

## Short Commentary

# Clinical Studies in HIV+ Patients Given Low-dose Oral Interferon (IFN)

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## Commentary

In November 1983, Dr. Buddy Brandt, a veterinarian, underwent extensive surgery in Houston with resulting complications requiring multiple blood transfusions. By January 1984, Dr. Brandt developed pneumonia requiring hospitalization. In retrospect, the pneumonia probably was his first Acquired Immunodeficiency Deficiency Syndrome (AIDS)-related illness. Shingles, genital warts, diarrhea, cold sores, mouth ulcers, respiratory infections, and weight loss were chronically experienced by Dr. Brandt. In February, 1986 AIDS-related complex was diagnosed.

In the spring of 1986, Dr. Brandt acquired low-dose oral human interferon (IFN) then approved in Texas as a treatment for dogs with parvovirus and cats with leukemia. Because of Dr. Brandt's success in treating feline leukemia with Pet Interferon Alpha, and because of Buddy's chronic weight loss and depressed CD4+ cell counts (less than 200 cells/cu.mm), Dr. Brandt experimented on himself with oral Pet Interferon Alpha. Four benefits seemed to result: 1) the CD4+ cell count increased from 153 to 319 cells, 2) his genital warts regressed, 3) his appetite improved, and 4) he gained weight. The Pet Interferon Alpha treatment was discussed with his physician who objected to treatment with oral IFN. This physician told Buddy to discontinue oral IFN and take Ribavirin. During 8 months of Ribavirin treatment, Buddy experienced weight loss and inappetence, and his CD4+ cell count decreased.

At the end of January 1987, Dr. Brandt restarted himself on Pet Interferon Alpha oral treatment and claimed he experienced appetite stimulation again; in February 1987, he gained 5 pounds. On February 26, 1987, one month after a previous blood sample, another blood sample was taken and analyzed for CD4+ cell counts; the count was only slightly increased from 189 to 232. From February to April, his CD4+ cell count decreased from 232 to 210, while his CD8+ cell count increased from 549 to 1050. From May to June (after taking bovine IFN $\alpha$ ), his CD4+ cell count rose to 520

and his CD8+ cell count increased to 1352. Another blood sample was tested June 29 and confirmed blood cell improvement which seemed to correlate with Dr. Brandt's clinical improvement.

These numerical increases in his blood counts may not have been meaningful; however, Dr. Brandt claimed he felt better than he had in 3 years and attributed his improvement to oral IFN treatment. He was able to continue working full-time, was active in 4-H, and kept a garden. In other words, he was able to maintain the quality of his life for many months, something he was unable to do before. His experience was reported in *Lancet*, December 26, 1987, p1530-1531. Buddy died when he failed to recover from additional heart surgery.

In October, 1989, ACM (anhydrous crystalline maltose) powder containing IFN $\alpha$  was carried from Japan to Kenya so Dr. Arthur Obel and Dr. Davy Koech could start treating AIDS patients. Dr. Obel reported that the first 6 patients were experiencing nausea.

Because of the nausea, Dr. Obel reduced the treatment to once a day instead of twice a day and reduced the amount of a single dose from "250 IU" to "200 IU". Frankly, it was not known exactly what dose was given because the powdered ACM-IFN $\alpha$  was given in tiny volumes measured by Dr. Koech with the clip off a Bic pen; this amount of powder was then rolled in aluminum foil. Subsequently it was learned that the ACM powder would only keep the IFN $\alpha$  stable if the moisture content stayed below 2%. Exposed to the air, the ACM powder rapidly attracted moisture.

After Dr. Obel reduced the dose in mid-October 1989, he reported remarkable clinical improvement in his patients. Patients with symptoms became asymptomatic and his patients reported improved appetite and increased sexual drive. Even more impressive were the laboratory reports of greatly improved blood counts. The "CD4+ lymphocyte counts," then the most accepted measure of progression of AIDS, were reported to improve from very low counts (<200 CD4+ cells per cu.mm) back to normal

(>800 CD4+ cells per cu.mm).

Dr. Koech completed a data set on 42 HIV+ patients (reported in *Molecular Biotherapy* 2:91-95, 1990). Drs. Koech and Okel, collected such impressive laboratory and clinical data, they had urged him to conduct a blinded, placebo-controlled clinical trial. After all, each patient in his present study knew he or she was receiving IFN $\alpha$ . Perhaps these patients were benefitting from a placebo effect. Dr. Koech agreed that a blinded, placebo-controlled study was needed and Hayashibara Biochemical Labs (HBL) in Okayama, Japan prepared placebo and different doses of HBL IFN $\alpha$  for such a trial. By January 1990, HBL prepared thousands of individually foil-wrapped lozenges containing placebo (white foil), 2 IU per lozenge (blue foil), 20 IU per lozenge (yellow foil) or 200 IU of HBL IFN $\alpha$  per lozenge (green foil), and they were delivered to Kenya. The color-coding was a flaw in the study design. All dose forms should look the same so patients and doctors could be “blinded.” Unfortunately, the eventual disposition of these lozenges became a mystery. Some of these placebo and active lozenges became commercially available and were sold in Kenya.

In November 1989, Dr. Koech made a public announcement that a remarkable new AIDS treatment had been discovered; he named the treatment KEO89. At the 10th anniversary of the founding of KEMRI, in February, 1990 Dr. Koech announced that the new AIDS “wonder drug” was to be called “KEMRON<sup>®</sup>.” The Kenyan press started carrying bewildering, inaccurate claims attributed by the press to Dr. Koech. KEMRON<sup>®</sup> was “manufactured in a secret Nairobi laboratory” in one report. In another story, the KEMRON<sup>®</sup> was “manufactured” and “invented” by Dr. Koech and the country of Kenya was going to benefit from royalties and recognition of this Kenyan invention. Suddenly there was great pride in Kenya that someone in “Black Africa” had developed a “cure” for African AIDS.

In the Spring of 1990, stories appeared that KEMRON<sup>®</sup> was selling for \$40 (US) per dose in Africa. Apparently, the lozenges I had delivered free for the double-blind, placebo-controlled study were being sold. The stories of KEMRON<sup>®</sup> sales and the claims in the press of an “African cure” for AIDS cast a cloud of suspicion over our dealings in Africa. A physician in Uganda had purchased KEMRON<sup>®</sup> in white and blue foil. The lozenges in white foil were placebo. He reported that the 4 patients who took the white lozenges died but that the 8 patients on blue foil wrapped KEMRON<sup>®</sup> (2 IU per dose) did very well. That single “blinded, placebo-controlled” report was the only firsthand report received from anyone regarding the thousands of lozenges sent to Kenya. Dr. Koech later explained that he did not want to give placebo to any patient because it was “unethical.”

In the Spring of 1990, Dr. Koech was told that WHO (World Health Organization) wanted to test KEMRON<sup>®</sup>. Dr. Koech delivered the green foil wrapped lozenges to WHO for a “multi-centre” clinical trial of 4 week’s durations. One hundred eight (108) patients were treated in 5 different countries in Africa (Ivory

Coast, Zimbabwe, Kenya, Cameroon, and Congo). The trial was designed to assess the patients after 2 and 4 weeks on “KEMRON<sup>®</sup>” treatments. The green foil wrapped lozenges were subsequently assayed at 183 IU per lozenge; the WHO patients all received that once daily dose for 4 consecutive weeks. The WHO reported (Report of a Meeting to Review the Results of a Multicentre Trial to Evaluate the Efficacy of Low Dose Alpha Interferon in the Treatment of AIDS) to the press in May 1990 that the results were “inconclusive” and “did not replicate” the beneficial reports from Kenya. However, WHO’s written report actually reported that many of the initial clinical signs and symptoms (oral candidiasis, fatigue/weakness, appetite loss, insomnia, night sweats, dysphagia, cough, diarrhea, pruritus) were ameliorated by the end of the study in over 60% of the patients. It is likely that a 6-month treatment, not a 4-week treatment, is required to produce a benefit in an AIDS patient.

In the spring of 1990, Terry Beirn of the American Foundation for AIDS Research (AmFAR) decided to test KEMRON<sup>®</sup>. Mr. Beirn recommended Toronto, Canada as a suitable test location where he wanted to demonstrate that clinical research could be conducted at the Community Research Initiative - Toronto (CRIT). With Mr. Beirn’s encouragement, some financial support from AmFAR, a cooperative Health Protection Branch of the Canadian Ministry of Health, and enthusiastic AIDS physicians in Toronto, a clinical trial in Canada was planned.

In July, 1990, Secretary General Nakajima of the WHO met with representatives of HBL and the Japanese Ministry of Health and Welfare (MHW). Mr. Nakajima demanded that the MHW deny HBL export approval for any more testing of HBL IFN $\alpha$  in AIDS patients. MHW and HBL wanted to honor Secretary General Nakajima’s request.

The immediate impact of Nakajima’s action was that HBL IFN $\alpha$  could not be obtained for the clinical trial in Toronto. After months of delay, Mr. Beirn of AmFAR wrote a FAX to WHO on Senator Ted Kennedy’s letterhead and demanded an explanation from WHO as to why WHO was blocking the CRIT study. WHO immediately replied denying any involvement in blocking of the CRIT study. In a few days, clinical supplies were released from Japan and the CRIT study began in early 1991.

Terry Bern was an energetic, innovative thinker and it was a great loss when he died of AIDS on July 16, 1991. The Community Program for Clinical Research in AIDS (CPCRA) was later named the Terry Beirn CPCRA to honor his pioneering efforts to generate research support for AIDS trials.

One hundred fifty (150) men participated in the Canadian study. For 8 weeks, these men took either placebo, or 50 or 100 IU of HBL IFN $\alpha$  daily. None of the benefits reported in Africa occurred in the population treated in Canada (*JAIDS* 5:1084-1090, 1992). We immediately began to question the dose and timing of administration of oral HBL IFN $\alpha$  and the influences of race, gender,

opportunistic infections and diet on the different studies. Why would black Africans respond differently from white Caucasians in Canada?

While the Canadian trial was in the planning stages, Brendon O'Regan in San Francisco representing an organization called the Institute of Noetic Sciences, asked if he could test low-dose oral IFN $\alpha$  in cancer patients in Nuremberg, Germany with Professor Gallmeier. Arrangements were made to deliver HBL IFN $\alpha$  to Germany with the expectation that cancer patients would be treated. However, because of the "hype" out of Kenya about oral IFN $\alpha$  and AIDS, Professor Gallmeier and his colleague Dr. Kaiser decided to use the lozenges on AIDS patients, instead of cancer patients. A study of 30 German patients was conducted for 12 weeks, 6 weeks on 200 IU IFN $\alpha$  once daily and 6 weeks on placebo. The results were disappointing as the Germans did not respond as the Kenyan population was reported to respond. Only a transient (at 2 and 4 weeks, but not 6 weeks) improvement in CD4+ cell counts was noted (data published AIDS 6:563-569, 1992). We wondered again why a black African population responded differently from white Caucasians in Germany.

A physician in New York state called to report on how to help oral IFN $\alpha$  work in HIV+ patients. "The patients need to eat kale," the doctor said. Dr. Obel reported that kale was a staple in the diet of Kenyans. Kale has been reported to have a positive effect on the immune system. See <http://nutritionfacts.org/video/kale-and-the-immune-system/>

Other AIDS studies using oral IFN $\alpha$  were conducted from 1989-1994 in Kenya, Zambia, Uganda, the Philippines, Thailand, New York, Puerto Rico, Japan and Canada involving over 1000 patients. A study at Mahidol University in Bangkok tested placebo and 100 or 200 IU of HBL IFN $\alpha$  given daily for 6 months. Dr. Prasert Thongcharoen who was the principal investigator in Thailand reported a significant weight gain and relief of symptoms in AIDS patients given 200 IU of HBL IFN $\alpha$  per day.

In a study conducted with Dr. M. Mukunyandela of the Tropical Diseases Research Center in Ndola, Zambia, a total of 150 HIV-positive patients were treated for 24 weeks with lozenges containing 150 IU of HBL IFN $\alpha$  or a matching placebo (J. Interferon Res. 14 (1) S140, 1994). One group of patients took active lozenges one week and placebo lozenges the next. One group took IFN $\alpha$  daily and one group took placebo daily. The treatment group that took 150 IU IFN $\alpha$  lozenges continually experienced significantly fewer new HIV-related opportunistic infections, compared to the placebo group, while both groups of IFN $\alpha$  treated patients tended to gain CD4+ cells, while the CD4+ cells of the placebo group remained flat.

From these many studies, data accumulated which allowed an IFN $\alpha$  dose to be chosen for the National Institutes of Health (NIH) oral IFN clinical trial (DATRI 022). A total of 560 AIDS patients were to be enrolled to three different sources of oral IFN $\alpha$  versus

placebo. After years of planning, it was announced in February 1995 by the AIDS Research Advisory Committee that the oral IFN $\alpha$  AIDS study was approved. In July 1995, the NIH ordered the clinical supplies for delivery to enroll patients. Unfortunately, because of slow enrollment, the study was halted in June 1998 and no meaningful results were possible. Because 560 patients were needed to provide sufficient "power" to analyze the data. NIH objected published their conclusion based on too few patients. The DATRI 022 data was published in the Journal of Acquired Immune Deficiency Syndromes (JAIDS). The summary in JAIDS concluded with the statement that "the small differences among the arms in the primary and secondary endpoints do not support claims of efficacy for the measures studied." Based on the power calculations for the trial, there were too few subjects enrolled and far too few subjects who finished 24 weeks of treatment to draw any definitive conclusions on treatment efficacy; and in those who did finish 24 weeks, significant differences were noted between treatment groups in CD4+ cell counts, depending on how the data are examined. There are additional areas of concern with the data, as detailed below.

The DATRI 022 study was designed to enroll 560 subjects to detect differences in treatments. It was reported in JAIDS that only 247 evaluable study subjects were enrolled and data on CD4+ cell counts of 89 subjects who completed 24 weeks were presented. Therefore, 44.1% of the necessary number of subjects were enrolled and only 15.9% of the projected 560 subjects completed the study. The JAIDS conclusion that these data "do not support claims of efficacy" for the measures studied therefore is not correct. The protocol design was such that a larger number of subjects was needed to detect a significant difference between treatment groups. It is a statistical truism that one cannot draw a definitive conclusion based on an underpowered clinical trial. That should have been acknowledged in the JAIDS publication and have tempered the conclusions. Due to the inadequate number of study subjects, definitive conclusions should not have been made.

Lozenges containing 150 IU of HBL IFN $\alpha$  were delivered to the WHO in 1991 so WHO could conduct a clinical trial of AIDS patients in Uganda. A total of 559 patients cooperated in the trial and were given either placebo or IFN $\alpha$  daily for up to 6 months; however, the majority of the patients were treated for 30 days or less. Many patients died during the study due to "diarrhea," tuberculosis and other complications associated with AIDS. Many patients had no or very few CD4+ cells (mean baseline CD4+ cell count was only 60 cells/cu.mm) upon entry to the study thereby forecasting a probable early death. Indeed, nearly a third of the patients died during the study. Even under the severe circumstances of the WHO study, a CD4+ cell count improvement was noted for 18 weeks, but the HBL IFN $\alpha$  therapy did not provide a beneficial effect on mortality. For months WHO was asked to share the data so we could determine if there was a subset of patients (e.g. - males with initial CD4+ cell counts >200) who might have benefitted

from treatment with oral IFN $\alpha$ . WHO did not provide the data for further analysis. They published their conclusions in *Sex Transm Inf* 74:265-260, 1998. Oral IFN $\alpha$  benefits are most readily induced in patients with baseline CD4+ cell counts >200 treated for 6 months.

There is probably no single agent, which can be given to AIDS patients with a CD4+ cell count of 60, which will seem beneficial. Many of the patients in the WHO study entered with CD4+ cell counts of zero. It is not surprising that nearly 1/3 of the patients died.

Even though low-dose oral IFN $\alpha$  therapy for AIDS patients was severely criticized by the AIDS “establishment,” Dr. Wilbert Jordan of Los Angeles used oral IFN $\alpha$  with beneficial effects that he reported in the *Journal of the National Medical Association* (Vol. 86, No. 4, p. 257, 1994 and Vol. 89, No. 10, p.647). Dr. Jordan tested HBL IFN $\alpha$  under a physician’s “IND” (Investigational New Drug Application). Dr. Jordan has given the oral IFN $\alpha$  technology

his support and has demonstrated his pioneering research spirit. Against all the critics who, without testing oral IFN $\alpha$ , deny the effects of oral IFN $\alpha$ , Dr. Jordan offers his years of clinical observations of its benefit.

## **AIDS Summary**

Orally administered IFN $\alpha$  has been tested in 23 studies of patients infected by HIV-1. The preponderance of data (review published in 2004 in *AIDS Vaccines and Related Topics*, pages 11-30) suggests that orally administered IFN $\alpha$  is useful in the management of opportunistic infections in HIV+ patients. AIDS is an epidemic out of control in some parts of the world. The clinical efficacy observed with oral IFN $\alpha$  in HIV+ patients, the ease of administration, lack of toxicity, room temperature stability and low cost of oral IFN $\alpha$  indicates that oral IFN $\alpha$  may have a role in helping manage AIDS.