AIDS
THE PARKLAND EXPERIENCE
1988-1991

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MEDICAL GRAND ROUNDS
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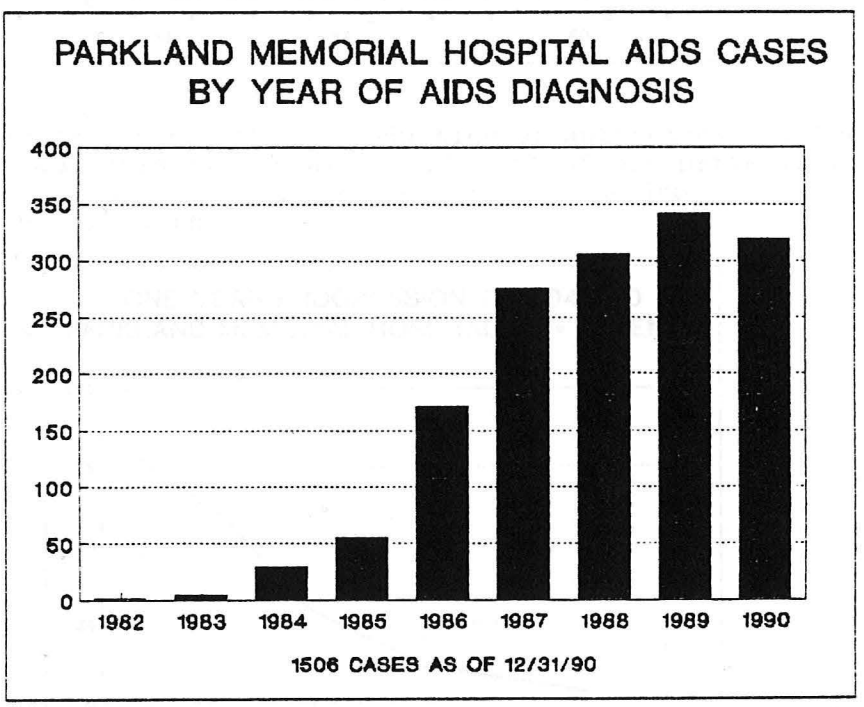
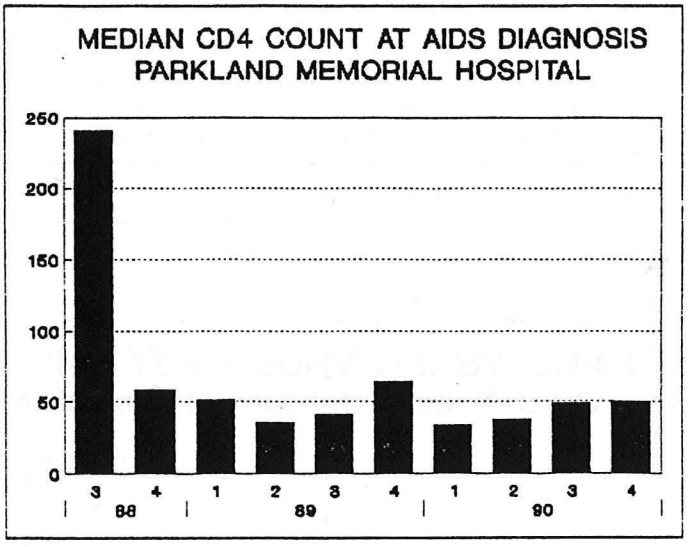
INTRODUCTION

By December 31, 1990, Parkland had treated 1506 AIDS patients. These patients comprise over half of all Dallas County residents with AIDS, and almost 1% of all United States residents with AIDS.

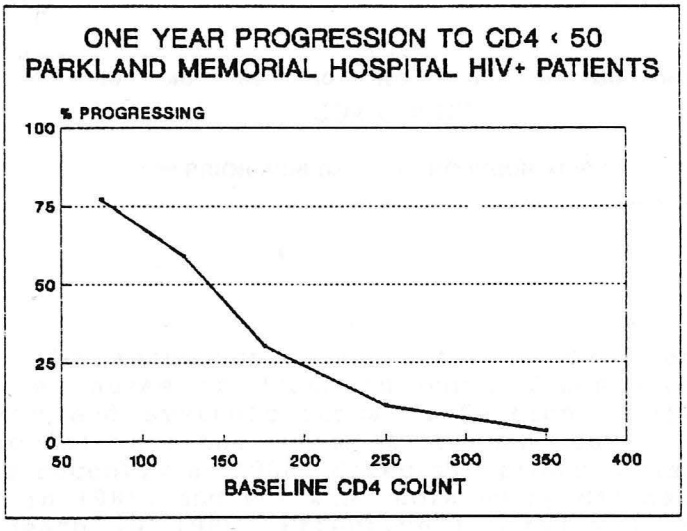
AIDS cases at Parkland increased exponentially between 1982 and 1987 and linearly thereafter. Numerous cohort studies have documented that transmission of HIV among gay men decreased substantially in the mid-1980s. The decrease in new AIDS cases after 1987 is almost certainly a consequence of this behavioral change.



However, the decrease in new AIDS cases after 1987 also reflects the introduction, in mid-1988, of antiretroviral therapy and antipneumocystis prophylaxis. Shortly after these therapies were introduced, the median CD4 lymphocyte count at the time of AIDS diagnosis in Parkland patients decreased from over 200/mm3 to under 50/mm3.

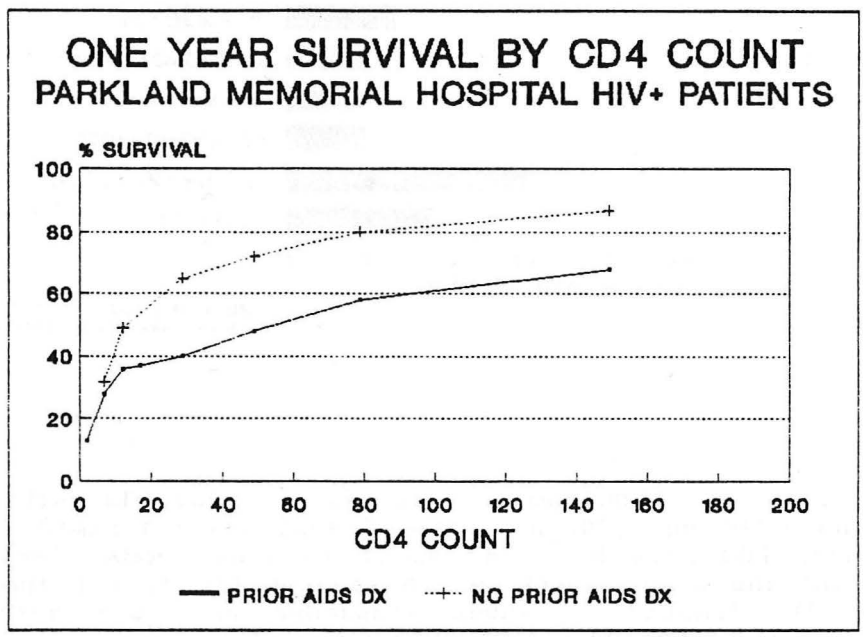


Furthermore, since the introduction of antiretroviral therapy and antipneumocystis prophylaxis, only 11% of our patients with a CD4 between 200 and 299/mm3 have experienced a drop in their CD4 count to < 50/mm3 within a year.

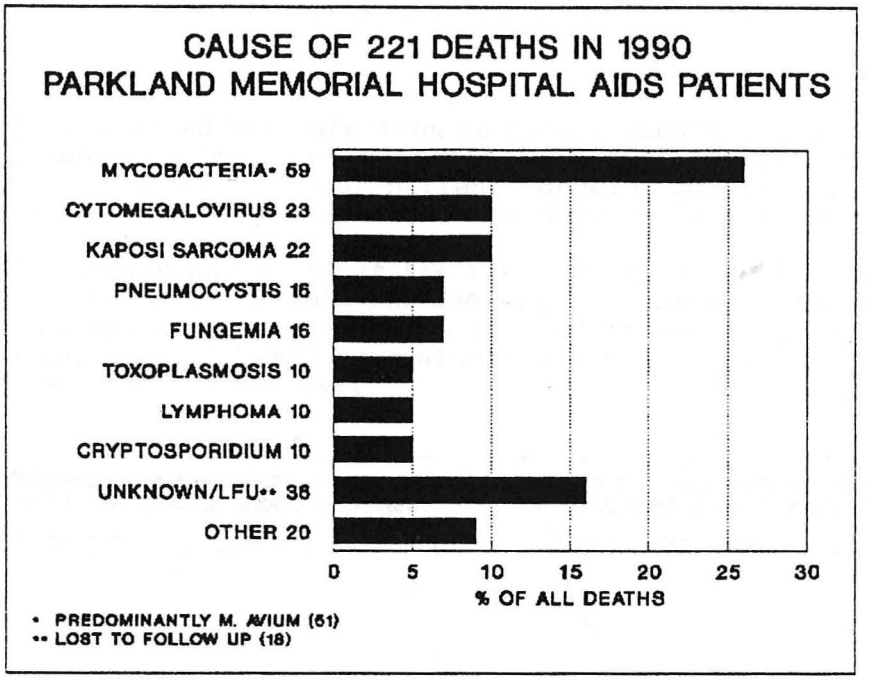


It would appear that while some of Parkland's AIDS cases have been prevented by behavioral change, others have only been postponed by antiretroviral therapy. The proportion of cases in the latter category remains to be determined.

Before 1988, the occurrence of an AIDS-defining event was the only generally accepted measure (other than death) of progression of HIV infection; the CD4 count was considered a "surrogate marker" of progression. The converse now seems closer to the truth; it is the AIDS-defining events, rather than CD4 counts, that seem to be the surrogate markers of the progression of HIV disease. In our patients, one year survival decreases exponentially after the CD4 count falls below 50/mm3.



Since the introduction of antiretroviral and prophylactic therapy, the causes of death in our HIV-positive patients have changed. PCP and systemic fungal infections (cryptococcosis and histoplasmosis) were the two most frequent causes of death in our patients as recently as 1988. Effective prophylaxis against PCP was introduced in 1988, and PCP was replaced by MAI as the most common cause of death in 1989. Effective prophylaxis against fungemia (vide infra) was introduced in 1990, and fungemia was replaced by CMV as the second most common cause of death in that same year. The incidence of Kaposi sarcoma in our patients has not changed, but patients with this opportunistic neoplasm are now more likely do die of it than with it. Deaths from toxoplasmosis, lymphomas, and cryptosporidiosis seem less common at Parkland than elsewhere.



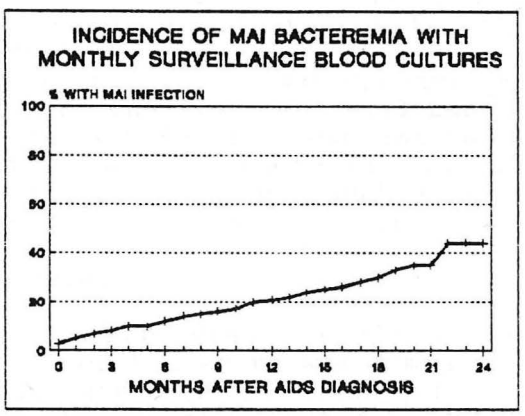
The median CD4 count at the time of our patients' deaths has been about 20/mm3 for the last 3 years; in 80%, the CD4 count has been < 50/mm3. About half of those who died with CD4 counts > 50/mm3 (about 10% of all deaths) did so from causes unrelated to HIV infection (such as substance abuse or trauma). There is presently some sentiment to use a CD4 count < 50/mm3 as an endpoint for clinical trials of antiretroviral drugs, rather than death or the occurrence of one or more AIDS-defining events. Our experience would support this approach.

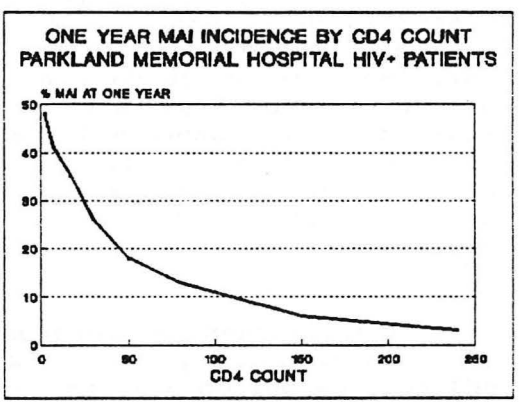
For clinicians, the most visible progress in the treatment of HIV-infected patients over the past three years has been in the treatment and prevention of four of the five most common causes of death in these patients: M. avium-intracellulare (MAI) infection, cytomegalovirus (CMV) infection, pneumocystis pneumonia (PCP), and disseminated fungal infections (cryptococcosis and histoplasmosis). This progress is reviewed below.

MYCOBACTERIUM AVIUM-INTRACELLULARE

Disseminated MAI infection is rarely identified at the time of AIDS diagnosis, but its incidence increases linearly thereafter. Twenty-two per cent of our patients develop MAI bacteremia within one year of AIDS diagnosis, and 44% develop it within 2 years.

The median CD4 count at the time MAI has first been identified in our patients is 12/mm3. The one-year incidence of MAI bacteremia is inversely, and exponentially, related to the CD4 count. Patients with a CD4 count < 5/mm3 have almost a 50% chance of developing MAI bacteremia within one year.





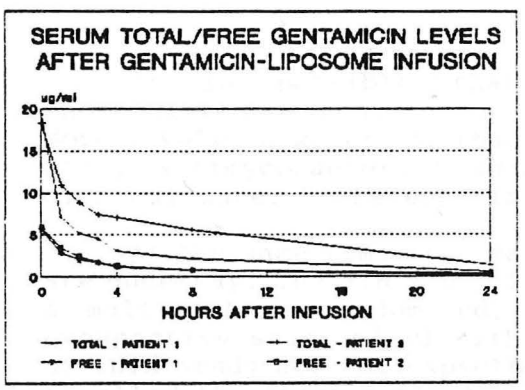
Patients with MAI may occasionally be asymptomatic, but most have loss of appetite, abdominal pain, diarrhea, weight loss, and/or night sweats. Anemia, neutropenia, and/or thrombocytopenia are common, and can be exacerbated by even small doses of zidovudine, ganciclovir, or sulfonamides. The cytopenias are initially responsive to erythropoietin and GM-CSF, but may become refractory to cytokines over time. Transaminases and alkaline phosphatase are usually about 5 times the upper limit of normal, and the liver and spleen are both usually enlarged.

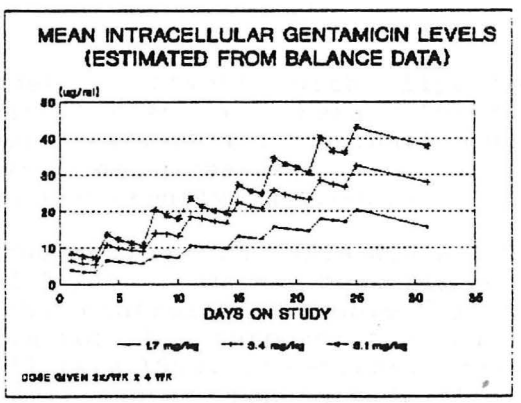
The median survival of our patients after the onset of MAI bacteremia has been only 5 months; the one-year survival has been only 12%. Survival has been marginally better for the small number of patients whose CD4 count was >30/mm3 at the time MAI bacteremia was first identified. We have not found that currently available drugs, including isoniazid, rifampin, ethambutol, pyrazinamide, ciprofloxacin, clofazimine, amikacin, or imipenem, alone or in various combinations, have benefited either symptoms or survival.

Four drugs are currently under active investigation for treatment of MAI. Very preliminary and unconfirmed reports suggest that rifabutin and clarithromycin, a macrolide related to erythromycin, may have benefited some patients with this infection. However, the patients in whom these benefits were claimed had much higher CD4 counts (mean 74/mm3 in the rifabutin series and mean 76/mm3 in the clarithromycin series) than we generally see in our patients. Azithromycin, a compound similar to clarithromycin, has been evaluated by Dr. Lowell Young and colleagues in a small number of patients; this data is scheduled for presentation at a national meeting later this year. Finally, we have performed a Phase I trial of liposome-encapsulated gentamicin in patients with MAI, and can report modestly encouraging results.

In HIV positive patients, MAI organisms are taken up by macrophages but not killed by them; instead, the MAI organisms appear to replicate easily within the macrophages. The rationale for our study was that liposomes, along with their contents, are also ingested by macrophages. At the lower pH of the intracellular fluid, the liposomes will burst, and release their contents at the site of infection. Gentamicin was chosen for encapsulation because it has antimycobacterial activity, because it is easily measured in clinical specimens, and because it is not known to be metabolized in vivo; the last attribute made it feasable for us to conduct a balance study in which we could estimate intracellular gentamicin levels.

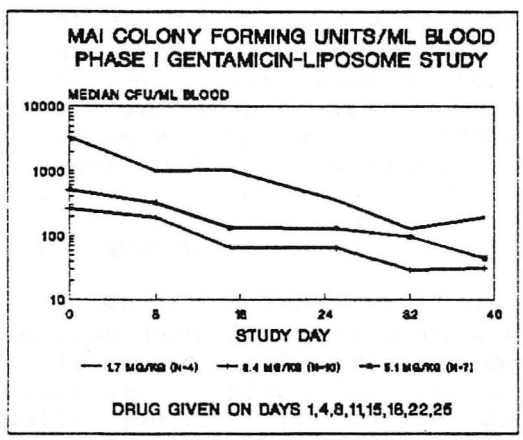
In our Phase I study, liposome-encapsulated gentamicin at 1.7, 3.4, or 5.1 mg/kg was administered twice weekly for four weeks to patients with MAI. Twenty-four hour urines were collected from the day before the first dose until seven days after the last dose.

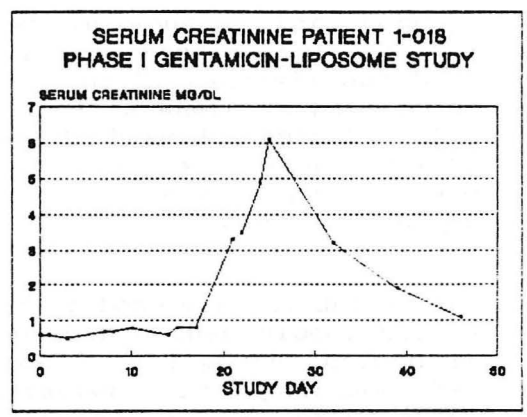




About one-third of the infused liposomes released their contents into the extracellular fluid, and about one-third of the infused gentamicin dose was excreted in the urine within 24 hours. The fraction of drug excreted over 24 hours did not vary significantly with the dose of drug or the number of prior doses administered. Since serum gentamicin levels were negligible at 24 hours, we assumed that gentamicin not excreted in the urine was in the intracellular fluid, and from this we calculated the mean intracellular gentamicin concentration.

At all three dose schedules tested, a statistically significant decrement in blood MAI colony forming units was observed. At the highest dose schedule tested, one patient developed reversible acute renal failure.





It is possible that longer treatment with liposome-encapsulated gentamicin may be effective as sole therapy for MAI. More likely, however, is that longer treatment and combination with other antimycobacterial agents will be necessary to achieve a clinical cure. These experiments are currently in progress.

At the same time, two major studies of prophylaxis against MAI are underway. The NIH AIDS Clinical Trials Group has recently begun a multicenter, randomized, placebo controlled, double-blinded, prospective study of clarithromycin for this purpose; the results of this study are not expected until late 1992. In February 1990 we enrolled the first patient into a multicenter, randomized, placebo controlled, double blinded, prospective study of rifabutin prophylaxis against MAI, sponsored by Adria Laboratories, and we have subsequently enrolled 82 of the 525 participants in it. The interim data analysis is scheduled for later this month.

HIV-positive patients with low CD4 counts often have cultures positive for "AFB", and the question then arises whether to give anti-M. tuberculosis therapy until the organism is identified. Because anti-M. tuberculosis therapy in this population is not effective against MAI, because this therapy frequently causes side effects, ranging from skin rash and nausea to hepatitis and aplastic anemia, and because these side effects can (and have) been fatal, we have adopted the following guidelines:

1) We do NOT treat "AFB" identified in routine surveillance blood cultures from HIV-positive patients with CD4 counts < 100/mm3 with anti-M. tuberculosis drugs. These organisms have invariably proven to be MAI, or rarely M. xenopi or M. chelonae; none of these are sensitive to anti-M. tuberculosis drugs. There have been no cases at Parkland in the past 2 years where M. tuberculosis or M. kansasii has presented in this manner.

2) We DO treat "AFB" identified in sputum, bronchoscopy specimen, stool, CSF, pleural fluid, or fine needle aspirate of a cyst or new growth. When M. tuberculosis or M. kansasii has been manifest in our patients, these are the sites where we have found them. However, in patients already known to have disseminated MAI, the likelihood that the newly-cultured organism will also prove to be MAI is very high. We have not yet encountered a patient who developed M. tuberculosis or M. kansasii infection after contracting MAI.

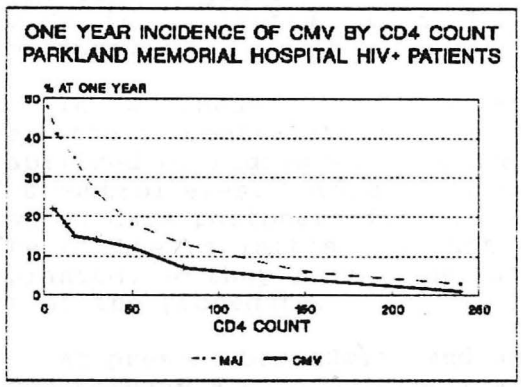
3) We do NOT treat "AFB" identified in bone marrow, unless AFB have also been identified in a specimen other than blood. MAI is usually identifiable in the bone marrow 2 or 3 months before it appears in the blood, and it has a characteristic appearance that usually permits it to be differentiated by an experienced pathologist from M. tuberculosis. There have been no cases in the past 2 years when M. tuberculosis has been found in the bone marrow but not coincidentally found in another site other than blood.

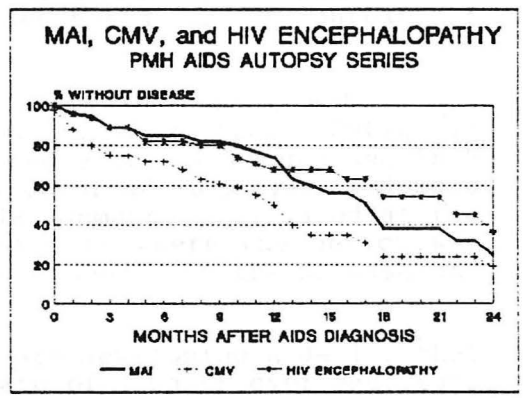
Most protocols for experimental anti-MAI therapy either require that subjects have never received and antimycobacterial therapy, or that they have not received such therapy for at least one month. We would welcome inquiries regarding patient eligibility for anti-MAI trials we are or will be conducting before those patients are begun on empiric anti-M. tuberculosis therapy.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is now second only to MAI as a cause of death in our patients. This rank may reflect our limited ability to diagnose this infection premortem rather than its true incidence. We do not establish the diagnosis of CMV infection unless we find retinitis, or unless we can demonstrate CMV in a biopsy specimen, usually from the gastrointestinal tract. For this reason, we rarely diagnose CMV pneumonitis, adrenalitis, or encephalitis premortem, but find them with some frequency postmortem.

CMV disease, like MAI infection, is uncommon early in the course of HIV infection, but is found with increasing frequency in its later stages. Our clinical and autopsy experiences both suggest that when effective therapy or prophylaxis for MAI infections is identified, CMV will almost certainly become the most common cause of death in our HIV-positive patients.





Current therapy with ganciclovir is partially effective but cumbersome. Ganciclovir must be given intravenously, and a central venous access is necessary. Because both ganciclovir and CMV infections cause neutropenia, catheter-related sepsis is a common complication of therapy. Over a one-year period in our AIDS Clinic infusion room, 8 of 23 patients receiving ganciclovir developed catheter-related sepsis, compared to only 3 of 51 patients who were receiving amphotericin B. Neutropenia and sepsis require at least temporary discontinuation of therapy, and this in turn limits the efficacy of the drug. For example, Fisher et al. from the Henry Ford Hospital found that the mean duration of ganciclovir therapy until visual deterioration was 7 months, and the mean duration of ganciclovir therapy until blindness was 15 months.

Alternative therapies for CMV infections should be available soon. We were participants in a multicenter study, sponsored by Schering-Plough, Sandoz, and Syntex, which found that patients who received recombinant human GM-CSF and ganciclovir had significantly longer interval before progression of their CMV retinitis than did patients who received placebo and ganciclovir. GM-CSF may become available in early 1992. Foscarnet, an alternative to ganciclovir, may become available in late 1991. Clinical trials of recombinant monoclonal anti-CMV antibodies for therapy and for prophylaxis of CMV infections are just beginning; it is too soon to tell if they will be successful in patients with far-advanced HIV disease.

In the past year we have, in association with Drs. Thomas Smith and Paul Ashton of the University of Kentucky Medical School and Drs. George Sanborn, Rajiv Anand, Robert Torti, and Richard Fish of the UT Southwestern Department of Ophthalmology, investigated the use of an intraocular slow-release ganciclovir drug delivery system for treatment of CMV retinitis. Drs. Smith and Ashton, who invented the device, have a potential financial interest in it; the UT Southwestern physicians do not. The device releases 6 mg ganciclovir at 2 ug/hr over a period of 4 months. The device is implanted under local anesthesia as an outpatient procedure.

In our Phase I study, 8 patients received an implant in one eye; their contralateral eye served as a control. Retinitis stabilized or regressed in all 8 treated eyes; it progressed in 5 of 8 control eyes. Retinal detachments occurred in 3 eyes, all more than 30 days postoperatively. These detachments originated at the site of the retinitis, and not at the site where the device was implanted, so they seem to be late consequences of the disease and not of the procedure.

At present Drs. Smith and Ashton are developing a device that would release 9 mg ganciclovir at a rate of 1 ug/hr over one year. They are also working with a pharmaceutical manufacturer to produce these devices under FDA-prescribed Good Manufacturing and Good Laboratory Practices, and in sufficient numbers for the conduct of a large multicenter trial. Both efforts have taken substantially longer than anticipated, but we hope to be able to proceed with further trials of this device before the end of 1991.

PNEUMOCYSTIS

The 30-day survival of Parkland's HIV-positive patients with a first episode of PCP is 85%. The most important determinant of survival in our patients has been how far their pneumonia had progressed before they first obtained medical care. Patients with a pO2 > 50 mm Hg on room air when first seen have a 95% 30-day survival; patients with a lower pO2 have a 50% 30-day survival. We hospitalize patients with a pO2 < 60 mm Hg, and discharge them when their pO2 is back over 60.

Our first choice for oral therapy is trimethoprim/dapsone for 21 days. We titrate the trimethoprim to 15 mg/kg/day; since our average patient weighs about 60 kg, and since trimethoprim comes in 100 mg tablets, this works out to 3 100-mg tablets 3 times a day. Dapsone can be given either as 100 mg/day or as 25 mg 3 times a day. Our first choice for intravenous therapy is pentamidine, 4 mg/kg/day until the patient can tolerate oral medications, at which time we switch to trimethoprim/dapsone. We prefer these regimens to trimethoprim/sulfamethoxazole because of the extremely high rate of adverse reactions our patients have to sulfamethoxazole.

Primaquine/clindamycin appears to be about as effective as trimethoprim/dapsone for PCP, and is a reasonable alternative for any patient who has had a prior adverse reaction to either trimethoprim or dapsone. There is much interest presently in a Burroughs Wellcome compound known as BW566C80, which is clearly effective against PCP; whether it, or primaquine/clindamycin, will prove to have fewer side effects than currently available therapies is still uncertain.

Steroids have been intermittently fashionable as adjunctive therapy for PCP; they are again in fashion as this is written. In several controlled trials, adjunctive prednisone (generally 40 mg 4x/day for 5 days, then 40 mg 2x/day for 5 days, then 40 mg/day for 11 days) has increased 30-day survival after PCP from about 80% to about 90%. Early reports describe only minimal complications of this therapy; this is almost certain to change. At present we use prednisone, in the dose given above, plus fluconazole 200 mg/day to prevent oral/esophageal candidiasis and ranitidine 150 mg 2x/day to prevent gastric ulceration, along with primary anti-pneumocystis therapy for patients with with PCP who have a baseline pO2 < 70 mm Hg on room air.

A major unresolved question is whether steroids benefit the roughly 20% of patients with PCP who have a coexistent bacterial, fungal, or viral infection. The potential danger of indiscriminate steroid therapy for PCP is that it will exacerbate disease due to coexisting pathogens, in the lungs or elsewhere. For example, almost all our patients treated with steroids for PCP have had reactivation of herpes simplex. Whether steroids will have a similar effect on MAI, CMV, or even HIV remains to be determined.

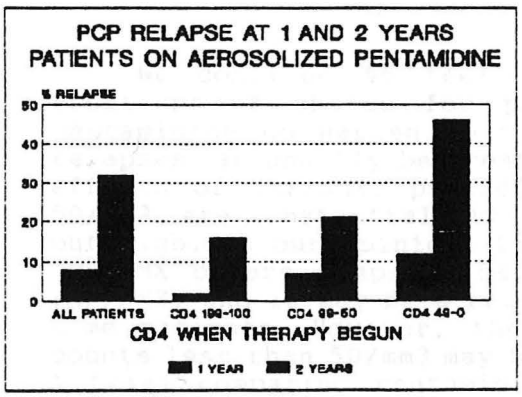
There are three widely used regimens for prophylaxis against PCP: trimethoprim/sulfamethoxazole (either one double-strength tablet a day, or one 3x/week), dapsone (at least 25 mg/day, but preferably at least 50 mg/day, and aerosolized pentamidine (300 mg/month). While several comparative trials of these regimens are under way, the performance characteristics of these regimens are now well known. The experience recently reported by Cox and colleagues at Harbor-UCLA Medical Center is typical:

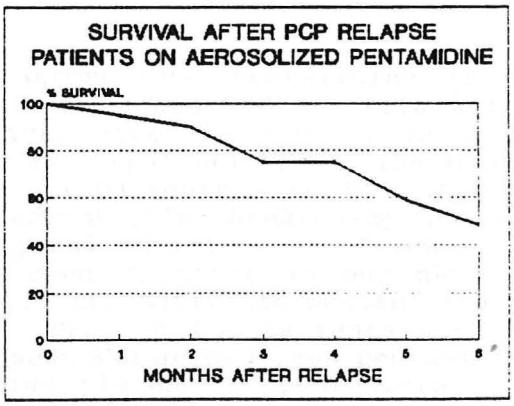
RETROSPECTIVE STUDY OF PCP PROPHYLAXIS
COX ET AL: HARBOR-UCLA MEDICAL CENTER

TMP/SMX 1DS BID 3D/WK	DAPSONE 25/D	PENTAMIDINE 300/MO
134 PTS, 981 PT-MO	79 PTS, 437 PT-MO	124 PTS, 1166 PT-MO
0 PCP (0/981 PT-MO)	5 PCP (1/82 PT-MO)	17 PCP (1/69 PT-MO)
70 (52%) ADV RXN	41 (52%) ADV RXN	2 (2%) ADV RXN

While there were no failures in their TMP/SMX group, the total experience is less than 100 patients-years; a larger series might find a few failures per 100 patient-years. The adverse reaction rate of 50% is typical. Dapsone was less effective at the low dose used in this series; at 50 mg 2x/day, dapsone is about as effective as TMP/SMX. However, the adverse reaction rate with the low dose dapsone was the same as for TMP/SMX. Pentamidine had a higher relapse rate (17%/year) but a low adverse reaction rate (2%).

Our experience with over 1000 patient-years experience with aerosolized pentamidine can be summarized as follows:





Our one year relapse rate, 8% for all treated patients, is the same as San Francisco General Hosptial's. As expected, the relapse rate varies with the characteristics of the patients treated and with the duration of therapy. However, the 30-day survival of our patients who were diagnosed with PCP while receiving aerosolized pentamidine is 95%.

Because pentamidine costs more than TMP/SMX, some centers have attempted to convert their patients from pentamidine to TMP/SMX. The San Diego Navy Hospital's experience was as follows:

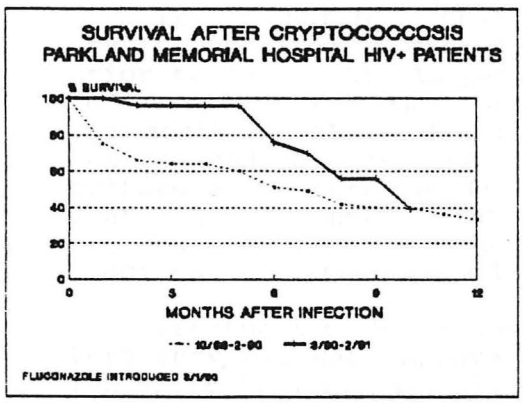
AP TO TMP/SMX FOR PCP PROPHYLAXIS
KENNEDY ET AL: SAN DIEGO NAVY HOSPITAL

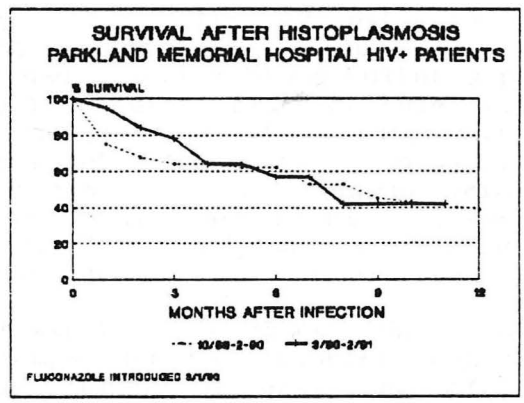
- 145 CANDIDATES; 19 EXCLUDED BECAUSE OF CYTOPENIA
- 38 FAILED CONVERSION (3 REQUIRED HOSPITALIZATION)
- OF 88 SUCCESSFUL CONVERSIONS:
  59% FEVER
  38% MACULOPAPULAR RASH
  27% MYALGIAS
  22% HEADACHES
  19% CHILLS
- MEAN FOLLOW UP 114 DAYS
- MEAN CD4 COUNT OF SUCCESSFUL CONVERSIONS 313

We continue to feel that aerosolized pentamidine is the treatment of choice for prophylaxis against PCP. Relapses on pentamidine do happen, but survival after relapse is good, and relapses can usually be treated on an outpatient basis. The adverse effects of TMP/SMX, particularly in patients with CD4 counts < 50/mm3, are substantial and often enough life-threatening that they outweigh, in our opinion, the marginal advantage in efficacy that TMP/SMX offers. Dapsone has not been as toxic in our hands as TMP/SMX, and it may be a reasonable alternative to pentamidine for some patients. However, the best approach for patients with CD4 counts less than 50/mm3 may be dapsone AND aerosolized pentamidine. A trial comparing pentamidine plus placebo to pentamidine plus dapsone, 50 mg 2x/day, is presently under way.

CRYPTOCOCCOSIS AND HISTOPLASMOSIS

Treatment of systemic fungal infections has improved substantially since the introduction of fluconazole.





FLUCONAZOLE THERAPY FOR HIV-ASSOCIATED SYSTEMIC FUNGAL INFECTIONS, 3/90 - 2/91

	CRYPTOCOCCOSIS	HISTOPLASMOSIS
NUMBER	30	21
AGE/SEX/RACE	34;97%M;72%W	34;100%M;71%W
MEDIAN CD4 AT Dx	38/mm3	20/mm3
MEDIAN CSF Ag	1:2048	
PRIOR AMPHOTERICIN	8	2
PRIOR FLUCONAZOLE	1	3
UNRESOLVED INFECTION AT DEATH/DEATHS	1/12 (LP - in 6)	10/10
RELAPSE ON 400/DAY	4/13	3/9
RELAPSE ON 200/DAY	4/12	7/10

Only 3 of the 8 patients with cryptococcosis who received amphotericin B received more than 150 mg; both of the patients with histoplasmosis who received amphotericin B received 1500 mg. The remainder received fluconazole, 400 mg/day by mouth, for the first 2 weeks of therapy. On the basis of this experience, we continue to recommend fluconazole in this dose as the initial treatment of choice for HIV-positive patients with cryptococcosis or histoplasmosis.

Eight of 25 patients with cryptococcosis had microbiological evidence of relapse. Six of these patients were not compliant with their medications; these patients did well after they resumed taking medications as directed. Relapses were equally frequent in patients taking 200 mg/day or 400 mg/day for maintenance therapy.

It is notable that only one of the 12 patients with cryptococcosis who died had any evidence of residual infection prior to death. All 12 patients had negative blood cultures prior to death, and 6 of these had negative spinal fluid cultures within one month of their death. The one patient whose infection was "unresolved" at the time of death had had a positive spinal fluid culture after three months of treatment and five months prior to death. He responded clinically to an increase in his maintenance fluconazole dose to 400 mg/day. His death was attributed to progressive wasting caused by cryptosporidiosis and MAI infections.

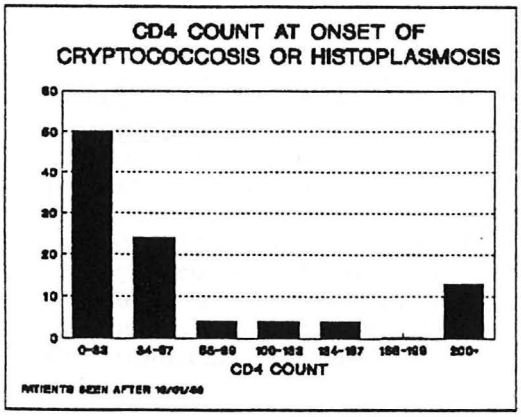
Treatment of histoplasmosis was less successful. While short-term survival was improved in comparison to historical controls, ten patients died, and all 10 had evidence of persistent infection at the time of death. Relapses were significantly more common in patients were given 200 mg/day for maintenance therapy.

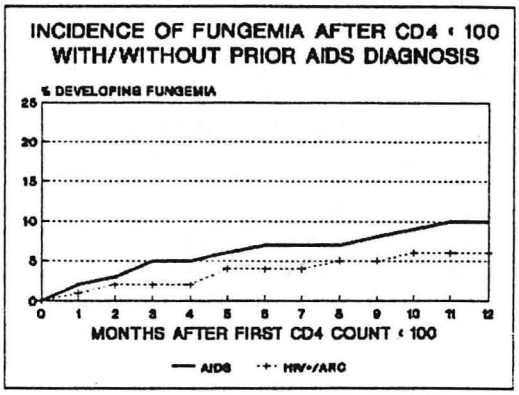
A comparative trial of fluconazole, 400 mg/day vs 800 mg/day, for treatment of AIDS-associated histoplasmosis is currently being organized. Until this study is complete, our experience to date leads us to recommend the 800 mg/day dose if the patient can tolerate this dose without side effects.

A congener of fluconazole, itraconazole, is also being evaluated as a therapy for AIDS-associated histoplasmosis. Preliminary evidence suggests that itraconazole may have about the same therapeutic efficacy as fluconazole for this condition.

At the same time, a trial of liposome-encapsulated amphotericin B for treatment of AIDS-associated histoplasmosis is also being organized. Preliminary experience with liposome-encapsulated amphotericin B suggests that it substantially less toxic than unencapsulated drug; its efficacy remains to be determined.

At the time fluconazole became available, we reviewed our experience with systemic fungal infections in HIV-positive patients. We found that three-fourths of our patients had CD4 counts < 68/mm3 at the time their infection was diagnosed, and that the incidence of systemic fungal infections from the time the CD4 count first fell below 100/mm3 was between 8 and 10%. For these reasons, we began to offer fluconazole, 100 mg/day, to our patients with CD4 counts < 68/mm3, both for treatment or prevention of oral/esophageal candidiasis and for its possible benefit as prophylaxis against systemic fungal infections.





FLUCONAZOLE PROPHYLAXIS OF DISSEMINATED FUNGAL INFECTIONS IN HIV-POSITIVE PATIENTS

	HISTORICAL CONTROL	TREATMENT GROUP
N	337	329
PATIENT-YEARS	157	145
AGE	34.7	34.7
% WHITE	75	69
% MALE	97	96
% AIDS	67	75
MEAN CD4	30	32
CRYPTO CASES	16	1
HISTO CASES	4	3
1-YEAR INCIDENCE	7.5 +/- 2.0	1.8 +/- 0.9
1-YEAR SURVIVAL	53 +/- 4	56 +/- 4
CRYPTO DEATHS	8	0
HISTO DEATHS	1	1

There were only 3 adverse events (2 rash, one reversible hepatitis) in the treatment group. There was a 95% reduction (16 to 1) in the incidence of cryptococcosis, but only a 25% (4 to 3) reduction in the incidence of histoplasmosis after fluconazole therapy was instituted.

Compliance was measured by the number of fluconazole prescriptions received from the pharmacy divided by the number of months of follow up. (Because of the cost of the drug, no patient received more than a one month supply of fluconazole at a time.) By this measure, 75% of the treatment group was 100% compliant with therapy. The four patients who developed systemic fungal infections were 100, 66, 60, and 40% compliant with therapy.

The controls in this study are historical, not concurrent and randomized, and this is a weakness of it. On the other hand, the study includes all patients who met the entry criteria; randomized trials rarely if ever meet this goal. The NIH AIDS Clinical Trials Group is presently conducting a randomized study (#981) of fluconazole 200 mg/day versus a non-absorbable antifungal for prophylaxis against systemic fungal infections in patients with CD4 counts < 200/mm3. We will be very suprised if this study does not support the observations presented above. Until the results of this study are available, we continue to recommend fluconazole, 100 mg/day, as prophylaxis against oral/esophageal candidiasis and against disseminated cryptococcosis for HIV-positive patients with CD4 counts < 68/mm3.

DISCUSSION

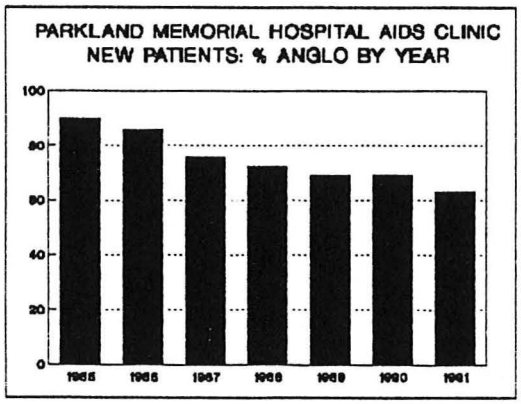
In the past 2 years substantial advances have been made in the treatment of systemic fungal infections, cytomegalovirus retinitis, pneumocystis pneumonia, and mycobacterium avium-intracellulare infections. If current trials of azithromycin or BW 566C80 are successful, there may be a substantial advance in the treatment of toxoplasmosis in the reasonably near future. ACT-UP's "Countdown 18 Months", a research agenda for the major opportunistic infections in HIV-positive patients that is scheduled for completion in June 1992, is on or even slightly ahead of schedule.

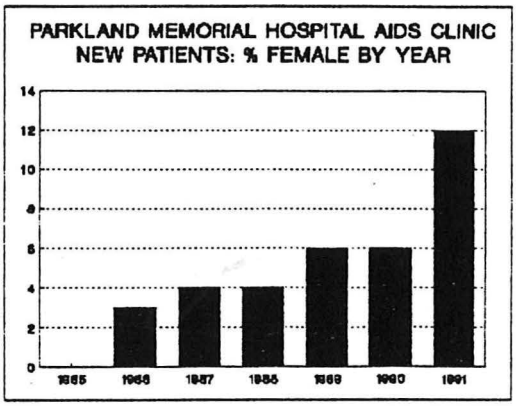
Advances in the treatment of HIV-associated neoplasms have been less substantial. Intralesional vinblastine injections are very helpful for cutaneous and oral Kaposi sarcoma. Interferon alpha has helped, though by no means cured, patients with Kaposi sarcoma and CD4 counts over 200/mm3. Unfortunately, most of our Kaposi patients have CD4 counts far below this level, where interferon becomes progressively less effective and more toxic. Fluconazole has increased our patients' tolerance to radiotherapy and chemotherapy, and we now get our lymphoma patients through more cycles of CHOP than we used to. The role of cytokines in the therapy of these neoplasms is just beginning to be explored at the clinical level.

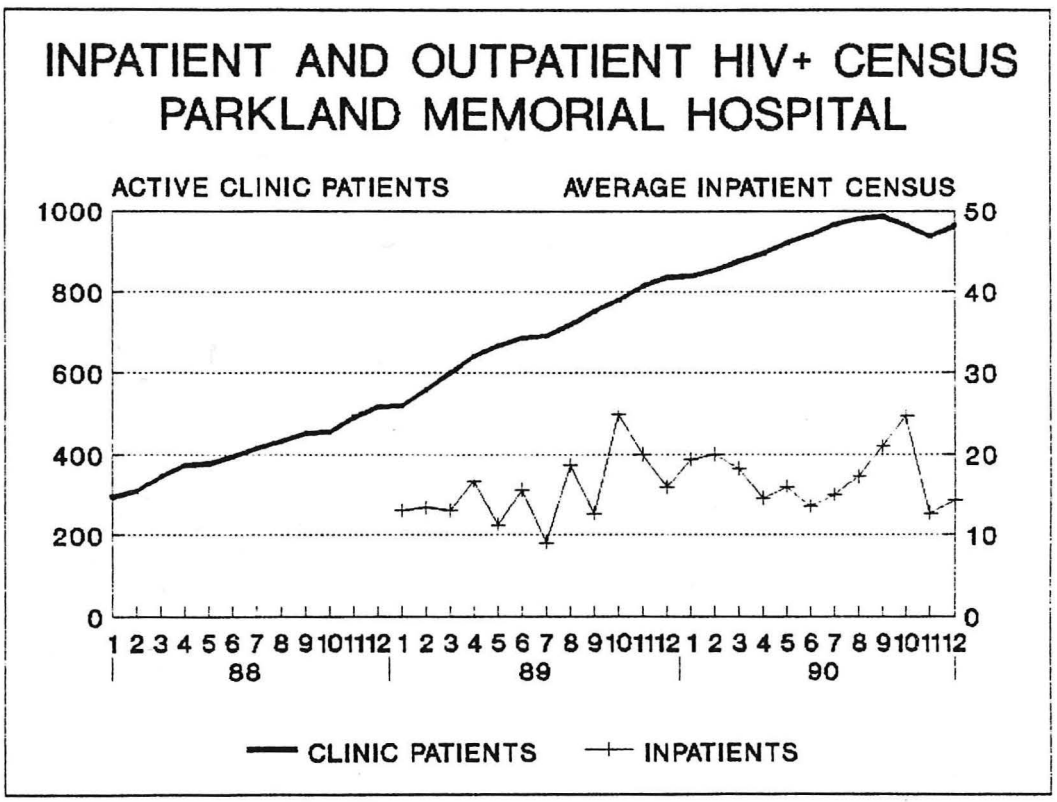
Advances in the treatment of HIV infection itself have been the most difficult to ascertain. AZT remains the center of our therapeutic regimen. The roles of ddI and ddC, alone or in combination with AZT, remain to be determined. The current buzz word in the industry is "gene therapy", but there is much basic science to be done before the gene surgeon replaces the pill pusher.

Over the past few years, the proportion of our patients that are Anglo has decreased gradually. Over the past few months, the proportion of our patients that are female has increased dramatically. At the same time, an increasing number of our new male patients are denying any prior homosexual contact or use of intravenous drugs. In our population, it appears that heterosexual transmission of HIV has become more common than homosexual transmission. This is not good news.

During the same time, Parkland's outpatient HIV-positive census has increased, but its inpatient HIV-census has remained stable. Our inpatient costs for HIV-positive patients are roughly $700/day, and our outpatient costs are roughly $700/month. Using December 1990 census figures, Parkland is spending roughly $4.3M/year for inpatient and roughly $8.4M for outpatient care of HIV-positive patients. The continued financing of this care may prove to be as great a challenge as finding a cure for this disease.


PARKLAND MEMORIAL HOSPITAL AIDS CLINIC
NEW PATIENTS: % ANGLO BY YEAR
100
80
60
40
20
0
1985
1986
1987
1988
1989
1990
1991


PARKLAND MEMORIAL HOSPITAL AIDS CLINIC
NEW PATIENTS: % FEMALE BY YEAR
14
12
10
8
6
4
2
0
1985
1986
1987
1988
1989
1990
1991


INPATIENT AND OUTPATIENT HIV+ CENSUS
PARKLAND MEMORIAL HOSPITAL
ACTIVE CLINIC PATIENTS
AVERAGE INPATIENT CENSUS
1000
800
600
400
200
0
50
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12
88
89
90
CLINIC PATIENTS
INPATIENTS