciclovir and foscarnet have significant toxicities which might have strengthened the case for a deferred therapy (or no treatment control) arm, but now that there are three FDA-approved treatments for induction therapy of CMV retinitis such designs appear highly questionable, possibly unethical and definitely anachronistic. While some may claim that there is no ultimate difference in the final visual outcome for patients in deferred therapy, every study demonstrates a dramatic difference in time to progression between immediate and deferred therapy arms:

Are Immediate vs. Deferred Studies Ethical in CMV Retinitis?				
		Median Time to Progression		
Study	***Drug***	***Immediate***	***Deferred***	***p-value***
ACTG 071	Ganciclovir	49.5 days	19.3 days	<0.001
Gilead 106	Cidofovir	78 days	21 days	0.001
SOCA/ACTG 281	Cidofovir	69 days	21 days	0.03
GCVI-606-NEI	Vitrasert	226 days	15 days	<0.0001

[Note: the more conservative FDA estimates were used for the Gilead 106 study. Time to progression in the Vitrasert study refers only to the implanted eye.]

In all four studies, the median time to progression in the deferred arm was a mere two to three weeks, demonstrating the rapidity of the progression of untreated CMV retinitis. We know that patients with any type of CMV retinitis will progress. Clear, rational and ethical reasons need to stated for designing immediate versus deferred studies for CMV retinitis. Quicker time to FDA approval is not one of them, and no one has presented a compelling case for continuing to conduct such studies. Alternative trial designs might include randomizing people to receive a new drug plus standard of care versus standard of care alone for induction, maintenance or relapsed CMV retinitis.

CMV PROPHYLAXIS

Considering the debate about the efficacy of oral ganciclovir for CMV maintenance documented above, it is no surprise that the use of oral ganciclovir for CMV prophylaxis is even more controversial, while other potential prophylaxes, such as valacyclovir or high-dose acyclovir, have either demonstrated an unacceptably high trend towards increased mortality (valacyclovir) or a lack of efficacy (acyclovir). Despite FDA approval of oral ganciclovir for this indication, many clinicians are not initiating oral ganciclovir for CMV prophylaxis , choosing instead more frequent ophthalmologic monitoring and CMV PCR testing.

Oral Ganciclovir

Oral ganciclovir is the only drug approved by the FDA for prophylaxis of CMV retinitis. Two randomized, placebo-controlled, Phase III studies have been completed (Spector 1996; Brosgart 1996). Syntex/Roche study 1654 suggested that oral ganciclovir was effective and reduced the risk of CMV end-organ disease by 49%. According to a study carried out by the Community Program for Clinical Research on AIDS , CPCRA 023, however, oral ganciclovir was no better than placebo in preventing CMV. Below is a comparison of the two studies, which both had a 2:1 ganciclovir to placebo design.

Syntex 1654 vs. CPCRA 023: Oral Ganciclovir (OGCV) vs. Placebo (PL) for CMV Prophylaxis		
	Syntex 1654	***CPCRA 023***
Ophthalmologic exams	Baseline, q2 months Ophthalmologist	After visual symptoms occur Primary care physician
Unit characteristics	Study site referral	Primary care
Demographics	81% white males	70% white males
Median CD4 count	21	34
Baseline CD4≤50	88%	65%
AIDS diagnosis	64%	45%
Acyclovir use	≤1 gm/day allowed	≤1 gm/day allowed
Ganciclovir/Placebo Hazard ratio (p-value)		
CMV disease	0.51 (<0.001)	0.92 (0.60)
CMV retinitis	0.51 (<0.001)	0.84 (0.37)
Death	0.81 (0.14)	0.83 (0.09)

Syntex 1654 vs. CPCRA 023: CMV Disease by Site						
CPCRA 023 (Follow-up 12 months)				***Syntex 1654 (Follow-up 18 months)***		
	OGCV	***PL***	***HR (p-value)***	***OGCV***	***PL***	***HR (p-value)***
N	662	332		486	239	
CMV retinitis	11%	13%	0.84 (0.37)	18%	39%	0.51(<0.001)
CMV colitis	3%	4%	0.83 (0.10)	2%	4%	0.68 (0.50)
Other sites	1%	2%	0.50 (0.17)	4%	5%	

CPCRA 023: Hazard Ratio for CMV and Survival Pre- and Post-Protocol Change			
	Median follow-up	***CMV HR (G/P)***	***Death HR (G/P)***
At time of DSMB review*	7.8 months	0.87	1.27
At protocol amendment	**9.0 months**	**0.86**	**0.96**

CPCRA 023: Hazard Ratio for CMV and Survival Pre- and Post-Protocol Change			
At study close	**15.0 months**	**0.90**	**0.83**
Follow-up censored at protocol amendment		0.93	0.90

* After Syntex 1654 was terminated early, CPCRA 023 patients were given the option of switching to open-label oral ganciclovir. At that time, exposure to oral ganciclovir was 9.3 months for patients randomized to oral ganciclovir and 2.1 months for patients randomized to placebo.

There were significant differences between patient management strategies in the two studies. Syntex 1654 patients were examined by an ophthalmologist at baseline and at every two months, while CPCRA 023 did not require a dilated eye examination by an ophthalmologist at study entry and only required patients to be examined by an ophthalmologist *after visual symptoms arose*. Thus, Syntex 1654 was likelier to detect CMV retinitis before it became clinically apparent, and CPCRA 023 only afterwards. CPCRA 023 was attempting to study a real-world scenario, equating "usual care" with ophthalmologic exams only after visual symptoms occur. However, this difference in patient monitoring may not have been the only determinant of the discordant results between the two studies. At the IX International Conference on AIDS, the CPCRA's Carol Brosgart presented a *post hoc* analysis of 023 prepared by the CPCRA Statistical Center, which found an unexpected negative interaction between oral ganciclovir and ddI. Patients who were on placebo and taking ddI had a very low rate of developing CMV, whereas patients in the oral ganciclovir arm on ddI had a high probability of developing CMV disease. The hazard ratio for developing CMV disease with oral ganciclovir versus placebo if on a ddI containing regimen was 7.48 ($p=0.02$). Of the 63 patients in the placebo arm taking ddI, only 1 patient developed CMV disease. Conversely, when other antivirals were used with oral ganciclovir versus placebo, the hazard ration was 0.62 ($p=0.04$). This drug interaction between oral ganciclovir and ddI has baffled many. Previously, there have been data indicating an approximate 70% increase in the area under the curve (AUC) of ddI when it is combined with oral ganciclovir. Likewise, the impressive suggested prophylactic results seen here with ddI (in the placebo patients) have not been documented before. In response, Spector reported that the Syntex/Roche 1654 team did a *post hoc* analysis of all their patients on ddI and did not find the same results seen in CPCRA 023. Brosgart stood by her team's analysis, but cautioned that the results should be interpreted carefully and that the supposed negative ddI and oral ganciclovir interaction should be investigated further (Brosgart 1996).

In a presentation at the 37th ICAAC, Spector presented a meta-analysis of Roche 1654 and CPCRA 023 indicating that oral ganciclovir may improve survival in patients with advanced AIDS ($p=0.04$). In the Roche study, according to Spector, CMV positivity at baseline increased the risk of CMV disease by 3.4-fold and the risk of mortality by 2.5-fold. 3,000 plasma samples from 553 of 725 patients from baseline and longitudinal visits were evaluated to correlate the impact of treatment on plasma CMV DNA. Spector divided those starting with CMV PCR positivity into responders and non-responders at two months. Responders' CMV PCR became negative, whereas non-responders' CMV PCR stayed positive. Mortality at twelve months was 20% for responders and 48% for non-responders (Spector 1997). A similar analysis should have been done among those in the placebo arm whose CMV PCR became negative.

Does Oral Ganciclovir Prophylaxis Cause Resistance?

Larry Drew presented resistance data on patients from Syntex 1654 who received at least 90 days of oral ganciclovir (Drew 1996b). Of 39 isolates taken from urine culture (mean ganciclovir exposure of 251 days; range 112 to 564 days), two were found to have resistant virus with an IC_{50} of more than 12 mcM. In this study, the estimated prevalence of resistance to oral ganciclovir after 8.3 months was less than 1%. However, other clinicians are skeptical of this finding. According to Mark Jacobson, 8 months is not long enough to be testing a CMV prophylactic agent now that we have potent antivirals that are allowing patients with CD4 counts below 50

to live longer. He contends, "If there's an exponential increase in resistance that we aren't catching [in eight months], then we're missing something very important" (Jacobson 1996b). Moreover, Drew believes that urine cultures for testing CMV resistance might not correlate with a patient's active retinitis. He acknowledges, "I don't think we know all the significance of PCR positivity and culture negativity. We may have levels of resistance that don't translate into culture positivity yet could be contributing to what's going on in the eye" (Drew 1996a).

Is Oral Ganciclovir Cost Effective?

Many studies have been conducted to determine the cost effectiveness of oral ganciclovir for CMV prophylaxis. In "The Cost-Effectiveness of Preventing AIDS-Related Opportunistic Infections," a study in this month's *Journal of the American Medical Association* (JAMA), Freedberg and colleagues compared the clinical impact, cost and cost-effectiveness of prophylaxis for PCP, toxoplasmosis, MAC, fungal infections and CMV, and found oral ganciclovir the least cost-effective prophylaxis:

Cost of Quality per Life Year (QALY) Saved by OI Prophylaxis		
Prophylactic Drug	***OI***	***$ Per QALY Saved***
TMP/SMX (Bactrim)	PCP & Toxo	$ 16,000
Azithromycin	MAC	$ 35,000
Rifabutin	MAC	$ 74,000
Oral ganciclovir	CMV	$ 314,000

(Freedberg 1998)

It is not surprising that oral ganciclovir is the least cost-effective. In the virology sub-study of Roche's Study 1654, **oral ganciclovir was *most effective in those patients who were CMV DNA PCR negative*** (14% developed CMV in the placebo arm vs. 1% in the oral ganciclovir arm). For those who were PCR positive, only those with fewer than 50,000 copies/µl benefitted from oral ganciclovir. There was no statistically significant difference between drug and placebo in those who were PCR positive (Spector 1996c). Using an expensive prophylactic drug that is only effective in patients at least risk will never be cost effective.

Lastly, the U.S. Public Health Service/Infectious Disease Society of America Guidelines Panel for the Prevention of OIs in Persons with HIV recently published its recommendation on the use of oral ganciclovir for CMV prophylaxis. It states:

> *Prophylaxis with oral ganciclovir **may** be considered for HIV-infected adults and adolescents who are CMV seropositive and who have a CD4+ T-lymphocyte count of <50 cells/µl Neutropenia, anemia, **limited efficacy**, lack of improvement in survival, and cost are among the issues that should be considered... (USPHS/IDSA 1997).*

EXPERIMENTAL CMV PROPHYLAXIS

Valacyclovir (Valtrex™, Glaxo-Wellcome)

ACTG 204 was a 1227-patient randomized, placebo-controlled, Phase III study of valacyclovir (VACV) versus two doses of acyclovir (ACV) for CMV prophylaxis in patients with advanced HIV disease (Feinberg 1998). VACV recipients had a 33% reduction in CMV endpoints compared to ACV recipients, and the time to confirmed CMV disease was significantly longer ($p=0.01$) for those in the VACV arm compared to all those pooled in ACV arms. The tables were turned on VACV arm in the final survival analysis where there was a trend ($p=0.06$) toward earlier

mortality for patients in the VACV arm compared to either ACV arm. This trend toward earlier mortality has never been completely understood and is disheartening because valacyclovir may help prevent CMV. Nonetheless, it is only by conducting randomized clinical studies that important – often life threatening – differences such as this one can be determined. With the increased mortality difference noted in ACTG 204, and because of a warning issued against its use in immunocompromised patients due to its association with hemolytic uremic syndrome / thrombotic thrombocytopenic purpura (potentially fatal bleeding in the kidneys) in this population (FDA Data 1996, Bell 1997), valacyclovir has been cast aside by almost everyone as a potential CMV prophylaxis for PWAs.

Valganciclovir (RS-790070, Pro-Ganciclovir, Hoffmann-LaRoche Inc.)

The ACTG is developing a CMV pre-emptive therapy (targeted prophylaxis) study that will use valganciclovir, the oral pro-drug of IV ganciclovir. Approximately 750 patients with high HIV viral loads and low (50 or less) CD4 counts will be enrolled. Patients will be followed with periodic CMV PCR tests (using Roche's assay) and opthalmologic exams. Those who test PCR positive will be randomized to pro-ganciclovir or placebo with the primary endpoint being development of CMV end-organ disease and a secondary endpoint of death. In this era of PPICT, finding 750 patients with high viral load and very low CD4 counts at ACTG trial sites may be a difficult and long process. Nonetheless, it is essential that this study be carried out. Validating the CMV PCR assay, the concept of CMV pre-emptive therapy, and the safety and efficacy of pro-ganciclovir will greatly help all PWAs at risk.

Adefovir dipivoxil (Preveon™, bis(POM) PMEA, Gilead Sciences)

Adefovir dipivoxil (Preveon™) is a nucleotide analog with *in vitro* activity against HIV, HBV, HSV-1 and -2, EBV, HHV-6 as well as CMV. Adefovir is now in phase III pivotal studies for HIV, as a CMV prophylaxis, and in phase II for HBV. PMEA (9-[2-(phosphonomethoxy)ethyl]adenine) is a nucleotide analog, differing from a nucleoside analog by virtue of a phosphate – the drug is one step closer to activation when it enters a cell, where it is phosphorylated twice, after which it inhibits the CMV polymerase. The fully phosphorylated nucleotide competes with adenosine, one of the building blocks of DNA, for incorporation into DNA. Adefovir or bis(POM) PMEA (bis(pivaloyloxymethyl)-9-[2-(phosphonomethoxy)-ethyl]adenine) is actually the prodrug of PMEA with improved oral bioavailability, tolerability and antiviral activity (by virtue of improved intracellular metabolism). Its side effects are predominantly gastrointestinal, such as nausea and diarrhea. Adefovir depletes levels of L-carnitine, necessitating supplementation with oral L-carnitine 500 mg/day. The drug's long intracellular half-life allows for once-daily dosing. Adefovir has a terminal serum half-life of approximately 5 hours. Its C_{max} is dose-proportional at the doses tested. It is renally excreted in unchanged form. There appears to be no drug accumulation over time. It is 30% bioavailable in a fasting state and 40% after eating. The dose under study is 120 mg/day. Two placebo-controlled Gilead studies are assessing the clinical impact of adefovir on HIV progression and the development of CMV disease.

Studies of Adefovir against HIV and CMV				
Study	*Sites*	*N*	*Population*	*Endpoints*
Gilead 407/CPCRA	USA	2,160	CD4<100	AIDS, CMV disease
Gilead 410/ADHOC	**Europe/Australia**	**2,000**	**CD4<100**	**Death, CMV disease**

(Dietz 1998)

Gilead is moving towards filing for FDA approval of adefovir, at least for the anti-HIV indication, sometime in 1998. In the meantime, the drug is available via expanded access by contacting 1.800.GILEAD.5 (Dietz 1998).

Lobucavir (Cyclobut G, BMS 180194, Bristol-Myers Squibb)

Lobucavir is another nucleoside analog – this one based on guanine – with broad-spectrum *in vitro* activity against CMV and other herpes viruses, HBV and HIV. Against HIV its activity appears confined to macrophages. Its bioavailability is 30-40%. Doses up to 400 mg orally four times daily seem relatively non-toxic and can render the urine of 60% of CMV viruric subjects CMV negative (Lalezari 1997a, Petty 1995). Despite some encouraging findings, lobucavir does not appear to be moving rapidly through the testing pipeline.

GW1263W94 & BDCRB (Glaxo-Wellcome)

Glaxo-Wellcome is in the early stages of developing GW1263W94 – an oral halogenated benzimidazole derivative with a unique mechanism of action and specific anti-CMV activity – as well as a related anti-CMV compound, BDCRB (Zacny 1997). GW1263W9's clinical development for CMV retinitis is in question because it does not seem to cross the blood-eye barrier well in animals. BDCRB does not appear to have as great a magnitude of anti-CMV activity as GW1263W94, but better crosses the blood-eye barrier in animals (Karen Biron, personal communication).

*

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CMV-ASSOCIATED NEUROLOGICAL DISORDERS

by Theo Smart

INTRODUCTION

Cytomegalovirus (CMV) can cause a number of distinct neurological syndromes (in addition to end-organ disease in the eyes, gut, lungs and elsewhere) such as mononeuropathy multiplex (inflammation or disease involving individual nerves in unrelated portions of the body), myelitis/polyradiculopathy (acute inflammation of a large number of the spinal nerves accompanied with pain, muscle wasting and paralysis), and two forms of encephalitis (brain disease): diffuse micronodular encephalitis (DME, scattered nodular lesions in the brain), ventriculoencephalitis (VE, inflammation of the brain's ventricles) (Morgello 1987; Vinters 1989; Said 1991; Cinque 1992; Fuller 1992; Kim 1993).

The actual rate of CMV infection of the central nervous system (CNS) is unclear. One two year study reported that CMV encephalitis is found in only 1% of patients with advanced AIDS (Gallant 1992). The figure may accurately reflect the rate of clinical diagnosis, but not the true incidence rate. In neurological autopsy studies, CMV infection of the CNS is found in between 20 and 28% of the brains studied (Morgello 1987; Cinque 1995).

Other figures have been produced by the AIDS Ocular Research Unit, University of California, San Diego, which calculated that CMV encephalitis occurs in around 42% of autopsied patients with CMV retinitis. The rate was almost 75% in more advanced cases of retinitis. In contrast, it was very uncommon in people without CMV retinitis (Bylsma 1995).

While there is no proof that all of the cases of CMV neurological disease detected upon autopsy were rapidly progressive or caused the patients' death, there is substantial evidence suggesting that patients are adversely affected by these undiagnosed infections. One study notes that even less advanced CMV infections may affect neurocognitive function. A team from the HIV Neurobehavioral Research Center at the University of California, San Diego, compared 16 patients with newly diagnosed CMV retinitis, but without clinical dementia to 32 matched controls with similar CD4 counts, age and education. They found neuropsychological impairment (most commonly attention and verbal deficits) in two-thirds of the patients with newly diagnosed CMV retinitis, and in about one-third of these cases the impairment was caused by CMV rather than HIV. Evidence of physical damage to the central nervous system detectable by magnetic resonance imaging (MRI) brain scans was approximately twice as frequent in the patients with retinitis than in the matched controls (McCutchan 1995).

While these findings are challenging, they do not prove a direct mechanism for CMV in neurological performance, since indirect mechanisms such as cytokine toxicity associated with CMV infection or visual interference in testing may explain the differences observed (David Clifford, personal communication). Researchers from San Diego's Neurobehavioral Center reported that the risk of cognitive impairment associated with CMV encephalopathy was seven-fold higher than of HIV encephalopathy (Ellis 1995). The authors concluded that "unrecognized CMV encephalitis may be an important cause of both mild and severe neurocognitive impairment in patients with advanced HIV infection."

CLINICAL MANIFESTATIONS AND NEUROPATHOLOGY

Mononeuropathy multiplex occurs when CMV infects the cranial and peripheral nerves resulting in face, wrist and foot palsies (Lipkin 1985). Mild forms that resolve spontaneously often strike patients fairly early in the course of HIV disease (So 1994).

Polyradiculopathy is strictly a late-stage AIDS event, caused by CMV infection of the nerve roots and spinal cord leading to axonal necrosis (Behar 1987). The condition may accompany or possibly lead to VE (McCutchan 1995). One case review of 23 patients reported that over a period of roughly two weeks, the condition began

with weakness, leg and back pain, and sensory loss in the legs in association with loss of bladder control (usually leading to urinary retention) or loss of anal-sphincter control. This is followed by an ascending paralysis of the lower extremities (So 1994).

The two CMV-encephalitic syndromes are distinguished primarily by their neuropathologies. DME is characterized by widely scattered small microglial nodules and inclusion-bearing cytomegalic cells primarily concentrated in the gray matter of the brain (McCutchan 1995). VE appears to be the result of an invasion by CMV via the CSF, beginning in the ependymal cells lining the ventricles and moving progressively layer by layer through the subependymal layers into the periventicular brain (Wiley 1986). This infection leads to necrosis of the cranial nerves and paraventricular parenchyma (Kalayjian 1993).

In both syndromes, dementia, delirium, confusion, apathy, and lethargy are common (Kalayjian 1993; Holland 1994). Some of the symptoms of DME depend upon the location of the nodular lesions, (as is often the case in toxoplasmosis, CNS lymphoma or PML) (Holland 1994). Patients with VE, meanwhile, often experience cranial nerve palsies and nystagmus (rhythmic, involuntary eye movement). Both conditions are rapidly fatal. In one study of patients with VE, the median survival was only 5 weeks (Kalayjian 1993), while those diagnosed with DME had a slightly longer median survival of 8.5 weeks in another study (Holland 1994). The full spectrum of DME has not been investigated, and milder forms with less rapid progression may exist.

DIAGNOSIS

In aggressive cases of CMV CNS disease, the onset of symptoms is so abrupt, and the progression so rapid, that the infection may dramatically progress within the time it takes clinicians to distinguish it from other AIDS-related neurological conditions. There are some distinctive features of CMV neurological disease, however. For example, CMV encephalitis occurs very late in the course of HIV disease, while signs of the most common alternate diagnosis, HIV encephalopathy, appear earlier and more gradually. Dementia was more commonly observed than cognitive or motor disturbances in one early autopsy study of patients with DME (Navia 1986). Holland and colleagues reported much higher levels of delirium, confusion, apathy, withdrawal and focal deficits among patients with CMV encephalopathy than in patients with HIV encephalopathy.

Other hallmarks of CMV CNS infection, such as electrolyte abnormalities, pleocytosis (cell infiltrates in the CSF) and enhancement of the brain ventricles on MRI brain scans suggest CMV infection, particularly in the presence of CMV retinitis (Holland 1994; McCutchan 1995). In cases of polyradiculopathy, an MRI shows a characteristic enlargement of the conus medullaris, and clumping of lumbosacral rootlets, or with gadolinium, contrast enhancement of the lower spinal cord leptomeninges (So 1994). The conditions are sometimes associated with CMV adrenalitis (infection of the adrenal glands, evidenced by reported electrolye abnormalities consistent with adrenal insufficiency (high levels of potassium, low levels of sodium) (Holland 1994; McCutchan 1995). These markers allow for a presumptive, but not a definitive diagnosis, since they also may occur in other neurological conditions as well.

Until recently, finding proof of active CMV infection in the CNS has been difficult without conducting a brain biopsy. Even though the CSF is believed to be the primary route through which CMV enters the CNS (particularly with VE and polyradiculopathy), the virus is rarely cultured from the CSF (So 1994).

Tests for CMV DNA by polymerase chain reaction (PCR) of the CSF may be diagnostic in the appropriate clinical setting. Some studies report that such assays are dramatically more sensitive than culturing and that the virus is usually only detected in cases of active CNS CMV infection (Cinque 1995). One study by Achim and colleagues (Achim 1994) found that the test was not as specific, since CMV DNA was detected by PCR in the CSF of 58% of the patients without CMV-associated neurological conditions. Limited experience using the new tests or use of post-mortem CSF samples may explain some of these contrasting results. Also, this was a study of autopsy specimens, and McCutchan points out that the virus could have entered the CSF post-mortem (McCutchan 1995).

It stands to reason that even if CMV DNA can be found in the CSF of people who do not have clinical CNS CMV disease, quantitative assays may provide a better indication of who is at risk for disease. A German study suggests that CMV DNA loads in the CNS were 10- to 1000-fold higher in patients with CMV neurological disease than in those without (Kuhn 1995). Researchers from Roche Molecular Systems and UC San Francisco reported in 1996 that CMV DNA was detected in 24 of 26 patients with polyradiculopathy and that levels were consistently above 1000 CMV DNA copies per milliliter (mL), except in one case of a patient on therapy (Long 1996). CMV DNA levels were generally under 100 per mL of CSF in patients with other CMV neurological conditions. Another group of researchers recently published data correlating the presence of CMV DNA in the CSF of all but one of 13 patients with CMV CNS disease, while no CMV DNA was found in control subjects. High levels of CMV DNA (1000 copies per mL) were associated with severe disease, VE in particular, and uniformly shorter survival (Arribas 1995).

TREATMENT

There have been no prospectively controlled studies of the treatment of CNS CMV disease, and the case reports are scant. Thus, there are no clear data on what is the best drug or dose to use, or what the duration of treatment should be. There are case reports of clinical responses to ganciclovir or foscarnet, but there is reason to believe that standard treatments of CMV retinitis may be inadequate as therapy for CMV infections in the brain. McCutchan and colleagues compared case studies of patients with polyradiculopathy who were treated to those of untreated patients and found that half of the treated patients survived for a median of 11 weeks while 7 untreated patients all died within four weeks (McCutchan 1995). It is hard to construe less than two months additional survival as a great success.

Furthermore, CMV encephalopathy often develops in patients receiving maintenance therapy for CMV retinitis (Mastroianni 1994, Paterson 1995, Berman 1994). Some treatment failures may be due to drug resistance. In two cases, CMV polyradiculopathy was associated by ganciclovir-resistant strains (Jokela 1994, Smith 1996). The degree of penetration by either ganciclovir and foscarnet into the CNS is unclear. The level of ganciclovir, in particular, in the CSF is substantially lower than in the plasma (Shepp 1985). On the other hand, Larry Drew of UCSF presented data in 1995 demonstrating that ganciclovir, with or without foscarnet can lower CMV load in the CSF (Drew 1995). Using the CMV bDNA assay, his team reported that treatment had antiviral activity in the CSF of 7 out of 8 patients with CMV neurological disease (Drew 1995). The lack of clinical response in these patients suggests that some of the nerve damage may be irreversible.

More promising data were presented by French researchers in 1996, reporting rapid clinical improvement (within 10-13 days) in four of four patients with CMV neurological disorders (three cases of encephalopathy and one myeloradiculitis) on a combination regimen of ganciclovir at 5 mg/kg every 12 hours, and foscarnet 60 mg/kg every 8 hours as induction therapy, followed by ganciclovir at 5 mg/kg, and foscarnet 90 mg/kg every day for maintenance. CMV DNA became undetectable in two out of two patients tested. No one stopped treatment due to toxicity, although one case of anemia and one case of leukopenia were observed (Couderc 1996).

These results support the rationale for ACTG 305, a six-month multicenter study of high-dose, aggressive combination foscarnet/ganciclovir therapy in at least 30 patients with recently diagnosed CMV encephalopathy or radiculomyelitis. Participants will be treated with 28 days of foscarnet 90 mg/kg and ganciclovir 5 mg/kg both twice daily followed by maintenance therapy with the same doses, but on a once-a-day basis. If they can tolerate it, those with prior experience on ganciclovir will receive higher ganciclovir doses (7.5 mg/kg twice a day for induction therapy and 10 mg/kg once a day for maintenance therapy). Up to ten patients who can not tolerate either agent will be treated with the alternate drug as a monotherapy. If patients fail on maintenance therapy, higher induction therapy doses will be reinitiated.

ACTG 305 seeks to answer many of the nagging questions surrounding CNS CMV disease. The study will evaluate both quantitative CMV DNA PCR and CMV bDNA as surrogate markers for disease severity, progression

and response to therapy. The study also will investigate the role of drug resistance in the evolution of CNS CMV disease, and in treatment failure. Finally, researchers will try to perform as many brain autopsies as possible on those patients who die during the study to determine the level of drug that actually penetrates the brain.

EXPERIMENTAL TREATMENTS

It is hard to predict what effect recent improvement in the treatment of CMV retinitis will have upon the development of CMV-related neurological syndromes. The addition of cidofovir to the approved anti-CMV armamentarium increases the number of treatment options, and lobucavir, adefovir, and other new compounds from Gilead Sciences and Glaxo Wellcome are waiting in the wings. It is unclear whether the use of oral ganciclovir will decrease the rate of extraocular disease or merely engender resistance by supplying suboptimal levels of drug. Finally, the growing use of localized therapies for CMV retinitis such as ganciclovir implants or intravitreal cidofovir injections may increase the rate of extraocular CMV disease, which was prevented before by the use of systemic anti-CMV therapy.

Even if the use of localized therapy does increase the incidence of CMV encephalopathy or polyradiculopathy, with viral load monitoring of the CSF and an increased awareness of the conditions, the prospects for the treatment of CNS CMV disease are improving. Increased diagnosis creates an opportunity to conduct prospectively controlled clinical trials that will eventually improve treatment. Furthermore, early detection may enable treatment to prevent permanent damage to the nervous system.

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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

by Theo Smart

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a rapidly progressive disease of the central nervous system (CNS). It is caused by the infection and destruction of oligodendrocytes and perhaps other brain cells by the JC virus (a papova virus — a family of viruses that also includes wart viruses). The oligodendrocytes produce the myelin that surrounds and protects nerve cells, and their loss leads to demyelination. In patients with HIV, the condition is often fatal within three to five months (Berger 1992).

PML was first described in the late 1950's in three patients, two with concurrent leukemia and one with Hodgkin's disease (Aström 1994). Since PML occurred within the context of immunosuppression, the authors suspected that an opportunistic viral infection was the cause. In 1971, the JC virus was cultured from the brain of a patient with PML, (Padgett 1971). The initials "JC" refer to this patient.

According to a 1995 review article, PML occurs in around 4% of AIDS cases and, at the time, the incidence had been increasing as people with AIDS lived longer with low CD4 cell counts (below 100). However, PML can also occur, less frequently, in patients with higher CD4 counts. It is the first AIDS-defining illness for half of the patients in whom it occurs (MacArthur 1995).

VIROLOGY & ETIOLOGY

The JC virus is very common in humans. Exposure occurs in about 50% of children by age 6 and 80% of adults by middle age (Padgett 1973). The primary illness associated with JC virus is unknown, although one case of meningoencephalitis has been observed in an immunocompetent teenage girl with rising JC antibody titers (Blake 1992).

After acute infection, the virus can remain latent in the kidney, lymphoid organs, bone marrow, and circulating B lymphocytes (Houff 1988; Major 1995). The virus is not believed not to dwell in the brain latently, but rather to be transported there by B cells upon reactivation (Mori 1991; Heinonen 1992; Sock 1993), which may be induced by a number of factors including aging, chemotherapy, immunosuppression and other viruses (Major 1995). The JC virus also can be transactivated by HIV-1 *tat* protein (Chowdury 1990), and replicated by the DNA polymerase of cytomegalovirus (CMV) (Heilbronn 1993). The CMV polymerase also permits the JC virus to grow in fibroblasts (collagen-producing cells) (Major 1995).

Variable regions in the JC virus genome may affect target cell tropism (Feigenbaum 1987; Tada 1990). The JC virus associated with PML lesions in the brain has unique genetic sequences which differ from classical or "archetypal" JC virus sequences found in the kidneys of the same patients (Loeber 1988; Yogo 1994). Neurotropic JC virus contains genes similar to those found in the host central nervous system (Amemiya 1992) which are absent in the archetypal virus (Tominaga 1992). While archetypal JC virus can be grown in glial cells from the brain (Major 1995), the neurotropism which leads to PML may be promoted by genetic changes in the JC virus. Upon entering the CNS, the virus primarily infects myelin-producing oligodendrocytes. Viral replication in the oligodendrocyte nuclei leads to cell death and demyelination. The infection spreads along myelin tracks to neighboring cells (Sweeney 1993).

CLINICAL MANIFESTATIONS

Although PML is pathologically a multifocal process, it may initially present as a unifocal disease. A unifocal lesion can quickly develop over days or weeks to become multifocal.

Persons with PML may initially experience any of a number of neurologic impairments including motor weakness, visual field defects, blurred vision, cortical blindness, double-vision, difficulty in speaking, hiccups and limb ataxia

(gait disturbance). Headache is uncommon. Gross dementia, paralysis and loss of all senses may occur in the end stages of disease (Sweeney 1993).

While progression is usually relentless, in patients with a higher a CD4 at presentation, spontaneous remissions have been observed. As CD4 counts drop, the PML usually returns (Berger 1988).

DIAGNOSIS

A definitive diagnosis can be made by brain biopsy, but this procedure can be harmful or fatal, so many clinicians rely on non-invasive imaging techniques such as axial computed tomography (CT) or magnetic resonance imaging (MRI). PML lesions usually do not enhance on CT or MRI. CT brain scans show hypodense lesions, without mass effect in the sub-cortical white matter (not in the deep white matter). Single and multiple lesions may occur in the cerebral hemispheres, cerebellum or brainstem, but are most common in the parietooccipatal area (Sweeney 1993).

In many cases, the more sensitive MRI may support a definitive diagnosis of PML. The MRI reveals the number and extent of asymmetric lesions, which can track along the contours of the grey and white matter and an intact cortical ribbon (MacArthur 1995). PML lesions are distinguishable from toxoplasmosis and lymphoma by the lack of mass effect or contrast enhancement. The multiple foci and asymmetry of the lesions are distinct from white matter changes seen in HIV encephalopathy (Sweeney 1993).

Detectable JC virus in the cerebrospinal fluid (CSF) is increasingly being used for diagnosis. Many researchers report that JC viral DNA can be detected by PCR only in the CSF of patients with PML (Moret 1993; Brouqui 1992; Weber 1994). JC virus detection in the CSF consistently correlates with positive diagnosis by brain biopsy. Such findings could make brain biopsies unnecessary in a large number of patients (MacArthur 1995; Major 1995).

A recent study by McGuire and colleagues in San Francisco looked for JC virus in the CSF of 26 patients with PML as well as in 114 HIV-positive controls and 16 HIV-negative controls. Using a sensitive PCR test that could detect one copy of JC virus in 50 microliters of CSF, the researchers found the virus in 24 of 26 patients with PML, 10 HIV-positive patients without PML (who will be closely monitored) and one HIV-negative participant with neurologic abnormalities, who happened to be on immunosuppressive therapy) (McGuire 1995).

Detection of JC virus in the plasma by PCR may also prove useful. In an ongoing study, a French team observed 165 people with HIV along with 65 HIV-negative immunocompromised persons and found that JC virus was detectable twice as often among HIV-infected persons as in the uninfected controls (28.9% versus 16.4% in the HIV-negative patients) (Dubois 1996). The individuals with both HIV and JC virus are being followed to ascertain what proportion of JC viremic patients develop PML. While clearly, 29 percent of HIV-infected persons do not develop PML, the study may determine whether a higher JC viral load or certain viral strains distinguish those people more likely to develop the condition.

ACTG 243, a study of the treatment of PML with high-dose antiretrovirals with or without cytarabine (Ara-C; see below) has gathered a large body of JC viral load data from both plasma and CSF. These data may help provide useful information on the pathogenesis and prognosis of PML.

TREATMENT

No treatment has proved effective for PML in controlled clinical trials. In the absence of any treatment proved effective, all efforts at treatment must be understood as experimental. A number of open-label non-randomized uncontrolled case reports and anecdotes have alleged responses to treatments such as cytarabine (Ara-C, O'Riordan 1990), alpha interferon (Colosimo 1992), vidarabine (Ara-A, adenine arabinoside) and idoxuridine (Sweeney 93). Such anecdotes must be viewed with skepticism, as spontaneous remission of PML can occur in the absence of treatment. A number of other case reports and open label studies recount the failure of these same therapies (Sweeney 1993). Treatment with high-dose AZT was reported to lead to responses (Conway

1990; Martin-Suarez 1994), but it is unclear whether improvement was due to an anti-JC viral effect or treatment of the underlying HIV infection. Another group reported two patients treated with AZT, alpha interferon and alpha interferon who survived more than 29 months after PML diagnosis (Smith 1994).

A once influential PML study by Carolyn Britton, who reported clinical improvement in 8 of 13 patients (mean CD4 count of 106) treated with intrathecal cytarabine (Ara-C). Other case reports and open-label studies recount the failure of cytarabine (Antinori 1994). In at least one case, the author suggested that cytarabine *caused* PML in a person with cancer, by suppressing the immune system (Hwang 1986). Furthermore, the drug may be neurotoxic at higher doses. Nevertheless, because of Britton's open-label studies, and because they have no other treatments to offer, many doctors and clinics have administered cytarabine to patients with PML. ACTG 243, the first well-controlled study performed in persons with PML, compared high-dose antiretroviral alone or with cytarabine administered intravenously or intrathecally (through a tube into the spinal fluid). During the summer of 1996 the study was closed when an interim analysis found that there were no differences in survival or neurological function between the three treatment arms. Thus, cytarabine should no longer be used for treating persons with PML.

More recent reports indicate that protease inhibitor containing combination anti-HIV regimens may significantly increase the survival for people with PML, not by anti-JC virus activity but rather, presumably, by the partial immune recovery attendant upon reduction of active HIV replication. Albrecht and colleagues conducted a retrospective analysis of 29 individuals with histologically or PCR-confirmed PML. The mean age was 39 years, and median CD4 count was 40. Fourteen patients (group A) never received or stopped antiretroviral therapy following diagnosis. Ten patients (group B) were treated with nucleoside analogues alone. Five patients (group C) were started on HAART including protease inhibitors. Group C survived significantly longer than groups A and B:

HAART Prolongs Survival Among Patients with PML		
Regimen	***N***	***Survival (days)***
Group A (No antiretroviral/stopped ARV)	14	123
Group B (Nucleoside analogues only)	10	127
HAART including protease inhibitor(s)	5	>403

(Albrecht 1997)

When the study was presented in fall 1997, four of the five HAART patients (80%) were still alive and were "either progressing less rapidly or have even experienced some improvement of their symptoms. CD4 count, age, gender, prior AIDS diagnosis, mode of HIV transmission, and therapy with foscarnet, ara-C or alpha interferon did not affect survival in this cohort." (Albrecht 1997).

EXPERIMENTAL TREATMENTS

Camptothecin derivatives — in particular, camptothecin, topotecan and irinotecan — can suppress the neurotropic JC virus in glial cell cultures (Kerr 1993; Kamil Khalili, personal communication, 1996). These chemotherapeutic drugs work by inhibiting topoisomerase I, an enzyme that uncoils strands of DNA, a necessary step in cell replication. These drugs are known to cause bone marrow suppression, diarrhea, nausea and other side effects. A number of patients now have been treated with topotecan (Colin Broom, personal communication). Two end-stage patients failed to respond. Another patient had remission of brain lesions and symptomatic improvement. Despite the bone marrow suppression caused by topotecan, which was treated with the growth factors G-CSF and EPO, the patient's CD4 count increased. However, this patient had also initiated anti-HIV therapy with a protease inhibitor six weeks earlier, so this response could have been due to immunologic

recovery. Nevertheless, the case has led SmithKline Beecham to design a study which will enroll at least 60 volunteers with biopsy-proven PML -- a hardy bunch -- who have been on stable antiviral therapy for six weeks. Trial participants will be randomized to receive topotecan or observation (no treatment). All in the latter study arm will be crossed over to the treatment arm when there is progression in disease, defined as growth in PML lesions of at least 25 percent as detected on MRI.

A paper by a team of Belgian researchers reported that cidofovir (HPMPC, Vistide™), a drug currently approved for the treatment of CMV retinitis, has activity against a murine (mouse) polyomavirus closely related to the JC virus (Snoeck 1995). The same group reported greater activity against SV40, a more closely related simian polyomavirus that causes a condition similar to PML in immunosuppressed monkeys with SIV (Andrei 1996). The team later treated one PML patient with 3 mg/kg of cidofovir once every ten days (Snoeck 1996). While after two infusions there was a reduction in the size of the lesion, there was continued neurologic deterioration. Treatment was discontinued after the fourth infusion and the patient died two months later. Because the lesion initially regressed, the Belgian team concluded that cidofovir had potential, but that further studies should use more frequent dosing. Several groups, including the ACTG, are currently planning controlled clinical studies of cidofovir for PML.

At the 37th ICAAC in fall 1997, Brosgart and colleagues reported on two individuals who developed PML in spite of having started HAART four and nine months previously. The first patient developed an undetectable HIV load but nonetheless developed PML; the second patient did not go undetectable. Both patients were treated with two months of intravenous cidofovir (5 mg/kg weekly for two weeks, then biweekly). "After two months on CD4, both patients regained use of all extremities and were living independently. In patient A, CD4 was stable and viral load remained undetectable." Patient B switched antiretroviral regimens. His viral load decreased from 192,000 to 38,000 copies/mL, but his CD4 count continued to decline. Nonetheless, at the time the study was reported, both patients were stable seven and nine months later (Brosgart 1997). ACTG 363, a 24 patient pilot prospective study of cidofovir for PML, is currently in development.

New combination antiretrovirals may turn out to be the most significant contemporary advance against PML. Numerous anecdotes suggest that some people with PML experienced lesion regression and clinical remission after starting treatment with potent antiretroviral regimens which include protease inhibitors. Potent antiretroviral combinations appear to be much better at limiting HIV replication and allowing at least partial immune recovery than past anti-HIV treatments, raising CD4 counts to levels at which spontaneous remission has been observed in the past. While no one knows the duration of the anti-HIV efficacy of the new regimens, all patients with PML should certainly be offered the best available anti-HIV agents, preferably ones to which they are not already resistant. Moreover, agents targeting the JC virus, especially cytotoxic or immunosuppressive ones which may actually aggravate their condition, should only be used in clinical trials which allow full use of contemporary antiretroviral regimens.

David Clifford, principal investigator of the Neurologic AIDS Research Consortium (NARC) at Washington University, is collecting natural history records on PML patients who are being treated aggressively with current antiretrovirals to determine as early as possible the impact of novel anti-HIV treatments. Patients and providers who wish to contribute data may contact Dr. Clifford at 314.362.9733.

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Bacterial Infections

MYCOBACTERIUM TUBERCULOSIS

by Steve Kass

INTRODUCTION

More people in human history may have died from tuberculosis (TB) than from any other single infectious agent. Nearly two billion persons worldwide are infected, and some three million people worldwide die each year from tuberculosis, making it the leading infectious cause of death, ahead of measles, malaria, and AIDS (Sepkowitz 1995). An important disease throughout human history, tuberculosis declined dramatically in developed countries during the last hundred years. In many developed countries, however, including the USA, this decline in tuberculosis morbidity and mortality has stopped and reversed dramatically, primarily as a consequence of the HIV epidemic.

More HIV-infected individuals die from tuberculosis than from any other cause (WHO 1997). Pulmonary tuberculosis is now an AIDS-defining illness. The re-emergence of TB has been dubbed an international public health emergency by the World Health Organization. Since 1992, the incidence of TB in the United States has again shown a decline, a result of the recognition of the relationship between HIV and TB and an increase in clinical and public health resources. (CDC 1997).

Up to 100,000 people in the US, and perhaps two million worldwide are co-infected with both HIV and the bacterium that causes tuberculosis, *Mycobacterium tuberculosis* bacillus (MTB). Outside the developed world, and in some urban populations within the developed world, tuberculosis is a common and serious opportunistic infection among HIV-infected persons, and HIV-infected persons everywhere are at some risk. In general, this chapter addresses tuberculosis as an opportunistic infection in the developed world.

Unlike many opportunistic infections, tuberculosis is neither new nor once rare. Effective prevention and treatment for tuberculosis exist, at costs affordable even in the poorest countries. But several factors complicate the management of tuberculosis as an opportunistic infection among persons infected with HIV.