TAG Does ICAAC

AIDS Research Highlights from the 35th Interscience Conference on Antimicrobial Agents & Chemotherapy (ICAAC)

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by

Mark Harrington and Michael Marco with Spencer Cox and Tim Horn

for the

Antiviral Committee Opportunistic Infections Committee

The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, pharmaceutical companies, and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

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Spencer Cox is TAG's Communications Director and chairs its Antiviral Committee. His FDA Regulation of Anti-HIV Drugs: A Historical Perspective was released in September 1995. Mark Harrington is TAG's Policy Director. He co-wrote and edited AIDS Research at the NIH: A Critical Review (with Gregg Gonsalves, 1992), Rescuing Accelerated Approval: Moving Beyond the Status Quo (1994) and Problems with Protease Inhibitor Development Plans (1995) and wrote The Crisis in Clinical AIDS Research (1993). Tim Horn is coordinating TAG's Wasting Syndrome Project, which will culminate in a report to be released in 1996. Michael Marco is Director of Opportunistic Diseases for TAG and is the author of The KS Project Report: Current Issues in Research and Treatment of AIDS-Related Kaposi's Sarcoma (1994) and The Lymphoma Project Report (1995). He will be editing TAG's Research Update on Opportunistic Infections Prophylaxis and Treatment for the 1996 Vancouver AIDS conference.

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INTRODUCTION

The 35th ICAAC was a more interesting conference than usual, with results from many important AIDS clinical trials being reported. Partly ICAAC benefitted from the lack of an international AIDS meeting in 1995, and partly perhaps from its location in San Francisco, a favorite junket site for physicians and activists alike. Spencer Cox, Mark Harrington, Tim Horn and Michael Marco attended the 35th ICAAC on behalf of TAG and we here summarize some of the more interesting new data reported there. Any errors of data transcription or interpretation are entirely ours and not to be blamed on the presenting investigator. ICAAC presentations have only the most pro forma of peer review, and hence some assertions made there may not end up being substantiated when data are recorded in the medical literature. As always, everything needs to be taken with a grain of salt.

PATHOGENESIS UPDATE

At the opening session at 7 p.m. Sunday night, September 17, David Ho introduced Beatrice Hahn of the University of Alabama at Birmingham (UAB).

Origins and Evolution of Primate LentivirusesBeatrice Hahn, UAB

There are five known families of related primate lentiviruses. They are endemic to certain species, which do not develop disease from the retroviral infection, but when they are introduced to another species they may cause fulminant disease. The primate immunodeficiency virus family has five branches:

* HIV and SIVCPZ (a chimp strain of HIV) * SIVSM (sooty mangabey), SIVmac (macaque) and HIV-2 * SIVAGM (African green monkey) -- not pathogenic in the native hosts * SIVMND (mandrill) * SIVSYK (Sykes' monkey)

Viral diversity among primate lentiviruses stems from several factors:

1. High mutation rate/no RNA proof-reading 2. Rapid viral turnover 3. Rapid escape from in vivo selection pressures

There are at least two distinct classes of HIV-1 clades, group M, which includes subtypes A-F (or is it G, H or I?) and the newly-discovered group O, which occurs in Central Africa (Cameroon and Gabon). Intra-clade isolates vary by 5-20% in their env and gag sequences, but group M viruses differ by 50% from group O. Group M's subtype B predominates in the Americas and in Europe. HIV-2 is endemic to Western Africa but may be spreading. Alarmingly, group O virus infection does not always elicit antibodies, yet the group O viruses can cause AIDS. Subtype E may have evolved to exploit heterosexual transmission, and says that type E has replaced type B in Thailand.

Dr. Hahn flatly resolved the long-standing controversy about the origins of HIV by stating that it was "the result of a zoonotic transmission from naturally-infected primates to man." Several primate species have non-pathogenic endemic lentiviruses. When they cross species they can become virulently pathogenic. This is what appears to have happened with HIV-1 and HIV-2 in man. Genotypic analysis suggests that there are at least five lineages of HIVs. HIV-2 appears to have been transmitted from some sort of macaque. Preston Marx has found that many sooty mangabeys are infected with SIVSMM in the wild. This strain is not pathogenic to sooty mangabeys, which live in West Africa, where they are hunted by humans and kept as pets. The geographic correlation between SIV and HIV-2 seems rather strong circumstantial evidence, and genotypic data supports a close relationship. HIV-1 appears to have been transmitted from a chimpanzee (which is rarely infected in the wild) or from some other primate species. Other documented examples of cross-species lentivirus transmission include from African green monkeys (AGM) to sooty mangabeys and white-crowned captive mangabeys.

Can retroviruses recombine in vivo? Yes. John Coffin discussed this in 1970. Because reverse transcriptase is error-prone it needs to skip to the complementary RNA copy sometimes, because there are nicks and deletions in the RNA sequence on one strand. There are at least three possibilities for recombination:

1. Multiple strains infect someone from multiple donors a. At time of initial infection b. After initial infection (superinfection') 2. Recombination of quasi-species within host

Some strains are subtype discordant across the genome. Hahn and colleagues found multiple mosaic' genomes. Every subtype was involved. These mosaics were taken from people in Africa and Brazil where multiple subtypes of HIV circulate. Hahn declares, "individuals can be superinfected," though she doesn't say whether they can be superinfected all at once or sequentially. "One cell can be infected by different viruses". What are the Darwinian implications of that?

Hahn concludes by saying that HIV strains have been diverging for awhile to form new lineages. She speculates that HIV-1 has been introduced at least twice by zoonosis and HIV-2 up to five times. Now that the viral population density in the human population has exploded, there are more opportunities for viral recombination within individual hosts, accounting for her new observations.

HIV Population Dynamics in Vivo John Coffin, Tufts University

Clinical latency is not unique to HIV, as seen in the dormant periods of herpesvirus infections, for example. However, the clinical latency period with HIV, as recent research has shown, is actually a period of high replication rates, broadening viral diversity and immune cell turnover. Shaw and Ho and colleagues showed that the viral turnover rate was somewhere between 1-1.5 days in the peripheral blood. This steady-state maintenance between viral load and immune function is balanced by the immune system's clearance of HIV particles and lysis of infected cells and activated target cells.

Coffin pointed out the assumptions underlying Shaw and Ho's papers: 1) viral burden in the peripheral blood reflects viral burden in the sites of its replication (principally the lymph nodes); and 2) the drug's impact in inhibiting replication is the only thing which perturbs the system as measured. (That is to say, both lymph node viral production and immune clearance are assumed rather than proved to be steady-state.

HIV genotypic diversity is so great that quasispecies resistant to any particular drug may be circulating in the body before exposure to such a drug. "All mutations will be there before you start the treatment. It's inevitable." This does not necessarily mean that the person was exposed to a resistant isolate. HIV goes through thousands of replication cycles in the years between infection and clinical illness, increasing the number of quasispecies. Even active treatments may just amplify out resistant strains, providing them with evolutionary cover in which to grow out and replace wild-type isolates. The hope is that one day such resistant virus strains may be less fit' or replication-competent than wild-type strains. This has yet to be seen with existing drugs.

Coffin presented a complicated equation to determine viral load and what it means. Viral load in peripheral blood (as measured by RT-PCR or bDNA) reflects R, the rate of viral production in the site of replication (the lymph nodes), T, the transfer efficiency (from the site of production to the site of sampling, the lymph nodes) and Kc, the clearance constant (the mechanism of clearance does not have to be specified; it could be antibodies, lysis of infected cells, complement binding, etc.).

Thus, Coffin declared:

$V = RT/KcC$

He continued:

1. The absolute number of virions is irrelevant per se (though it may relate to transmissibility); virus counts go up to 1012/ml 2. Viral burden in peripheral blood (PB) is not a measure of the rate of replication and is unrelated to the rate of genetic diversity 3. Viral burden is important as a relative measure within one person of the number of virus-producing (actively-infected) cells [though this assumes infected cells produce a fixed rather than a variable amount of HIV] 4. There is a reasonable but untested assumption that PB viral burden is related in a steady-state fashion to a clearance constant 5. If so, viral load reflects the number of productively infected, actively virus-producing CD4+ T lymphocytes.

Coffin concluded:

"Proviral DNA is a very misleading measure of viral activity and genetic composition."

He proposed that PB viral burden is an indirect measure of the number of [actively] infected cells.

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TREATMENT TRENDS

Survival trends, 1990-1994 (I168)

J.W. Ward and colleagues from the CDC's Adult/Adolescent Spectrum of Disease study correlated survival with treatment patterns by reviewing medical records of 8,622 persons diagnosed with AIDS from 1990-1994. The median survival for PWAs was 35 months (95% c.i., 33-36 months). After controlling for CD4 count, age and risk, antiretroviral treatment, Bactrim, Dapsone and MAI prophylaxis with either Rifabutin or Clarithromycin, but not aerosolized pentamidine, were associated with improved survival:

AIDS treatments reduce the risk of mortality

Risk of death (hazard ratio) 95% c.i.

Antiretrovirals 0.4 (0.4-0.5) PCP prophylaxis Bactrim 0.7 (0.6-0.7) Dapsone 0.8 (0.8-0.9) Aerosolized pentamidine 1.3 (1.2-1.4) MAI prophylaxis 0.5 (0.4-0.5)

Persons who were prescribed antiretroviral treatment, PCP and MAI prophylaxis had the longest survival (47 months, 95% c.i., 44-52 months).

Use of treatments among PWAs dying of AIDS

1990 1994

N 99 359 Antiretrovirals 68% 83% PCP prophylaxis 75% 91% MAI prophylaxis 0% 33%

"The prescribed use of antiretroviral treatments and prophylactic antimicrobials has increased over time and may have increased survival."

Antiviral Therapy Use (I19)

Researchers from the Centers for Disease Control and Prevention (CDC) presented data on antiretroviral use in 1,632 HIV-infected patients. During 18 months of study, charts were reviewed from 9,311 office visits. Of the total number of patients, 53% had AIDS, and 88% had at least one CD4+ count of <500 (and were, therefore, eligible for antiretroviral therapy). During clinic visits, 68% of potential candidates were taking AZT, 34% were taking ddI, 26% were taking ddC, and 22% were taking d4T. Only 35% of patients taking antivirals were taking combinations. Women were somewhat less likely to be taking AZT, ddI or d4T, but had a slightly higher mean CD4+ count. Gay men were more likely to receive d4T than injection drug users (p=0.002), and privately insured patients were more likely to be taking combination antiretroviral therapy than publicly ensured patients (p=0.05). Privately insured patients were also more likely to be taking combination therapies (44% vs. 25%).

Incidence trends in AIDS-related opportunistic illnesses (I21)

J.L. Jones and colleagues from the CDC presented an overview of changing incidence of AIDS-associated OIs in gay men diagnosed with AIDS between 1990-1993 and part of the Adult/Adolescent Spectrum of Disease project in 10 U.S. cities. About 2,648 men were in the study each year. Trends included:

1990 1991 1992 1993 p-value (trend)

PCP 20.4% 19.6% 18.3% 18.3% <0.002 Esophageal candidiasis 9.1% 10.3% 7.1% 6.9% <0.001 Kaposi's sarcoma 9.3% 9.1% 8.6% 8.3% 0.04

There were no significant trends for CMV, CMV retinitis, cryptosporidiosis, cryptococcal meningitis, HSV, toxoplasmosis or pulmonary or extrapulmonary TB. They speculate that these men who have sex with men were becoming more adherent to prophylaxis for PCP and candida, and don't understand the apparent (but slight) decrease in KS. They should have presented data on all risk and demographic groups rather than simply men who have sex with men. See "Who is not receiving PCP prophylaxis?" below.

Who is not receiving PCP prophylaxis? (I20)

Sandra Schwarcz and colleagues from the San Francisco Department of Public Health reviewed case records of patients resident in San Francisco whose AIDS-defining diagnosis was PCP in 1993. 321 patient records were examined. Only 35% had received PCP prophylaxis.

* "Non-whites were significantly less likely to have received primary PCP prophylaxis than were white patients (23% vs. 40% respectively, p=0.03). * Individuals who lacked health insurance were less likely to have received primary PCP prophylaxis than were individuals who had health insurance (16% vs. 41%, p=0.001)." * There were no sociodemographic differences in secondary prophylaxis use. * The most common reasons cited by patients for not seeking PCP prophylaxis were lack of awareness of their HIV infection or lack of regular medical care.

Incidence trends in AIDS-related deaths (I22)

R.M. Selik and colleagues from the CDC presented changing mortality trends in AIDS from 1987-1992, based on analyses of death certificates listing HIV infection and any opportunistic infection listed in more than 1% of cases:

AIDS: Cause of Death

1987 1993

Decreasing mortality PCP 32.5% 13.8% Cryptococcosis 7.7% 5.0% Candidiasis 2.3% 1.7% No change in mortality Unspecified pneumonia 17.6% 18.6% KS 10.4% 12.1% Increasing mortality MAC 6.7% 12.2% CMV 5.2% 9.9% Bacterial septicemia 9.0% 11.5% NHL 3.9% 5.7% Tuberculosis 2.9% 4.1% PML 0.8% 1.9% Bacterial pneumonia 1.2% 2.1% Toxoplasmosis 5.0% 5.3% Cryptosporidiosis/isosporiasis 0.7% 1.2%

Clearly the introduction of PCP prophylaxis has had a dramatic effect on overall causes of AIDS mortality. Similarly, the introduction of Fluconazole appears to have reduced mortality from candida and cryptococcus. Most alarmingly, perhaps, non-pneumocystis pneumonias are now the second most common cause of AIDS-related deaths, and bacterial septicemia comes third (after PCP).

Non-traditional therapy use (I61)

N. Singh and colleagues from the Pittsburgh VA Hospital quizzed 56 HIV+ patients on their use of non-traditional therapies. 30% reported such use including meditation, herbal therapy, special foods, vitamin therapy and acupuncture. Non-traditional therapy takers were older, more likely to be homosexual, more assertive, had greater community support and less hopelessness. Race, education, duration of positivity, disease stage and CD4 counts did not correlate with non-traditional therapy use. "On followup, CD4 count decline, HIV progression and mortality were similar for [the] two groups."

I. ANTIRETROVIRAL THERAPY

A. Nucleoside analogues: AZT, ddI, ddC, d4T, 3TC

ACTG 175 + Delta study results(LB-1) "This is the first [sic] study with long-term follow-up in which survival has been changed dramatically... It establishes once and for all that antiretroviral drugs can prolong life. The idea that you only need to do surrogate marker trials is blown sky-high by Delta. Delta shows how important clinical endpoint studies are."

-- Brian Gazzard, Delta Principal Investigator

"I mean, it's not like I live for bad news. It looks like we're making some progress."

-- Spencer Cox

Results of ACTG 175, a comparison of AZT alone, ddI alone, AZT/ddI and AZT/ddC in 2,467 HIV-infected participants starting without AIDS and with CD4 counts ranging from 200-500, were released on Thursday 14 September 1995 and presented at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) on Monday 18 September 1995 in San Francisco. Results of the European Delta study comparing AZT alone to AZT/ddI and AZT/ddC in 3,214 participants with starting CD4 counts ranging from 50-350 were released on Tuesday 26

September 1995 at the Fifth European Conference on Clinical Aspects and Treatment of HIV Infection in Copenhagen, Denmark.

A Comparison of ACTG 175 and Delta

ACTG 175 Delta

Regimens AZT alone (600 mg/d) AZT alone AZT/ddI (600/400 mg/d) AZT/ddI AZT/ddC (600/2.25 mg/d) AZT/ddC ddI alone (400 mg/d) -- N (CD4 range) 2,467 (200-500) 3,214 (50-350) AZT-naive N/median baseline CD4 1,067 (40%) 372 2,131 (66%) 212 AZT-exp. N/median baseline CD4 1,400 (60%) 338 1,083 (34%) 189 % with AIDS at baseline 0% (except mild KS) 12-17% Average follow-up 35.7 months 26 months Lost to follow-up (%) 19% 12-15% Off study drug (%) 53% ? DSMB action Extended by 6 months Stopped early

ACTG 175 Results

AZT alone ddI alone AZT/ddI AZT/ddC Global p-value

AZT-naive N 269 268 263 267 Death 18 (7%) 11 (4%) 11 (4%) 9 (3%) p=0.23 (NS) AIDS/Death 32 (12%) 23 (9%) 20 (8%) 16 (6%) p=0.074 (NS) CD4/AIDS/Death 63 (23%) 46 (17%) 37 (14%) 27 (10%) p=0.001

AZT-experienced N 350 352 350 348 Death 36 (10%) 18 (5%) 20 (6%) 31 (9%) p=0.023 AIDS/Death 64 (18%) 48 (14%) 45 (13%) 60 (17%) p=0.091 (NS) CD4/AIDS/Death 133 (38%) 90 (26%) 76 (22%) 93 (27%) p<0.001 ACTG 175 Overall N 619 620 613 615 Death 54 (9%) 29 (5%) 31 (5%) 40 (7%) p=0.007 AIDS/Death 96 (16%) 71 (11%) 65 (11%) 76 (12%) p=0.021 CD4/AIDS/Death 196 (32%) 136 (22%) 113 (18%) 120 (20%) p<0.001

ACTG 175: Immediate vs. Delayed Combination Therapy

Immediate Delayed Global Combination Combination p-value

AZT-naive N 530 537 Death 20 (4%) 29 (5%) p=0.27 (NS) AIDS/Death 36 (7%) 55 (10%) p=0.069 (NS)

AZT-experienced N 698 702 Death 51 (7%) 54 (8%) p=0.63 (NS) AIDS/Death 105 (15%) 112 (16%) p=0.47 (NS)

ACTG 175 Overall N 1,228 1,239 Death 71 (6%) 83 (7%) p=0.31 (NS) AIDS/Death 141 (11%) 167 (13%) p=0.11 (NS)

Background of ACTG 175. The study was controversial from the beginning. Originally the brainchild of ACTG Primary Infection barons Martin Hirsch of Harvard and Thomas Merigan of Stanford, 175 was designed in 1991 at the height of optimism about the use of CD4 as a surrogate marker and about the promise' of combination therapy. ACTG 175 was designed to build on the results of ACTG 016 and 019 suggesting that early AZT delayed progression. AZT would be the control arm and new regimens -- AZT/ddI, AZT/ddC and perhaps ddI and ddC alone -- would be compared with AZT in an 019-like population. To do such a study with clinical endpoints would have required over 3,000 participants and consumed perhaps half of the ACTG's resources for some time to come. Therefore, Hirsch and Merigan determined upon using CD4 changes as the primary endpoint. As Doug Richman was fond of saying in those years, "ACTG 155 will be the last clinical endpoint study." ACTG 175 was to be the first of a new breed of surrogate endpoint standard-of-care studies. Hirsch offered the position of study chair to Deborah

Cotton, the ddI skeptic who didn't believe in surrogate markers, but Cotton had no power to change the already-agreed upon structure of the study, and so she resigned. Hirsch and Merigan then named two junior researchers from their sites, Scott Hammer and David Katzenstein, respectively, to chair ACTG 175. Plans for a ddC monotherapy arm were dropped after ACTG 114 showed that ddC monotherapy was twice as bad as AZT for survival. ACTG 175 was finally opened as a stratified, four-arm study in the fall of 1991 amidst a chorus of howls from many activists and from other AIDS researchers. The study over-enrolled its projected target accrual by some 400 in order to achieve gender parity. Most of the extra enrollees were AZT-experienced, reflecting the American practice of starting AZT at 500 CD4 cells. In 1993, following release of the results of Concorde and ACTG 155, the ACTG 175 protocol team retrofitted the study, moving progression and death back to the status of primary endpoints -- especially for the planned comparison of immediate vs. delayed' combination therapy -- and, following the advice of the Data & Safety Monitoring Board (DSMB) extending the study for six months to provide more clinical endpoints. As the study wore on, it was plagued by dropouts (53% were off study drug before follow-up ended) and losses to follow-up (19%, still far less than in the higher CD4 cohort of ACTG 019, in which it was 35%). Many activists and scientists predicted the study would show nothing clearly. We were wrong.

Clinically Significant Differences in Delaying Progression and Death in ACTG 175. The study chairs, assisted by chief statistician Michael Hughes of Harvard's Statistics & Data Analysis Center (SCAC), presented a balanced assessment of the surprising and provocative results of ACTG 175. While two combination regimens were better than AZT alone, they refused to conclude that combination therapy per se was therefore better than monotherapy in general, because participants on ddI monotherapy did just as well clinically as those randomized to immediate combination.

Hazard ratios (95% c.i.) Death AIDS/Death CD4 drop/AIDS/Death

ACTG 175 Overall AZT/ddI vs. AZT 0.55 (0.36,0.86) p=0.008 0.64 (0.46,0.87) p=0.005 0.50 (0.39,0.63) p<0.001 ddI vs. AZT 0.51 (0.32,0.80) p=0.003 0.69 (0.51,0.94) p=0.019 0.61 (0.49,0.75) p<0.001 AZT/ddC vs. AZT NS (p=0.10) NS (p=0.085) 0.54 (0.43,0.68) p<0.001

ddI alone and AZT/ddI each conferred a clear clinical benefit, as well as a benefit when measured by the composite endpoint of CD4 drop, AIDS or death. The composite endpoint figures are driven by the CD4 endpoints, which made up 399/565, or 70%, of the total first endpoints. The only statistically significant benefit with AZT/ddC combination therapy depended on the composite endpoint. Immediate versus deferred comparisons were non-significant overall

AZT-Naive Cohort AZT/ddI vs. AZT NS (p=0.19) NS (p=0.082) 0.55 (0.37,0.82) p=0.003 ddI vs. AZT NS (p=0.11) NS (p=0.11) 0.64 (0.44,0.94) p=0.023 AZT/ddC vs. AZT NS (p=0.084) 0.49 (0.27,0.89) p=0.016 0.39 (0.25,0.62) p<0.001

All three regimens are significantly superior to AZT monotherapy when measured by the CD4 composite endpoint, but AZT/ddC jumps out in the composite clinical (AIDS/death) endpoint whereas the other two only show trends. Remember the small number of clinical events in this cohort (16 on AZT/ddC vs. 20 on AZT/ddI, 23 on ddI, 32 on AZT). Statistical significance does not always equal clinical significance. Nonetheless, Roche will probably try to make this a pivotal confirmatory' subset study for AZT/ddC combination. There was no significant difference in immediate versus delayed combination therapy in this cohort. ACTG

175 lacked the statistical power to detect the optimal first-line therapy; its overall results are driven by the AZT-experienced cohort.

AZT-Experienced Cohort AZT/ddI vs. AZT 0.52 (0.30,0.91) p=0.019 0.65 (0.44,0.95) p=0.025 0.48 (0.36,0.63) p<0.001 ddI vs. AZT 0.48 (0.28,0.85) p=0.010 NS (p=0.080) 0.59 (0.45,0.77) p<0.001 AZT/ddC vs. AZT NS (p-0.40) NS (p=0.60) 0.60 (0.46,0.79) p<0.001

In this cohort, AZT/ddI beats AZT alone by any measure. ddI alone beats AZT alone by the composite endpoint and by extending survival. AZT/ddC together only improve surrogate marker outcomes and do not appear superior to AZT alone vis-…-vis clinical outcomes in this cohort. Once again, there is no significant difference between immediate and delayed combination therapy.

ACTG 175: Virology + Immunology. At ICAAC, David Katzenstein presented preliminary virology and immunology results from ACTG 175 (LB-2). At 60 weeks, all three arms except AZT alone had median CD4 counts above baseline. They measured viral load with quantitative microculture and by RT-PCR in a subset of 348 patients (196 naive, 162 experienced). There were significant differences in the time viral load too to return at baseline at weeks 8, 20 and 56 but not at weeks 80 or 104 (possibly due to smaller sample size at those time points). AZT-experienced patients randomized to AZT monotherapy displayed no antiretroviral response to AZT There was a statistically significant change in viral load changes between AZT and AZT/ddC in the AZT-naive group. The two combination arms reduced viral load by a median of 0.7 log copies of plasma RNA. While combination reduced viral load by a greater magnitude than ddI alone, the duration of response appeared similar, and ddI alone conferred similar clinical benefits. Katzenstein and Hughes cautioned me (personal communication) that neither viral load nor CD4 changes have yet been validated in this study. Further case-control analyses are ongoing.

Conclusions of ACTG 175

* ACTG 175 suggests that for patients with CD4 counts between 200-500, it is better to start therapy with ddI alone, AZT/ddI or AZT/ddC than to start with AZT alone. However, it does not say whether starting therapy at this time is better than waiting. * AZT 175 suggests for the first time that initiating antiretroviral therapy in this population with ddI alone, AZT/ddI or AZT/ddC can delay death as well as progression as compared with starting AZT monotherapy. * ACTG 175 suggests for the first time that ddI-containing regimens can improve survival as well as delay progression (cf. ACTG 116B/117). * ACTG 175 suggests that for pre-AIDS patients with no AZT experience, clinical outcomes can be improved by starting with AZT/ddI, AZT/ddC or ddI alone as opposed to starting with AZT alone (cf. ACTG 152 in children). * ACTG 175 suggests that for pre-AIDS patients with AZT experience, clinical outcomes can be improved by switching to ddI monotherapy (cf. ACTG 116B/117) or AZT/ddI combination therapy, and that switching to AZT/ddC may not be clinically beneficial (cf. ACTG 155). * ACTG 175 shows that medium-term studies measuring clinical progression and survival are possible in intermediate-stage patients. * ACTG 175 shows that there were no significant differences among the four treatment arms in recorded adverse events; however, 25% were lost to follow-up in the naive arm, compared with 15% in the AZT-experienced arm, suggesting that up to a quarter of AZT-naive, healthy patients find the drug(s) unbearable even without manifesting ACTG-graded toxicities. Of note, the losses to follow-up were lowest in the ddI monotherapy arm. * The losses to follow-up in ACTG 175 are lower (19%) than in the higher CD4 stratum of ACTG 019 (35%), suggesting that it is possible to improve long-term follow-up still further. * ACTG 175 did not have the power to

distinguish which of the three alternative regimens (ddI alone, AZT/ddI, AZT/ddC) is optimal first-line or early second-line therapy. * ACTG 175 could not show any benefit to starting with combination therapy as opposed to monotherapy. AZT monotherapy was worse than the combination regimens, while ddI monotherapy appeared to be equivalent to them. * ACTG 175 shows that it is a mistake to rely on surrogate markers such as CD4 level changes to establish the standard of care; the study will be convincing only because it shows statistically significant differences in delaying progression and death, not just CD4 declines. * ACTG 175's results indicate that Debbie Cotton was right to resign from the study as originally designed, with CD4 declines as the sole primary endpoint. Only the post-Concorde addition of progression and death, and the DSMB's extension of the study by six months, saved the study from irrelevance.

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Delta Study Results

AZT alone AZT/ddI AZT/ddC Total Delta 1 (naive) N 703 702 708 2,113 Died 17% 10% 12% NS Progressed/Died 28% 18% 23% SS

Delta 2 (experienced) N 355 362 366 1,083 Died 26% 23% 26% NS Progressed/Died 39% 38% 38% NS

Delta Overall N 1,058 1,064 1,074 3,196 Progressed/Died 28.4% 17.6% 23.3% SS

[SS = statistically significant; NS = non-significant]

In Delta overall, combination therapy reduced the relative risk for progression and death by 25%. The study was driven by the highly significant results in Delta 1; there was no significant difference in Delta 2. We have less information at this time about Delta than we do about ACTG 175, so it's harder to go into the ins and outs. However, some important differences strike one immediately:

Differences between ACTG 175 and Delta.

Different populations with different stages of disease. ACTG 175 population started out with many more CD4 cells (338-372) and less full-blown AIDS (0%) than Delta (189-212 CD4 cells and 12-17% AIDS at baseline). Different amounts of AZT experience. Whereas only 40% of the 175 population was AZT-naive, 66% of the Delta population had never taken AZT before. Thus, the results of 175 were driven principally by progression and death occurring in the AZT-experienced arm, whereas the results of Delta were driven by the more advanced, but still AZT-naive population's experience. Different levels of drop-outs and losses to follow-up. ACTG 175 had higher drop-out rates, losses to follow-up and participants switching off study drug before reaching clinical endpoints than Delta. Different strategies for stopping the trials. However, ACTG 175 was also extended for six months to strengthen its ability to measure clinical endpoints after Concorde cast doubt on the use of CD4 changes. By contrast, Delta was stopped early after a statistically significant overall difference progression and survival emerged. This was an unexpected reversal from the prior pattern, in which Europeans ran trials through to their planned conclusions and Americans stopped them early whenever a hint of efficacy emerged. Different approaches to announcing study results. Also striking was the difference between the measured caution of the American investigators when presenting their results at ICAAC -- no press conference and no immediate rush to consecrate combination therapy -- with the very un-British hype and hysteria of the Delta team's press release

calling their data the "most important trial results ever." "Two drugs better than one," trumpeted the Medical Research Council (MRC)'s press release, while the ACTG investigators were careful to note that ACTG 175 did not prove that combinations were better than monotherapy per se, but simply that anything -- including ddI monotherapy -- appeared to be better than long-term first-line AZT monotherapy use. Delta lacked a ddI monotherapy arm, which provided the most provocative and surprising part of the results of ACTG 175. Since Delta lacked a ddI monotherapy arm its investigators concluded that combination was superior to monotherapy, but 175 suggests that ddI monotherapy may be equivalent to AZT/ddI in combination. Still outstanding are the results of CPCRA 007, a.k.a. "NuCombo," another comparison of AZT/ddC, which will not shed further light on the ddI monotherapy question, since its regimens are the same as those used in Delta.

*

Long-term follow-up of children in ACTG 076 (I1)

Children born to mothers treated with AZT in ACTG 076 were followed for at least 60 weeks (n=274, AZT-treated n=151, placebo-treated n = 123). Apart from a mild anemia in AZT-treated children, no significant differences were seen with respect to weight, length, head circumference, CD4+ and CD8+ counts.

In another presentation (I5), researchers compared viral burden in women treated with AZT during pregnancy as compared to women not treated with AZT. AZT treatment was stopped after birth. No difference in viral burden were found during pregnancy, however AZT use during pregnancy was associated with an increase in viral load six months after delivery (p=0.01).

In a study of AZT resistance at transmission (I274), researchers studied 60 patients within 12 months of seroconversion. At baseline, 16% carried the mutation at codon 15 that confers resistance to AZT, 4 had the mutation at codon 41 that is associated with the 215 mutation, and 7 had mutation a codon 70.

ddI (VidexTM, didanosine) (A27)

The combination of ddI and Ganciclovir increases the availability of both drugs. This may increase the risks of toxicities associated with use of these drugs.

Hydroxyurea + ddI (I110, I111)

Based on in vitro data suggesting a synergistic inhibition of HIV using ddI and hydroxyurea, some researchers in Portland, OR presented a poster with results from a phase I study of the combination. The study looked at six HIV+ patients (median CD4+ = 79, range 27-198) who were treated with 500 mg hydroxyurea and 200 mg ddI/bid. Viral burden was assessed using the Chiron bDNA assay at days 1, 3, 5, 7, 10 and 17 following initiation of therapy. The combination was well-tolerated by all patients, and 3/6 patients had substantial reductions in viral burden by day 7.

d4T (ZeritTM, stavudine) (I169, I170, I171, I263)

Bristol-Myers Squibb presented data from A145-019, a randomized, multi-center study of AZT vs. d4T in patients who'd had at least six months of previous AZT treatment. The study compared 40 mg d4T twice daily to 200 mg AZT three times daily, and was stratified by site and baseline CD4+ cell count (<100, 101-300, >300). Primary endpoints were death, new or recurrent AIDS-defining

opportunistic infection (OI), or drop to < 50% of baseline CD4+ cell count. Patients were followed after their first endpoint to death or the end of the study. There was an 8% loss to follow-up.

BMS A1445-019: AZT vs. d4T

AZT d4T

Baseline criteria N 418 426 Age 36 35 Gender 89% male 87% male

Clinical status Asymptomatic 38% 35% Symptomatic 48% 52% AIDS 14% 16% Median CD4+ 255 238 p-value Outcomes Median follow-up 115 wks 114 wks NS Median time on therapy 54 wks 79 wks <0.0001

Endpoints CD4+ drop, AIDS or death 0.0002 AIDS or death 26 32 0.007 Death 79 53 0.07 Mean CD4+ drop @ 93w -79 cells -53 cells Study cessation (total) 260 295 Study cessation due to perceived progression 54% 34% <0.0001

Adverse Events Nausea/vomiting 178 160 <0.01 Myalgia 139 132 0.04 Dyspepsia 48 58 0.05 Neuropathy 18 56 <0.0005 Retreated 59% 63% Med. tx post-neuropathy 29 wks 23 wks Discontinued due to PN 9 28 0.02

Anemia, neutropenia & leukopenia were more common with AZT. Mild liver enzyme increases were more common on d4T, however there was no difference between the two arms with respect to severe liver enzyme increases or amylase increases.

In addition, the company presented data from its large, simple trial of high-dose d4T (40 mg bid) vs. low-dose d4T (20 mg d4T). Patients with advanced HIV disease, and no alternative therapy were eligible to participate. 11,784 patients received d4T for a median of 22 weeks.

Outcomes on d4T Parallel Track / Large Simple Trial

High-dose d4T Low-dose d4T p- value Death 7% 8% 0.03 (NS) Hospitalizations 0.08 (NS) PN requiring dose-modification 23% 17% <0.0001 PN requiring discontinuation 13% 11% NS

[PN = peripheral neuropathy]

In addition, 30 children have been treated with d4T for 1-3 years with a median duration of 84 weeks. Average dose has been 2 mg/kg/day. The investigators found no unusual adverse events, and no peripheral neuropathy.

AZT + d4T (I118)

Because in vitro tests suggest that AZT and d4T compete for the same binding site, many people have thought that these drugs could not be used in combination with each other. A study of 40 HIV-infected patients in France (CD4+ <100 = 27 patients, CD4+ 100-200 = 13 patients) compared d4T to AZT+d4T. In the group of sicker patients, the combination reduced rate of OIs (p=0.03) and death (p=0.05) as compared to d4T monotherapy. The researchers conclude that the combination provides an acceptable alternative to monotherapy.

3TC brand lamivudine

Members of TAG, GMHC and AIDS Action Baltimore met with representatives of Glaxo Wellcome to discuss its New Drug Application (NDA) for 3TC. In particular, we

expressed concern that the company is proposing that the drug be approved in combination with AZT as front-line therapy for patients with <500 CD4+ cells, but their "confirmatory study" is in antiretroviral-naive patients with <300 CD4+ cells. The company felt that this was the most efficient way to evaluate the clinical efficacy of their product, and that it would be possible to extrapolate to the healthier patients based on surrogate-response studies. The activists disagreed. Glaxo Wellcome suggested that, rather than trying to answer the question of "early vs. late" treatment using just one drug, it would be more efficient to develop a plan to address the larger conceptual question in combination with other major pharmaceutical companies. We agreed that we would feel much better about their proposed indication if we felt that a substantial effort was in place to resolve this controversy. Both sides emphasized the importance of developing cost-effective models for large-scale research. A model was proposed that looked suspiciously like the earlier Rebecca Pringle-Smith/AmFAR/Donald Abrams ComPACT study. Glaxo Wellcome agreed to initiate discussions regarding such a study, while the activists agreed to begin discussions with the Kaiser Foundation about some pilot efforts to integrate third-party payment with post-marketing research.

B. Protease Inhibitors

InviraseTM brand Saquinavir (Roche)

Extended treatment with Saquinavir, AZT and ddC-containing regimens (ACTG 229 follow-up) (I173)

Ann Collier of the University of Washington in Seattle presented long-term follow-up data from ACTG 229, the 302-patient study comparing AZT/ddC to AZT/Saquinavir and AZT/ddC/Saquinavir. Over its first six months, there were modestly greater CD4 and viral load changes in the triple-drug arm compared with the double-drug arms, with no measurable clinical differences. 94% of participants completed the initial 24-week study and 244/302 (82%) of these completed an additional 24 weeks of follow-up; 218/302 (73%) remained on study until completion.

ACTG 229 Follow-Up: Data at Week 48

AZT/ddC/SQV AZT/SQV AZT/ddC p-value

AIDS or death 3 8 7 NS CD4+ count over baseline 111 74 72 0.013 RNA titers under baseline -0.5 log -0.25 log -0.25 log NS Grade 3/4 toxicities 15 26 31 NS

CD4 percentages returned to baseline in the triple combination group at week 44. C.J. Hopper and colleagues also presented a poster attempting to correlate CD4 changes with viral burden changes in 201 patients from ACTG 229. 107/201 patients had no significant decrease in RNA or infectious units area under the curve (AUC). The median CD4 AUC was +4.4 cells/æl. 51 had a decrease in RNA AUC > 2.5 log and 7 had a decrease in IUPM AUC >0.5 log. The median CD4 AUC increased by 16 and 16 cells/æl in these groups. 36 patients having decreases in both RNA and IUPM AUC had a median increase in CD4 AUC of 48 cells/æl ($p<0.001$). "The trend of CD4 cell count rise correlating with RNA suppression reached statistical significance in all three treatment arms ($p<0.038$), but only patients on triple therapy had an association between increased CD4 count and decreased IUPM ($p=0.043$)... Patients with the greatest decrease in viral load, especially those with drops in both plasma viremia and cellular infectivity, had the greatest and most enduring increase in CD4 count." (I152)

Higher doses of Saquinavir (LB-5)

Jonathan M. Schapiro of Stanford presented an open-label study of two higher doses of Saquinavir. 20 patients each were randomized to receive 3600 or 7200 mg Saquinavir daily for 24 weeks. Mild liver function test elevations, confusion, GI upsets were reported at the higher dose. CD4 counts rose by an average of 72/mm3 at 4 weeks and by 121 at 20 weeks. Two critical mutations at codons 48 and 90 are associated with the development of resistance to Saquinavir. 13/40 developed the 48 or 90 mutation over the course of the study, with the suggestion but not proof that the higher dose delays the emergence of the mutation(s) as opposed to the lower dose.

Resistance to Saquinavir (I174)

L48V and L90M are two mutations in the protease gene which clearly induce a Saquinavir-resistant phenotype, however Saquinavir-resistant HIV remains susceptible to six other protease inhibitors. In a European study at 25 weeks 50% have low-level resistance and the rest develop it by 12 months. In the three-drug arm of ACTG 229 only 22% had resistance at one year.

Second Saquinavir Lottery

Roche announced on 18 September a second lottery for 2,280 persons with CD4<300 to receive Saquinavir. 60% of the slots are for those with CD4<50 and the rest for those <300 who cannot tolerate available agents (although they're encouraged to use such agents in the expanded access program). Patients not selected in the first lottery are automatically eligible for the second. Information is available by calling 1.800.332.2144. Registration forms must reach the Roche Data Coordinating Center at Parasol by 5:00 p.m. EST 3 November 1995.

Registration plans for Saquinavir

Roche applied in September for accelerated approval for Saquinavir. The FDA Antiviral Drugs Advisory Committee will consider Roche's application, along with 3TC and d4T, on 6-8 November 1995.

CrixivanTM brand Indinavir sulfate (Merck)(LB-6, I172, I176)

In an oral presentation, researchers from Merck presented data on 16 patients who crossed over after a 24 week comparison of the Merck protease inhibitor (MK-639) vs. AZT. These patients had constituted the AZT arm, and were given MK-639 (600mg q6h) following cessation of the randomized study. All patients were p24+ at baseline, with median CD4+ of 110 and a viral load over 50,000 (later changed to over 20,000); the actual average viral load was around 100,000 copies. At weeks 12, 24 and 36, median CD4+ was increased from baseline by 104, 105 and 126 cells respectively. Median CD4+ was sustained above baseline at 52 weeks. At 8 weeks, there was a median 1.98 log reduction in serum HIV RNA levels. 1/3 of patients have a greater than 2 log RNA reduction, and about 1/3 have sustained decreases in RNA at 24 weeks. Median viral load returned to baseline at 24 weeks. Four patients developed urolithiasis (stones in the urinary tract) and were rechallenged. At a dose of 400 mg/q6h, transient increases in billirubin occurred in about 15% of patients, and one patient developed crystallized drug in the kidney.

There are 9 residues associated with phenotypic resistance, of which at least three are required for in vitro resistance (M46I, L63P and V28T). In some treated patients, as many as 23 residues have shifted. By week 24, most patients

have at least 1/9 mutations associated with resistance. Appearance of the resistance mutations correlates with increasing viral burden. However, "simply counting the viral copies cannot predict the extent of the immune damage. Maybe we're selecting less virulent virus." This would explain the apparent dissociation between the return of RNA copy count to baseline at 24 weeks with the more sustained CD4 rises at 52 weeks.

Data were also presented on MK-639 in combination with IL-2 in patients with <300 CD4+ cells. The study had three arms: (A) 12 MIU IL-2 for 5 days out of every 2 months and MK-639 at 600 mg qid, (B) 12 MIU IL-2 for 5 days out of every 2 months in combination with 600mg MK-639 qid for 10 days every 2 months (pulsed dose) and 600mg MK-639 alone qid. Values were assessed at baseline (T0), 2 weeks after beginning MK-639 but before beginning IL-2 (T1), 1 month after the first IL-2 cycle (T2), at the time of the second IL-2 cycle (T3) and one month after the second IL-2 cycle (T4).

Results of IL-2 + MK-639 Combination Study

Group A Group B Group C (IL-2 + MK) (IL-2 + pulsed MK) (MK-639) N 7 5 6 Median CD4 T0 242 175 138 T1 322 160 261 T2 436 195 295 T3 396 168 241 T4 263 223 251

CD4+ increase of >50% T1 4/7 0/5 3/6 T2 6/7 1/5 5/6 T3 5/7 1/5 4/6 T4 2/3 3/5 4/4

(IL-2 + MK) (IL-2 + pulsed MK) (MK-639)

HIV RNA by bDNA (x103) T0 190 379 395 T1 123 633 86 T2 234 455 24 (n=6) T3 170 (n=6) 507 97 (n=5) T4 107 (n=3) 658 (n=4) 415 (n=2)

Hyperbilirubinemia, rash and aseptic meningitis each occurred in one MK-639 patient, but did not recur following rechallenge

ABT-538 Ritonavir (Abbott) (I282, LB-7)

D. Norbeck presented data on Abbott's Ritonavir (ABT-538). Monotherapy data indicates that viral levels rebound at 8 weeks with doses from 3-400 mg. With higher doses such as 600-800 mg, however, the reduction is sustained at 0.8 logs for 28 weeks. The emergence of resistance to Ritonavir is a multistep process. Seven mutations have been correlated with the development of reduced in vitro HIV sensitivity to Ritonavir (at codons 82, 20,36,46,54,71 and 84). The codon 82 mutation seems to be the primary resistance mutation, while the other codon changes enhance resistance. Only two of these sites (82 and 84) are predicted by X-ray crystallography to interact directly with protein substrates or competitive inhibitors. In rapid succession Norbeck presented two provocative claims about Ritonavir. First, he described a French triple-combination study carried out by Jacques Liebowitch (I think). Participants were given AZT/ddC/Ritonavir. Their CD4s went up by 110 and their plasma RNA went down by 2.5 logs at 20 weeks. Over the subsequent weeks, he claimed, an increasing proportion of participants became viral culture negative -- which is to say, they could not culture infected cells from the blood. "Some became PCR and culture negative, which suggests that the viral reservoir was empty." Abbott helpfully distributed a slide which it claimed contained the data substantiating this claim:

Viral Load Reductions in Patients Treated with Ritonavir, AZT + ddC

Infectious titer PBMC Plasma HIV RNA 99.9% 100% N 99% 100%

0.5 months 8% 0% 29 4% 4% 1 months 12% 4% 28 12% 8% 2 months 30% 18% 27 20% 20% 3 months 54% 39% 26 24% 30% 4 months 58% 30% 24/25 33% 24% 5 months 48% 23% 19/20 55% 35%

He rushed on from this irresponsible, unsubstantiated claim, to present data on an interaction between Saquinavir and Ritonavir. In vitro cross-resistance between these agents is rare. On its own, Saquinavir is poorly absorbed (some estimates suggest as little as 4% of the drug actually makes it into serum). However, Ritonavir appears to slow down the metabolism of Saquinavir 290-fold, enhancing its bioavailability. Both Saquinavir and Ritonavir are metabolized by the kidneys. When rats were treated with both drugs, the concentration of Saquinavir in the blood increased by 18-fold, and substantially enhanced the serum half-life of Saquinavir. There was no effect on the pharmacokinetics of Ritonavir. If this pans out in vivo it could enhance Saquinavir's antiretroviral activity, while increasing the chance that resistant mutations would develop more frequently.

Several TAG members met with Abbott Laboratories to discuss its expanded access program, which is expected to begin enrollment in January. TAG recommended that Abbott add a data collection component to their program, analyzing survival on all patients who apply for participation through the National Death Index. Abbott has expressed interest, and is considering the proposal. ViraceptTM brand AG1343 (Agouron) (LB-3, LB-4)

Graham Moyle summarized results of an English pilot phase II study of two doses of AG1343. 20 antiretroviral-naive HIV+ subjects with viral load over 20,000 copies and a median of 400 CD4 cells received total daily doses of 770 mg or 1030 mg in capsule form for four weeks. Viral load dropped by around 1.2 logs at 20 days at the higher dose level. Diarrhea occurred in 5-8 per arm (13/20 = 65%), fatigue in 6/20 (30%). They managed nausea with castor oil. Six patients (the responders') continued receiving drug after completion of the study. In these six, the level of virus remained under pre-treatment levels by at least 90% for up to 120 days.

Marty Markowitz of the Aaron Diamond AIDS Research Center presented data from a pilot phase II study of AG1343. 30 antiretroviral-naive HIV+ subjects with viral load over 20,000 and CD4s between 200-500 were given one of three daily doses of AG1343 in tablet formulation for four weeks at ADARC or at the Conant Medical Group in San Francisco. Twice daily doses of 500 mg, 600 mg or 750 mg of AG1343 resulted in average maximum reductions in plasma HIV levels of 90%, 94% and 93% respectively. 40% of participants experienced diarrhea.

U-103017 Protease Inhibitor (Upjohn) (A128)

In addition to a great deal of pre-clinical data on the Upjohn Protease Inhibitor (I121, I122 and 123), a poster presented by researchers from Upjohn Labs detailed results of a Phase I pharmacokinetic study of its protease inhibitor (U-103017). Three different formulations were tested in "healthy" volunteers, including an oral solution, a free-acid in capsules, and a di-sodium salt in capsules. All formulations were well-tolerated, although the oral solution was reported to have a bitter taste, like that of the Abbott PI. Bioavailability was good for the first two formulations, but not so good for the di-sodium salt version. Half-life was 8-15 hours. VX-478 Protease Inhibitor (Vertex) (I278)

In vitro studies suggest that an I50V mutation is necessary but not sufficient to induce resistance to VX-478.

C. Novel antiretroviral compounds

Allelix Biopharmaceuticals tat Inhibitor (ALX40-4C)

Allelix Biopharmaceuticals presented a phase I study of a new tat inhibitor. In a phase I dose-ranging study of 28 people with HIV, the top two doses (0.56 mg/kg and 0.70 mg/kg) achieved doses above the IC50 for HIV. No dose-limiting toxicities were seen.

Chinese Herbs (I143)

A study by Dr. Robert "Chip" Schooley in concert with X.Q Zhang and colleagues from the Chinese Academy of Medical Sciences determined that seven herbs commonly co-administered as a single prescription have potent anti-HIV activity in vitro, with relatively low cytotoxicity. The herbs include two extracts each from Scutellaria baicalensis and Salvia miltiorrhiza.

GEM 91 Antisense (I177)

David Sereni of Hybridon Europe presented data on 30 patients given GEM 91. 9 received 0.5 mg/kg/day, 9 received 1.0 and 12 received 2.0. Infusions last for two hours every other day for 27 days (14 infusions total). CD4 counts ranged from 100-500 and RNA copies were greater than 25,000. So far the two lower doses have been well-tolerated. Nausea was reported in the high-dose arm. No changes in HIV RNA levels have been observed.

New Antiretroviral Drugs -- Preclinical Development

Pre-clinical data were presented on a new protease inhibitor from Ciba-Geigy (U-103017, I121-124), the NCI's protease inhibitor KNI-272 (I125), a new protease inhibitor from Parke-Davis (5,5-Dihydro-2H-Pyran-2-ones), several metabolites of Merck's CrixivanTM (including one compound with more potent protease inhibition in vitro than the parent compound, I126), Ciba-Geigy's proteases CGP-57813 (I127) and CGP-53437 (I128), a naturally occurring antifungal/antibiotic from Parke-Davis called Cerulenin which may also be able to inhibit protease cleavage (I129, I137), antisense oligonucleotides (AS S-ODN, I139), two nucleoside analogue reverse transcriptase inhibitors (RTIs) from Glaxo Wellcome [159U89 (I109) and 54W91], a new non-nucleoside RTI from Eli Lilly (LY300046-HC1, I130), a new compound PRO 2000 that disrupts CD4/gp120 binding in vitro from Procept (I131), a dextran sulfate analogue called D2S that doesn't yet seem to have a sponsor (I132-33), several zinc finger inhibitors being studied by the NCI intramural program (I134-136), a tat peptide-DNA that may inhibit tar RNA (I140), a foscarnet analogue, (I141) an aminoglycoside called Hygromycin B (I144), several acyclic nucleoside analogues with boronic acid moieties (I145), and a quinolone derivative called Vesnarinone (II106, I146).

Immune-Based Therapies Roundup

Interleukin-2 (IL-2) (LB-8)

NIAID's Joe Kovacs presented some data from the ongoing NIAID intramural randomized comparison of IL-2 plus standard of care (SOC) versus standard-of-care alone. 60 patients were randomized, with average CD4 counts of 416. 31 received IL-2, 29 didn't. 42% of IL-2 recipients reported fatigue. Only 2/31

(6.5%) IL-2 patients completed the trial without an IL-2 dose reduction. The mean dose used then was about 9 million units/day for 14 days per two month period.

Clinical Endpoints: Randomized IL-2 Study

IL-2 No IL-2 OI CD4 month OI CD4 month

MAC/PML 51 6 Bartonella 216 8 Cryptosporidiosis 202 16 Toxo/lymphoma 74 14 Hodgkins' lymphoma 792 16 PML 144 18

Surrogate Marker Changes: Randomized IL-2 Study (mean change per month)

IL-2 No IL-2 p-value

CD4 change +37 -5 <0.001 CD8 change - 5 -9 .05 (?) p24 Ag change + 5 -0.7 .22 bDNA count 5,300 6,400 .83

Mean CD4 counts went from 400-1,000 in the first ten months on IL-2 and stayed at baseline (~400) in the no IL-2 group. Kovacs said, "IL-2 is safe with dose reductions on this regimen at one year. It raises CD4 counts but not CD8s and does not increase viral load in the lymphoid tissue."

Viagene's HIV-IT(V) elicits anti-HIV cytotoxic T lymphocytes (CTLs)(I75-76)

Viagene researchers R. Haubrich and J. Merritt presented two studies of intramuscular HIVIIIB env/rev encoding retroviral vector [HIV-IT(V)] administered by intramuscular infections once a month for three months to 37 asymptomatic HIV+ persons with CD4 200-500. In the first study (N=16), the mean CD4 count rose from 516 to 558. 4/8 patients with low CTL pre-therapy had an increase in CTL from 3-1-5.6 times baseline. 3 were unchanged. 1/8 patients with high pre-treatment CTL activity showed an increase. There were no changes in viral burden. The vector appeared to be safe and well-tolerated. In the second study (N=21), placebo was compared with three doses. 0/6 placebo-takers and 0/5 at 106 injected at one site responded, 1/4 responded at 106 injected at four sites, and 4/5 at 107 cfu administered at 4 sites responded. "Response" meant an increase in anti-HIV CTL activity. CD4 counts and HIV RNA levels were stable. Question: Why are they using HIVIIIB?

Novel interferon may be superior to IFN-à2b as an anti-HIV agent(I77)

Interferon-àn3 is a purified mixture of multiple IFN-à species from Sendai virus-treated human lymphocytes. It is 1,000-fold more effective than recombinant IFN-à2b (Schering's Intron-A or Roche's Roferon-A) against HIV in vitro. In this study by Monte S. Meltzer and colleagues from the Walter Reed Army Institute of Research, 20 HIV-infected patients with over 400 CD4 cells were given 1 million units, 5 million units or the maximum tolerated dose (37 MU) subcutaneously three times weekly for 12 weeks. The flu-like syndrome associated with IFN-à2b was absent and toxicities were few. The IFN-àn3 was not immunogenic and patients developed no antibodies to it. Anti-HIV activity was dose-dependent. CD4 counts after 21 months of follow-up were 538. Further studies are warranted.

Soluble TNF receptor fusion protein inactive (I78)

12 HIV+ patients with CD4 counts below 200 were given three doses of sTNFr (Immunex Corp.). It was well tolerated. No improvements occurred in immunologic or virologic parameters.

Thymopentin reduces viral load in acutely SIV-infected rhesus macaques(I81)

J. Blanchard of Tulane University randomized 20 macaques to receive Thymopentin 25 mg or placebo subcutaneously thrice weekly for four weeks and then infected them with 50 animal infectious doses of SIV. Thymopentin was continued thrice weekly until death. By day 28 post-infection 5/9 Thymopentin macaques had infectious viral cultures, and 10/10 in placebo. These titers were lower in the Thymopentin macaques. Progression and survival data were not presented.

II. OPPORTUNISTIC DISEASES: PROPHYLAXIS + TREATMENT

Opportunistic infections increase viral load (I236)

C.E. Bush and colleagues from Henry Ford Hospital, Detroit, Michigan, monitored HIV ICD p24 antigen and RNA levels with Chiron's bDNA assay over three years. 10 patients experienced AIDS-defining events. "There was a striking and significant increase in the level of plasma RNA with the advent of an opportunistic disease in 8/8 patients with detectable RNA levels." The median pre-OI RNA level was 18,000/ml. The median increase was 36,000 copies/ml ($p=0.01$). With recovery from the OI, mean RNA levels decreased by 30,000 ($p=0.013$). Neither CD4 counts nor p24 antigen levels appreciably changed during an acute OI and during recovery. "There was a consistent burst of HIV plasma RNA during an opportunistic event."

A. Viral Infections

Herpes simplex I + II (HSV-1, HSV-2), Varicella zoster virus (VZV, shingles)

HSV (genital herpes)

K. H. Fife presented a head-to-head comparison of Valacyclovir vs. Acyclovir for the first episode of genital herpes in 643 HIV-negative subjects (H11). 323 patients were randomized to receive 100 mg Valacyclovir twice daily and 320 to receive 200 mg Acyclovir five times daily. Duration of HSV-2 shedding, duration of pain, duration of symptoms and time to healing were similar in the two groups; there was no statistically significant difference between the two arms.

This study showed Valacyclovir as effective but not more so than Acyclovir. Valacyclovir is the pro-drug of Acyclovir and reportedly provides a 5 fold higher bioavailability than Acyclovir, many expected Valacyclovir would be more efficacious. This, however, was not the case.

Mark Loveless of Oregon Health Sciences University presented data on of 951 HIV-negative patients in three separate studies comparing various doses of Famciclovir (250, 500, 750 mg thrice daily) to Acyclovir (200 mg five times daily). Using the same dosings in all studies, one compared treatment over five days and another compared treatment over ten days. 70% of patients were female, 30% male, HSV-1 positive and 68% HSV-2 positive. Using duration of shedding, healing or loss of symptoms as criteria, there was no statistically significant differences between the two drugs. There was also no difference in any of the three doses of Famciclovir. Both treatments were found to be easily and equally tolerable. (H12)

The results of this Famciclovir study seem to be on par with the results of the Valacyclovir vs. Acyclovir study. While Famciclovir is reportedly more bioavailable than Acyclovir (77% as compared to 15-30%) and has a longer intracellular half-life, it only worked just as well and not significantly better.

Acyclovir ineffective for VZV retinitis (I50)

I. Cochereau and colleagues from the CHU Bichat-Claude Bernard, Paris, presented retrospective data on 7 patients with ocular VZV infection. The median CD4 count was 15. IV Foscarnet or Ganciclovir was the treatment of choice; the retinitis resolved within 6 weeks but most eyes subsequently went blind. Early treatment improved prognosis. 3 patients died within one month. CNS involvement was found in four patients concurrent with retinitis.

Cytomegalovirus (CMV)

N. Bernard and colleagues from the Group d'Epid,miologie Clinique du SIDA en Aquitaine presented a retrospective survey of 3,525 HIV-infected patients from 1985-1994, 158 patients presented with 168 first episodes of CMV infection. 68% already had AIDS with a median CD4 count of 42/mm3. CMV viremia was positive in only 24%. The probability of developing CMV disease rose from 3.9% to 17.5% between one and five years after CD4 counts declined below 200. 55.2% were dead within six months of the CMV diagnosis and 78.8% after one year. Note: these figures should be taken with some caution since they encompass a period before and after the development and dissemination of effective treatments for CMV disease, e.g., Ganciclovir and Foscarnet. Current mortality is probably lower. (I46)

CMV treatment

Chiron Vision's intraocular Ganciclovir implant (I215)

B.D. Kupperman presented efficacy data on Chiron's intraocular Ganciclovir implant. This treatment study -- using time to CMV progression as its endpoint -- tested two doses of intraocular Ganciclovir implant (1ug/hr or 2 ug/hr) vs. IV Ganciclovir. With 188 patients evenly divided in the three arms, the intraocular implant at 2 ug/hr was found to prevent progression for 182 days vs. IV treatment which prevented progression for 72 days ($p = 0.0001$). The rate of fellow eye involvement (CMV disease occurring in the other eye), was 40% for the implant group and 16% for the IV group ($p = 0.2789$). Extraocular disease (CMV disease developing elsewhere in the body) occurred in at least 15% of the patients in the implant group, which was statistically significant ($p = 0.010$). There were no statistically significant differences between the implant groups and the IV group in survival (140 days implant vs. 158 days IV; $p = 0.2340$).

Complications arising from the implant surgery were pronounced. There was a 1.7% incidence of endophthalmitis (blindness) as well as 21 cases (11.9%) of retinal detachment. Moreover, patients with the implant initially experienced a approximate four week period of blurry vision.

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

endophthalmitis. Much of this discussion will need to take place before and during the FDA's hearing of Chiron's NDA .

Cidofovir (HPMPC) (LB-9)

J. Lalezari presented data from a 60 patient study comparing two maintenance doses (3 mg/kg vs. 5 mg/kg) of Cidofovir after induction for the treatment of relapsed CMV retinitis. Data showed no statistically significant difference with the 5 mg/kg maintenance dose at 115 days to progression vs. 49 days for the 3 mg/kg dose. Renal toxicities, as is the usual for Cidofovir, were pronounced: 18% proteinuria (high levels of protein in the urine) and 12% creatinine increase. Because of these renal toxicities, Probenecid must be administered with Cidofovir. Probenecid, a sulfur drug, helps with the renal toxicities, but 40% of the patients in this study had a reaction to it. Lalezari also threw in old data from Gilead's immediate vs. deferred study which demonstrated 120 days until progression for Cidofovir versus 22 days for those on placebo. The fact that Cidofovir helped prevent progression of CMV disease more than placebo was not news to anybody. A number of researchers, including William Powderly, are now coming out against the use of placebos in immediate vs. deferred studies of acute CMV retinitis. He believes that using placebos is unethical when have a drug with known activity and patients on their way to full blown CMV disease. Gilead's recent filling of an NDA for Cidofovir seems premature at this time with only these two small studies, no studies versus the standard of care (Ganciclovir or Foscarnet) or any drug interaction studies. Moreover, the fact that this drug will always have to be used with Probenecid -- which is intolerable to half who take it -- is problematic.

SOCA sits on sight-saving data (ACTG 228)

NIAID's Michael Polis gave a state-of-the-art mini-lecture on "New Therapies for Cytomegalovirus Diseases" state-of-the-art minilecture. When it came time to discuss the best therapy for patients who relapse on CMV retinitis maintenance treatment, Polis ironically was only able to present the schema of ACTG 228. ACTG 228, the CMV Retinitis Retreatment Trial, was a phase III study which tested Ganciclovir and Foscarnet alone versus Ganciclovir and Foscarnet together for patients who had relapsed on either maintenance treatment. The study was designed by the Studies of the Ocular Complications of AIDS (SOCA) program and carried out by SOCA and the ACTG. It was closed by the DSMB in mid April 1995 and results were dicussed with ACTG Executive Committee and all SOCA investigators just a few weeks later. These are the only people who have been privy to the treatment results because of SOCA's policy not to publicly present study data until a paper is published in a medical journal. This has irked a number of ACTG investigators (who paricipated in the joint ACTG/SOCA study) who have (between April and now) been unable to show slides or mention the results of 228 when they have given lectures at conferences. Many believe that these data are important in understanding the standard of care. This exorbitant wait -- due to SOCA's policy -- will be challenged this week and in the months to come by many ACTG investigators and AIDS activists. Below are some of the results of ACTG 228:

ACTG 228: Median time to first CMV retinitis progression

Ganciclovir/Foscarnet together 4.8 months Ganciclovir alone 2.1 months (p=0.00002) Foscarnet alone 1.6 months

For patients originally on monotherapy (median of 1.6 relapses), swithching to an alternate drug was no more effective than staying on the same drug. The

adjusted relative risk of progression (switchers versus non-switchers) was 0.89 (p=0.576). Approximately 70% of the 271 patients in ACTG 228 were Ganciclovir-experienced. One third of them were randomized to receive Ganciclovir monotherapy. Having the Ganciclovir arm come out second best considering the majority had already taken Ganciclovir is encouraging. It indicates that drug penetration rather than resistance may account for some proportion of retinitis relapses. No difference could be detected in visual acuity outcomes. However, visual field loss and retinal area involvement on fundus photographs both paralleled the progression results with the most favorable results seen in the combination group.

ACTG 228: Rates of visual field loss

Combination 160/month Ganciclovir 180/month (p=0.003) Foscarnet 310/month

ACTG 228: Rates of increased retinal area involved by CMV

Combination 0.85%/month Ganciclovir 1.44%/month (p=0.003) Foscarnet 2.57%/month
Mortality was similar for all three arms.

ACTG 228: Median survival time

Combination 7.8 months Ganciclovir 8.6 months (p=0.790) Foscarnet 8.4 months

ACTG 228: Adjusted mortality rate

Combination 0.80/year Ganciclovir 0.90/year (p=0.196) Foscarnet 1.20/year

Quality of life was a major issue. Combination therapy and Foscarnet monotherapy patients had a poorer quailty of life than those on Ganciclovir monotherapy.

ACTG 228: Adjusted mean change in treatment impact (QOL) scores Combination - 10.22 Ganciclovir - 0.82 (p=0.049) Foscarnet - 4.58

ACTG 228: Adjusted mean changes in quality of life (QOL) scores from baseline

Combination - 7.16 Ganciclovir - 2.93 (p=0.046) Foscarnet - 8.17

Most discouraging were the cognitive function scores of the patients on combination therapy, who sored worse than either monotherapy arm.

CMV prophylaxis

CPCRA 023 sheds doubt on oral Ganciclovir for CMV prophylaxis(LB-10)

The most important CMV data to come out of this ICAAC conference was Carol Brosgart's late-breaking presentation of CPCRA 023 study, a randomized, placebo-controlled trial of the safety and efficacy of oral Ganciclovir for prophylaxis of CMV disease in HIV-infected individuals. Anticipation of this presentation was great since NIAID's CPCRA had sent out the executive summary a week earlier, concluding that "the CPCRA CMV study does not support use of oral Ganciclovir at a 3 grams per day dose as prophylaxis for symptomatic CMV retinal or gastrointestinal disease."

How could this be, many thought. An apparently similar study, Syntex 1654 was terminated early (after 20 months) by the Data Safety Monitoring Board (DSMB)

because it study showed a reduction of CMV retinitis by approximate 50% for the patients in the oral Ganciclovir arm.

CPCRA 023, a 26-month study, however, showed no statistically significant difference between oral Ganciclovir and placebo. Below is a summary of the CPCRA 023 study data plus a direct comparison of both studies. (Note: both studies had a 2:1 Ganciclovir to placebo design in which 662 patients were in the oral Ganciclovir arm and 322 patients were in the placebo arm.) CPCRA 023: Baseline Characteristics

Oral Ganciclovir Placebo p-value

N 622 332 -- Median CD4 35 33 0.80 % previous progression 44 48 0.29 Mean age 40 40 0.80 % white 72 70 0.81 % women 4 6 0.027 Gay/bisexual 87 83 0.07 IDU history 11 14 0.36

023: Summary of CMV and Death Events

Hazard Oral Ganciclovir Placebo ratio (G/P) p-value

N 622 332 -- -- CMV disease 99 55 0.90 0.53 Death 221 132 0.83 0.10 CMV or death 270 158 0.84 0.09

Breakdown of CMV disease

Hazard Oral Ganciclovir Placebo ratio (G/P) p-value

CMV retinitis 74 44 0.84 0.37 CMV colitis 21 12 0.83 0.10 Other sites 8 8 0.50 0.17

Hazard Ratio for CMV and Survival Pre- and Post-Protocol Change

Median CMV hazard Death hazard follow-up ratio (G/P) ratio (G/P)

At time of DSMB review 7.8m 0.87 1.27 At protocol amendment 9.0m 0.86 0.96 At study close 15.0m 0.90 0.83 Follow-up censored at protocol amendment 0.93 0.90

Adverse Experiences on Blinded Study Drug Hazard Oral Ganciclovir Placebo ratio (G/P) p-value

Any adverse experience 246 95 1.40 0.0007 Grade IV AE 185 75 1.33 0.05 AE requiring discontinuation 143 48 1.62 0.005

Comparison of Syntex 1654 and CPCRA 023

Syntex 1654 CPCRA 023

Ophthalmologic exams Baseline, q2 months After visual symptoms occur Ophthalmologist Primary care physician Unit characteristics Study site referral Primary care Demographics 81% white males 70% white males Median CD4 count 21 34 Mean CD4 count 26 44 Baseline CD4<50 88% 65% AIDS diagnosis 64% 45% Acyclovir use <1 gm/day allowed <1 gm/day allowed

Comparison of Syntex 1654 and CPCRA 023 Results

Syntex 1654 CPCRA 023 G/P hazard G/P hazard ratio (p-value) ratio (p-value)

CMV disease 0.51 (<0.001) 0.90 (0.53) CMV retinitis 0.51 (<0.001) 0.84 (0.37) Death 0.81 (0.14) 0.83 (0.10)

While 023 and 1654 trial designs were superficially similar, there were significant differences. The only true similarity was the fact that they used a 2:1 allocation of study drug (oral Ganciclovir) vs. placebo. The study designs in all other terms were different. That was mostly intentional. 1654 required patients be examined by an ophthalmologist every two months as compared to 023 which only required patients be examined by an ophthalmologist only after visual symptoms arose. Thus, Syntex 1654 was likelier to detect CMV retinitis before it became clinically apparent, and CPCRA 023 only afterwards. 023 was attempting to a real world scenario, equating "usual care" with ophthalmologic exams by clinicians only after visual symptoms occur.

Could such a difference in study design (patient management) account for the discordant results seen in both studies? Many researchers say, "yes." Thus, discussions regarding 023 and 1654 do not center on whether or not oral Ganciclovir is effective for prophylaxis, but on trial design (how to evaluate a CMV prophylactic drug), CMV patient management (what is "real world" or "usual care"), and treatment of asymptomatic vs, symptomatic CMV disease (when to treat).

Many are concerned with 023's decision not to require baseline screening for retinitis if patients did not complain of symptoms. Moreover, if 023 patients did complain of symptoms, their CMV diagnosis would not be determined by an ophthalmologist, but at the their clinic by a nurse or clinician looking through an ophthalmoscope. Thus, many critics of 023 are asking "how do we know that some patients did not already have asymptomatic CMV retinitis when they entered the study, during the study, or when they went off study?"

Some clinicians are concerned about the study design and its belief that they were providing "usual care" in the "real world." In fact, one clinician who was interviewed was troubled by the study design, saying "they [CPCRA study designers] are pretending when they say it is real world, because how they manage the patients is not how I manage patients in the real world.' The appropriate thing in the real world is to have patients with very low CD4 counts see an ophthalmologists for screening visits frequently."

She also believed that this style of patient management was dangerous, commenting, "They are making the claim that that is standard of care out in the community. My contention is that that is malpractice. I think that most people who take care of patients feel that way about it. If you miss the boat detecting CMV retinitis because you think you are good enough just looking into somebody's eyes with a routine ophthalmoscope in the office I think you are fooling yourself and the patient."

This study leaves us with a number of questions underlying how little is still known about the natural history of CMV end-organ disease in people with AIDS:

* How important is treating patients with asymptomatic CMV disease? * How detrimental is waiting until symptom occur? * Should all patients with low CD4 counts see an ophthalmologist for routine screening for detection of asymptomatic disease? * Can all patients in the "real world" afford to see an ophthalmologist? * Can all patients with low CD4 counts afford oral Ganciclovir for prophylaxis?

Does oral Ganciclovir prophylaxis cause resistance? (H-135)

UCSF's Larry Drew, co-chair of the 1654 study, presented resistance data on patients from Syntex 1654 who received at least 90 days of oral Ganciclovir. Of 18 isolates tested with a mean Ganciclovir exposure of 10.1 months (range: 4.4-18.6 months), one was found to have resistant virus with an IC50 of more than 12 mcM. This data confers that the estimated prevalence of resistance to oral Ganciclovir is less than 1%. This data dovetails with Drew's 1991 analysis of patients treated with IV Ganciclovir in which he described 7.6% of the patients tested were resistant to Ganciclovir. The numbers in this IV treatment study are, of course, higher due to the fact that patients had active CMV disease vs. those patients who were merely prophylaxing.

Drew's data on oral Ganciclovir prophylaxis are positive and may put to rest some of the concerns about the occurrence of resistance. The possible threat of resistance is one of the major reasons why some clinicians are apprehensive of using oral Ganciclovir as prophylaxis. In the absence of resistance, it appears that failures on Ganciclovir prophylaxis or maintenance may reflect primary the oral form's low bioavailability, high pre-treatment CMV levels in the body, and inadequate penetration into the eyes.

The retelling of Acyclovir vs. Valacyclovir for CMV prophylaxis (ACTG 204)(I214)

Judith Feinberg presented updated data on ACTG 204, a Phase III study of Valacyclovir versus two doses of Acyclovir for CMV prophylaxis in patients with advanced HIV disease. This study was originally presented in February 1995 at the 19th ACTG meeting, mere days after the study was closed early due to an apparent excess of deaths on the Valacyclovir arm. The ICAAC presentation, however, included all endpoints through July 1995. By July, 490 patients had died and there was a trend towards more severe mortality on Valacyclovir (p=0.06).

ACTG 204 was a 1227-patient randomized, placebo-controlled study with two-thirds enrolled at U.S. ACTG sites and the rest internationally. Valacyclovir (2 grams four times daily) was tested against high dose Acyclovir (800 mg four times daily - HACV) or low dose Acyclovir (400 mg twice daily - LACV) using a 1.5:1:1 randomization. (The total blinded study medication was 18 pills a day.) The diagnosis of CMV retinitis was based on clinical examination by an "experienced" study ophthalmologist at scheduled visits every 6 months or at visits precipitated by symptoms. Retinal photographs were used to confirm a diagnosis of CMV retinitis. The three arms were balanced for baseline characteristics with a median CD4 count of 32 overall and two-thirds below 50.

ACTG 204: CMV Endpoints Valacyclovir Both Acyclovir Arms Total

N 523 704 1227 Confirmed CMV 51 (11.7%) 123 (17.5%) 184 (15.0%) Unconfirmed CMV 12 (2.3%) 25 (3.6%) 37 (3.0%) Rejected CMV 10 (1.9%) 19 (2.7%) 29 (2.4%)

Diagnosis of CMV retinitis was based on clinical examination by experienced study ophthalmologists at scheduled visits every six months or at a visit precipitated by symptoms. Retinal photography was used to document and confirm retinitis. 11.7% of patients on VACV had a confirmed CMV endpoint versus 17.5% in the pooled ACV arms, representing a 33% reduction for VACV recipients.

ACTG 204: CMV Disease by Organ

CMV by organ Valacyclovir Both Acyclovir Arms % of total endpoints

Retinitis 51 (9.8%) 95 (13.5%) 79.3% Upper GI 4 (0.8%) 11 (1.6%) 8.2% Lower GI 3 (0.6%) 10 (1.4%) 8.7% Encephalitis 1 (0.2%) 5 (0.7%) 3.3% Radiculomyelopathy 1 (0.2%) 2 (0.3%) 1.6% Pneumonitis 1 (0.2%) 0 0.5%

The results indicate a one-third reduction in CMV endpoints for the VACV recipients. The proportional reduction seen for retinitis for the VACV recipients was also seen across all end-organ disease. Most importantly, 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.

In the survival analysis, the tables turn on VACV arm. The final analysis (as of July 1995), there was a trend (p=0.06) toward earlier mortality for patients in the VACV arm compared to all pooled patients in the ACV arms. This trend, unlike the survival difference seen at the February 1995 interim analysis, did not reach statistical significance. Comparing three arms showed higher mortality only for the comparison of VACV to LACV (p-0.02) and no difference between the two doses of ACV. There were no differences in primary causes of death between the three arms (lymphoma 3.6%, non-PCP pneumonia 3.6%, MAC 3.4%, wasting 3.1%, PCP 2.9%, sepsis 2.7%, KS 2.6%). 490 deaths were reported through July.

There were significant differences in duration of treatment and reasons for treatment discontinuation. Some of this might be due to the high rate of gastrointestinal toxicity reported in the VACV arm.

ACTG 204: Differences in Follow-Up, Treatment Discontinuation

Overall VACV HACV LACV p-value

Weeks on treatment 33 29 36 40 Weeks on study 57 57 56 60

Reasons for discontinuation

Treatment toxicity 4.0% 0.3% 1.4% 0.0005 Clinical endpoints 8.4% 12.2% 16.5% 0.001 % > grade 3 GI toxicity 19.5% 14.2% 17.1% 0.034

The re-analysis of ACTG 204 confused some and raised many questions. Further studies may be required to determine whether Valacyclovir's apparent effect on CMV outweighs its toxicity and apparent excess mortality. In any case, we must answer these questions:

* Can we still achieve this protective effect with a lower, less toxic dose? * Why was there such a survival difference between VACV and LACV? * Is ACV a placebo making VACV harmful or do we believe that ACV increases survival in HIV positive patients so the differences are not important?

CMV PCR substudy of ACTG 204 (H119)

The 16 European and Australian 204 sites enrolled 310 trial participants in a sub-study, presented by P.D. Griffiths, with the objective of describing the baseline CMV virological status of patients as measured by PCR. Both urine and blood baseline samples were obtained for 244 patients. 49% of these patients were found to be CMV positive by PCR in urine and or blood. Only 20% of them were found to be viremic (CMV in the blood), whereas 40% were excreting virus in their urine.

Interestingly, in the urine assay group, patients were equally distributed regardless of study drug (VACV or ACV), however fewer VACV recipients were CMV-positive in their blood.

ACTG 204: Baseline Blood and Urine CMV PCR Status

Urine CMV+ Blood CMV+

VACV 44% 14% HACV 42% 29% LACV 38% 20% All ACV 40% 24.5%

There was also a difference in the blood and urine PCR results with regard to patient's baseline CD4 counts. While CD4 counts did correlate with PCR positivity in their urine, the patients with a mean CD4 count of 27 or below were found to PCR positive in their blood. The conclusions drawn from this sub-study can (and should) be used for future CMV prophylaxis studies. They are:

* Agents would be considered "prophylactic" for those who were PCR negative in their blood and urine. * Agents would be considered as "suppressive or pre-emptive therapy" if they were PCR positive in their blood and/or urine. * Future clinical trials of CMV prophylaxis should consider using baseline PCR status as part of their entry criteria.

E.F. Bowen and colleagues used PCR to detect CMV viral load in the blood and urine of 32 patients on Ganciclovir therapy (H118). At baseline, 25 had detectable virus in either blood (n=15) or urine (n=10). The median load in the blood was 1.9 x 105 genome/ml and in urine 5.84 x 104 genomes/ml. All patients with positive baseline urine samples and 12 of the 15 with positive blood samples had undetectable levels of virus after 3 weeks of induction Ganciclovir, or a 104-106 reduction in CMV load.

A Kaplan-Meier survival analysis of the 15 patients with positive baseline blood samples showed that a viral load presentation greater than a median of >1.90 x 105 genome/ml was associated with increased mortality ($p = 0.03$). While this is a relatively small study, the results do suggest that PCR viral load detection might be effective in determining the pathogenesis of CMV and in determining the prognosis of patients.

William Powderly, during a Pathogenesis of OIs lecture, presented some of Stephen Spector's CMV PCR data. This data came from samples of CMV treatment study participants before they had developed their CMV disease. Spector noticed that these patients had a viremic burst in CMV two to three months before they developed retinitis. This spiking of CMV viral load -- which quickly returned to a negative baseline level -- might be the "seeding of the eye" which ultimately becomes CMV retinitis.

This data deserve follow-up attention on a large number of patients. Syntex/Hoffmann-LaRoche should work closely with Spector to confirm this pathogenesis hypothesis. If confirmed, we might be able to detect patients who are most in need of prophylactic or pre-emptive therapy.

Kaposi's sarcoma herpesvirus (KSHV)/human herpesvirus 8 (HHV-8)

KSHV: how it got there and what it means

Since December 1994, a great deal of controversy has centered around the Chang and Moore's discovery of the Kaposi's Sarcoma Herpes Virus (KSHV). At that time, many --- believed -- including Chang and Moore -- that KSHV was a new

herpesvirus, Human Herpes Virus 8 (HHV-8). Until it could be widely confirmed, and until an international committee on virus nomenclature can name it human herpes virus 8 (HHV-8), Chang and Moore settled on naming it KSHV because the initial discovery came from Kaposi's sarcoma-derived tissues. A myriad of prominent labs around the world have attempted to confirm their research in Kaposi' s sarcoma. During that time, many have found KSHV in other cancers including body cavity based lymphoma's of HIV-positive individuals and HIV-negative individuals(BCBLs), basal cell carcinoma, and Castleman's disease. In fact, Sandra Colombini from the Laboratory of Tumor Cell Biology (LTCB) and Peter Biberfeld from Sweden's Karolinska Institute found KSHV in feral Cynomolgus macaques infected with SIV (as well as those uninfected with SIV) who went on to develop lymphomas.

Some of this follow-up research suggests that KSHV is not specific to KS cells, nor perhaps to HIV-positive patients. It may be a newly-discovered, but already widely prevalent, herpesvirus. Whether or not it is a ubiquitous virus -- like most of its viral cousins -- is now the central question. Moore says that it is not. The most important new KSHV data came from T.J. Spira of the of CDC (H4). He attempted to address whether or not KSHV was in the semen of HIV positive men and, if so, was that the way it has been spread for a number of years. This hypotheses falls in line with the general belief that the KS-agent may be sexually transmissible since over 90% of those infected with KS are gay men. Also, data overwhelmingly shows that most of the few women with KS had sex with homosexual or bisexual men. Jay Levy and colleagues from University of California, San Francisco were unable to detect KSHV in the semen of HIV-positive patients with KS, but there is the possibility that Levy's assay was insensitive.

Nevertheless, the CDC's data is interesting and highly sophisticated. They took Chang and Moore's published PCR primers and probes (233 base pairs) and amplified it to 720 base pairs. This made the probe highly sensitive and assured better detection. Of 30 men who were found to have had KSHV in their semen, only 13 (43%) developed KS. Of three HIV-negative men who also had KSHV in their semen, none of them developed KS. CD4+ T-cell count did not correlate with those with KSHV positivity.

This study also attempted to correlate CMV culture positivity with the development of CMV disease. The CDC found that only 13 of 30 (43%) HIV- positive patients were CMV- positive based on PCR while 26 of 39 (67%) were CMV by culture. None of the 15 patients had CMV detectable in their semen. Of the 26 patients that were CMV culture-positive, 10 developed CMV, and 3 of the 13 (23%) who were CMV culture-negative, also developed CMV disease. For these subjects, CD4+ T-cell counts were significantly inversely correlated with CMV culture positivity.

Another presentation concerning KSHV was delivered by M.J. Glesby for the Multicenter AIDS Cohort Study (MACS, LB-16). This MACS study attempted to determine whether or not the use of antiherpes drugs such as Acyclovir, Foscarnet or Ganciclovir lowered the risk of developing KS. Data from a cohort of 935 homosexual men demonstrated that neither Acyclovir use for HIV infection (OR 0.84; 95% CI 0.56-1.26; P = 0.39) nor Acyclovir for any indication (odds ratio 1.02; 95% c.i. 0.76,1.38; p=0.23) was associated with a reduced risk of KS as an initial AIDS diagnosis. Likewise, Acyclovir was not protective in against developing KS after a person has already had one AIDS-defining event.

For the patients in the cohort who developed CMV disease and were treated with either Ganciclovir or Foscarnet, the was a non-statistically significant reduced

relative risk (RR) of developing KS. In the Ganciclovir treated patients, there was an RR of 0.56 (95% c.i. 0.22,1.44; p=0.23) and for the Foscarnet-treated patients there was an RR of 0.40 (95% c.i. 0.051,3.10, p=0.38). Glesby implied that there was a protective trend with the patients treated with Foscarnet even though it was not statistically significant. Note: if patients hadn't developed KS by the time they developed CMV disease they might not have lived long enough to develop enough KS afterwards for the alleged treatment effects of Foscarnet or Ganciclovir to become apparent.

The idea that Foscarnet might have activity against KSHV and the development of KS was also presented this summer by Rachel Humphrey from Robert Yarchoan's lab at the 1995 annual meeting of the Laboratory of Tumor Cell Biology. Her data indicated that approximately half of the small number of patients on Foscarnet cleared KSHV from their peripheral blood mononuclear cells (PBMC).

Such claims that Ganciclovir or Foscarnet might have activity against KSHV are at best unsubstantiated and could wind up being harmful for AIDS patients. First, there is no statistically significant retrospective data that proves either agent has protective activity against KS or against KSHV. Second, Ganciclovir is the most powerful drug in our moderately effective arsenal of drugs to treat (and possibly prevent) CMV retinitis. There are data showing that patients can become resistant to Ganciclovir, although we still do not know how many nor the overall significance. It would be unwise to use Ganciclovir for hypothetically unproven KS/KSHV prophylaxis because patients who go might go on to develop CMV disease might have already developed resistance. Furthermore, Foscarnet is extremely toxic and expensive. Finally, researchers have yet to show whether these drugs inhibit KSHV in vitro, or whether there is active KSHV replication in people with KS. These antiherpesvirus drugs would not be active unless the virus were replicating, and even if it were, they might not have strong enough anti-KSHV activity.

Finally, Alvin Friedman-Kien presented data that his lab found KSHV in the endothelial cells and spindle cells of lesions (using in situ hybridization) of HIV-positive patients. Friedman-Kien's data are controversial. Numerous labs have attempted to find KSHV in endothelial cells or spindle cells, and have been unsuccessful.

Human papilloma virus (HPV)

Province-wide surveillance for cervical dysplasia in HIV+ and HIV- women(I44)

British Columbia has a province-wide surveillance system for cervical dysplasia. "All cytology is read centrally, colposcopy is performed in controlled clinics, and dysplasia managed uniformly by the BC Cancer Agency." D.R. Burdge of the UBC generated lifetime cervical cytology data on 75 HIV+ women and compared it with 490,985 British Columbian women.

Canadian Province-Wide Cervical Cytology

Negative Mild Moderate Severe Invasive

BC (N=490,985) 89.1% 6.9% 1.7% 0.6% 0.02% HIV+ (N=75) 68% 24% 7% 0% 1% HIV+ mean CD4 381 401 166 NA 286

"No patients progressed subsequent to HIV diagnosis. Cervical dysplasia was more prevalent in the HIV-infected women... In the HIV cohort most dysplasia was mild or moderate and progression was not noted."

Imiquimod cream for genital and perianal warts (H2)

3M Pharmaceuticals has a nifty cream, Imiquimod (IQ), a heterocyclic amine which stimulates the production of interferon and possibly other antiviral cytokines. S. Spruance of UCSF and colleagues compared 1% and 5% IQ cream with placebo in 279 patients with genital and perianal warts, 125 women and 154 men. Treatment was given daily for 16 weeks or until clearance or warts.

5% and 1% Imiquimod (IQ) cream versus placebo for genital warts

5% IQ 1% IQ Placebo p-value

Enrolled 94 90 95 Analysis group 69 79 75 Complete clearance 49 (71%) 13 (16%) 3 (4%) p<0.0001 Time to clearance (w) 9 7 12 Recurrences 9/48 (18.7%) 2/12 (17%) 0/3 p>0.50

Clearance rates were higher than women than men. Local skin reactions were common.

JC virus / progressive multifocal leukoencephalopathy (PML)

S. Moreno and colleagues from the Hospital General Universitario Gregorio Mara¤¢n, Madrid, Spain, presented a retrospective chart review of 22 PML cases (13 of them biopsy-proved), of whom 8 received cytarabine (Ara-C, 2 mg/kg/day for 5 days every 4 weeks). One each developed a rash and vomiting. Clinical and/or radiological improvement was noted in 3/8 Ara-C patients and 0/5 non Ara-C patients. There were no differences in duration of survival by AZT use. Moreno and colleagues claimed median survival was 100 days for those receiving Ara-C and 36 days for those with no therapy. Such retrospective studies are highly biased. (Maybe the non-Ara-C receiving patients didn't live long enough to get the drug.)

B. Bacterial Infections

Mycobacterium tuberculosis

The CDC reports that TB incidence declined by 5% annually from 1953-1984, rose by 20% between 1985-1992 and has decreased between 1992-1994 by 8.5% (S57) Two billion humans worldwide and 15 million American residents are infected with mycobacterium tuberculosis (S60).

TB conversion rate among health care workers (I84)

Fred Gordin and colleagues from the CPCRA followed 776 health care workers who had contact with TB-infected patients and who had PPD tests done every six months. 19 health care workers (2 per 100 years of follow-up) converted. Median follow-up was 15 months. 1.6% converted at 6 months, 2.1% at 12 months, 2.8% at 18 months at 3.8% at 24 months. There were no differences in conversion rates between New Yorkers and non-New Yorkers or those involved in direct or indirect patient care. Those who performed cough-inducing procedures had a higher conversion rate than those who didn't (4.1% vs.2.3%).

Drug-resistant tuberculosis

Fred Gordin and colleagues from the CPCRA surveyed risk factors for susceptible and multiple-drug resistant tuberculosis (MDR-TB) in 425 New York City cases and

948 other sites. 79% of the New York cases were HIV-positive and 29% of the non-New Yorkers. Drug resistance was 29% in New York and 16% elsewhere, MDR was 14% in New York and 2% elsewhere (p<0.001 for both comparisons). (I82)

Risk factors for MDR-TB

OR 95% c.i. p-value

Asian 4.58 (2.88,7.29) <0.001 Prior TB therapy 2.88 (2.03,4.09) <0.001 NYC area 1.85 (1.31,2.61) <0.001 HIV+ 1.76 (1.18,2.62) 0.005 HIV unknown 1.15 (0.77,1.71) 0.495 HIV- 1.00 -- -- Age >50 0.65 (0.44,0.95) 0.026

[OR = odds ratio, hazard ratio, relative risk of MDR/risk of drug susceptible TB = 1.0]

J. Dobkin and colleagues from Columbia University monitored the incidence of multiple drug resistant TB (INH + Rifampin-resistant) and Rifampin-resistant TB from 1990 to 1994. The incidence of MDR-TB rose from 3.6% to 8.0% while the incidence of resistance solely to Rifampin rose from 0% to 7.6% in 1992 and fell back to 0% in 1994. "The decline in mono-resistance probably reflects decreasing secondary resistance resulting from better treatment compliance." (C100)

Mycobacterium avium-intralellulare (MAI)

Mycobacterium avium complex (MAC) is common in people infected with advanced HIV infection. While only 5% of pediatric and 7% of adult patients reported to the CDC have MAC as their first AIDS-defining disease, recent studies suggest that the prevalence in adult and children with AIDS is greater than 20%, and its incidence is up to 50-60% in some post-mortem studies. Before the onset of the AIDS epidemic, treatment results of chronic pulmonary disease due to MAC were poor, especially for patients with relatively extensive pulmonary involvement. Disseminated disease due to MAC (dMAC) was uncommon prior to the AIDS epidemic, and treatment, for the most part, ineffective. While dMAC remains potentially life-threatening for people with AIDS/HIV, significant progress has been made in recent years in developing more effective regimens for treatment and prophylaxis.

MAC is typically caused by two common atypical, non-tuberculous mycobacteria. Mycobacterium avium and Mycobacterium intracellulare are widespread in the environment, with high concentrations found in water, soil, food, water, and aerosol droplets. Mycobacterium avium occurs much more commonly than M. intracellulare as a cause of disseminated disease in AIDS patients. Of 28 serotypes of Mycobacterium avium, types 4 (40%), 8 (17%) and 1 (9%) are most commonly isolated from patients with AIDS.

In people with HIV/AIDS with dMAC, almost any organ can be involved. The most common organs afflicted are those with many mononuclear phagocytes, including liver, spleen and bone marrow. Symptoms are generally nonspecific, such as fever, night sweats, weight loss, weakness, and anorexia. Diarrhea, malabsorption and abdominal pain are symptomatic of gastrointestinal involvement; enlargement of the liver and spleen is common. Laboratory findings often include anemia, neutropenia, and elevated alkaline phosphatase levels. Respiratory symptoms and pulmonary involvement are uncommon in AIDS-MAC.

The diagnosis of dMAC is often indicated in the presence of any of the symptoms listed above. While it is possible to culture MAC from stool samples, this may not be the most sensitive assay to use. While MAC colonizes itself (asymptomatic reproduction of MAC bacteremia) in the gastrointestinal tract and nasal passages

of many people with AIDS/HIV, a definitive correlation between colonization and symptoms has not yet been made. The most sensitive assay used to determine MAC infection, albeit time-consuming, are blood and/or bone-marrow cultures (measuring for MAC CFU, colony-forming units).

Predictors of MAC (I92)

C.R. Horsburgh (CDC) and colleagues performed a case-matched controlled study of 270 HIV-infected persons with similar CD4 counts, 90 with MAC bacteremia and 180 without. They found several highly significant laboratory abnormalities in those with MAC, indicating that "specific signs, symptoms and laboratory abnormalities are seen in persons with MAC when compared to persons with advanced AIDS without MAC. The appearance of such associations before a positive MAC blood culture suggests that bacteremia occurs after a period of localized infection."

Signs & Symptoms: Case-Control MAC Survey

MAC No MAC p-value

N 90 180 -- Hemoglobin (gm) 10.9 12.0 0.001 Fever 48% 26% 0.001 Weight (kg) 66.3 71.1 0.01 Karnofsky score 74.3 83.8 0.01 Abdominal pain 33% 22% 0.04 Diarrhea 37% 27% 0.07 Alkaline phosphatase 203 148 0.08

Improved treatment regimens for MAC

There is still no standard treatment regimen for disseminated MAC. Most clinicians currently use multidrug therapy to maximize efficacy and to minimize the likelihood that resistant organisms will emerge. Up until recently, most studies of therapy for dMAC have been relatively small and have not been designed to assess quality of life, duration of survival or long-term benefit.

While there is no standard treatment regimen for the treatment of dMAC, the United States Public Health Service (US PHS) recommends a drug combination consisting of at least two drugs, including a macrolide (Clarithromycin at 500 mg twice daily or Azithromycin 500-1000 mg daily). Ethambutol (15 mg/kg daily) is commonly prescribed as the second drug, alone or in combination with Clofazimine (100 mg daily), Rifabutin 300-450 mg daily [higher doses have been known to cause uveitis, inflammation of the cornea of the eye]), Rifampin (600 mg daily), Amikacin (10-15 mg/kg daily), and Ciprofloxacin (500-750 mg twice daily). Providing an effective combination has been chosen, clinical responses are typically seen in 4 to 6 weeks. While MAC cultures will often remain positive after clinical symptoms have diminished, sterilization of MAC CFU can occur with prolonged treatment.

Although combination therapy is clearly more effective that monotherapy for the treatment of AIDS-related disseminated MAC, there are still no conclusive data about which combination is the most effective in treating clinical symptoms of dMAC and clearing MAC bacteremia. Furthermore, there are limited survival data from previous trials. Lack of survival data from dMAC prophylaxis studies, either with Rifabutin or Clarithromycin, posed serious questions for all current and projected studies.

At this year's 35th ICAAC, several presentations and posters attempted to shed more conclusive light on the efficacy of various combination regimens for the treatment of dMAC.

Clarithromycin + Clofazamine vs. Clarithromycin, Rifabutin + Ethambutol for treatment of MAC bacteremia (LB-19)

Dr. Toubur May presented the results of a French trial of 2 Clarithromycin-containing combination regimens for MAC treatment were reported. This randomized open-label trial compared the combination of Clarithromycin (2000 mg every day for 2 months then 100 mg every day) and Clofazamine 9200 mg ever day then 100 mg every day) versus Clarithromycin (2000 mg every day for 2 months then 1000 mg every day) and Rifabutin (450 mg every day) and Ethambutol (1200 mg every day) for the treatment of MAC infection. Endpoints (success) were survival, symptom reduction and negative blood cultures. In June of 1995, an intent-to-treat analysis was performed. 123/132 patients were evaluable. The median CD4+ counts was 14 cells/mm3.

CLARI + CLO CLARI + RIFAB+ ETHAM

N Success Failure N Success Failure p-value

Month 2 49 36 13 46 32 14 0.51 Month 6 25 7 18 26 12 14 0.51 Resistance 14 2 <0.01

There was no difference in survival distribution between the two groups. 18 patients in the double combination group had relapse infections between month 2 and month 6. The investigators felt that the combination of Rifabutin + Ethambutol dramatically ($p<0.01$) reduced the incidence of Clarithromycin-resistance.

3 drugs better than 4 for treating MAC bacteremia (LB-20)

A second trial was presented by S.D. Shafran of the Canadian MAC Study Group. The study, started in November of 1992, was a 16 week randomized open-label trial comparing the CCTG four-drug regimen -- Ciprofloxacin (750 mg twice daily), Ethambutol (15 mg/kg daily), Rifampin (600 mg daily) and Clofazimine (100 mg daily) -- versus Clarithromycin (1000 mg twice daily), Rifabutin (600 mg daily) and Ethambutol (15 mg/kg daily) in HIV+ patients with MAC infection. The primary endpoint was eradication of bacteremia in 2 consecutive cultures. Evaluable data was available in 187/229 patients enrolled. The dose of Rifabutin was lowered to 300 mg every day due to 24 cases of uveitis reported in the three-drug combination arm.

3 Drugs Better than 4 for Clearing MAC Bacteremia and Prolonging Survival

3-drug combination 4-drug combination p-value

MAC clearance Overall 67 (69%) 26 (30%) <0.002 High-dose Rifabutin (79%) (22%) <0.001 Low-dose Rifabutin (58%) (36%) <0.05 Median survival 8.7 months 5.2 months <0.001

The combination of Clarithromycin (at 300 mg every day), Rifabutin at either dose and Ethambutol is superior to the four drug combination. Higher doses of Rifabutin help clear MAC more rapidly but also cause an unacceptable amount of uveitis. This study is important because it proves that better MAC regimens are associated with longer survival, something not previously demonstrated in MAC treatment studies.

Clarithromycin + Clofazamine with or without Ethambutol (I201)

Dr. Mark Dube of the California Collaborative Treatment Group presented. Data from an randomized study of Clarithromycin (2000 mg every day) plus Clofazimine (100 mg every day), with or without Ethambutol (800 mg every day), for treatment and prevention of relapse of disseminated MAC. There was no significant difference in sterilization of MAC cultures between those patients treated with the addition of Ethambutol versus those who weren't. However the development of Clarithromycin resistance was higher in the group treated without Ethambutol (14% vs. 27%). This result was not statistically significant.

GM-CSF may potentiate MAC killing by Azithromycin (G109)

In a tiny eight-patient study, C. Kemper and colleagues from the Santa Clara Valley Medical Center randomized 8 HIV+ patients with MAC bacteremia to receive Azithromycin 600 mg daily with or without GM-CSF 250 æg/M2 for six weeks. The hypothesis was that the GM-CSF would stimulate macrophage-mediated killing of MAC organisms. Median log differences in viable intracellular MAC and median % reductions in colony-forming units (CFU) were:

Reductions in MAC CFUs: Azithromycin with or without GM-CSF

Azithromycin alone Azithromycin+ GM-CSF

N 4 4 Baseline 0.4 (11%) -0.04 (7%) Day 14 -0.15 (28%) -0.76 (82%) Day 28 -0.11 (22%) -0.94 (88%) Day 42 -0.19 (28%) -0.47 (60%)

One patient in each arm became culture negative. GM-CSF may warrant further exploration as adjunctive therapy for MAC. William Rich of AMGEN stated (Michael Marco, personal communication) that G-CSF is helpful in clearing MAC infection in a nude mouse model. AmGEN is pursuing this finding further in a clinical trial.

MAC prophylaxis improves survival

Two preventive treatments have been shown to be effective in reducing the incidence of MAC bacteremia. Rifabutin (300 mg daily) is approved by the Food and Drug Administration (FDA) as prophylaxis for dMAC in HIV+ people with CD4+ counts below 200 cells/mm3 based on two controlled trials. Clarithromycin (500 mg twice daily), while not indicated by the FDA as prophylaxis for dMAC, has shown to be effective in preventing infection.

Two presentations, one late-breaker presentation and one poster, specifically dealt with the correlation between survival and MAC prophylaxis with either Rifabutin or Clarithromycin.

Clarithromycin as MAC prophylaxis improves survival (LB-18)

In a late-breaker session report from Dr. Mark Pierce of Abbott Laboratories, the effect of MAC and its prevention on survival in patients with advanced HIV infection was reported. 682 participants (CD4+ counts <100 cells/mm3) enrolled in a prospective, randomized, double-blind multicenter trial conducted in the United States and Europe of Clarithromycin for the prevention of MAC. 341/682 (50%) patients were randomized to Clarithromycin (500 mg twice daily):

Clarithromycin Placebo p-value

Developed MAC (pts) 19 53 <0.001 Death 106 136 Median Survival (days) >700 573

Placebo-receiving patients who developed MAC culture positivity had an increased relative risk of death of 2.6 compared to those who were MAC negative ($p<0.001$). 60% of Clarithromycin recipients who developed MAC had high-level resistance to Clarithromycin. The incidence of resistance to Rifabutin on prophylaxis is far lower, because of absorption problems, lower antimycobacterial activity or both.

TAG's Michael Marco asked Connie Benson of Rush Medical College in Chicago to comment on the Abbott Clarithromycin survival data. She commented:

...clearly using Clarithromycin as prophylaxis was beneficial in reducing the incidence of MAC bacteremia by about 68-69%. The original Rifabutin study showed about a 50% reduction in MAC bacteremia. Since these weren't head-to-head comparisons you can't say that with some certainty that Clarithromycin is 20% better than Rifabutin. What you can say is that both drugs have shown a clear benefit and the proportion of people who got MAC bacteremia was lower for those on the Clarithromycin than for Rifabutin.... Clearly it was effective in reducing MAC bacteremia, but a small proportion of patients did develop MAC bacteremia while receiving Clarithromcin. And this Clarithromycin study did show a significant survival benefit for those receiving Clarithromycin for prophylaxis..

Because Clarithromycin has been found to be efficacious as both a treatment and prophylaxis treatment against dMAC, it is important for clinicians to examine these data in light of resistance data. According to Dr. Benson, clinicians may want to consider preserving Clarithromycin for patients who have very advanced immunosuppression or who develop dMAC infection.

Clarithromycin-resistant MAC may be resistant to Azithromycin(C93-94)

Macrolide antibiotics display varying abilities to inhibit MAC. Clarithromycin appears to permeate the cell membrane at concentrations 2-3 times higher than Erythromycin (C93). MAC isolates with a minimum inhibitory concentration (MIC) > 16 æg/ml are defined as resistant to Clarithromycin; those with an MIC > 128 æg/ml as resistant to Azithromycin. Nash and Inderlied from USC/Childrens Hospital Los Angeles determined that macrolide-resistant MAC isolates were derived from pre-treatment strains and that the key mutations appeared to occur in the MAC ribosomal RNA (rRNA) 23s gene. "Furthermore, Clarithromycin resistance appears to always cross to Azithromycin resistance." (C94) In a small retrospective survey by D. Asmith and colleagues from University of Texas, Galveston, breakthrough cases of MAC after prophylaxis were associated with macrolide resistance (Clarithromycin, 2/9, 22%, Azithromycin, «, 50%), whereas breakthroughs on Rifabutin were not (0/9, 0%). (E1)

Rifabutin as MAC prophylaxis improves survival (I204)

A second presentation at this year's ICAAC reporting survival data from MAC prophylaxis was Drs. Richard Chaisson and Richard Moore's poster on prophylaxis with Rifabutin. The poster reported a survival analysis of two controlled trials of Rifabutin prophylaxis against MAC in AIDS. This is the first time survival data has ever been presented showing a survival benefit to using Rifabutin. Cox proportional hazards analyses were performed on 1146 patients enrolled in 2 Rifabutin clinical trials to determine survival. The median treatment time in both trials was 185 days with an open-label follow-up in both trials (median 217 days).

Relative Hazard of Death (Rifabutin vs. Placebo) 95% c.i. p-value

Overall 0.70 0.57, 0.85 p<0.001 CD4+ count <50 0.75 0.58, 0.96 CD4+ count >50 0.60 0.42, 0.8

Rifabutin: Hazard of Death (12 and 18 months)

Rifabutin No Rifabutin (95% c.i.)

12 Months 0.20 (0.17,0.24) 0.28 (0.24,0.32) 18 Months 0.31 (0.26,0.36) 0.45 (0.29,0.50)

When asked about the Rifabutin prophylaxis study, Dr. Benson replied:

The original study reached the required number of endpoints and resulted in the drug being approved. The original analysis really was based on a short duration of follow-up and, therefore, the original study was not able to show any statistically significant survival difference.

Several current trials will attempt to provide more conclusive data on survival and MAC prophylaxis. Follow-up data (18 months) to ACTG 196, a randomized study of Clarithromycin vs. Rifabutin for the prevention of dMAC, should yield interesting news. Also, the Pfizer/CCTG Azithromycin prophylaxis study (Azithromycin vs. Rifabutin vs. Azithromycin + Rifabutin), which was rejected as a late-breaker at this year's ICAAC, will be presented at the January, 1996, ASM Human Retrovirus conference.

C. Protozoal Infections

Pneumocystis carinii

Bactrim desensitization regimen (I221b)

Stanford's J.L. Carl and colleagues tried to desensitize 39 HIV+ patients who had experienced an allergic reaction to Bactrim (trimethoprim-sulfamethoxazole). They used an eight-day regimen of serial dilutions of the pediatric oral suspension. 37%% (15) completed desensitization and continued on Bactrim; 32% (13) completed desensitization and did not continue on Bactrim (because of non-allergic side effects) and 27% (11) failed to complete the regimen because they developed recurrent allergic reactions. "Only one-third of these patients were successfully desensitized." AmFAR is using a similar regimen in its planned desensitization study.

Toxoplasma gondii

GM-CSF may potentiate anti-Toxoplasmosis treatment (I225)

E. Sennevile and colleagues from Grenoble, reported on 34 HIV+ patients with CNS toxoplasmosis who were randomized to receive either standard treatment (Pyrimethamine 75 mg/d + sulfadiazine 6g/d) or standard treatment plus GM-CSF (3 æg/d). Patients with P/S/GM-CSF experienced less neutropenia and higher ANC counts than those on standard therapy, and fewer bacterial infections (6% vs. 25%). Clinical and tomographic resolutions were 12% on GM-CSF, 6% on no GM-CSF; deaths were 3 on GM-CSF, 6 on no GM-CSF, and 3 and 4 patients respectively were non-evaluable.

Cryptosporidium parvum

V. Cama and colleagues from the University of Arizona, Tucson, administered Paromomycin and Clarithromycin alone and together to cryptosporidial cultures and to infected nude mice. The drugs were active alone and synergistic in combination. (E43) Five antimicrotubule ditronaniline herbicides were used for in vitro evaluation of anti-cryptosporidium parvum activity by J.R. Mead and colleagues from Emory University and the CDC. Growth inhibition exceeded 99% for the compounds fluchloralin, pendimethalin, profluralin and trifuluralin at 5 æM and for nitralin at 10 æM. Pendimethalin was a log more effective than the next most active compounds (EC50 of 0.19 æM). No cellular toxicity was observed. (E42)

D. Fungal infections

Candida albicans

Itraconazole Oral Solution vs. Fluconazole for Oral Candidiasis I(I219)

G. Frechette from the Clinique M,dicale l'Actuel Inc., Montreal Canada presented Effects of Itraconazole in the Treatment of Oral Candidosis in HIV Patients: A Double-Blind, Double-Dummy, Randomized Comparison with Fluconazole. Two regimens of Itraconazole oral solution (100 mg twice daily for 7 days or 100 mg daily for 14 days) were compared to 100 mg/day of oral (pill) Fluconazole to treat oral candidiasis. 244 patients were recruited.

7 vs. 14 days Itraconazole vs. Fluconazole for Oral Candidiasis

7 days Itra 14 days Itra Fluconazole

N 79 79 78 Cured/markedly improved 84% 91% 91% Relapse within 18 days 24% 20% 22%

Itraconazole daily for 14 days appears equivalent to Fluconazole; Itraconazole twice daily for seven days appears inferior to Fluconazole.

Itraconazole Oral Solution vs. Fluconazole for Oral Candidiasis II(I220)

J.R. Graybill of the University of Texas Health Sciences Center, San Antonio, Texas, presented Itraconazole Oral Solution versus Fluconazole Treatment of Oropharyngeal Candidiasis. Itraconazole oral solution is a new cyclodextrin formulation of Itraconazole with greater bioavailability. 190 HIV+ patients with oral candidiasis were randomized to receive Itraconazole solution (IS) 200 mg/d for seven days, 200 mg/d for 14 days, or Fluconazole 100 mg/d for 14 days. 179 patients were evaluable. The median CD4 count was 146. 96% of isolates recovered at baseline were candida albicans.

7 vs. 14 days Itraconazole Oral Solution vs. 14 Days Fluconazole for Oral Candidiasis

7 days Itra 14 days Itra 14 days Flu

Clinical success 50/60 (83%) 57/59 (97%) 52/60 (87%) Mycological cure 31 (52%) 52 (88%) 46 (77%) Relapse (N=144) 27/46 (59%) 23/52 (44%) 23/46 (50%)

Four 7-day Itraconazole recipients, three 14-day Itraconazole recipients and one Fluconazole recipient stopped treatment due to toxicity. 14 days of Itraconazole oral suspension is at least as good as Fluconazole for treating oral candidiasis.

Oral Suspension Fluconazole vs. Topical Liquid Oral Nystatin for Oral Candidiasis (I221a)

Vincent Pons of UCSF presented a Comparative Clinical Study of Oral Suspension Fluconazole versus Topical Liquid Oral Nystatin in the Treatment of Oropharyngeal Candidiasis in AIDS. 136 patients with AIDS-related oral candidiasis were evaluable after being randomized to receive 100 mg/day of oral suspension Fluconazole (N=68) or 500,000 units of topical liquid oral Nystatin (N=68), which they were to "rinse, retain and swallow" daily for 14 days.

Oral Suspension Fluconazole vs. Topical Liquid Oral Nystatin for Oropharyngeal Candidiasis

Fluconazole Nystatin

Clinical resolution @ 14d 85% 48% Clinical failure @ 14d 4% 34% Relapse by day 28 18.6% 48% Relapse by day 42 40.6% 54.5%

Despite the fact that Nizoral is the most commonly prescribed treatment for oral candidiasis, Fluconazole is much more effective. Perhaps concerns about the potential development of Fluconazole-resistant candida organisms account, at least in part, for the continuing use of Nizoral, along with the latter's low cost.

Cryptococcus neoformans

ACTG 159/MSG 017 Part I: Amphotericin-B alone or with Flucytosine (5FC) for the Treatment of AIDS-Related Acute Cryptococcal Meningitis(I216)

Charlie Van Der Horst of the University of North Carolina presented a step 1 of Randomized Double-Blind Comparison of Amphotericin B (AMB) plus Flucytosine to AMB Alone (Step 1) Followed by a Comparison of Fluconazole to Itraconazole (Step 2) in the Treatment of Acute Cryptococcal Meningitis in Patients with AIDS. ACTG 159/Mycoses Study Group (MSG) 017 was a collaboration between two NIAID-funded clinical research networks. It addressed two questions:

1. Does adding Flucytosine (5-FC) to Amphotericin-B as induction therapy for cryptococcal meningitis improve 2- or 10-week survival compared to induction with Amphotericin-B alone?

2. Is Itraconazole as effective as Fluconazole in suppressing relapse of cryptococcal meningitis during the maintenance phase of treatment?

Amphotericin-B was administered at 0.7 mg/kg intravenously with or without 25 mg/kg oral Flucytosine every six hours for two weeks. Participants were then re-randomized to their maintenance regimen. ACTG 159 built on the regimen established in ACTG 059, which showed that there was 8% mortality within 2 weeks of starting therapy, and 14% mortality at 10 weeks on the Amphotericin-B regimen. This led to the recommendation to start with Amphotericin B and then switch to Fluconazole maintenance after two weeks.

They enrolled 381 participants with acute cryptococcal meningitis and so had 99% power to detect a 20% increase or decrease in cerebrospinal fluid (CSF) clearance of cryptococcal antigen. Participants' starting CD4s averaged around 20/mm3; it had to be their first episode of meningitis; 60% were culture positive for cryptococcus neoformans and 50% were African-American.

Results of ACTG 159/MSG 017 Part I: AmB/5FC vs. 5FC for Induction Therapy of Acute Cryptococcal Meningitis

AmB/5FC AmB alone p-value

Culture positive @ 2 weeks 60% 51% p=0.06 Culture negative @ 2 weeks 23% 30% ? Cultures not done 17% 11% -- Proportion dead @ 2 weeks 5% 6% NS

There was no significant difference in percentage who cleared culture positivity from their CSF between the two arms. There was no significant clinical difference between the two arms either. In sum, according to this study, Flucytosine plus Amphotericin-B does not improve acute outcomes for induction of cryptococcal meningitis over Amphotericin-B alone. The overall death rate in this part of the study was just 5.5%, a significant reduction from the 8% death-rate in ACTG 059, suggesting that the regimens to reduce intracranial pressure (which were used in both arms) may have reduced mortality in this group. Van Der Horst thanked study participants, showing a slide of a young woman who participated.

Reducing elevated intracranial pressure (ICP) may reduce mortality in acute cryptococcal meningitis. Although this part of the study was not randomized, it may be the most important new' result of ACTG 159. Both induction regimens included measures to reduce intracranial pressure (ICP) in patients with the worst symptoms. These measures were developed in collaboration between ACTG infectious disease specialists and neurologists such as David Clifford. About 200 of the participants in ACTG 159 had their pressure measured. If the intracranial pressure was above 250 ml of water they recommended taking measures, which were mandatory if the ICP was over 350 or if the patient displayed symptoms related to high blood pressure -- severe nausea, severe headache -- particularly when moving -- or papilledema. The three steps were as follows:

1. Daily removal by lumbar puncture of 25-30 cc's of fluid from the CSF by putting in a drain; 2. Administration of Acetazolamide (Diamox) which is believed to inhibit the production of CSF; it's a mild diuretic also used for glaucoma; 3. Inserting an intraventricular shunt, although no one needed it.

Of the 200 whose ICP was measured, about 30-40% had abnormally high ICP. It may be possible to use information on outcomes in this population to develop new guidelines for the management of high ICP during acute cryptococcal meningitis. The Mycoses Study Group (MSG) and ACTG have been discussing a consensus conference on the optimal management of AIDS-related fungal diseases.

2. Is Itraconazole as effective as Fluconazole in suppressing relapse of cryptococcal meningitis during the maintenance phase of treatment?

ACTG 159/MSG 017 Part II: Itraconazole vs. Fluconazole for Maintenance Therapy of AIDS-Related Cryptococcal Meningitis (I217)

Michael Saag of the University of Alabama at Birmingham presented step II of ACTG 159/MSG 017. Of the 381 participants who entered part I, 306 were able to be analyzed for outcomes in part II, the maintenance section of the study. Participants were randomized to Fluconazole or Itraconazole. Endpoints were CSF culture negativity at week 10 and resolution of symptoms at week 10.

Results of ACTG 159/MSG 017 Part II: Fluconazole vs. Itraconazole for Maintenance of Cryptococcal Meningitis

Fluconazole Itraconazole Difference Culture negative 72% 60% -12% Symptoms resolved 68% 70% + 2% Death 2 5 Not significant (NS) Major toxicity 5 5 NS

The null hypothesis (that Fluconazole was at least 15% better than Itraconazole) could not be rejected for CSF culture negativity, but it was rejected for clinical outcomes; Itraconazole recipients did at least as well clinically as those maintained on Fluconazole. There were no statistically significant differences in mortality at 10 weeks or at 12 months. They looked at patients according to both randomizations together; figures shown are for those whose cultures went negative at 10 weeks.

AmB/ITR AmB/5FC/ITR AmB/FLU AmB/5FC/FLU

CSF +/- @ 10w 30/43 32/50 18/54 23/56

MSG 025: Fluconazole vs. Itraconazole as Maintenance of AIDS-Associated Cryptococcal Meningitis (I218)

UAB's Michael Saag also presented Mycoses Study Group 025: Comparison of Fluconazole versus Itraconazole as Maintenance Therapy of AIDS-Associated Cryptococcal Meningitis. 107 patients who had been successfully treated for AIDS-related CM were randomized to 200 mg/day of either Itraconazole (N=55) or Fluconazole (N=52) and followed for documented CSF-culture-positive relapses. There were no mortality differences and no toxicity differences between arms.

Whereas ACTG 159 looked at 2- and 10-week clearance of acute cryptococcal meningitis, MSG 025 looked at time-to-relapse after treatment of an acute episode. 107 people with AIDS who had survived a bout of acute CM were randomized to receive Fluconazole or Itraconazole as maintenance. Median follow-up was nine months.

MSG 025: FLU vs. ITRA for Preventing Relapse of Cryptococcosis

Fluconazole Itraconazole p-value

CM recurrence 2/52 (3.8%) 13/55 (23.6%) 0.003 Death 11/52 (21%) 8/55 (14.5%) NS

There was no mortality difference here because no one died of the cryptococcal relapse. Interestingly, there were two separate predictors of failure in MSG 025: not getting Flucytosine (5-FC) in the induction period, and getting Itraconazole during the maintenance period. Thus, with longer-term follow-up, the apparent inefficacy of Flucytosine and the apparent efficacy of Itraconazole seen in ACTG 159 were both undermined in MSG 025.

Putting the two studies together, the implication is that the greater initial microbiological efficacy of Fluconazole to Itraconazole (72% vs. 60%) confers a later benefit in delaying time to relapse, or in eradicating the organism more successfully and for a longer time.

William Powderly of Washington University in St. Louis, who chairs the ACTG Complications of HIV Disease Research Advisory Committee (RAC), said, "I think Itraconazole is inferior to Fluconazole for [maintenance treatment of] cryptococcal meningitis. If you had someone who couldn't tolerate Fluconazole, perhaps due to occasional skin rashes, you could try them on Itraconazole. Fluconazole-resistant cryptococcus is still very rare. I also think, based on MSG 025, that 5FC should be used with Amphotericin-B during induction. There's no extra toxicity and it reduced the risk of relapse in MSG 025. Most failures

on maintenance are due to imperfect absorption or eradication and not to resistance. At ICAAC I asked Janssen [makers of Itraconazole] for their interpretation of these results. They haven't seen all the data yet, but feel that the Itraconazole failures may be an absorption problem not a resistance problem." Higher dose Itraconazole (e.g., 400 mg/day) could yet prove better than 200 mg did in MSG 025.

Histoplasma capsulatum

Histoplasma capsulatum is a fungal organism endemic to the Ohio and Mississippi River Valleys, in parts of the Caribbean and in Latin America. People breathe spores through the lungs and may develop acute or chronic pulmonary disease. Once infected persons may carry the organism for life, with reactivation of infection into disseminated disease when immunosuppression sets it. Amphotericin-B is used for induction therapy in severe cases, and Itraconazole in milder ones; Itraconazole is the treatment of choice for maintenance. According to histo maven L. Joseph Wheat, of Indiana University, relapse occurs in 5-20% of patients with AIDS. Antigen levels should be monitored about every four months from urine and serum specimens during maintenance treatment to re-induce if necessary to prevent relapse. Wheat's Histoplasmosis Reference Laboratory can provide overnight antigen test results. Two new azole compounds have demonstrated in vitro activity against histoplasma -- U46 and U51 from Uriach & Cia., Barcelona, Spain (B70, F84-85).

Invasive aspergillus

Aspergillus species include over 300 types of soil-borne fungi, a few of which infect humans, the most common being A. fumigatus. The disease may present as a dense mass in the lung or elsewhere (aspergilloma) or in disseminated form. Aspergillosis is relatively common among neutropenic cancer chemotherapy patients and those receiving immunosuppressive therapy for organ transplants. It is still rare, but increasingly common, as a late-stage manifestation of AIDS. Treatment of choice is resection (excision) for aspergilloma along with Amphotericin-B, and Amphotericin-B with Itraconazole (200 mg twice daily) for disseminated disease. Serum levels of Itraconazole should be monitored since the drug is not always well-absorbed. Note: Janssen researchers reported in a poster that PWAs drinking Itraconazole with a cola beverage increase absorption of the drug because the cola beverage reduced gastric pH. (A31)

New and emerging fungal infections

Gerald Bodey of the University of Texas described several new or previously rare fungal infections which are becoming increasingly common in the United States. Two pathogens in particular, Fusarium and Trichosporon, have been found at seven hospital centers in the U.S. They infect the lungs and sinuses. 8/11 evaluable patients died. Preliminary efforts are underway to assess Amphotericin-B and Fluconazole against these pathogens in open-label, unrandomized studies. (S9)

New azole antifungal agents

UK-109,496 is a new, wide-spectrum triazole derivative made by Pfizer Central Labs, UK. They tooled around with the Fluconazole molecule until they came up with something more active against aspergillus. It's also active in vitro against candida and cryptococcus. In vivo (in neutropenic guinea pigs) it was more active than Itraconazole against Fluconazole-resistant candida. It's up to 90% bioavailable, is extensively metabolized, and less than 1% leaves the body intact in urine. Pfizer enrolled several HIV-positive men in Britain with

oropharyngeal candidiasis to receive 200 mg/day or twice daily for 7 days. 80-100% of patients cleared their symptoms. 8-10% of patients experienced mild-moderate visual disturbances (enhanced awareness of light) while on the drug; several had elevated liver function tests and one developed a rash. Two studies were done in aspergillosis, one in acute disease and the other in chronic. 75% in the acute study responded (27/36) and 69% (9/13) in the chronic study. Uncontrolled phase I drug company studies often show higher response rates than emerge from later, more objective, randomized studies. (F69-F81).

SCH-56592 from Schering-Plough is a new orally active broad-spectrum antifungal agent. In vitro it appears equivalent to or stronger than Fluconazole and Itraconazole, and approximately equivalent to Amphotericin-B. It has particularly good activity against aspergillus species (MIC ~ 0.1 æg/ml compared with Fluconazole's 400), as well as equal activity against Fluconazole-sensitive and resistant candida strains and cryptococcus neoformans. It's bioavailable in five animal models and appears slated to go into clinical trials by 1996. (F61-F68).

UR-9746 and UR-9751 (a.k.a. U46 and U51) are two novel azole derivatives with a morpholine ring discovered by Uriach & Cia., Barcelona, Spain. They display good in vitro activity against histoplasma and U51 appears particularly active against coccidioides immitis, as well as against the usual thrush and meningitis fungi. Animal model studies are ongoing; the drugs have good activity. (B70, F84-85). Other new agents ready for clinical trials include the new azoles T-8581 from the Toyama Chemical Company, ER-30346 from Tsukuba Research Laboratories and D0870 from the Mochida Pharmaceutical Company, all of Japan. ER-30346 has good activity against aspergilla; all have respectable but not spectacular activity against candida. Animal studies are underway. (F82-F94).

In Vitro Activity of Novel Azole Antifungal Agents (MIC, æg/ml)

Fungal organism FLU ITR SCH-56592 UK-109,496 U46 U51 T-8581 ER-30346

Aspergillus fumigatus 400 0.25-1 0.1 0.09-0.25 NA NA 16-128 .006 Blastomyces dermatitidis 8.41 <1.97 <0.40 <0.03 ND ND ND ND Candida albicans <.5->64 .004-.03 0.25 ND 2-16 <0.5-8 .125-.5 .013 FLU-resistant C.albicans >64 ? 0.20 ND ND ND ND Coccidioides immitis 6.25 ? ND ND 25 3.13 ND ND Cryptococcus neoformans <0.5-32 0.1 0.06-0.25 <0.03 2-8 <0.5-2 ND .025 Histoplasma capsulatum 6.25 ? ND ND 0.78 0.78 ND ND

[NA = not active (against that organism). ND = not done.}

FLU = Fluconazole (Diflucan, Pfizer); ITR = Itraconzole (Sporonox, Janssen); SCH-56592 = a new Schering compound (F61-F68); UK-109,496 = a new Pfizer compound (F69-F81); U46 and U51 are being developed by Uriach & Cia., Barcelona, Spain (B70, F84-85); T-8581 is being developed by Toyama Chemical Co., Japan (F82-83); ER-30346 is being developed by Tsukuba Research Labs, Japan (F91-94).

New non-azole antifungals

There are also some non-azole potential antifungal lead compounds which are being looked at, mainly in vitro, including Riloprox, Hoechst's fungicidal hydroxypyridone (E78), Cecropin A, a lytic peptide that is not lethal to human cells (E79), Eli Lilly & Co.'s , a semisynthetic echinocandin B analogue, L-733460, a novel lipodepsipeptide agent from pseudomonas syringae, Syringomycin E and Abbott's A-39806 lanosterol 14à demethylase inhibitor (F102-106). Two Amphotericin-B derivatives, lipid nano-sphere encapsulated AMB and KY-62 are

also being looked at. (F98-F110). Bill Powderly told us that Bristol-Myers Squibb has a new intravenous antifungal, not an azole, which uses a new mechanism of action. He said they are planning phase I studies in the winter. There was no evidence of Bristol's new compound at the ICAAC. Macrophages appear to synergize with Fluconazole in killing candida albicans, and N-acetyl-cysteine (NAC) appeared to inhibit fungal spore germination against aspergillus. (E81, E82).

Resistance to antifungal agents

News about emerging antifungal resistance was contradictory but nonetheless alarming (I101-105). Barchiesi and colleagues passaged candida albicans organisms cultured from AIDS patients pre- and post-Fluconazole therapy, infected mice with the isolates, and monitored whether Fluconazole could prolong their survival. Fluconazole worked on the pre-treatment isolates, but not on those after several months of Fluconazole therapy. This could be a good animal model for resistant thrush. (B66). Maria Lynch and colleagues from Wayne State University examined candida isolates from 49 women with recurrent vulvovaginal candidiasis (RVVC). Isolates remained susceptible to all agents tested, suggesting that "azole antifungal resistance does not contribute to episodes of RVVC caused by candida albicans." (E66) However, R. Pelletier and colleagues from the NCI Pediatric Branch found that the emergence of resistance to Clotrimazole in 87 isolates from HIV-infected children correlated with a loss of clinical efficacy not only of Clotrimazole but also of Fluconazole, Itraconazole and Ketoconazole. The emergence of resistance also correlated with clinical failure. 6/15 (40%) children with Clotrimazole-resistant organisms had to receive IV Amphotericin-B for recurrent thrush , versus only 4/72 (5.5%) whose isolates remained sensitive. (E67).

While Fluconazole-resistant candida species have been well known for quite some time, only recently have reports begun to emerge of Fluconazole-resistant cryptococcus. Alarmingly, S.L. Koletar and colleagues from Ohio State University reported the emergence of cryptococcus resistance between 1991 and 1994 in patient isolates from their unit. Over those years there was no increase in resistance to Amphotericin-B and Flucytosine (5FC), but in 1991 6/11 pretreatment cryptococcus neoformans isolates had an MIC to Fluconazole of <2 æg/ml and all had an MIC <16 æg/ml. By 1994, however, only 9/20 had MICs<16 æg/ml and 11/20 had MICs >32 æg/ml. 13/14 isolates with high MICs had previous Fluconazole therapy. (E70). A CDC study of DNA subtypes and antifungal susceptibilities in recurrent (relapsed) cryptococcosis showed 73% of cryptococcus isolates from patients with recurrent meningitis had no changes, and only one patient each experienced increasing MICs to Amphotericin-B, Flucytosine and Fluconazole respectively. (E77).

The jury is still out on Fluconazole-resistant cryptococcus, but the dangers of resistant thrush are becoming all too apparent, and this has given rise to a controversy over whether to use Fluconazole as ongoing candida-suppressive therapy or for prophylaxis of invasive fungal diseases. The ACTG 981 study clearly showed that Fluconazole prophylaxis reduced the risk of invasive fungal diseases by 75% (from 10% in the Clotrimazole control arm to 2.5% in the Fluconazole arm), but most such serious diseases occurred in patients with under 25 CD4 cells. Therefore, some physicians are hesitant to start patients on long-term antifungal prophylaxis until they either have a series of recurrent episodes of thrush or a very low (<25-50) CD4 count. There is also the question of the expense of Fluconazole. According to Bill Powderly, if everyone in the U.S.A. with CD4<100 were given Fluconazole it might cost $250-500 million a year; if only symptomatic episodes are treated the cost would be about $15

million. This crucial can only be answered through a properly randomized trial comparing two strategies -- for example, comparing treatment of each thrush episode with continuous prophylaxis and monitoring the incidence of recurrent thrush, resistant fungi and invasive fungal diseases. One study being discussed to address the question is an ACTG/Mycoses Study Group collaboration which would compare intermittent versus chronic Fluconazole for candidiasis.

E. Wasting Syndrome

Epidemiology and prognosis of wasting syndrome and weight loss (I56-57)

C. Gibert and colleagues from the CPCRA presented survival data on 2,066 persons with CD4<500, mean 89.4, mean weight 158 pounds and average follow-up of 1.3 years. Baseline weight, N, proportion dying and similar data for weight change over first four months were presented:

Baseline weight and weight change over 4 months as predictors of mortality

Baseline % weight change weight N % dying @ 4 months N % dying

<120 125 49.6% <-9% 138 53.6% 120-139 388 36.1% -8 to -6% 143 44.8% 140-159 635 27.9% -5 to -3% 251 36.3% 160-179 533 23.5% -2 to -1% 482 25.1% 180-199 247 26.7% +0 to +2% 540 23.9% >200 138 18.1% + > 3% 511 22.7%

Lower weight (p=0.003), 4-month weight loss (p=0.02), disease progression before baseline (p=0.0005) and disease progression during follow-up (p=0.0001) were each significantly correlated with a higher risk of death. (I56). D. Wheeler et al., also of the CPCRA, presented the effect of weight change on the risk of various OIs, using data from 2,066 CPCRA patients (I57):

Relative risk of OI for a 5% weight loss versus no weight loss over 4 months

OI N events RR p-value

Any OI 772 1.27 0.0001 PCP 226 1.22 0.0005 MAC 199 1.16 0.012 CMV 187 1.41 0.0001 Candidiasis 167 1.10 0.17 Wasting 89 1.51 0.0001 Dementia 76 1.19 0.08

The two studies together validate the philosophy of Diseased Pariah News: "Get fat, don't die!"

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