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The Spectrum of Access

By Bob Huff

The accessibility of quality HIV care, with and without antiretroviral therapy (ART), varies widely across the globe. As drug prices have fallen in resource-poor areas, dozens of small pilot programs are now proving that that therapy is effective, feasible and subject to problems familiar in the rich countries. Meanwhile, in the U.S., several hundred thousand people are estimated to have HIV and not know it or want to deal with it. Many of these people have limited access to care and may finally enter the system only after symptoms develop. Barriers to care, such as stigma, lack of knowledge, and lack of money, cut across hemispheres and time zones.

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At the International AIDS Society's *2nd IAS Conference on Pathogenesis and Treatment*, held in Paris this summer, 17 abstracts reported on the experience of treating over 2,400 patients with ARV in 11 countries in Sub-Saharan Africa. Additional reports of successful treatment programs in Latin America and Asia peppered the conference abstract book. This is up from the handful of papers presented at 2002's much larger International AIDS Conference in Barcelona. Clearly a lot has been accomplished in the intervening 12 months, but of the estimated 300,000 people receiving ART in the developing world, half are in Brazil and fewer than 30,000 are thought to be on treatment in Africa. With at least 4 million people in need of treatment in that region alone, the often-stated goal of treating 3 million worldwide by 2005 seems to be slipping out of reach.

Not so, says Paulo Teixeira, the architect of Brazil's successful ART program who has just taken over as the new chief of HIV/AIDS at the World Health Organization (WHO), the body that set the target at 3 million. "My belief is that it is absolutely feasible, despite the magnitude of the task," Teixeira told Reuters. The daunting reality is that achieving WHO's goal means treating 100,000 new people every month from now until the end of 2005. Yet, despite the slow pace to date, there are signs that treatment programs are poised to accelerate as costs decline and funding increases. Here are a few selected reports from the Paris conference that sketch the outlines of what is possible and where problems persist.

Generally, the reports of pilot treatment programs tell stories of improved CD4 counts, fewer deaths and fair adherence. At the 2002 International AIDS Conference in Barcelona, the Heineken brewing company reported that providing ART to employees and spouses was affordable, if not strictly justified on a cost/benefit basis. A year later the company has presented an analysis of changing costs in AIDS-associated medical expenses, absenteeism and death after the

institution of their treatment program at a brewery in Burundi. They now find that the benefits do justify the costs.

Thirty-one persons have started treatment since the Heineken program began in September 2001. Hospitalization for opportunistic infections declined from an average of 20 per year (1997-2000) to 10 in 2001 to only 6 in 2002; deaths declined from 11 to 2 to 1 during the same periods. Time off due to illness also declined. Meanwhile, voluntary HIV testing increased from an average of 13 per year (1997-2000) to 123 in 2001 and 140 in 2002. Overall costs were 58,188 euros ($66,000), including 47,207 for drugs, 7,927 for travel and training, and 3,154 for diagnostic tests. Overall, medical expenses increased by only 5,233 euros between 2001 and 2002, suggesting that the costs of treatment were almost entirely recovered by savings in hospitalizations and other losses. (Gahimbaza)

Reports of pilot treatment programs tell stories of improved CD4 counts, fewer deaths and fair adherence.

But government involvement will be essential if treatment programs hope to reach the huge numbers of people without jobs or family income. In Cameroon, with nearly 1 million infected, the government is now providing ART for 7,000 people. Médecins Sans Frontières (MSF), the international medical organization, reported on a collaborative pilot project in a military hospital in Yaounde that has treated 117 people since 2001. With effective therapy and good monitoring, and despite advanced disease in many patients, the authors observed outcomes comparable to those obtained in rich countries. (A complete listing of worldwide MSF ART programs is on page 7). (Mougnutou)

A researcher at a care center in Mumbai, India reported on the struggle to provide antiretroviral drugs to people who need them when few can afford them. Simply following the "Hit Early, Hit Hard" paradigm, he says, would result in bankruptcy. To accommodate the reality of limited resources, the author studied ways to modify treatment protocols, dosages, combinations and follow-up to increase affordability, adherence and survival. During the period from 1995 to 2002, 4100 people with HIV/AIDS were managed by the clinic, and although 943 were eligible to receive ART by local standards, only 570 could afford generic drugs. Most who began drug therapy took an NNRTI and two NRTIs; the rest were given supportive therapy and treatment for symptoms and opportunistic infections (OI). "CD4 count, clinical status, incidence of OI were studied, but viral load was dispensed with." Further cost-saving measures included extending the follow-up interval by an average of 3.7 months and reducing dosages by 25–50 percent according to body weight. The author observed no difference in outcomes between patients treated on this austerity plan (about $30 per month) and those who received a PI-based regimen. In this clinic, lowered drug prices, reduced follow-up costs and simplified patient care protocols resulted in improved access to ARV. (Gilada)

While costs may be managed, and affordable ART delivered where there are institutional or corporate resources, the situation when individuals are on their own is not as bright. One study looked at the economic status of those who able to receive ART in Cote d'Ivoire. Not surprisingly, higher personal income was associated with greater access to treatment. Physicians conducted interviews with 173 patients receiving ART in five outpatient clinics in Abidjan during a four-day period in November 2002. The patients had a median age of 34 years and had been attending the clinic for a median 9 months; over half were women (59%). Of those surveyed, 23 percent had no personal income; 37 percent received less than $76 per month; 26 percent received between $77 and $288 per month; and 14 percent had incomes over $288 per month. Of those with incomes, 61 percent were employed, while the rest reported receiving an allowance from relatives. The 31 patients (18%) taking ARV had a significantly higher monthly income than those not being treated (>$76 monthly: 68% vs. 48%, P=0.05). Only 2 patients received ARV for free. The rest had to pay for all or part of their medication, with 46 percent paying up to $45 per month; 41 percent paying between $46 and $107 per month; and 14 percent paying more than $107 per month. Relatives contributed to ARV costs for 45 percent of those surveyed. (Sauvageot)

But there are barriers to receiving care beyond affordability, among them lack of empowerment, lack of knowledge, social stigma and fear of disclosure. HIV-positive women in Lusaka were asked via questionnaire about how accessible they perceived HIV therapy to be for them. Seventy-one percent had heard about antiretroviral therapy but did not know exactly what it was; and 14 percent had purchased drugs—usually Indian generics—and were taking them. The expense of medications was the most common reason given for not buying ARV (85%), with 62 percent saying they would rather spend the money on household expenses. About a quarter of the women said they had not disclosed their HIV status to their partners for fear of being blamed for bringing the disease into the household. Two-thirds of the women said they were dependent on their spouses for income and 72 percent said the felt the traditional role of

women in society was a factor in making it difficult of them to obtain access to treatment. (Shumba)

Provider knowledge may be another barrier to effective care, even where drugs are available. India is a huge, sprawling country with many cultural traditions that include a range of practitioners of different medical systems such as ayurveda, homeopathy, Unani, naturopathy, and modern Western medicine. With over 4 million HIV-infected persons in India, many of these doctors are increasingly called upon to practice HIV medicine. A researcher from a government hospital conducted a survey among 300 family physicians and 60 consultants from both high- and low-HIV prevalence regions, concerning their level of knowledge about providing antiretroviral therapy. About three-quarters of the participants were modern medical practitioners, 20 percent ayurvedic physicians and 8 percent homeopaths. In the low-prevalence states, 99 percent had no knowledge of the parameters for initiating HIV therapy and 70 percent were unaware of diagnostic tests. Although 70 percent had heard of AZT, there was no knowledge of adverse drug reactions, patient monitoring or pre-therapy counseling.

In high-prevalence areas the results were somewhat better, though still abysmal. Although 80 percent of doctors were able to write the names of two or three drugs, the majority were unaware of parameters for starting therapy. And although most had heard of the CD4 count as an HIV test, few understood the significance of CD4 results. The author notes that physicians in India often prescribe antiretroviral therapy "to pacify the patients without proper protocol or scientific basis," thereby risking the development of drug resistance. Currently, there is no laboratory in India to detect or monitor emerging drug resistance. (Deshpande)

And lest we think that drug access disparities only occur in faraway places, the San Francisco Department of Health reported on the uptake of a new generation antiretroviral, tenofovir, in a setting where free treatment is guaranteed to all who need it. Using citywide surveillance data, the authors conducted a retrospective review of 6,898 people living with AIDS during the period of 1999 to 2002 and identified 403 (5.8%) people who had ever received tenofovir. About a quarter of these had received the drug prior to approval, which suggests participation in a clinical trial or expanded access program. Those never receiving tenofovir were more likely to be non-white, injection drug users, homeless and have no insurance. Individuals from upper-income areas were more likely to have had access to tenofovir than those from lower-income areas. The authors concluded that their "findings highlight a disquieting inequity of the American healthcare system that cannot be corrected simply by making AIDS treatment affordable or free." (Chen)

Finally, as a counter example to the situation in India and elsewhere, one can look to the description of a model, comprehensive primary care HIV clinic provided by the Community Health Network of Rochester, NY to grasp what state-of-the-art care can entail. Started over 13 years ago, the federal, state and locally funded clinic serves about 800 patients with five HIV specialist physicians, six social workers and two aides, five clinical nurses, a research nurse, a care coordinator, a dietician, and a treatment adherence counselor. They also have available a psychiatrist, a therapist, a gynecologist, an optician and a part-time pharmacist. (Perhaps some of these experts would volunteer to spend next winter teaching in sunny Lusaka. Contact the International HIV Clinician's Exchange Program: www.iceha.org) Also important to note is the patient-centered approach to care that the Rochester clinic supports with services such as issue-driven patient group meetings, a patient care-committee and a patient library. (Corales)

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Access to care depends on many factors ranging from income to empowerment and from price to patient and provider knowledge. As drugs become more available, access to information and commitment to equitable availability are emerging as crucial factors for obtaining good outcomes from HIV care, wherever it is provided.

All abstracts are from The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 13-16 July, 2003 and are published in Antiviral Therapy, Volume 8, Supplement 1, 2003.

Gahimbaza L. Costs and benefits of the antiretroviral therapy in the private sector: the experience of Brarudi, Burundi. Abstract 668.

Mougnutou R. Evaluation of a HAART pilot study in Yaounde, Cameroon: 24 months follow-up. Abstract 686.

Gilada I, Comprehensive cost-efficient model of HIV care from India most suitable for resource-poor settings. Abstract 639.

Sauvageot D. Access to antiretroviral (ARV) drugs in five outpatient clinics in Abidjan, Cote d'Ivoire. Abstract 642.

Shumba CD, Kwalombota M, Accessibility of HIV therapy to women living with HIV/AIDS in Lusaka, Zambia. The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, 2003. Abstract 772

Deshpande A. Is India poised for HAART? Abstract 569.

Chen SY. Disparities in community uptake of tenofovir in San Francisco, California. Abstract 643.

Corales RB. The comprehensive HIV primary care clinic model: one stop shop. Abstract 648.

ARV in Sub-Saharan Africa: 17 Reports

By Bob Huff

The descriptions below relate experiences treating adults with antiretroviral (ARV) medicines in Sub-Saharan Africa and were presented at the 2nd IAS Conference on Pathogenesis and Treatment, Paris.

Seventeen abstracts described clinical outcomes, adherence, and costs of treating 2442 adult patients in 10 African countries. In addition to these, a number of other papers discussed treatment experiences in Asia and Latin America. Most studies were retrospective chart reviews; no randomized treatment trials were reported. Numbers refer to published abstracts; full references at end of article.

Seventeen abstracts at IAS described clinical outcomes, adherence, and costs of treating 2442 adult patients in 10 African countries.

Abstract 112—A treatment program in two hospitals and 10 clinics in the Chiradzulu district, Malawi run by the Ministry of Health and Médecins Sans Frontières (MSF) reported on treating 464 adults since August 2001 with an NNRTI-based regimen. From a baseline of 109, median CD4 cell counts/mm^3 increased by 142 at 6 months and by 133 at 12 months. During the period 64 patients died, 15 were lost to follow-up, 4 were non-compliant and 9 went off treatment due to toxicity or OI treatment. At time of last visit, 93% reported taking at least 80% of their prescribed therapy.

Abstract 629—The Nigerian national treatment program reported on the 12, 24 and 36-week experience of 74 patients receiving generic nevirapine, lamivudine and stavudine at three centers during March to December, 2002. Women comprised 35% of the patients. The mean CD4 cell count/mm^3 increased from 214 at baseline to 298 at week 12, and 348 at week 24. Median weight increased from 51.7 kg at baseline to 55.7 kg at week 12, 63.6 kg at week 24, and 62.7 kg at week 36. At baseline, 20.8% had TB and one patient died from TB within one week of starting treatment. The most common adverse events were peripheral neuropathy and rash. Cost was identified as a barrier to regular follow-up.

Abstract 636—The Benin national treatment program conducted a chart review to assess characteristics of 448 patients who were receiving ART during a period between December 2001 and February 2003. A PI-containing regimen (indinavir or nelfinavir) was prescribed for 55% and an NNRTI regimen (efavirenz) for 45%. Women comprised 47% of those reviewed. Most patients were infected with HIV-1 (98.4%) with 0.6% having HIV-2 and 1% having both. BMI was less than 18.5 for 35%. The most frequent OIs were wasting, 86%; oral candidiasis, 49%; and dermatitis, 46%. TB was reported in 4% of patients. The delay from diagnosis to treatment was less than 6 months in 56%; between 6 and 12 months in 14%; from 1 to 2 years in 18% and over 2 years in 12%.

Abstract 668—A company-sponsored treatment program for employees of the Heineken brewery in Braudi, Burundi reported the costs and benefits after 18 months experience treating 31 persons. Hospitalizations declined from an average of 20 per year prior to ART to 10 in 2001 and 6 in 2002. Deaths declined from 11 prior to ART to 2 in 2001 to 1 in 2002. Program costs were almost completely recovered by savings in medical care.

Abstract 686—A treatment project at a military hospital in Yaounde, Cameroon reported on the 24-month experience of a pilot program treating 117 persons with a nevirapine-based regimen. Nelfinavir was substituted in 5 cases and efavirenz in 4 cases. The median length of follow-up was 10.5 months. Women comprised 69% of the patients. The median CD4 cell count/mm^3 increased from 151 at baseline to 250 at 12 months. Viral load became undetectable in 85.2% of cases. The median BMI increased from 23.2 to 25.2. Eleven patients changed treatment due to adverse events and 1 due to nevirapine resistance. Nine patients died, with a median time to death of 9 months.

Abstract 690—A clinical research center in Kampala, Uganda assessed adherence in 28 persons starting treatment with Triomune (generic NVP/3TC/D4T) using multiple techniques including self-report, visual analog scale (VAS), MEMS and unannounced pill counts. Patients were followed for 1 to 6 months (mean 3.1). Results from the various techniques were well correlated with each other; mean adherence ranged from 87% to 91%.

Abstract 693—A clinical research center in Kampala, Uganda reported on therapeutic responses to a regimen containing efavirenz, zidovudine and lamivudine in 11 patients with non-B subtype HIV-1 (A, D), many with baseline viral loads above 100,000 copies/mL. At 12 weeks, 89% were below detectable levels of HIV RNA; at 31 weeks, 71% were undetectable. At 31 weeks the median CD4 count had increased by 183 cells/mm^3.

Abstract 697—A clinical research center in Lagos, Nigeria reported on 24-week experience treating 226 persons with generic nevirapine, lamivudine and stavudine. Median viral load decreased from 4.7 log copies/mL at baseline to 2.7 at week 24. Median CD4 count increased by 170 cells/mm^3 and median BMI increased from 21.5 to 23.8. Adherence was reported as "good" in 74% of patients.

Abstract 700—A care center in Pointe-Noire, Congo conducted a medical chart review of 49 patients who had received ART during a period from April 2002 to January 2003. The majority (65%) received a PI-containing regimen and 35% received an NNRTI-regimen. The mean CD4 cell count/mm^3 rose from 97 to 215 at six months; the proportion of patients with CD4 below 50 fell from 45% to 4%. Mean patient weight increased by 4.5 kg. Seven patients had side effects that required a change in treatment. Side effects included disabling peripheral neuropathy and acute pancreatitis.

Abstract 701—Three primary care facilities in the South African township of Khayelitsha run by MSF and the provincial government reported on clinical outcomes for 288 adults who have received ART since May 2001. Most patients started treatment with CD4 counts below 50 cells/mm^3. An 18-month survival estimate was 85%. Those starting treatment with CD4 under 15 cells/mm^3 had poorer survival outcomes.

Abstracts 705, 1118—A hospital pharmacy in Dakar, Senegal assessed adherence and causes for ART interruption in 158 adult patients over a three-year period. NNRTI-based regimens comprised 51% of prescriptions; PI-based regimens, 43%; dual therapy, 4%. Ten percent of participants died and 2% withdrew. High adherence was defined as mean monthly adherence of 95% or greater. The proportion of highly adherent patients decreased as the duration of treatment exceeded 12 months, as the monthly cost of treatment exceeded 15 euros ($17), or with the use of PI-containing regimens in patients with advanced disease.

Abstract 759—A hospital in Maun, Botswana evaluated predictors of adherence with a review of 176 randomly selected patient records

Access to Care through Research: After the love is gone

In 1988, New York ACT UP treatment activist Jim Eigo argued, "For the person with no other options, a research study means access to healthcare." This was a time in the U.S. when the only way to get experimental treatments to prevent certain deadly opportunistic infections was by joining a clinical trial. The activist critique of the coercive nature of such research led to a revolution in drug development and clinical trial practice, including the assurance of active controls and the innovation of expanded access programs. The availability of marketed and experimental treatments has improved considerably in the U.S. since then, at least for those who participate in the healthcare system. But in many resource-poor parts of the world, a research project may be the only way to access lifesaving HIV healthcare — with or without sophisticated antiretroviral medications.

One of the central ethical questions about performing research in resource-limited settings is what happens once the research is complete, recognizing that the influx of money, skills and opportunities that come along with Western-supported research can profoundly affect quality of life and expectations in a place with few services. It's generally agreed that research projects should strive to leave behind improved capacity to continue the benefits of research-associated services, but the reality of what happens when the clinic closes is not often reported.

A study recently detailed what happened to participants when a long-term research project that provided primary health care for participants in Lusaka, Zambia closed for seven months. During the study, beginning in 1995 and continuing with one break until 2002, serodiscordant couples were enrolled and followed at three month intervals. The study has previously reported that counseling and testing reduces the incidence of HIV transmission in discordant couples by two-thirds. Couples who entered the study were given primary healthcare at the research clinic, which was lost when the study was interrupted.

In the report about the seven-month closing, death rates and HIV and syphilis incidence were compared before, during and after the closing during the period between December 1988 and June 1999. After the study reopened, 531 participants (about 75% of those enrolled when the study was stopped) returned and answered questions about their experience during the closing. Most (82%) respondents reported continued condom use and the incidence of new HIV and syphilis infections during the closure did not differ from rates before or after. Yet the majority of participants reported that the closing had a negative impact on them, primarily due to the withdrawal of medical services. Most strikingly, the death rate among HIV-positive participants doubled from 6.7/100 patient years (PY) before the closing to 12.4/100 PY during the closing, then went back to 7.5/100 PY after the study reopened.

This finding suggests the crucial role that medical management can have on the outcome of HIV infection, even in the absence of treatment. It also underlines the importance of assuring the sustainability of interventions that accompany research projects and for planning for the transition of study participants to alternative sources of healthcare when project funding ends.

Shutes E. What happens when a research project closes: HIV incidence, mortality, and perceptions in a couples' cohort in Lusaka, Zambia. The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, 2003. Abstract 111

of individuals who had received ART for 3 months or more. Adherence measures included 7-day recall questionnaires and pill counts, which were validated with pill identification tests, interviews and monthly pill calendars. Overall, monthly average adherence was 24.9 adherent days per month (83%). Factors that promoted adherence were adherence partners, pharmacy counseling and pill counts. Non-adherence was attributed to forgetting, lack of access, and lack of privacy.

Abstracts 1212, 1213, 1216—The Botswanna national ARV therapy program performed a retrospective chart review to analyze the experience and outcomes of the first 306 people to receive ART in Gaborone beginning in January 2002. All HIV-positive adult citizens of Botswanna with CD4 counts below 200 cells/mm^3 are eligible to receive an NNRTI-based regimen for free, containing either nevirapine (47.5%) or efavirenz (52.4%) plus Combivir. Women comprised 57% of the patients. At baseline the mean CD4 count was 81 cells/mm^3 and mean viral load was 5.65 log copies/mL. The median time of follow-up was 283 days. CD4 cell count/mm^3 increased by 166 at six months and by 204 at nine months. Viral load fell below 400 copies/mL in 84.5% of patients at six months. Anemia (grade 3 or 4) occurred in 8% of those receiving Combivir; four patients died (mean time to toxicity 11.6 weeks). Severe nevirapine-associated rash occurred in 3.42% (mean time to toxicity 28 days). Nevirapine-associated hepatitis developed in 2.7% with two deaths (mean time to toxicity 12.6 weeks). Efavirenz-associated CNS complications were reported in 4.45%. The overall death rate to February 2003 was 10.7% (33 of 306) with an average time to death after starting treatment of 2.4 months. Of those who died, 72% were women. The overall baseline CD4 count of patients who died during the period was 60 cells/mm^3 (66% were below 50). The causes of mortality among the 33 patients was wasting with chronic diarrhea (21.2%); wasting without chronic diarrhea (9%); pulmonary TB (18.1%); AZT-induced anemia (12.1%); nevirapine-induced hepatitis (3%); cryptococcal meningitis (9%); TB meningitis (6%); Kaposi's sarcoma (9%); PCP (3%); pseudomonas pneumonia (3%); non-AZT-induced anemia (3%); and suicide (3%). The authors note that limited blood supply for transfusion are reflected in the high rate of AZT-associated anemia. More frequent monitoring of hemoglobin for patients on AZT may also be beneficial.

Abstract LB53—The incidence of severe morbidity among members of a research cohort in Abidjan, Cote d'Ivoire was compared between 126 patients who had received ART after 1998, and 166 patients with CD4 <200 who had received cotrimoxazole and were followed between 1996 and 1998. The ART group composed of 81% women, had a baseline median CD4 count of 137 cell/mm^3 and were followed for a mean time of 21 months. The non-ART group was composed of 60% women, had a baseline median CD4 count of 100 cell/mm^3 and was followed for a mean time of 16 months. The most frequent causes of severe illness in the groups were acute unexplained fever (ART vs. non-ART, per 100 patient years): 12.2 vs. 9.1, severe bacterial diseases: 9.2 vs. 25, non-specific enteritis: 9.1 vs. 23 and tuberculosis: 2.4 vs. 6.9. The incidence of malaria was the same in both groups (2.4 per 100 py).

References:

Durier N, Treatment of HIV disease with HAART in Chiradzulu District, Malawi. Abstract 112.

Ekong E, The Nigerian accelerated antiretroviral drug initiative – evaluation of nevirapine, lamivudine and stavudine in ARV naive patients. Abstract 629.

Azondekon A, HAART in Benin initiative: what have been used and for whom? Lessons from 448 patients elected one year later. Abstract 636.

Gahimbaza L. Costs and benefits of the antiretroviral therapy in the private sector: the experience of Brarudi, Burundi. Abstract 668.

Mougnutou R, Evaluation of a HAART pilot study in Yaounde, Cameroon: 24 months follow-up. Abstract 686.

Oyugi JH. Self-reported adherence measures are feasible and valid compared to multiple objective measures in kampala, Uganda. Abstract 690.

Kebba A. Therapeutic responses to AZT+3TC+EFV in advanced ARV-naive HIV-1 infected Ugandans. Abstract 693.

Idigbe EO. The use of generic copies of ARVs in the management of HIV infections in Lagos, Nigeria: a 6 month follwo-up study. Abstract 697.

Kibangou N. Pointe-Noire, Congo-Brazzaville: ARV therapy assessment, an evaluation following 6 months of prescription. Abstract 700.

Boulle A. Early outcomes and lessons from a public sector ARV treatment programme in South Africa. Abstract 701.

Diop K. Adherence to ART in Senegal: assessment at the pharmacy level. Abstract 705

Laniece I. Determinants of adherence among adults receiving ARV drugs in Senegal (ANRS cohort study). Abstract 1118.

Nwokikr JI. Baseline data and predictors of adherence to ART in Maun General Hospital, Maun, Botswana. Abstract 759.

Ndwapi N. Preliminary analysis of mortality and causes of death among the first ARV-treatment naive HIV-1C-infected persons receiving HAART under the Botswana national ARV treatment program. Abstract 1212.

Wester W. Preliminary analysis of toxicity and tolerability among the first ARV-treatment naive HIV-1C-infected persons receiving HAART under the Botswana national ARV treatment program. Abstract 1213.

Ndwapi N. Response to the Botswana national ART program - preliminary analysis of the first 306 treatment -naive adults receiving HAART via the national program. Abstract 1216.

Seyler C. Morbidity causes in HIV-infected adults before and after the ART era in Abidjan, Cote d'Ivoire: Data from the Cotrame ANRS 1203 cohort study. Abstract LB53.

Médecins Sans Frontières (MSF) Antiretroviral Treatment Projects Worldwide

This is an excerpt from an MSF report entitled, *Positive Replications*, which can be found in its entirety online at: www.accessmed-msf.org

The challenge of scaling up

There are many real and perceived barriers to expanding treatment to large numbers of people in the developing world. Among those most often referred to are lack of political will, the high price of ARVs; the lack of trained staff and other elements of healthcare infrastructure; the complexity of treatment protocols and laboratory monitoring.

Médecins Sans Frontières (MSF) believes these should not be viewed as reasons to accept the status quo. Despite facing many of these problems in its HIV/AIDS treatment projects around the developing world, MSF is showing that these barriers are not insurmountable. In July 2002, MSF was treating 2,300 patients in ten countries. At the Barcelona conference, MSF set itself the goal of doubling the number of patients it treated by the end of 2003. Now MSF has 23 projects in 14 countries with 4,447 patients (310 of these are children) receiving ART.

MSF's most frequently used first-line regimen is stavudine, lamivudine and nevirapine and fixed dose versions of these combinations are being used in a majority of projects. In MSF projects the price of first-line therapies ranges from US $277 (Cameroon) to US $593 (Ukraine) per patient per year.

Médecins Sans Frontières has been caring for people living with HIV/AIDS in developing countries since the early 1990s, and the first ARV treatment projects began in 2000. As of June 2003 more than 5,000 people have received ARVs in MSF projects. Eighty eight percent of these are still on treatment.

Although the places and contexts are very different for each of these treatment projects, a certain number of common denominators exist: MSF focuses on offering care to the poorest and most destitute people; and to ensure that a maximum number of people can be treated and that programmes are sustainable, efforts are made to identify the least expensive sources of medicines. In many cases, this means using generic versions of ARVs.

MSF does not offer ART in a vacuum, but instead aims to integrate treatment into a continuum of care: projects include prevention efforts (health education, prevention of mother-to-child transmission of HIV), voluntary counselling and testing (VCT), treatment of opportunistic infections, ART and nutritional and psychosocial support.

MSF treats people with antiretroviral drugs in its projects in the following countries (June 2003 figures):

Country	Place	All patients	Children
Cambodia	Phnom Penh, Siem Reap, Sotnikum	736	28
Cameroon	Yaoundé, Douala	281	7
Guatemala	2 projects in Guatemala City; Costepeque	421	0
Honduras	Tela	118	17
Kenya	Homa Bay, Mathare, Nairobi	461	29
Malawi	Chiradzulu, Thiolo	731	59
Mozambique	2 projects in Maputo; Tete; Angonia	130	3
South Africa	Khayelitsha	480	60
Thailand	Bangkok, Surin	717	86
Uganda	Arua	305	1
Ukraine	Odessa, Mykolayiav, Crimea	20	20
New country projects			
Burkina Faso	Ouagadougou	20	0
Burma	Kachin, Rangoon, Shan, Rakhine states	25	0
Indonesia	Merauke	2	0
Total number of patients		4,447	310

Notes on Hepatitis C Infection from the IAS Paris Conference

By Tracy Swan

Two Viruses, One Clean Syringe and a Condom

Hepatitis C infection is prevalent among injection drug users around the world, and in the United States, as many as 90 percent of the people who acquired HIV from injection drug use also have hepatitis C virus (HCV). Overall, 16–25 percent of people with HIV in the U.S. are also coinfected with HCV. In China, 96 percent of HCV infections resulted from injection drug use and/or illegal blood donation; in Tunisia, injection drug use was reported by 83.7 percent of coinfected people, and in Brazil, male and female HIV-positive injection drug users were far more likely to be coinfected than people who acquired HIV from sex.

Overall, sexual transmission of hepatitis C appears to be low, but has been reported more frequently among men who have sex with men (MSM). In England, researchers have tracked cases of acute hepatitis C infections between 1997 and 2002 among a group of MSM. Of the 28 cases identified, 26 were in HIV-positive men, and 20/26 reported no risk factor other than unprotected anal intercourse. Another group of researchers in England identified 20 cases of acute HCV in HIV-positive men between October of 2002 and January of 2003. All 20 had had unprotected anal intercourse; 15 of the 20 reported fisting. Although the possibility of sexual transmission of HCV has been debated in the past, clearly, HCV prevention messages targeted specifically for MSM are now overdue.

As prevention, education and treatment programs for HIV begin to scale up in the developing world, the challenge of HCV must not be forgotten. At a minimum, access to clean injection equipment should be included in prevention and treatment initiatives. But scaling-up of prevention efforts is urgently needed here in the United States as well. Clean injection equipment must be readily available to all who need it in sufficient quantities with minimal legal and bureaucratic barriers to access. Imagine what would happen to the HIV infection rate be if obtaining protection required exchanging used condoms on a one-to-one basis!

HIV, HCV, Injection Drug use and Survival in the HAART era

End-stage liver disease has become a leading cause of death among HIV-positive people in Europe and the United States, and the liver damage caused by hepatitis C disease progresses more rapidly in HIV-positive people. One study found advanced liver disease among a third of 914 coinfected individuals, all of whom had a similar estimated duration of infection (16 years). Heavy alcohol intake and increased age (over 35) were the only variables associated with the progression of fibrosis, the tissue scarring that accompanies HCV infection.

Reports of HIV/HCV coinfection prevalence from around the world

Region		HCV Prevalence*
Abidjan (West Africa)	pregnant women: 501 HIV-positive pregnant women: 501 HIV-negative	1.2% (6/510) HIV/HCV 1% (5/501) HCV only
Cameroon	pregnant women: 217 HIV-positive pregnant women: 2,337 HIV-negative	1.8% (4/217) HIV/HCV 1.9% (45/2337) HCV only
China		56.9% (136/239)
Indonesia (Jakarta)		62% (74/162)
Southern Brazil (Porto Alegre)		28.5% (321/1128)
Spain		64.6% (973/1506)
Thailand	pregnant women: 1437 HIV-positive pregnant women: 448 HIV-negative	2.9% (42/1437) HIV/HCV 0.5% (2/448) HCV only
Tunisia		43% (80/186)

*all HIV-positive except where indicated

A French group evaluated a decade of data from 2, 710 HIV-positive individuals, and analyzed the impact of HAART, HCV coinfection and injection drug use on survival before and after 1996. During the HAART era, five-year mortality rates were higher for coinfected people than for those with HIV alone, and higher yet for coinfected injection drug users. Although HCV coinfection did not significantly increase the risk of death at five years, coinfection plus injection drug use did, with the risk of death almost three times greater for coinfected injection drug users than for people with HIV alone.

These differences in survival may be attributed to several factors. Some studies have reported that coinfected people have a blunted immune response to HAART which might mean they are more susceptible to death from AIDS. Also, coinfected individuals are at greater risk for developing liver toxicity from antiretroviral therapy and they may experience more frequent switches or discontinuations of drug regimens. Access to treatment for HIV and HCV is a significant problem for coinfected injection drug users, who often receive HAART later than non-users. Until 2002, injection drug use was a contraindication for HCV treatment and although the 2002 Consensus Statement on Management of HCV has revised this recommendation, many physicians are still reluctant to treat injection drug users. Even when HCV treatment is prescribed, access is not guaranteed; under-funded AIDS Drug Assistance Programs can't afford to add expensive HCV treatment to their formularies, leaving many coinfected people without a way to pay for HCV therapy, which costs as much as $40,000 for the 48-week course of treatment. These factors, plus the primary risks of using injection drugs probably all contribute to higher death rates for this vulnerable group.

Lack of access is not the only barrier to HCV treatment. Eligibility can be limited; a Spanish study reported that 60.6 percent of 1,006 coinfected individuals had contraindications for HCV treatment. Furthermore, the side effects of interferon and ribavirin may be especially severe in coinfected persons. In the studies presented at the IAS conference, the rate of treatment discontinuations ranged from 15 to 24 percent and adverse events reported included psychiatric toxicities, pancreatitis/lactic acidosis, hepatic decompensation, severe neutropenia, thyroid dysfunction and retinopathy.

HCV treatment does not appear to work as well in coinfected people regardless of CD4 cell count or HIV virus load. In one study, only 21 percent (28/132) of individuals treated for HCV achieved a sustained virologic response six months after completion of a 48-week course of standard interferon plus ribavirin. Disappointingly, with pegylated interferon and ribavirin, only 26 percent (15/58) of individuals achieved a sustained virologic response. The only predictive marker that has been significantly associated with sustained virologic response to treatment remains infection with HCV genotype 2 or HCV genotype 3.

References:

Kilani B. Seroepidemiology of HCV-HIV Co-Infection in Tunisia. Abstract 952.

Yin N. Epidemiology and Distribution of Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV) Among Intravenous Drug Users and Illegal Blood Donors in China. Abstract 954.

Bhagani S. Acute HCV in a Cohort of HIV-Positive Homosexual Men in a London Clinic-Risk Factors and Outcomes. Abstract 955.

Voirin N. Survival of Patients infected with HIV and HCV in the era of highly-active antiretroviral therapy. Abstract 956.

Berenguer J. Interferon Alpha and Ribavirin Therapy for Chronic Hepatitis C in HIV-Infected Patients (GESIDA 28-02 Study). Abstract 960.

Njouom R. Seroprevalence of HCV Among HIV-Positive and HIV-Negative Pregnant Women in Yaounde, Cameroon. Abstract 967.

Hernández S. Estimation of the HCV-HIV Co-Infected Population Eligible for Anti-Hepatitis C Treatment or Liver Transplant in Spain (GESIDA 28-02 Study). Abstract 970.

Parra-Ruiz J. IT78047 Trial. A Randomized, Multicentre Study of Pegylated Interferon Plus Two Different Does of Ribavirin in the Treatment of Patients with Chronic Hepatitis C and HIV Infection. Abstract 971.

Browne RE. Increasing Incidence of Acute Hepatitis C in HIV Positive Men Secondary to Sexual Transmission: A New Epidemic? Abstract 972.

Hopkins S. HIV-HCV Co-Infection: To Treat or Not to Treat. Abstract 973.

Msellati P. Prevalence of Hepatitis B and C Viruses and HCV Genotypes in HIV-Positive and Negative Pregnant Women in Abidjan, Ivory Coast (West Africa). Abstract 974.

Voigt E. Factors Related to Outcome of Treatment with Pegylated Interferon Alpha 2b (PEG INF) Plus Ribavirin (RBV) in HCV/HIV Co-Infected Patients. Abstract 976.

Slim J. Neutropenia as an Adverse Drug Reaction in Patients Co-Infected with HIV/HCV Receiving Interferon and Ribavirin Therapy. Abstract 977.

Sprinz E. Hepatitis C Virus Infection in a Southern Brazilian Cohort of HIV-Infected Patients. Abstract 978.

Martin-Carbonero L. Fibrosis Progression in 914 HIV-HCV Co-Infected Patients is Strongly Related With Age: A European Collaborative Study. Abstract 984.

Pacheco R. Clinical and Epidemiological Characteristics of Hepatitis C Infection in a Large Cohort of HIV-Infected Patients in Spain (GESIDA 29/02 Study). Abstract 985.

Birowo NR. Prevalence of HIV and HCV Co-Infection Among Drug Users. Abstract 987.

Ngo-Giang-Huong N. HIV-1/HCV Co-Infection in Pregnant Women and Their Infants in Thailand. Abstract 994.

Preventing HIV/AIDS in India: Points to Ponder

By Maitreya

These notes were prepared on the occasion of the International Conference of South Asian Parliamentarians (SAARC) meeting on the "Advocacy Role of Elected Representatives in Prevention of HIV/AIDS", August 1-2, 2003, Ashok Hotel, New Delhi (India).

The person writing this letter has some experience gained in prevention activities against the spread of HIV/AIDS in India during the last eight years. Initially the Government and funding agencies came along in a big way addressing the issue of HIV through prevention projects. During the course of implementing these top down projects, myself and my organization felt some severe inadequacies starting with the conceptualization, to the implementation and down to preparations on the ground. In short, in project lingo, these are lessens learned.

The condoms supplied to female sex workers are male condoms, which means they have to ask the clients, under harrying conditions, to wear them.

Targeted intervention among "high-risk groups"

This is a highly effective intervention strategy. Since HIV is transmitted through blood and sexual intercourse, to address the high-risk groups (sex workers; injecting drug addicts; mobile work force, such as truck drivers, construction workers etc.) on a war footing before HIV percolates into the general public would seem effective. But we failed miserably in preparing the ground for intervention. Take for example, the case of sex workers; we never addressed the laws criminalizing sex work and its premises, stigma attached to sex work, human rights violations both by the public and police, gender-power relations in sexuality and differences among the different segments of sex workers. No project can work effectively in a criminalized atmosphere. The projects existed in India as clandestine activity just like contrabands. There never developed a co-ordination between the law making/implementing authorities and the health departments.

The projects were designed in the context of brothels in Europe or U.S., where there is relative freedom for the inmates in deciding their personal matters. But here the situation was of slave trade and there is no organization of sex workers for collective bargaining either with the brothel owners or with the clients. Without a sex worker's organization they can never bargain with clients; if one denies, another should not cater. Except perhaps in few pockets like Sonagachi in Kolkata, or in some fifty-odd sites in West Bengal, Sangli in Maharashtra, sex worker's organizations are non-existent in India. Here again, we could see the relative freedom of sex workers running the brothels to decide the matters. But the Government's policy is still against the sex worker's rights and organizations.

Again, the projects drawn in the situation of brothels are used to address the situation of street-based sex workers, for example in Kerala, where there is no red-light area or permanent brothel. All the parameters and monitoring systems are for brothels, which makes it ridiculous. (For example, in a brothel situation, condom tracking with a waste basket outside a room can provide some information, but in the street, this exercise is a joke—still the project reports will be full of condom tracking.) In the absence of brothels, drop-in-centers are a must for executing the projects. But as there was no ground preparation from the part of Government in supporting the drop-in-centers, it vanished from the projects in the course of implementation. This means there is no collectivity and hence no bargaining in condom use. There is only a nascent organization in Kerala, but projects go on in papers.

In the absence of collective bargaining the only alternative is using condoms oneself. But the condoms supplied to the female sex workers are male condoms, which means they have to ask the clients, under harrying conditions, to wear them. The power relations in sexuality are against the women; all they could do is wear something themselves. If the Government promoted female condoms in targeted interventions it would have succeeded immensely. They will cite the prohibitive cost but mass production and subsidy could have brought down the cost. In a study, it is shown that tampons can reduce the rate of infection in women. So the Government should also provide these along with female condoms in the projects and ensure their availability in the market.

There is still no concept of Male Sex Workers (MSW) but only of Men Seeking Men or Men having Sex with Men (MSM). This stems from the assumption that sex workers are only women; again no one sees it as sex work but only as exploitation of women, because if you

admit the reality of sex work, then the strategy and policy will have to change. So the authorities just shut their eyes conveniently against the reality. But those who are involved in sex work, whether they are male or female, know it as work. So we should understand that there is a distinct category of male sex workers, who should be addressed independently. (We are not talking of gigolos, a minuscule category, which caters to rich independent women.) We should also know that we can't address all gay men as sex workers or vice versa. Right now there is confusion in these MSM projects.

Again, archaic crininalizing laws coined in the name of "unnatural offences" hinder all activities among the male sex workers as well as within the gay community. There are instances of health activists getting arrested on these charges. The concept of needle exchange among IV drug users is still being debated. With the existing laws, as in the case of sex workers, no project can be implemented with effectiveness. Change of law is a must in these situations.

Condom promotion

The concept of A (Abstinence) B (Be faithful to one partner) C (then use Condoms if you can't stick to the other two) in prevention projects ran high. All the IEC (information, education and communication) materials produced by the State Aids Control Societies (SACS) had this moral overtone in it. I must say they created fear and shame in people on the whole. Now it is backfiring. People are rejecting their kith and kin and in the case of strangers they even go to the extent of lynching them. The presumed "Indian Culture" and morals are actually fallout of our colonial past. The Indians, and for that matter people of other countries also, have a rich tradition in sexuality and a practice quite diverse. But the prudish postures our administrators take make them fit enough to be living in 19th Century Victorian England. Because of this "right" moral approach, people hide their sexuality and pretend otherwise. The existence of several million female sex workers along with millions of all other varieties in India show that we have a highly promiscuous way of life. We all pretend that we have the barest minimum of sexual life and only the "westerners" are indulging in sex. If it is true, then how come we Asians have two-thirds of the world population? We should know that we are more active in sex and for that matter, more in penetrative sex, and for that matter, more active in unsafe sex than all the people in the world. So it is imperative to promote condoms in every way possible and also to teach non-penetrative sex. Think about promoting kissing in the movies and tell people to indulge in non-penetrative sex. Make sexuality a pleasurable act, which could be safely practiced instead of keeping it as an act of procreation. Keeping sex as an act of procreation, as religion preaches, is keeping people in the animal state. Because, Westerners were able to conceive sex as pleasure in their culture they have brought the burgeoning population in their countries under control. Here, even after thirty years of condom promotion in the family welfare scenario, condoms have failed to click because of the opposite understanding. For us sex first means procreation and penetrative sex. Just think about all the literature like Kamasutra and all the temples of Khajooraho and Konark, what a fall! A real fall from heaven. What we call now Western is Indian and what we call Indian is Western.

We should invent different varieties of condoms, especially different colors to suit the Asians. We can do away with the white variety altogether, or maybe keep a few for the pale skin people.

When we talk of condoms, we have to think about varieties. We should invent different varieties, especially different colors to suit the Asians. We can do away with the white variety altogether, or maybe keep a few for the pale skin people. We must immediately produce flavored condoms and thus promote oral sex, another safe sex activity. As I said earlier, we must produce female condoms and tampons to give our women a defense against the penetrative sex culture of the males. This will remain as a viable alternative for the meek and submissive "wives" and "girl friends".

Look at the varieties now available in the market, ribbed condoms, spotted condoms, dotted condoms etc. The idea of friction inside the vagina is behind all this, which the male thinks is a necessity for women. Poor women have to bear all this thrusting and just burn inside. Can't these fellows who design these condoms, just ask the women? Haven't they heard about a protuberance called clitoris in women? Didn't they know about the Grafenberg spot (G-spot) in women's vagina? Ignorance of women's sexuality is the principal input in the designs of men's condoms now. We have to consult women when designing male condoms. Similarly, we should consult men when designing female condoms!

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Stumbling Forward: New Drugs Bring New Questions

By Bob Huff

Viread, Viread, Viread

Viread (tenofovir disoproxil fumarate) has come under a lot of scrutiny this summer after reports of pharmacokinetic interactions, creatinine increases, and a strange case of bad clinical chemistry with abacavir and 3TC set off a flurry of "Dear Doctor" letters.

First, Viread is turning out to have more pharmacological interactions than were understood at first. An interaction with Videx EC (ddI) has been recognized to raise ddI levels and a letter from Bristol-Myers Squib (BMS) recommends separating Viread dosing by two hours before or one hour after taking ddI. Some doctors have reduced dosing of Videx EC from 400mg to 250mg once-a-day taken simultaneously with Viread, but, so far, there is no clinical trial data to validate this approach.

In the mad race to achieve reliable once-daily dosing with novel combinations, more victims are being left on the roadside.

Bristol also issued a Dear Doctor letter advising of a pharmacokinetic interaction between tenofovir and the new BMS protease inhibitor, atazanavir (Reyataz). This is strange because tenofovir is excreted through the kidneys and was not expected to affect drugs metabolized by the liver. A BMS-funded study found that, 24 hours after taking a dose, when blood levels are lowest (Cmin), concentrations of atazanavir (400mg) coadministered with tenofovir were 40 percent less than when given alone in uninfected persons. The wide variability of the Cmin of atazanavir was a topic of concern for the FDA antiviral advisory committee that evaluated the drug prior to approval. Some members of the panel were worried that atazanavir Cmins would be too low in too many people to prevent virologic breakthrough.

BMS advises that clinicians should use caution when administering atazanavir with tenofovir. As once-a-day drugs, the two seem like natural allies but the unboosted combination should probably be avoided until someone can definitively explain what's going on and how to dose around the problem. The letter also reported that blood levels of tenofovir were raised by coadministration with atazanavir, although no increase in tenofovir-associated toxicity was noted at 24 weeks.

But all may not be lost. Preliminary data from BMS has shown that boosting atazanavir with ritonavir (300mg/100mg) raised Cmins to more comfortable levels. A study by a French group cited in the BMS letter found that the Cmin of boosted atazanavir was decreased by about 23 percent in people with HIV. BMS advises that if atazanavir is to be coadministered with tenofovir "consideration should be given to administering Reyataz 300mg with ritonavir 100mg until additional data are obtained." The drugs should be given as a single daily dose with food.

As an aside, at the IAS Conference in Paris, data was presented that suggests that the 100mg ritonavir booster dose, while compromising atazanavir's benign lipid profile a little bit, does not have a huge effect and that the combination may be more tolerable than Kaletra. Still, there is not enough being done to get the message out that unboosted atazanavir poses a big risk for someone who's been on PIs in the past and may harbor resistance mutations. For an individual coming off of a treatment interruption or a PI-sparing regimen a current genotype might not show hidden PI-resistant strains waiting to bloom once atazanavir is started. Activists are concerned that with all the hoopla about once-daily convenience, these dosing concerns will be overlooked.

The Tenofovir / Abacavir Debacle

In the mad race to achieve reliable once-daily dosing with novel combinations, more victims are being left on the roadside. There was a peculiar little study presented at the IAS Conference in Paris that set off alarms about combining Viread and Ziagen (abacavir) and 3TC (Epivir, lamivudine) in a QD combo. A 19-person, non-randomized, uncontrolled pilot study was undertaken by Charles Farthing of the AIDS Healthcare Foundation. Patients were put on a once-a-day triple-NRTI combination of abacavir, tenofovir and 3TC and then observed to see what would happen. It failed spectacularly. Within 8 weeks over half of the people in the trial had virological failure and the study was stopped.

Simultaneously, GlaxoSmithKline (GSK), the maker of abacavir and 3TC was performing a much larger, randomized, but no less peculiar study comparing tenofovir to efavirenz, each with a background of abacavir and 3TC. Again the tenofovir/abacavir combination collapsed with about half failing at the 8-week mark and the 200-person study was stopped. Another French study is rumored to report similar results soon.

There are a number of aspects to the design of these studies that are disconcerting. First, aba-

cavir was used as a once-daily drug with little data to support that. Second, this particular triple combination hadn't been properly studied even as a twice-daily regimen. Finally, a number of the people enrolled had viral loads in excess of 100,000 copies—a population not expected to do well on a marginally potent regimen. The result is that several patients now have resistance to 3TC, abacavir and tenofovir.

In justification of these studies, it could be said that many people expected this should have been a potent and convenient combination, and it's one that some clinicians had already been using in the absence of data. For Glaxo, an added incentive for undertaking the multi-million dollar trial was to generate some numbers that would make Viread look bad. Who seriously thought tenofovir was a match for efavirenz? But with a coformulated tenofovir and FTC tablet expected from drugmaker Gilead Sciences next year, Glaxo may have been seeking ammunition to protect its market-dominating Combivir from an upstart. As for AHF, some have speculated that the failed study was actually a ploy to discourage abacavir use or a petulant bid to avoid AZT. Last year AHF sued Glaxo, ostensibly over their AZT patents (the original case was tossed), in a move some say was a tactic to punish Glaxo for refusing to fund the Foundation's international expansion. (AHF has launched clinics in Uganda and South Africa, which are in the process of scaling up to treat over 1000 people.)

To Glaxo's credit, when it realized there was a problem, the company issued a Dear Doctor letter warning about the combination. According to Glaxo, their study began enrolling in January of 2003 and by the last week in June, the first few reports of virologic failure had been received. At that time, the company amended the protocol to call for more frequent monitoring and the study continued. Then, on July 3, one doctor called and said he had 9 patients who appeared to be failing the tenofovir arm. This sent Glaxo into a state of alert and the company began collecting patient data for a preliminary analysis. That same day the IAS abstract book was published and the company learned that the title of Farthing's talk scheduled for July 14th seemed to confirm that there was a problem. On Thursday, July 10, with most of the Glaxo investigators in Paris for the IAS conference, the emergency data analysis reported that the catastrophe was real and the study's global safety board ordered the trial stopped. Gilead was informed of the situation and they reported that they had heard rumors that a French study was having similar results. By Friday, July 11, Glaxo began notifying study investigators and briefed U.S. community representatives on Sunday the 13th. On Monday, Glaxo met with Farthing to show him the data supporting his findings and he included a reference to the larger trial during his presentation that afternoon.

Farthing would have submitted his abstract for the July conference sometime before the deadline in March. Gilead says they became aware of his results in the Spring but decided not to tell Glaxo because they thought it would be dangerous to draw conclusions based on that small amount of data. Yet had Glaxo known they might have increased their vigilance for problems and could have begun investigating the mechanism sooner.

The reason for the bad outcomes with this combination are subject to wide-ranging speculation pending further research. Gilead said they did a small pharmacokinetics study of tenofovir and abacavir but didn't observe an interaction. Farthing offered that the problem may lie with once-daily dosing of abacavir or perhaps 3TC. Glaxo suspects a shared resistance pathway of abacavir and tenofovir may be the culprit and cites evidence from a successful study of tenofovir plus Trizivir (abacavir/3TC/AZT) to suggest that AZT may play a protective role in preventing resistance. It would be welcome news if a credible, fourth party stepped into this question to figure out what is really going on. Glaxo will present a case-by-case analysis of their study at the ICAAC conference in September.

It would be welcome news if a credible, fourth party stepped into this question to figure out what is really going on.

Yet More on Viread

As for tenofovir on its own, new concerns have been raised about the drug's effects on the kidneys after a large cohort study reported frequent mild elevations of creatinine levels. Julio Montaner conducted a study of 310 patients in Vancouver who received tenofovir on expanded access during 2002 and compared them to 404 patients who started abacavir during the same period. Within six months of starting therapy creatinine elevations greater than 1.5 times above baseline were seen in 8.4 percent of those starting tenofovir and in only 3.6 percent of those who stated abacavir. A lower baseline CD4 count was associated with a greater risk of a creatinine elevation. Nephrologists that examined the Canadian cohort data saw no indication of Fanconi's syndrome or serious kidney impairment, yet physicians are now advised to pay careful attention to creatinine levels and to be vigilant for signs of kidney problems in patients on Viread.

Will Miracles Never Cease?

Gilead was reportedly slapped on the wrist by the FDA for sloppy statements made by sales reps downplaying the potential for developing lactic acidosis and hepatic steatosis while on tenofovir. All NRTIs carry an FDA warning about the rare but deadly possibility of developing these NRTI-associated conditions. In another incident, Reuters reports that Gilead sales reps were cited by the FDA for pitching Viread as a "miracle drug." There are no clinical data to support the claim.

Emtriva Approved

In happier Gilead news, Emtriva (FTC, emtricitabine) was approved by the FDA on July 2. The drug is a nucleoside analog reverse transcriptase inhibitor (NRTI) comparable to 3TC (Epivir) in its resistance profile but with somewhat increased potency and a longer half-life allowing for comfortable once-daily dosing. The drug also exhibited less toxicity to mitochondria in laboratory tests. Despite the similarity to Epivir, more needs to be learned about Emtriva and its resistance profile. The sooner FTC is added to the commercial phenotypic assay panels and clinical cutoffs start to become clear, the sooner we may begin to appreciate the nuances of Emtriva's particular resistance characteristics. All in all, the incremental benefits of FTC over 3TC should make Emtriva a welcome addition to the HIV medicine shelf, although caution is always warranted when a new drug is released since rare side effects may not show up until the drug has been in broader use over longer periods of time. One odd side effect that has been reported is a spotted discoloration on the palms of the hands of people taking Emtriva.

By all accounts the guidelines development process can be a political snake pit, with industry partisans lobbying for this drug or that.

Fuzeon Forges Ahead

Four months after its FDA approval, prescriptions for Fuzeon (enfuvirtide, T-20) are being filled at a steady pace, says Roche. Interestingly, after all the concern about having enough T-20 to meet the demand, Roche has announced that production capacity has been increased and was now capable of supplying Fuzeon to nearly 20,000 people by the end of 2004.

Reports on 48-week data from the large, pivotal TORO 1 and TORO 2 trials confirmed 24-week results with about twice as many Fuzeon patients experiencing a greater than 1.0 log reduction in viral load as those receiving optimized background therapy without Fuzeon. The median time to virologic failure was 32 weeks for patients receiving Fuzeon vs. 11 weeks for patients receiving the background regimen alone. However, while 47 percent of Fuzeon recipients had achieved at least a 1.0 log reduction at 24 weeks, at 48 weeks this proportion had dropped to 34 percent which indicates the fragile durability of these salvage regimens.

Julio Montaner presented an analysis of factors that predicted success with Fuzeon in the TORO trials at the 24-week mark. Patients with CD4 counts over 100 and those with at least two active drugs in their background regimen were less likely to have virologic failure. This analysis reinforces the problem with finding a therapeutic niche for T-20: those who need it most are less likely to have an optimal outcome, and those who will be most likely to do well on Fuzeon may be unwilling to undergo the burdens of twice-daily injection. Other factors that predicted success were viral load below 100,000 and no prior exposure to Kaletra.

One oddity uncovered in the TORO trials was that the incidence of bacterial pneumonia, which had been recognized in earlier reports, was now 10 times higher in Fuzeon patients (6.6% vs. 0.6%) reaching 10 percent in those with CD4 counts under 200. Possible reasons for this are under investigation. In the meantime, Roche should be reminding doctors to watch for early symptoms of bacterial pneumonia in people who are starting Fuzeon.

Tipranavir Access Improves Slightly

According to Boehringer Ingelheim, enrollment in the RESIST Phase III trials for tipranavir is on track for completion by the end of the year. An open label safety study (OLSS) is now accepting persons who could benefit from tipranavir but were unable to participate in the large studies. The capacity of the OLSS has recently been doubled, which will allow 600 patients worldwide to enroll during 2003. Still, drug supply problems make a less-restrictive expanded access unlikely until the first part of 2004 when the company expects to be able to add an additional 50 persons per month. By the middle of 2004 the expanded access program is projected to be able to add 100 patients per month until approval sometime in 2005. As Julio Montaner's analysis suggests, access to tipranavir will be especially crucial for individuals considering starting Fuzeon if they are not susceptible to other available protease inhibitors.

Wrong Path for Guidelines?

The U.S. guidelines were released during the IAS meeting where they made nary a ripple. The biggest news is that now only efavirenz or Kaletra-based regimens are recommend for first-line,

first-time therapy. And, despite mounting evidence and clinical consensus that d4T is not the best choice for treatment-naïve patients with healthy immune systems, Zerit was still listed among the preferred drugs with only an asterisk to indicate its association with lipid abnormalities. By all accounts the guidelines development process can be a political snake pit, with industry partisans lobbying for this drug or that. At a minimum the guidelines reflect a reasonable, conservative take on how to approach therapy and what not to do. For those who take time to read them, they provide an education in the complexities behind making treatment decisions. The problem is that many physicians may never read them thoroughly. Table 12a (Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral Naïve Patients) is such an easy pill to swallow. That's where you can catch the new first-line drug recommendations at a glance. This table is destined to appear on a thousand power-point slides. Already I have received an email from a PR firm repping Abbott that included a disembodied copy of Table 12a. Oddly, the stavudine asterisk was in place but it led nowhere. So there was the take-home message untroubled by messy footnotes: Kaletra plus Epivir and AZT or Zerit highly recommended, and the lipids be damned.

The new guidelines had been expected at the Retrovirus Conference in February. It's unfortunate that they arrived just as several new products hit the market. With few of 2003's new drugs mentioned (Fuzeon is discussed in the context of treating ARV-experienced patients), and efficacy still paramount, the new guidelines seem to lag behind the times a bit. For a set of authoritative guidelines that catches up with more contemporary thinking, consult the British HIV Association, which doesn't mince words when it comes to Zerit: "For initial therapy, combinations including D4T are not recommended because of increasing evidence of its role in the development of lipodystrophy and abnormal lipid profiles."

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South Africa Relents on HIV Drugs

...continued from back cover

the AIDS community by announcing the formation of a Presidential AIDS Advisory Panel populated by a handful of dissident scientists who disputed the link between HIV and AIDS. With the medical and scientific worlds' attention finally turning to South Africa and hopes running high that the raging epidemic there could be muted, it was becoming horrifyingly clear that the country's leadership was embracing a policy of denial and refusal. The surreal pronouncements of the President and his Minister of Health variously ran: "The cause of AIDS is not known; the treatments are deadly in themselves; and, no matter, since we can't afford to treat everybody, we won't treat anybody." Whether explained by paranoia, Soviet science, intellectual stubbornness or cold political calculation, Mbeki seemed entrenched. The growing activist movement, now joined by Mandela, regretfully found itself pitted against a government that had liberated them less than a decade before.

It's been over three years since the Durban conference and the world has changed in many strange ways. In developing nations, resistance by the pharmaceutical industry has retreated, money from the U.S. and a Global Fund has been promised to buy life for HIV-infected Africans, pilot programs have shown that treatment works as well as it does in rich countries, and affordable and practical combinations of generic drugs are now available, with prices continuing to fall. In South Africa, after years of legal challenges, demonstrations and civil disobedience led by TAC, the government has apparently now withdrawn its objection to saving its citizens and a plan is being readied to make antiretroviral treatment widespread. Hopefully, South Africans will soon be free to start the next, perhaps more difficult phase of their struggle. Last month, as disease began to rob him of his strength, Zackie Achmat decided to accept HIV medicines. If the tragic farce of denial and obstruction in his country has truly come to an end, he may soon be joined by a million of his comrades.

Progress at Last?
South Africa Relents on HIV Drugs

By Bob Huff

An announcement has been made. Is that enough to finally stop the river of death in South Africa? After years of refusal, the government there has asked that a plan be developed to bring antiretroviral drugs to several million of its citizens who will surely die if their HIV disease continues untreated. At a pace of over 1000 deaths per day in a country twice the size of Texas, the mortality rate in South Africa has not yet peaked, and hundreds of thousands more will surely die before the plan is written, the implementation rolled out, and the drugs begin to flow to hospitals and clinics.

It's still only an announcement to make a plan, but it feels like a glacier has tumbled into the sea. The battle to treat the dying in South Africa has been long and tragically unnecessary. This is a country where apparently nothing comes easily, but persistence is rewarded. After an 80-year struggle to defeat the institutionalized racism of apartheid, a new government finally emerged in 1994 led by a freedom fighter schooled on a windswept prison island in Capetown's Table Bay. Nelson Mandela, a hero and living saint, led the country through the transition to freedom with vision and magnanimity—and South Africa survived. But as liberation found its feet, HIV was flourishing, scarcely noticed, sweeping through the cities, townships and countryside.

Unfortunately, Mandela's presidency never seriously addressed HIV as infection rates ran unchecked and prevalence soared to a quarter and then to half of the population in some areas. Because AIDS is a slow disease, the stark horror of the rising death toll was deferred until Mandela had been succeeded by a new president, Thabo Mbeki, a political leader who had been formed, not on Robben Island, but in the best European and Russian schools of economics and revolution.

In the late 1990s, seeing that the miracle of antiretroviral drugs was preventing death in the rich, northern countries, groups of doctors and activists began to call upon the South African government to recognize the crisis and avert millions of deaths by finding a way to bring medicines to the townships. A new generation of heroes emerged to take up this struggle, most famously Zackie Achmat, who vowed to not treat his own HIV disease until antiretrovirals were available to all his countrymen.

The challenge was immense. The prices for AIDS drugs in the North were completely unaffordable for South Africa, and the international drug makers resisted coming to a practical accommodation because they feared that their markets in the rich countries would be hurt if cheap drugs were diverted to Northern pharmacies. They also were bound to serve and protect the emerging international system of intellectual property protection that was being designed by the World Trade Organization. Already, Brazil was tackling its own HIV crisis by ignoring patents and making affordable generic copies of AIDS drugs at home to treat its hundred thousand citizens who would die without them. Generic makers in India were gearing up to make the drugs available for pennies on the dollar of what the majors charged. Threatened, the corporations blindly fought back without a thought for the cost.

The activist Treatment Action Campaign (TAC) began to graphically demonstrate that HIV treatment was crucial and feasible in South Africa. Achmat and others smuggled generic fluconazole from Thailand to help people dying horrible deaths from AIDS-related cryptococcal meningitis. Pfizer, the official maker of fluconazole, refused to make the drug available at a reasonable rate until TAC's defiance and publicity exposed their stance. When it came to HIV drugs, the pharmaceutical industry responded with a policy of obstruction and disinformation. They dismissed claims that prices or patents were the problem, arguing that clean water and infrastructure of the sort found in industrialized nations needed to be in place before complicated antiretroviral drugs could be introduced. Industry apologists in the U.S. government publicly doubted if Africans could learn to tell time. In South Africa, led by GlaxoSmithKline, the big pharmaceutical companies joined a lawsuit to defend their market and block affordable generic drugs from entering the country.

Taken alone, the deadly obstruction of the drug industry could have been surmounted. Eventually, as generic drugs became available, market forces, activist pressure and public opinion compelled the big companies to drop the lawsuits and lower prices. Affordability unlocked a wave of small pilot treatment programs using generic drugs that demonstrated that antiretroviral therapy in a resource-poor setting was feasible and effective. A few lives were finally being saved. But, tragically, the South Africans faced a much more formidable obstruction in one who should have been an ally: President Thabo Mbeki.

In 2000, a year when the International AIDS Conference was finally to be held below the equator in the heart of South Africa's epidemic in Durban, and just as the world seemed poised to respond to the wildfire consuming the region, Thabo Mbeki revealed that he had found evidence on the Internet saying that HIV was not really what was killing so many of his people; that the problem was actually poor nutrition and tragic history; "a uniquely African catastrophe." He soon stunned

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