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TreatmentUpdate 19

By
Sean Hosein
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I. ANTI-HIV AGENTS

A. AZT: 3,000 mg/day

Although AZT (Azidothymidine, Zidovudine or Retrovir) has been shown to inhibit HIV infection in laboratory experiments, its efficacy with human subjects appears to be of limited duration. AZT by itself (or other anti-retroviral agents by themselves) has not been able to cause a complete and/or sustained reconstitution of the immune systems of people with AIDS or less advanced forms of HIV-disease. Clearly, combinations of anti-retrovirals with other agents may become necessary for the treatment of HIV infection.

Since bone marrow transplants of healthy cells have been found useful in correcting the immunodeficiency seen in some disorders unrelated to HIV infection, attempts have been made to rebuild the immune systems of subjects with AIDS, using interferons, transfusions of white blood cells, and bone marrow transplants. At best, the effect of these therapies by themselves on HIV-disease progression has been temporary.

Several years ago, scientists at the National Institutes of Allergy and Infectious Diseases (NIAID, Bethesda, Maryland) theorized that if high doses of AZT were combined with a subsequent bone marrow transplant then perhaps the immune systems of treated subjects would be able to regenerate. A course of high-dose AZT would serve two basic functions: it would likely cause severe bone marrow damage (destroying any HIV-infected bone marrow and perhaps providing "space" for the new, transplanted marrow), and it might inhibit HIV replication in almost all cells of the body.

The NIAID enrolled 16 HIV-infected males, each subject with a healthy, non-HIV-infected twin. Nine subjects had AIDS, 5 had persistently swollen lymph glands, 1 had fatigue and night sweats, and 1 was symptom-free. All subjects were given AZT in a dose of 500 mg/4 hours per day (for a total daily dose of 3,000 mg) for 12 weeks. The dosage of AZT was adjusted "as necessary": in 7 subjects the dose was reduced during the first 12 weeks, although what the adjusted dose became was not stated. In the 10th week, transfusions of lymphocytes from their identical twin were given to the subjects, and again in the 12th week. At the end of the 12th week, a bone marrow transplant

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from the identical twins was done. Thereafter, subjects were given either AZT (100 mg/4 hrs per day for a total daily dose of 600 mg/day) or placebo. At this point the subject who was symptom-free at study entry was no longer given AZT.

After the bone marrow transplant most subjects experienced worsening symptoms of HIV disease. Six subjects died and 2 developed AIDS. Interestingly, 1 subject experienced a complete remission of his symptoms of Kaposi's sarcoma (KS) lesions which continued for 2 years. Readers should bear in mind that KS is known to spontaneously regress, so whether or not the disappearance of KS in this particular case was due to the combination therapy is unknown. According to the study researchers, "no obvious differences in clinical, immunologic, or virological outcome could be discerned between patients assigned to AZT and those assigned to placebo". Some subjects who were assigned to the placebo arm managed to maintain their CD4+ count. According to the researchers, subjects in this study did not "appear to benefit" from the use of AZT. Despite these findings, the study physicians think utilizing this form of therapy earlier in the course of HIV disease could lead to better results. **Annals of Internal Medicine 1990;113:512-519.**

B. AZT: 600 mg for AIDS

Clinical trials of AZT in subjects with advanced ARC/AIDS have produced results indicating that the drug prolongs survival and reduces the number and severity of opportunistic infections, although subjects often experienced severe and sometimes life-threatening anemias. Another problem is that the most effective dose of AZT remains unknown. Some doctors have wondered whether or not 500 to 600 mg/day would be just as effective in subjects with advanced HIV disease. The everyday experiences of doctors suggest that this is likely and a clinical trial we are reporting on here confirms it.

This trial enrolled 524 HIV-infected subjects (average CD4+ count 87 cells) who had had a confirmed first time episode of PCP at least 2 weeks before study entry. Initially, subjects were not allowed use of preventative agents against PCP. The study protocol was later amended to allow PCP prophylaxis after a second episode of PCP. Eventually, use of aerosolized pentamidine was allowed in any subject.

Subjects were randomly assigned to one of two regimens: AZT 250 mg/4hrs (for a total daily dose of 1500 mg/day), or 200mg/4hrs (1200 mg/day) for 1 month followed by 100 mg/4hrs (600 mg/day). Equal numbers of subjects were assigned to both the high-dose and the low-dose arms of the trial. No statistically significant differences were noted between the 2 groups in terms of pre-study values (CD4+ counts etc). At least half the subjects were followed for up to 26 months. Thirty-seven subjects were lost to follow-up.

In total, 357, or 68% of the subjects in this trial died. Initially, there was a difference in survival rates between the two groups, with the low-dose group experiencing better survival than the high-dose group. These differences were statistically significant at 1, 1.5, and 2 years into the study. However, at the 26th month, the survival graphs indicate that the percentage of subjects surviving was more or less the same in both groups.

Four hundred and twenty-nine subjects experienced another opportunistic infection during this trial, virtually equal numbers from each arm of the study. The difference between the two groups in terms of "length of time to another opportunistic infection" was not statistically significant. Nor were the types of opportunistic infections different between the two groups.

Fifty-six percent of subjects (291) received PCP prophylaxis (131 subjects in the high-dose group and 160 in the low dose group). Interestingly, the time to development of a new bout of PCP did not differ significantly between the groups during the study period when PCP prophylaxis was forbidden. Analysis of the data from surviving subjects, at 6, 8, and 10 months, showed no difference in terms of survival between those subjects who received PCP prophylaxis and those who did not. This may be due to the relatively late use of PCP prophylaxis in the study.

The CD4+ count increased in both groups compared to pre-study levels, however, by the 3rd month of AZT administration the values had peaked and by the 6th month they had fallen below pre-study levels. They continued to fall throughout the rest of the trial. There was no statistically-significant difference between the two groups in terms of CD4+ cell decline, either in the number of cells or as a percentage of cells. In 205 subjects, HIV p24 antigen was detected before AZT administration, a result which suggested viral replication was taking place. Declines in p24 levels occurred at week 8 and generally persisted in these subjects for the duration of the study. Of the 146 subjects who were tested for HIV p24 antigen and found to be negative prior to the study, 9% later became p24 positive.

The major toxicities of AZT were more frequent in the high-dose group compared with the low dose group. Nearly all toxicity differences between the two arms were statistically significant. Headache was a more frequent complaint in the low-dose group. One hundred and thirty-four subjects (65 in the high-dose arm and 69 in the low-dose arm) received transfusions of red blood cells to counteract the anemia caused by AZT.

The physicians/investigators who conducted this trial concluded that low doses of AZT were just as effective as 1500 mg/day. It is interesting to note that while there were statistically significant differences in the survival rates between the 2 arms of the trial in the first and second years, after the second year there was no difference. It is unclear why there was an initial survival difference. During long-term follow up increasing numbers of subjects died, suggesting that the beneficial effects of AZT decrease over time. However, the decline in efficacy

may be due to the cumulative toxicity of the drug, the development of AZT-resistant strains of HIV, or other as yet unknown factors. Because HIV is a chronic viral infection, in which levels of viral replication increase with time, the use of the high dose induction period (1200 mg/day for 1 month) is not thought to be necessary as the lower dose seems just as effective. No differences were noted between the two dosage groups in terms of brain dysfunction/neurologic complications. But it would appear that the optimal dose of AZT for HIV-related neurologic disease, indeed for HIV disease itself, has yet to be found. **New England Journal of Medicine 1990;323:1009-1014.**

C. AZT:300 mg/day in ARC

In an effort to extend the usefulness of AZT, doctors are combining it with one or more anti-viral agents such as ddC, ddI, and acyclovir. French researchers have reported that acyclovir inhibits HIV replication in laboratory experiments, and preliminary reports from France suggest a short-term effect of acyclovir in treated subjects although this has not been confirmed by others.

In one study, investigators compared different doses of AZT with or without 4.8 g/day of acyclovir. (In **TreatmentUpdate 15** we reported on an oral summary of this information.) All subjects had ARC [defined as mild to severe constitutional disease--that is, night sweats, fatigue, progressive weight loss, CD4+ counts between 200 and 500 cells, and either detectable p24 antigen or HIV]. A total of 67 subjects were enrolled and 28 subjects assigned to low-dose AZT (300 mg/day), 24 to 600 mg/day, and 15 to high-dose (1500 mg/day).

Subjects receiving 300 mg or 600 mg experienced a greater easing of their symptoms of HIV disease compared to the group on 1500 mg. Weight gain of at least 2.3 kg was seen in 17 of 47 subjects with no significant difference between those on acyclovir and those not. Eight subjects developed AIDS and 5 experienced progressive declines in CD4+ cells. Differences in the rates of progression among the 3 dose groups were not statistically significant. Between weeks 12 and 36, the "number and severity of symptoms...did not change" in the groups.

Subjects in the 300 mg AZT group had a decrease in HIV p24 antigen equal in timing and magnitude to that seen in the other dosage groups. Of the 47 subjects who tested positive for HIV antigen, only 13 became negative at some time while on AZT. Simultaneous use of acyclovir did not increase the anti-HIV effect of AZT. During a 28-week period after the initial 12 weeks of the study, subjects had an increase of at least 14% in the level of HIV replication regardless of AZT dosage. During the trial, some of the subjects were switched to a different dose of AZT (people on 300 mg were switched to 1500 mg, those on 600 mg were switched to 1500 mg, and those on 1500 mg were switched to 300 mg). Increasing or decreasing the dose had no effect on HIV antigen levels during the 8-week crossover period. Toxicity was always worse in the higher dose groups compared to the 300 mg group.

In subjects treated for 12 weeks with 300 mg/day, the CD4+ count rose from 321 cells at study entry to 412 cells (statistically significant). Changes in the other two dose groups were not statistically significant. At week 36, the CD4+ count of the 300 mg group was 354 cells, but by week 48 it had declined to 249 cells. There were few subjects in the higher dose groups after week 24. Because of the potential clinical benefits seen at 300 mg/day (stabilization of CD4+ counts, increases in weight and decreased fatigue) the study investigators suggest that more trials using 200 to 300 mg/day AZT appear to be justified. **New England Journal of Medicine 190:323:1015-1021.**

II. INFECTION FIGHTERS

A. Steroids and PCP

Even though physicians are now better able to identify people at risk of developing PCP, and to stream them into prophylactic regimens, the incidence of PCP continues to increase. It is also thought that even if breakthroughs in the development of better anti-PCP agents occur, use of the new drugs would not likely change the lung damage resulting from PCP.

People dying with PCP have lungs which are inflamed and swollen with fluids. This results in reduced levels of oxygen reaching the blood. During attacks of PCP a type of white blood cell known as the neutrophil tends to accumulate in the lungs as a response to infection. Unfortunately, neutrophils produce various enzymes which attack and destroy lung tissue. Corticosteroids, commonly called steroids but not the same as the drugs used by some athletes, decrease the ability of neutrophils to move into sites of inflammation. Steroids also disrupt the inflammatory process in several ways. Thus, it was thought that steroids could be used in early PCP to decrease the severity of the disease. Small studies conducted over the past 3 to 4 years gave incomplete information about steroid use and PCP. Because steroids do cause immune suppression, some clinicians were hesitant to use them because they thought that there would be an increase in the development of life-threatening opportunistic infections, the spread of Kaposi's sarcoma would increase, and/or HIV replication would be greatly enhanced.

Five randomized clinical trials have recently been conducted, and although one of them was done in Canada, most investigators have focused on the larger American trial (called the CCTG) because it had the largest number of subjects (see B on page 4). The analysis used data on 251 subjects in the CCTG who had AIDS and PCP and who were receiving standard treatment--Bactrim/Septra, intravenous pentamidine at 3 or 4 mg/kg of body weight per day or oral dapsone (100 mg/day) with 15 to 20 mg/kg of trimethoprim per day. The subjects were randomly assigned to either steroids or no additional therapy. Those assigned to steroids received prednisone 40 mg twice/

day for 5 days, then 20 mg/day for 5 days. This was reduced to 20 mg/day for the rest of the time they were being given anti-PCP drugs. Subjects who could not take oral prednisone were administered intravenous methylprednisolone at 75% of the oral dose.

Sixteen percent, or 41 subjects of the 251 died during attacks of PCP; 40 of these deaths were due to PCP. Seven other subjects had to be put on mechanical respirators, and another 7 subjects had such a low amount of oxygen in their arteries that they were considered to have respiratory failure. So respiratory failure occurred in 55 subjects, mostly within the first 4 days of their being put into the trial. The cumulative risk of respiratory failure on the 21st day was greater in the standard treatment group than in the steroid group, and this was statistically significant, i.e. highly unlikely a result of chance. More subjects given steroids were better able to tolerate their anti-PCP regimens for a longer period of time compared to those subjects not receiving steroids. In the steroid group, it was noticed that after day 84 in the study there was a higher incidence of reactivated herpes virus infection in 32 of 123 subjects compared with 19 of 128 subjects in the standard treatment arm. There was also a tendency toward increased incidence of oral thrush in the steroid group. The incidence of other HIV-related opportunistic infections was not different between the two groups. These researchers found that the use of steroids in early PCP infection cut the risk of death by nearly 50%. Survival benefits were sustained for nearly 84 days. **New England Journal of Medicine** 1990;323:1451-1457.

B. *Consensus on Steroid use*

The National Institutes of Health/University of California expert panel for steroids as adjunctive therapy for PCP made several recommendations after reviewing the data from the 5 trials, although more weight was given to the CCTG study because of its size:

· adults or children older than 13 years with proven or presumed HIV-related PCP should be given steroid therapy if they have moderate or severe pulmonary dysfunction (pulmonary dysfunction was defined by measurement of oxygen in the arteries). Patients with mild disease could benefit from steroid therapy but this has not been proven.

· steroid therapy should be initiated at the same time as anti-PCP therapy (i.e. as early as possible). No benefit has been found for patients given steroids 72 hours after anti-PCP therapy has began.

· because the dose regimen used in the CCTG study has been tested in more subjects, this dose and schedule of steroids is recommended although it is not known if this is the best regimen.

The panel said that it seemed reasonable to consider use of steroids in pregnant HIV+ positive women who have PCP. **New England Journal of Medicine** 1990;323:1500-1504.

C. *Fluconazole and fungal infections*

In North America, infection by the fungus Cryptococcus neoformans (C. neoformans) is the most common life-threatening fungal disease among people with HIV disease. This fungus usually causes meningitis. In the US approximately 10% of patients with AIDS develop cryptococcal meningitis and as many as 60% of these people die as a result. The standard treatment is amphotericin-B (AmB) with or without flucytosine and survival rates can initially be as high as 80%. However, while AmB (with or without flucytosine) may prevent death, its use is associated with serious kidney and bone marrow toxicity. Patients often experience side effects with each dose of AmB. Thus, effective anti-fungal agents which can improve the quality of life experienced by HIV-infected patients are urgently needed. Several new investigational anti-fungal agents are undergoing testing in Canada, the US, and the European Community. These agents include itraconazole, fluconazole, and SCH 39304. In the fall of 1990, fluconazole, made by Pfizer/Roerig, and sold under the brand name Diflucan, was licensed for use in Canada.

Several articles in this issue of **TreatmentUpdate** focus on clinical trials of fluconazole to treat meningitis and candida infections. As yet, the optimal regimen for some of these conditions is uncertain, but clinicians may wish to use results from these trials as a guide. Fluconazole is well absorbed when given orally, taken with or without food or anti-ulcer drugs such as cimetidine (Tagamet). Fluconazole remains in the blood for a prolonged period, which means the drug only has to be taken once a day. Fluconazole works in part by inhibiting an essential fungal enzyme without affecting the equivalent enzyme in humans. Fluconazole does interact with drugs such as phenytoin, cyclosporin, and warfarin. **Drugs** 1990;39(6):877-916.

D. *Fluconazole versus Amphotericin B for cryptococcal meningitis*

In this trial, 26 subjects were enrolled if they had evidence of cryptococcal meningitis, defined as headache and a positive test for C. neoformans from blood or CSF. (CSF is cerebrospinal fluid; the fluid that surrounds the brain and spinal cord). Subjects were randomly assigned to fluconazole or amphotericin B (AmB). Fluconazole was given orally 400 mg/day for 10 weeks. Those subjects who had AIDS were then given 200 mg/day as a maintenance dose after the 10-week period. If urine samples were positive for the fungus during the maintenance phase, the dose was increased to 400 mg/day. AmB was administered intravenously in a dose of 0.7 mg/kg per day in the first week and then reduced to 3 times per week for the next 9 weeks. All subjects on AmB were given flucytosine orally 150 mg/kg per day in four divided doses for the first 10 weeks. Once

diagnosed, subjects were followed for 62 weeks or until death, failure of the study drug, or withdrawal from the trial.

Within the first 10 weeks, there were 4 deaths in the 14 subjects assigned to the fluconazole group, compared with no deaths in the AmB group (not statistically significant). In 2 of these subjects, death was caused by cryptococcal meningitis, one death was caused by bacterial pneumonia, and one death was from respiratory failure. Three other subjects were withdrawn from the study as they were found to have the fungus in their CSF. Two other subjects, although completing the 10-week course of high-dose fluconazole, were also found to have fungus in their CSF at week 10. Despite continuing on 400 mg/day of fluconazole, they did not do well on the drug. By week 10, fluconazole had failed in 8 of 14 subjects (57%). This is in contrast to the results from the 6 subjects assigned to AmB - flucytosine, who survived the 10-week period and had negative blood and CSF tests for the fungus, although 2 of them had positive urine tests for C. neoformans. The difference in outcome between the two groups was statistically significant.

Two of 4 subjects in the fluconazole arm who were considered cured at week 10 relapsed during the follow-up period. Subjects receiving fluconazole took longer to test negative for the fungus in their CSF compared to those on AmB (statistically significant). The more frequent and serious side effects all occurred in the AmB group.

Readers should note that this trial used only a small number of subjects. Even though subjects were randomly selected into the two trial arms, the average CD4+ cell count of those subjects in the fluconazole arm was 44 cells and in the AmB arm 97 cells (statistically significant). This may have accounted for some differences in outcome between the two groups, although the subjects were matched for disease severity. This trial did not demonstrate a superiority of fluconazole over AmB-flucytosine. In the future, higher doses of fluconazole may allow it to be used as a primary treatment. **Annals of Internal Medicine 1990;113:183-187.**

Dr. Robert Larsen (University of Southern California Medical School), who was one of the investigators in this trial suggests that for the treatment of cryptococcal meningitis a 2 to 4 week course of AmB-flucytosine should be administered, followed by maintenance therapy with fluconazole 200 mg/day. He suggests that primary therapy with fluconazole should be reserved for patients with "mild clinical symptoms" and low CSF levels of the fungus. **Journal of Infectious Diseases 1990;162:727-730.**

E. Fungal infections, HIV, and Women

Initially, research on the clinical symptoms of HIV infection in North America focused on males, but as the disease began to appear in different communities more and more women became affected. In the US and France, HIV infected women are reported to experience faster disease progression than men. There are several factors which may account for this. First of all, many of the women in the first wave of HIV infection were injection drug users and/or sex trade workers, people not generally incorporated into the health care system. Women were not usually seen as being "at risk" for AIDS, meaning their initial symptoms were often overlooked. Thus, women are not diagnosed with HIV until much later in the course of their disease, missing the opportunity for early intervention. The majority of HIV-infected women are generally of lower socio-economic status and this often hinders their getting access to good health care and treatments. But these reasons may only be part of the explanation for possible accelerated disease progression.

The interaction between HIV and the immune system may result in a different manifestation of symptoms in women compared to men. For example, although thrush (candida) is a fairly common opportunistic infection seen among HIV-infected patients, candida infections appear to affect more women than men.

The male-female differences may be hormonal and ultimately genetic. Part of HIV resembles the hormone estrogen, high levels of which are found in women. Some scientists think that when antibodies are produced against HIV they "cross-react" and attack parts of the body which resemble HIV, in this case estrogen. This may, in part, cause a more serious disruption of the body's functioning in women than in men. For more details of this issue and Tamoxifen, a potential therapy, please see **TreatmentUpdate 12.**

To examine and understand the different effects HIV infection can have in women, researchers at Brown University, Rhode Island, enrolled 66 HIV-infected women for a 3-year study. Subjects were grouped according to their CD4+ cell counts. All subjects with CD4+ counts below 200 cells were given a total daily dose of 1000 mg AZT. This was reduced to 500 mg/day in 3 subjects because of worsening side effects (anemia and muscle inflammation). Later, all subjects with CD4+ counts below 200 cells were given PCP prophylaxis with aerosolized pentamidine 300 mg/month or either Bactrim or Septra (brand names of the drug combination trimethoprim/sulphamethoxazole) 800/240 mg/day.

For treatment of vaginal candida infections, subjects were given nystatin 100 mg vaginal suppositories placed once nightly for 2 weeks or clotrimazole 100 mg vaginal tablets for 6 days. In the case of oral candida infections, nystatin lozenges 500,000 units four times daily for 1 week or clotrimazole lozenges 10 mg 4 times per day for 1 week were used. If the candida lesions failed to resolve by the end of the week, ketaconazole was given as a single 200 mg dose for 7 days. Should the candida have penetrated into the throat and deeper into the body, then clotrimazole lozenges 10 mg 4 times daily and oral ketaconazole 400 mg/day for 10 to 14 days were administered.

The researchers found that 33 women noticed either new or

more frequent vaginal candida infections before any other signs/symptoms of a suppressed immune system. All of the subjects who experienced more frequent vaginal candida infections had at least 4 such infections per year. It is interesting that out of this group of 33 women, 17 noticed new or more frequent vaginal candida infections for between 6 to 36 months before their previous doctors (outside the study) even considered a diagnosis of HIV infection. Twenty-five of the 66 women experienced severe oral candida infections. Of these 25 women, only 2 had not previously experienced new or more severe vaginal candida infections. Nor had the presentation of new or more severe vaginal candida infections ever led to the diagnosis of HIV disease by the pre-study doctors. In only 7 cases did oral candida infections lead pre-study physicians to test for HIV infection.

As measured by CD4+ cell counts and CD4/CD8 ratios, the level of immune suppression closely correlated with "the location and severity of candida infections" according to the study investigators. For instance, symptom-free subjects tended to have CD4+ counts around 700 cells. Subjects with candida infections restricted to the vaginal area tended to have approximately 500 CD4+ cells and a CD4/CD8 ratio of 0.9. Subjects with oral candida infections had an average of approximately 230 CD4+ cells and a ratio of 0.29. Subjects with candida in the throat and down the tube connecting the mouth with the stomach (esophageal candidiasis) had an average of 30 CD4+ cells and a CD4/CD8 ratio of 0.07. These differences were statistically significant.

A breakdown of the figures showed that oral thrush was found in 21/26 subjects with 300 CD4+ cells or less. All subjects with esophageal candidiasis had fewer than 100 CD4+ cells. Although the number of subjects in this study is relatively small, perhaps the close correlation between CD4+ cell counts and a different presentation of HIV disease could help indicate those women potentially at risk for candida infections. As the immune deficiency in these subjects worsened, the number of infection sites increased. With increased immune suppression, infections often recurred and became more difficult to treat. Perhaps the CD4+ ranges found in this study could be used as guidelines for prophylaxis of candida infections in women. In this regard, fluconazole which, unlike ketaconazole, does not interfere with hormonal synthesis and is unlikely to cause liver damage might become a candidate for an ideal low toxic, prophylactic, anti-candida agent. The prevention of esophageal candidiasis is seen to be of greater concern as this very painful condition often results in weight loss. Because oral candida sometimes presages the development of esophageal candida, the study doctors recommend treatment of oral candida in patients having fewer than 100 CD4+ cells with ketaconazole or fluconazole combined with local therapy for the mouth. **American Journal of Medicine** 1990;89:142-146.

F. Fluconazole vs. clotrimazole for oral fungal infections

Fungal infections are a major problem for people with HIV infection, oral infections, particularly candida, being a recurrent complication. Oral candida infections can also spread beyond the mouth into the throat and stomach depending on the level of immune suppression. The standard drugs for oral candida infection are ketaconazole and clotrimazole. Ketaconazole may cause problems for some patients as it can cause liver toxicity. Clotrimazole must be taken several times daily and some patients may find this inconvenient. The newly-licensed anti-fungal agent, fluconazole, may offer several advantages over traditional anti-fungal agents because of its low toxicity and the long time it remains in the body.

Researchers at Ohio State University randomly assigned 39 subjects with HIV-related candida to 100 mg/day fluconazole (1 capsule) or 10 mg clotrimazole lozenge, 5 times per day. Both protocols were for 14 days. Both groups were similar in terms of immune suppression, previous anti-fungal therapy, AZT usage and severity of candida. Subjects were evaluated on the 3rd, 7th and 14th days of the study. Eventually 17 subjects in the fluconazole arm and 19 in the clotrimazole arm were evaluated according to the protocol. At the end of the 2-week period, fluconazole was found to be the more effective and resulted in statistically significant greater disappearance of candida than clotrimazole. Follow-up after the trial showed that 2 weeks later 87% of the subjects in the fluconazole arm had not relapsed compared with 29% in the clotrimazole group (statistically significant). There were no serious side effects seen in either arm of the trial, although 3 subjects from each group reported nausea. Compliance of subjects with the protocol in the clotrimazole arm was poor. Many of these subjects did not take all of their doses for various reasons, including "forgetfulness, inconvenience of taking multiple doses and altered taste sensations." Compliance in the fluconazole arm appeared to be excellent. The optimal dose, length of treatment and ultimately, prophylaxis of candida using fluconazole remain unknown. **Antimicrobial Agents and Chemotherapy.** 1990;34(11):2267-2268.

G. Fluconazole: maintenance therapy for oral candida

HIV-infected patients who are successfully treated for oral candida infections (thrush) eventually experience relapses because of their continuous immune suppression. Although effective treatment doses of fluconazole have been found for this condition, the best or optimal dose for maintenance has not yet been determined. Italian researchers have recently conducted a clinical trial to determine the optimal prophylactic regimen for oral candida with fluconazole.

The trial enrolled 60 HIV-infected subjects all of whom were

being given AZT. The subjects were classified into 2 groups of 30 subjects based on their stage of HIV disease. The first group were subjects experiencing their initial bout of oral candida while the second group already had candida infections in the past and were classified as having AIDS. All subjects were considered cured of their oral candida infections after getting 100 mg/day fluconazole for 2 weeks. After this treatment phase, all subjects were randomly assigned to 1 of 3 suppressive dose-schedules of fluconazole: 50 mg/day, or 50 mg every other day, or 150 mg in a single one-time dose. The subjects were assessed weekly for a 3-month period.

The researchers found that the optimal dose of fluconazole depended on the stage of HIV disease. In subjects with less-advanced HIV disease and in their first episode of oral candidiasis, 50 mg/day or every other day resulted in suppression of the fungus. By the first month of prophylaxis with 150 mg/day, 80% of subjects with less advanced disease did not relapse. In contrast, subjects with advanced HIV disease, and who had had prior candidal infections, responded best to 50 mg/day fluconazole as prophylaxis. **AIDS 1990;4(10):1033-1034.**

H. Fluconazole: once per week as prophylaxis for candida

In using fluconazole, different doses have been tested against candida infections. At least 3 properties of fluconazole may give it an advantage over traditional anti-fungal agents. The first is the prolonged time fluconazole stays in the blood. This allows for less frequent doses and likely greater patient compliance. The second is its relatively low toxicity. The third property is that the absorbtion of fluconazole is not affected by low levels of stomach acid which have been reported in patients with AIDS.

Twenty-four subjects with AIDS/ARC who had oral candida were put into a 2-part study. In the first part all subjects were given fluconazole 50 mg/day orally for 2 to 4 weeks, depending on how long it took to cure the fungal infection. Those subjects who were "clinically cured" and who could tolerate the drug were then put into the second phase of the study. Here subjects were randomly assigned to either fluconazole 150 mg/week or placebo for up to 6 months.

At the end of the first part of the study, 21 subjects could be assessed. Of these 21, 17 or 81% were clinically cured, 2 improved and 2 subjects did not get better. Laboratory analysis indicated that 53% of subjects had no fungus and 33% had relatively low fungal counts. Of the 17 subjects clinically cured, 14 were entered into the second phase of the study. Four of 5 subjects assigned to placebo relapsed within 3 weeks compared to 7 of 9 subjects on fluconazole, who remained symptom-free for 6 months. The doctors concluded that fluconazole (150 mg/week) was effective as prophylaxis against oral candida. **Journal of Infection 1990;21:55-60.**

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CDC AIDS Weekly/DAITS
P. O. Box 5528
Atlanta, GA
US, 30307

Critical Path AIDS Project
2062 Lombard Street
Philadelphia, PA
US, 19146

Info-Traitements
Comité des personnes atteintes du VIH du Québec
3600, avenue de l'Hôtel-de-Ville
Montréal, Québec H2X 3B6

Notes from the Underground
PWA Health Group
31 West 26th Street, 4th Floor
New York, New York
US, 10010

Project Inform
347 Dolores Street, Suite 301
San Francisco, CA
US, 94110

PWA Coalition Newsline
PWA Coalition, Inc.
31 West 26th Street
New York, NY
US, 10010

PWAlive
P.O. Box 10034
Minneapolis, MN
US, 55458-3034

Sida 91
ARCAT-SIDA--CIVIS
57, rue Saint-Louis-en-l'Isle
75004 Paris, France

Test Positive Aware
1340 West Irving Park Rd.,
Box 259
Chicago, IL
US, 60613

Treatment Issues
Gay Men's Health Crisis
129 West 20th Street
New York, New York
US, 10011

Washington HIV News
Whitman Walker Clinic
1407 "S" Street NW
Washington, DC
US, 20009