Executive Summary: "Immunotherapy and Beyond"

Immunotherapy and Beyond is a review of scientific literature compiled by Dr. Victoria Wulsin at the request of the Heimlich Institute between August and December 2004.

Dr. Hank Heimlich, inventor of the Heimlich Maneuver, contended that AIDS, which attacks white blood cells in the human immune system, might be countered when white blood cell production was intensely stimulated in response to malaria. He found precedent for this hypothesis in vaccination—the long-established medical practice of exposing patients to disease in a controlled environment in order to enhance their bodies' immune responses.

However, Dr. Wulsin concluded in her review that "The preponderance of evidence indicates that neither malaria nor Immunotherapy will cure HIV/AIDS."

As Thomas Francis reported in Radar Online in November 2005, "the day after issuing a draft of her report…Wulsin was fired" by the Heimlich Institute.

In her review, Dr. Wulsin raised the following objections:

- A review of the related scientific literature showed a "trend over time of decreasing support for Immunotherapy."
- There was "complexity and inconsistency of data apropos of the effect of malaria" on AIDS.
- "Patients must be informed of – and understand - the relative costs and benefits to Immunotherapy and its alternatives. …Research protocols must be approved by local (operating) and donor (managing) institutional review boards. These authorizations should be readily available for examination by any critics, patients, potential collaborators, or others."

In summary, Dr. Wulsin informed the Heimlich Institute that their research on Immunotherapy should not go forward unless they:

- Clarified the ethical and scientific details of past studies.
- Ensured that future studies conformed to strict ethical standards.
- Acknowledged the ever-growing scientific consensus that Immunotherapy was ineffective for fighting AIDS, and were willing to engage in "transparent discussion [of their research] with scientists, physicians, and other stakeholders."

She also warned that the Heimlich Institute would face a credibility and sustainability crisis if it continued to pursue its current path. She suggested that it consider more promising avenues of AIDS research, such as highly active antiretroviral therapy, while insisting that it could not do effective research until it overhauled its research and operating methods.

Dr. Wulsin's involvement with the Heimlich Institute and Immunotherapy was strictly limited to this literature review. At no point was she involved in the Institute's clinical research. Dr. Wulsin discussed her interactions with—and ultimate dismissal by—the Institute in a November 11, 2005 Radar Online article, "Outmaneuvered" (www.radaronline.com/web-only/radar-investigates/2005/11/outmaneuvered-part-ii.php).

Immunotherapy and Beyond

Heimlich Institute

D – R – A – F – T

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I. Background

Three months ago I began a consultancy with the Heimlich Institute [HI] for two reasons. First, I was to evaluate the viability of Malariotherapy Therapy as a focus for HI and to recommend to HI's Board of Directors the requisite next steps in developing it as a life-enhancing &/or life-prolonging intervention for persons living with HIV/AIDS. Second, I would identify the comparative advantage ("market niche") of the Heimlich Institute in developing Immunotherapy or any aspect of life-enhancing &/or life-prolonging interventions.

II. Methods

My approach to resolving the issues was approved by my two supervisors – Dr. Henry J. Heimlich [HJH] and Mr. Thomas Powell. Approximately every two weeks I have presented formal status updates to them and Dr. Eric Spletzer [ES] to ensure corroboration. I have modified my activities to comply with their recommendations from each of these sessions.

Three approaches comprised my methods. First and most importantly, I reviewed the literature on the public health significance of AIDS, malaria, and co-infection, the scientific significance of relationship between AIDS and malaria, and specifically, the evidence for Immunotherapy. The types of investigation included ecological surveys, *in vitro* analyses, animal research, epidemiological studies, and clinical trials. Immunotherapy for HIV/AIDS has undergone both phase I (safety) and phase II (effect) clinical trials. A question to answer during this consultancy was whether HI could now move into phase III (efficacy) and phase IV (population-based effectiveness) trials.

I reviewed over two hundred articles, dating from 1984 to 2004. In addition to summarizing the key findings of each, I noted the author/s, the institution with which they were affiliated, the reputation of the journal where the article appeared, whether original data were analyzed (versus secondary analyses or review articles), and the date of publication. I further critiqued the articles using standard epidemiologic criteria: sample size, type of study, direction of association, magnitude of association, dose-response, reliability, confounding variables, rigor of analysis, potential bias, and statistical significance.

Secondly, I would conduct independent analyses on available data that had not been published. I have been unable to glean additional data from China, but have obtained raw data from East Africa. Thirdly, I planned to speak to as many of the leaders in the field of Immunotherapy as possible, beginning with HJH and ES, and leading to a site visit of ongoing trials in China and/or East Africa. I have succeeded in speaking directly with several scientists involved with malaria, HIV/AIDS, and/or Immunotherapy, but was unable to speak to key contacts in China and East Africa.

The site visits did not materialize due to severed relations (China) and logistical difficulties (East Africa).

The relative weight given to each of the following criteria may be subjective, but all must be considered:

1) Evidence
2) Ethics
3) Feasibility
4) Alternatives

III. Results: Literature Review

The public health significance of AIDS, malaria, and co-infection with both is not controversial. At the beginning of the AIDS pandemic, the major concern regarding co-infection stemmed from the transmission of HIV through the blood transfusions required to treat anemia secondary to malaria. Before testing for HIV in donated blood became routine, contaminated transfusions were a major source of HIV, particularly in childhood

To understand Immunotherapy, the history of malaria must be reviewed. In the New World, malarial interventions focused on eradication of the vector, the *Anopheles* mosquito. By the late twentieth century, malaria in the USA arises from imported cases. Many countries in Latin America destroyed the *Anopheles* mosquito population through extensive DDT campaigns in the 1960s.

In Asia and Africa, interventions focused more on individual behavior: avoiding mosquitoes and treatment of infection. However, highly effective and relatively inexpensive treatment with chloroquine became ineffective in the 1980s as resistance appeared around the world. As early as 1989, the case fatality of 21.1% among children was in no small part due to chloroquine-resistance.[1]

Because of the high prevalence of malaria in Africa, where HIV prevalence has been highest throughout the history of the AIDS pandemic, public health officials anticipated that malaria would be a leading cause of death among AIDS patients. However, early reports found no association[2] between the two diseases, with the exception of transfusion-related HIV infections.[3] Interestingly, other parasites have been also identified as *not* being associated with HIV infection, including Trypanosoma brucei and its clinical presentation of sleeping sickness.[4] Reports of improved outcomes of children with HIV who had malarial infections appeared at an international conference in 1990[5] and in peer-reviewed literature the following year.[6]

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[1] Greenberg 1989
[2] Nguyen-Dinh 1987; Colebunders 1990; Fleming 1990; Muller 1990; Butcher 1992
[3] Hedberg 1993
[4] Fleming 1990
[5] Davachi 1990
[6] Greenberg 1991

This salutary effect inspired further investigations by laboratory researchers, immunologists, and epidemiologists. Although the three areas overlap, the findings are arranged according to their most salient category.

Relationship between Date and Support for Immunotherapy

While reviewing the extensive and diverse literature related to AIDS and malaria, I noticed a trend over time toward an increasing number of negative reports compared to positive reports. I decided to quantify this trend by dividing the articles into six groups defined by date of publication. The time periods are uneven because the number of relevant articles varied widely year by year, and I wanted at least 15 articles and at least 1½ years per group. Table 1 catalogs my analysis of the first 207 articles reviewed.

Table 1: Trend over Time of Decreasing Support for Immunotherapy

Group	Dates	# Years	# Articles	Vote			Ratio P:N
				P	N	Other	
1	1984-1989	6	18	6	1	11	6.0
2	1990-1992	3	25	7	3	15	2.3
3	1993-1998	6	32	6	5	21	1.2
4	1999-2000	2	27	2	8	17	0.3
5	2001-2002	2	33	0	9	24	0.0
6	2003-2004	< 2	72	3	13	56	0.2
Total			**207**	**24**	**39**	**144**	**0.6**

P = Positive
N = Negative

The “other” categories included those that did not provided particularly relevant information [n=55]; those that were not clearly encouraging [positive] nor unsupportive [negative] of further scientific investigation of Immunotherapy [n = 46]; those that discussed alternatives to Immunotherapy for focused attention by the Heimlich Institute [n=28]; and those that I deemed neutral [n=15].

Overall, fewer articles supported Immunotherapy than countered it [P:N ratio = 0.6]. Prior to 1990, six times as many articles supported Immunotherapy [P:N ratio = 6.0] whereas in the past 1½ years, five times as many articles did not support it [P:N ratio = 0.2]. The intervening 13 years demonstrated a somewhat consistent pattern of increasing disapproval over time.

Laboratory Analyses

Both *in vitro* analyses and animal research have demonstrated the complexity of the relationship between HIV and malaria. Not only do humans and mice have differences as well as similarities,[7] the specific chemicals involved with the immunologic response have different effects on the host. For example, some cytokines ameliorate and others worsen malarial infection.[8]

Another source of complexity is the difference in biological response depending on the length of time since infection. For example, *in vitro*, HIV-1 replication increases by one or two orders of magnitude (ten to a hundred times) in peripheral blood mononuclear cells exposed to malaria antigens or malaria pigment.[9] This effect, mediated by enhanced expression of the cytokine tumor necrosis factor, appears to be short-lived. Likewise, in mice, death due to cerebral malaria was prevented by murine AIDS [MAIDS, the type of AIDS to which mice are susceptible], "but the onset of antimalarial immunity is increasingly hindered as the virus-induced immunodeficiency progresses."[10] Furthermore, "following injection of the [malarial] parasite into profoundly immunosuppressed mice, certain manifestations of MAIDS were partially reversed…including a…50% weight loss of lymph nodes."[11] However, no difference in virus load was observed in mice that were infected with MAIDS and those not infected. The authors note "…these rodent models clearly show that interactions exist between viral and malarial infections. ***These are complex, their nature depending on the stage each pathogen has reached in evolution of disease***."[12] [Emphasis added.]

Immunologic Evidence

Entering the realm of human immunologic studies compounds the complexity and inconsistency of data apropos of the effect of malaria, or either of its main infectious agents, *Plasmodium falciparum* and *Plasmodium vivax.* This section is divided into three parts. First, the effects of malaria on white cells (e.g., CD4) and human cytokines are summarized and compared to the effects of other infectious agents on specific immunologic markers. However, studying the immunologic effects only indirectly predicts the likely effects on HIV. "CD4 cell counts can't be counted on to predict progression [of HIV to AIDS or AIDS to death] in the absence of viral loads."[13] Hence, second, the reported effects of malaria on HIV load itself are reviewed. Third, the effects of HIV on malarial infection are briefly documented, because of the relevance of malarial infectivity of HIV-positive patients with malaria on both HIV-positive and HIV-negative contacts.

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[7] Harpaz 1992
[8] Harpaz 1992
[9] Corbett 2002
[10] Marussig 1996
[11] Marussig 1996
[12] Marussig 1996
[13] Hennessey 2000

How Malaria and Other Parasites Affect Immunologic Components

Malaria has been reported to elevate[14] and to lower[15] CD4 count, the cells that are host to the human immunodeficiency virus. Both *Plasmodium falciparum* and *Plasmodium vivax* cause elevations of Interleuken-2R [IL-2R], a cytokine associated with increased immunologic vigor. Other parasites have the same effect on IL-2R, and the most potent has been found to be visceral leishmaniasis.[16] The increase in IL-2R is indirectly associated with age (probably because adults have partial immunity) and directly associated with clinical severity.[17] The elevation in IL-2R lasts only a few days or weeks - not months. "High circulating levels of IL-2R might be able to bind IL-2 and be responsible for the immunosuppression observed during the acute phase of malaria. Whether this increase has beneficial or negative (as Tumor Necrosis Factor) effects also remains to be clarified."[18] Some cytokines protect, others worsen malarial infection.[19]

How Malaria Affects Viral Load

An increase in viral load is correlated with proinflammatory cytokine response.[20] However, the relationship between CD4 counts and HIV load is not uniformly predictable. "Of those subjects with CD4 T-cell counts measured within thirty days of viral load quantification, there were statistically significant negative correlations between HIV-1 load and CD4 counts for groups with asymptomatic infection and for AIDS, but not for patients with symptomatic infection."[21] Hence quantification of viral loads is a necessary aspect of analyzing the effects of malaria on clinical HIV/AIDS.

Acute malaria can up-regulate HIV replication, leading to higher plasma viral loads.[22] The HIV burden has been reported to be higher in patients with *Plasmodium falciparum* compared to controls, leading one author to suggest that "suppressing malarial infection may lower HIV viral burden."[23] More recent information corroborates this proposition: "If present observations of a transient increase in viral load during malaria episodes, and its reversibility with effective treatment of malaria, hold in prospective studies, malaria control may be beneficial in curbing HIV-1 transmission and the rate of disease progression."[24] Malaria as a co-infection

[14] Heimlich 1996
[15] Chirenda 1999
[16] Josimovic-Alasevic 1988; Fleming 1990
[17] Nguyen-Dinh 1988
[18] Deloron 1989
[19] Harpaz 1992
[20] Lawn 2004
[21] Ho 2000
[22] Rowland-Jones 2002
[23] Hoffman 1999
[24] Corbett 2002

increases HIV load.[25] However, in one controlled[26] and one uncontrolled[27] series, viral loads returned to baseline following temporary increases (as much as seven times baseline in the controlled study) during malarial infection. In fact as early as 1992, Estambale reported that *Plasmodium falciparum* might favor more rapid evolution of the HIV infection.[28] Quantitatively, a 116% higher viral load has been reported in patients with malaria parasites at baseline leading one author to conclude: "Although the long-term effects of malaria on viral load are unknown, prevention of malaria among people living with HIV1 should be given the highest priority."[29]

How HIV Infection Affects Malaria

Recent evidence demonstrates that persons with HIV are more liked to experience clinical malaria than those without HIV.[30] Among HIV+ persons, parasitemia is more common, lower CD4 counts are associated with higher parasite densities, and clinical malaria is more common.[31] Quantitatively, the mean parasite density has been reported to be 12-fold higher in HIV-positive compared with. HIV-negative patients.[32] A recent review concluded that "Multiple cross-sectional studies…showed no association between malaria & HIV….more recent studies find higher parasitemia in HIV+ pregnant women…and more clinically diagnosed malaria among HIV-positive Ugandan adults."[33]

Epidemiologic Studies

Like the laboratory and immunologic work discussed previously, the epidemiologic data are also conflicting. Because many studies are cross-sectional, it is difficult to separate the effect of HIV on vulnerability to malaria (infection, progression, duration, severity, and prognosis) from the effect of malaria on vulnerability to HIV (infection, progression, duration, severity, and prognosis). For example, among children HIV infection appears protective to malaria [Prevalence Ratio = 0.72-0.94]: that is, children with HIV are *less apt* to be infected with malaria than children without HIV.[34] However, HIV in children is associated with severe, complicated malaria,[35] [Odds Ratio = 2.3] and death [Odds Ratio = 7.5].[36] Among adults, HIV has been reported to have a positive [Prevalence Ratio = 0.69] and a negative[37]

[25] Lawn 2004
[26] Corbett 2002
[27] Chen 2003
[28] Estambale 1992.
[29] Kapiga 2002
[30] Rowland-Jones 2002; Harms 2002
[31] Whitworth 2000
[32] Birku 2002.
[33] Holmes 2003
[34] Chandramohan 1998
[35] Grimwade 2003; Grimwade 2004
[36] Grimwade 2004
[37] French 2000; French 2001; Corbett 2002; Khasnis 2003

[Prevalence Ratio = 3.3;[38] Adjusted Odds Ratio = 9.75[39]] relationship to malaria. Malaria has been found to be more frequent[40] and more severe among HIV-positive persons.[41] Data from Africa indicate that the risk of developing severe malaria is 2.35 times among those with HIV compared to HIV-negative individuals.[42]

Mother-to-Child-Transmission of HIV

Recent reports of increased morbidity,[43] mortality,[44] or both[45] among pregnant HIV-positive women exposed to malaria have led researchers to investigate the effect of malaria on the mother-to-child-transmission [MTCT] of HIV. Data conflict regarding the change in rate of transmission. MTCT is not increased in the presence of malaria despite the increased morbidity and mortality among the mothers.[46] Similarly, elevated rates of malaria and placental malaria among pregnant women with HIV were not associated with *in utero* or peripartal transmission of HIV.[47] Others report an approximate threefold rate of transmission, controlling for viral load.[48] This particular group warrants further investigation to elucidate the immunologic relationships among HIV, malaria, and pregnancy.

Immunotherapy

Immunotherapy was used effectively as a treatment for neurosyphilis until improvements in public health, such as follow-up of partners, precluded its necessity.[49] Although the mechanism of action is unknown, more recent publications indicate that the malaria works as a stimulating factor boosting the patient's immunologic capabilities.

In 1991 Dr. Henry Heimlich proposed Immunotherapy for the treatment of AIDS. In 1993 he began collaborating with Chinese investigators to conduct a Phase II Clinical Trial. Eight patients demonstrated increased CD4 cell counts for two years following a single treatment [3-4 week course] of Immunotherapy.[50] Viral loads were not available. The course during the subsequent eight years is unknown, because the study was designed to follow the patients for two years only. [The H.I. ceased collaboration when the Chinese insisted that funding for more studies be sent prior to

[38] Chandramohan 1998
[39] Francesconi 2001
[40] Chirenda 2003
[41] Chirenda 2003
[42] Chirenda 2000
[43] Huff 2001
[44] Corbett 2002
[45] Rowland-Jones 2002
[46] Corbett 2002
[47] Inion 2003:
[48] Brahmbhatt 2003; Cohen 2003
[49] Chernin 1984
[50] Heimlich 1996

results being obtained.] The mechanism of action is not known but postulated to be due to a general immunologic stimulation due to malaria.

The Chinese have continued to study Immunotherapy. In a total of 20 subjects, side effects, such as organomegaly [increased size of spleen &/or liver] in 75-95% of patients disappeared within one month.[51] In 12 subjects, CD4 counts and viral loads were not adversely affected by malaria.[52] Results of this Phase II Clinical Trial indicate that patients with CD4 counts greater than 500 are not suitable candidates for Immunotherapy because of sub-optimal outcomes.[53] The authors write in their most recent article, "In conclusion, malariotherapy [sic] benefited some of the HIV-infected patients [with CD4 counts at 200 – 499] as they experienced increases of CD4 cell counts and percentages and their HIV viral load remained relatively unchanged for at least 1-2 years after therapy."[54] They end with the hypothesis that highly active antiretroviral therapy [HAART] plus malariotherapy [sic]may eradicate HIV *in vivo.*

IV. Results: Independent Analyses

Recent data from a nine-month follow-up of a small (n = 8) series of HIV+ patients infected with *Plasmodium falciparum or Plasmodium vivax* in East Africa have been shared with the Heimlich Institute. These infections were acquired naturally, but not treated for at least two weeks following the first fever. These eight patients were among many patients interested in trying this novel therapy. Patients with CD4 counts in the range of 200 – 500 were considered ideal. Patients with CD4 counts less than 200 were excluded, with the exception of the first volunteer who was particularly keen to participate. Viral loads, history of malaria, age, and pregnancy status were not considered as inclusion or exclusion criteria. The potential risks and benefits were explained to the patients. In addition to these 8 patients, 4-5 others underwent malarial infection, but were lost to follow-up.

Clinically, the eight patients continue to do well. Patient #1 has had a secondary infection, treated with antiretroviral drug therapy [HAART]. Patient #8 has been treated with "Bactrim" for tuberculosis but is now well. All eight report weight gain and feeling well, and none has progressed to AIDS.

Drs. Spletzer and Heimlich state that naturally acquired malaria *does have* the same immunologic effects as Immunotherapy. The difficulty in using naturalistic epidemiologic studies is twofold. First, the infection needs verification. (Our East African colleagues are currently verifying the malarial infection in the eight subjects.) Second, treatment can confound responses, because usual treatment for malaria (chloroquine) has some antiretroviral effects.[55]

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[51] Chen 2003b
[52] Chen 2003a
[53] Chen 2003a
[54] Chen 2003a
[55] Corbett 2002

Seven of the eight patients have marked reductions in viral loads without any antiretroviral therapy. Among four, the level is below detectable limits (LDL means a viral load < 50 copies/microliter). Unlike HAART, malarial infection sustained these low levels nine months – without any antiretroviral therapy in seven of the eight patients. Follow-up is continuing to determine how long the reductions in viral load last. Changes in CD4 counts were neither marked nor consistent. Key data are summarized in Table 2 below.

Table 2: CD4-Counts and Viral Loads among HIV-positive Patients Infected with Malaria

#	Sex	Age		Pre-malaria	Post-malaria	6 weeks	3 months	6 months	9 months
1	M	42	CD4	124	178	71			
			Viral load	2,046,614	101,286	445,217			
2	F	27	CD4	548	324	459	468	412	360
			Viral load	793,600	661,383	144,659	278,828	3388	4,012
3	F	24	CD4	589	504	273	460	395	340
			Viral load	23,386	49,072	10,128	20,654	6600	1,699
4	F	25	CD4	364	454		345	341	376
			Viral load	5,306	7,320		LDL	LDL	LDL
5	F	27	CD4	505	794	746	577	639	661
			Viral load	1,693	9,109	1,025	2,646	3,960	LDL
6	M	30	CD4	598	324	366	440	289	441
			Viral load	257,306	326,421	163,334	594,650	37,620	40,585
7	F	22	CD4	605	405		334	550	544
			Viral load	12,874	24,444		4269	667	LDL
8	F	21	CD4	764					1076
			Viral load	1,365					LDL

The reported salutary effects of malaria on the immune system ("immune boosting") appear to be similar to those of other microbiological agents, scrub typhus and *Schistosoma mansoni*.[56] In fact, some of the positive effects, including increased CD4 counts [p = 0.005] and decreased viral loads [not statistically significant] have been reported in HIV-positive individuals infected with helminthes.[57]

Other microbiological agents indeed boost the immune system, but only the parasite that causes malaria [*Plasmodium vivax*] has been proven safe as a therapeutic agent. In addition to treating neurosyphilis, Immunotherapy has decreased the size of tumors among cancer patients followed at the National Cancer Institute of Mexico, Dr. Heimlich reported.[58]

[56] Lacroix 1998
[57] Elliott 2003
[58] Heimlich 2004

V. Ethics

"First, do no harm," is a fundamental *sine qua non* of medical training. Not surprisingly, Immunotherapy has received sporadic, but not inconsequential, criticism from the medical establishment as well as others. Institutional review boards (IRBs) at research establishments serve the purpose of protecting patients from over-zealous scientists who might, with the best possible intentions, nevertheless unnecessarily expose vulnerable and disempowered patients to risky and potentially life-damaging or life-shortening treatments, procedures, and interventions. "Informed consent" from study subjects is a necessary but insufficient component of accepted clinical research.

The political atmosphere surrounding HIV/AIDS patients is particularly sensitive, in large part due to a) the terminal nature of the disease; b) the societally-censured major modes of transmission (sex and injecting drug use); c) its higher prevalence among marginalized groups such as homosexuals, persons of color, Africans, and commercial sex workers; and d) controversy and the perception of inconsistent or inadequate measures to stop its spread.

Research in Third World countries, notably in Africa, has notoriously neglected sanctions from operational (usually local) and supporting/donor (often First World) institutions through IRB approval. Given the discrepancy in standard of care between the First and Third Worlds, clinical trials should be conducted only with approval from both local and donor IRBs.

VI. Feasibility

Protecting patients is one reason that scientific investigations typically follow four discrete stages. Practical considerations such as time, personnel requirements, funding, side-effects, etc. also support conducting research in stages. Phase I trials demonstrate the <u>safety</u> of the proposed intervention on a handful of persons – often healthy volunteers (including laboratorians themselves) to be sure that the medical credo "Do No Harm" is observed. Phase I trials are sometimes omitted when the intervention has been proven safe in other milieus. However, investigators must be cautious lest the putative reason for intervention sufficiently alters the host/s that previous peripheral experiences do not pertain.

Phase II clinical trials study the hypothesized <u>effect</u> of the intervention among enough patients to convince donors to support further research. Phase II trials are typically small (~ 10-20 patients) because "venture capital" in an untested intervention is very limited. Despite their small size, Phase II trials typically satisfy standard operating procedures of design, analysis (including statistical significance), individual (informed consent) and institutional (IRB approval) protocols. However, control subjects are not required. Both the Chinese and East African pilot studies of Immunotherapy qualify as Phase II trials.

During Phase III trials clinical efficacy is demonstrated. That is, under special circumstances – those of a research environment – the intervention makes a significant[59] improvement in patients' outcome. Phase III trials almost always include a control group: patients as identical to those receiving the experimental therapy as possible. "Randomization" and "blinding" study subjects and investigators further strengthens the comparability between the two groups. Successful completion of a Phase III trial leads to the gold standard: a Phase IV study of effectiveness. Clinical effectiveness refers to "real world" situations in which the hypothesized improvement can be utilized consistently and reliably.

Some key issues of feasibility affect every phase of Immunotherapy trials:

- Stigma surrounding HIV status.
- Prejudice against Immunotherapy.
- Sensitivity about conducting research in Africa or other Third World areas while not doing the same in the USA.
- Financial cost of recruitment, infection, course of malaria, laboratory and clinical follow-up.
- Palliative care while the patient suffers from malarial symptoms.
- Efficiency of infection with either naturally-acquired or injected *Plasmodium vivax*.
- Potential selection bias.
- Potential confounding by treatment[60] for malaria.
- Minimum follow-up period of 9 months.
- Optimal follow-up period of at least 24 months.
- Loss to follow-up during extended time period.
- Malarial contagion from patients undergoing therapy to others.
- Difficulty of randomization of study subjects.
- Impossibility of blinding study subjects and investigators.

Issues specific to individual phases of Immunotherapy trials are:

- Phase I: safety of *Plasmodium falciparum* as a therapeutic agent.
- Phase II: logistics of infecting, treating, and following-up study subjects.
- Phase III: availability of a control group.
- Phase IV: availability of alternative therapies, including but not limited to HAART.

These general and specific issues of feasibility are taken into account in the projections summarized in Table 3 (see pages 15-16).

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[59] A note regarding the often-overused term "significance." Statistical significance, a requisite for scientific credibility, depends on three crucial factors: 1) absence of bias or confounding variables; 2) magnitude of the difference in effect between groups; and 3) sample size of the groups. On the other hand biological significance refers to a more subjective, less quantitative but no less important, characteristic of scientific results. Biological significance is determined by the impact the intervention has on the disease in question.

[60] Corbett 2002

VII. Alternatives

The major alternative to Immunotherapy as a treatment for HIV/AIDS is the currently accepted standard of care using highly active antiretroviral drugs. HAART's disadvantages are obvious: cost, growing microbiological resistance with consequent diminution in usefulness, side-effects, accessibility, clinical and laboratory follow-up, especially in settings with substandard health infrastructure, and most significantly: lack of curative effectiveness. Nevertheless, the international community, led by the World Health Organization and its integrated AIDS program UNAIDS, is committed to treating 3,000,000 HIV-positive patients by 2005. This "3 by 5" target is strikingly optimistic when viewed against the current number of cases receiving HAART being less than 200,000.[61]

Recently, costs for the drugs themselves have lowered to $140 per patient per year.[62] However, ancillary costs including clinicians' and laboratory fees, transportation, lost-time from work, and treatment for opportunistic infections and palliative care are not included in this calculation.

VIII. Discussion

Reviewing the results of this consultation is limited by several key questions that remain unanswered.

1. What is the infectious agent of malaria in the East African pilot series?
2. What is the financial cost of treating an individual patient with Immunotherapy?
3. What is the optimal number of patients in a treatment group?
4. How can the Heimlich Institute re-establish collaboration with the Chinese investigators?
5. How should the Heimlich Institute utilize the findings from the East African Phase II clinical trial?

Evidence

The literature review and the independent analysis of the East African Phase II clinical trial provide interesting information regarding the relationship between malaria and AIDS, the history of Immunotherapy, and the potential for malarial infection to boost the immune system in certain HIV-positive patients.

The "Relationship between Date of Publication and Vote" is interesting, but only partially helpful, for several reasons. First and foremost, the vast majority (144 of 207, about 70%) of the articles did not clearly support or oppose further work in Immunotherapy. Secondly, the value of articles is not noted in this rough analysis. For example, articles with original data are generally more significant than reviews, but are given equal weight here. The trend over the past ten years of publications being increasingly negative about Immunotherapy may be a result of increased

[61] Gutierrez 2004
[62] James 2004

knowledge about its relative costs vs. its potential benefits. However, the trend may result from political factors that are not based in science. Such political factors must be taken seriously, despite their subjectivity.

The preponderance of evidence indicates that neither malaria nor Immunotherapy will cure HIV/AIDS. Few data address clinical changes during and following malaria and Immunotherapy. The data regarding improving indicators of immune status, such as CD4 counts and HIV load, are inconsistent. The original Chinese studies reported a consistent rise in CD4 counts, sustained over a 24-month period.[63] More recent follow-up indicate some CD4 counts rise and others decline.[64] The East African data are similarly erratic. Overall, five counts decline (Patients 1, 2, 3, 6, and 7) and three (Patients 4, 5, and 8) rise [see Table 2]. Furthermore, during the nine-month follow-up period the levels fluctuate: inconsistently but not unexpectedly.

The possible combinations of levels, durations, and ratios of cytokines associated with the human immune response are infinite. The single best laboratory indicator of HIV progression is probably the viral load itself. This is why the data from East Africa are so valuable. Unfortunately, the only other Phase II trial does not report similar findings.[65] Reasons for the discrepancies include: different infectious agent (*Plasmodium vivax* in China, probably *Plasmodium falciparum* in East Africa); different lengths of time of malarial infection; different treatment of malaria; additional medications; different nutritional or immunological status of study subjects; different sub-type ("clade") of HIV; different underlying immune status vis-à-vis malaria; different mode of transmission of HIV (primarily through injecting drug use in China, heterosexual transmission in East Africa); and different mode of transmission of malaria (injected in China, naturally acquired from mosquitoes in East Africa). Variations in laboratory technique or accuracy could also explain the divergent findings. Nevertheless, the potential for success of Immunotherapy in making a substantial (both statistically and biologically significant) improvement in the lives of HIV-positive patients, based on the East African trials, warrants verification and elaboration.

Ethics

Studies of Immunotherapy are ethically justifiable as long as three conditions are met.

1. Patients must be informed of – and understand - the relative costs and benefits to Immunotherapy and its alternatives.
2. Research protocols must be approved by local (operating) and donor (managing) institutional review boards. These authorizations should be readily available for examination by any critics, patients, potential collaborators, or others.
3. Research protocols should be designed prior to operations. "Fishing expeditions" for possible benefits are no longer warranted. Specific outcomes should be investigated. Any deviations from research protocols must be accounted for.

[63] Heimlich 1996; Chen 1999
[64] Chen 2003a
[65] Chen 2003a

Feasibility

The overwhelming issue related to feasibility is the time required to move from "idea" to "results." Table 3 demonstrates how nearly a decade was required for each of the first two phases of Immunotherapy trials. Extremely optimistic projections (***green*** in Table 3) conclude that another seven years would be the least amount of time required to conclude a Phase III trial. More realistic predictions (***blue*** in Table 3) would put the required time at an additional ten years. *The forecasts are italicized.*

Table 3: Immunotherapy Timetable[66]

Year		Accomplishment/Event
1	1986	CDC agrees to provide *Plasmodium vivax* to the Heimlich Institute to utilize in studies of Immunotherapy for cancer.
2	1987	The Heimlich Institute makes arrangements for studies of Immunotherapy for cancer patients.
5	1990	Davachi reports "Decreased Mortality from Malaria in Children with Symptomatic HIV Infection" at the VI International Conference on AIDS.
		Heimlich suggests Immunotherapy to treat Lyme Disease. His article is published as a letter to the editor of *The New England Journal of Medicine*, arguably the most prestigious medical journal in the world.
		CDC writes to state epidemiologists that Immunotherapy is not recommended for Lyme Disease.
6	1991	Greenberg reports "Plasmodium Falciparum Malaria and Perinatally Acquired Human Immunodeficiency Virus Type 1 Infection in Kinshasa, Zaire," in *The New England Journal of Medicine*. Its abstract concludes "In this study malaria was not more frequent or more severe in children with progressive HIV-1 infection and malaria did not appear to accelerate the rate of progression of HIV-1 disease."
8	1993	CDC circulates another missive with five key points. 1. The effectiveness of Immunotherapy for neurosyphilis is inconclusive. For Lyme disease it is not effective. 2. Clinical malaria has no salutary effect on HIV progression. 3. Neither hyperthermia nor fever improves HIV progression. 4. Malaria and Immunotherapy have measurable risks to patients. 5. Ethics precludes Immunotherapy.
		The Heimlich Institute collaborates with the Department of AIDS Control and Prevention of the Guangzhou, China Center for Disease Control and Prevention. They begin an 18-month follow-up of two Chinese HIV-positive patients treated with Immunotherapy.
9	1994	The Chinese and the Heimlich Institute add six patients to their cohort.
10	1995	24-month and 6-month follow-ups of Chinese patients are completed.
11	1996	The results of the eight Chinese patients are analyzed, discussed, and submitted to *Mechanisms of Ageing & Development*.

[66] Items in *green* and *blue* are projections. Note: years without relevant events are not included.

		Dr. John Fahey, Director of the Center for Interdisciplinary Research in Immunology and Disease, of UCLA agrees to collaborate with the Heimlich Institute.
		Dr. Chen Xiao Ping, chief Chinese collaborator, works with Dr. Fahey at UCLA.
12	1997	*Mechanisms of Ageing & Development* publishes the Chinese results.
13	1998	Follow-up of the eight patients continues in China.
14	1999	Heimlich co-authors the publication of "Phase-1 Studies of Malariotherapy for HIV Infection" in *Chinese Medical Journal* on first eight patients, now followed 24-30 months.
15	2000	An American sponsor initiates discussions with the Heimlich Institute regarding Immunotherapy for East Africans.
16	2001	The Heimlich Institute's collaboration with the Chinese investigators terminates.
		The Chinese add twelve patients to their trial of Immunotherapy.
17	2002	Heimlich presents "Malariotherapy: An Affordable and Accessible Treatment for HIV/AIDS" at the PanAfrica 2002 AIDS Conference in Nashville.
		Michele Ashby of The Denver Gold Group, an international trade association of gold mining companies, introduces Heimlich to twelve CEOs that operate in Africa and other locations, during the Mining Investment Forum 2002 in Denver.
		Three physicians from two mining companies come to the Heimlich Institute in the fall of 2002. Neither company chooses to collaborate at the time.
18	2003	Two publications appear in *Chinese Medical Journal* on all 20 Chinese patients.
		An American sponsor commences infection with malaria among 12-13 HIV-positive East African patients.
19	2004	The Heimlich Institute engages Wells to review Immunotherapy.
		Nine-month follow-up on eight of the East African cohort is shared with the Heimlich Institute.
		Consultation with Dr. Greenberg of the CDC (see 1991) reveals that absence of statistical significance in the sentinel paper obviate its authors' commitment to further study of the possible benefit of Immunotherapy.
20 1	*2005*	*18-24 month follow-up on pilot series of 8 patients concludes with extremely positive results.*
21 2	*2006*	***East African Phase II Clinical trial is published and/or presented and received with enlightened enthusiasm. East African investigator/s and the Heimlich Institute attain IRB approvals.*** ***East African Phase II Clinical trial is published and presented and received with guarded interest.***
22 3	*2007*	***East African investigator/s and the Heimlich Institute [H.I.] enroll initial 75[67] patients.*** ***East African investigator/s and the H.I. attempt to attain IRB approvals.***
23 4	*2008*	***Year 1 follow-up. East African/H.I. study enrolls additional 20-30 patients.*** ***East African investigator/s and the H.I. attain IRB approvals.***

[67] The East African Phase II trial has lost approximately 4 patients to follow-up during its first 9 months. Using this rate, I extrapolate requiring a minimum of 75 patients for an adequate follow-up sample of 50. More conservatively, because loss to follow-up will continue through the final 15 months of the study, we should recruit 100 patients at the beginning.

24 5 5	*2009*	***Year 2 follow-up. East African/H.I. enrolls final 30-40 patients.*** ***East African/H.I. study enrolls initial 20-30 patients.***
25 6 6	*2010*	***Results finalized, analyzed, discussed, submitted for review.*** ***Year 1 follow-up: East African/H.I. study enrolls additional 20-30 patients.***
26 7 7	*2011*	***Results published and presented.*** ***Year 2 follow-up. East African/H.I. enrolls additional 20-30 patients.***
27 8	*2012*	***East African/H.I. enrolls final 40-50 patients.***
28 9	*2013*	***Results finalized, analyzed, discussed, submitted for review.***
29 10	*2014*	***Results published and presented.***

Alternatives

HAART therapy is not the only alternative to Immunotherapy that the Heimlich Institute may want to explore. However, it would require a minimum of a commitment of 7-10 years – similar to the Phase III clinical trial of Immunotherapy – to gain the requisite human, technical, and financial resources to even *begin* credible research focused on HAART.

IX. Conclusion

Immunotherapy: Past, Present, Future

Immunotherapy claims a fascinating history of effectiveness for another largely sexually transmitted epidemic.[68] Its safety was demonstrated over much of the twentieth century, precluding the necessity of Phase I clinical trials for replicating its use for HIV. Phase II clinical trials have resulted in positive, though discrepant, results in 20 Chinese and 8 East African HIV-positive individuals. Currently the Heimlich Institute has no formal association with either of these trials, although the sponsor of the East African work maintains contact with the Heimlich Institute and shares results regularly. No written protocol is available for this innovative work in which patients acquire malaria naturally and are followed thereafter.

Further field studies of Immunotherapy, including Phase III and IV clinical trials, require the verification of the encouraging results from East Africa, elaboration on discrepancies between them and the results from the Phase II trial in China, and professional dissemination and transparent discussion with scientists, physicians, and other stakeholders.

The Heimlich Institute: Strengths, Weaknesses, Opportunities, Threats

A summary of the strengths, weaknesses, opportunities, and threats ("SWOT") of the Heimlich Institute can open the door for a more detailed, relevant, and exhaustive analysis to guide its strategic, operational, and administrative plans. The strengths of

[68] Chernin 1984

the Heimlich Institute center on Dr. Heimlich himself: his brilliance, his creativity, his passion, his reputation, and his development of the Heimlich Maneuver that has saved thousands, if not millions, of lives. Dr. Heimlich does not shy away from controversy and has improved the world on account of his courage and persistence. He has constructed a strong, independent Board of Directors and established a working relationship with a multi-million-dollar non-profit institution, the Deaconess Associations Incorporated.

The weaknesses revolve around the limited personnel and other resources that the Heimlich Institute has had to forge relationships, generate research, and most importantly: publish findings. Even internal documents, such as research protocols and business plans are not obtainable. These limitations lead logically to the opportunities readily available to the Institute: building and re-building scientific and programmatic collaborations, expanding research, and disseminating results.

Three issues loom as potential threats to the vigor of the Heimlich Institute. First, Dr. Heimlich wishes to reduce his role as the leader of the Institute but has not instituted a "succession plan" to sustain the Institute. Second, the financial and institutional affiliations with the Deaconess Associations Incorporated are currently being discussed. The Institute may be in jeopardy of losing ground in these negotiations. Third, previous and current controversies with journalists, scientists, and other stakeholders have not been fully resolved. This may deleteriously affect decision-makers, particularly funders, as the Heimlich Institute moves ahead in the third millennium.

Sustainability: Programs, Finances, Institution

Management theory often divides sustainability into three interlinking components.[69] Programmatic sustainability refers to the strength of the organization's activities to last beyond the leadership of the organization itself. Programmatic sustainability can be further divided into the capacity to conduct each required step of operations: assessment, planning, design, implementation, monitoring, evaluation, adaptation, replication, and dissemination.

Financial sustainability refers to the ability of an institution to fund – and continue funding – salaries, supplies, and support to enact its programmatic agenda. A diverse funding base is generally preferable to a dominant donor or single source of income. Non-profits such as the Heimlich Institute are typically supported through donations from individuals, private foundations, corporations, and public agencies. Generally, the greater the proportion of funding from public agencies – most notably the National Institutes of Health or the United States Agency for International Development – the more productive is the institution. With productivity comes justified prestige. This convention has changed slightly in recent years as private foundations, specifically the Bill and Melinda Gates Foundation, have become substantial players in the arena of scientific research, education, and interventions.

[69] CSTS+ Sustainability Handbook

Institutional sustainability is the third side of the sustainability pyramid. This requires high-quality personnel, with appropriate job descriptions and policies regarding human resources; a vigorous, effective, and diverse board of directors; transparent and trustworthy decision-making; and most importantly, a solid, inclusive, effective, flexible, and scientific strategic plan supported by all the major stakeholders involved in the organization.

X. Recommendations vis-à-vis Immunotherapy

Brainstorming leads to a host of potential actions the Heimlich Institute could take. These are meant for discussion only. They are not meant to be prescriptive.

Programmatic Next Steps

1. Write a strategic plan for the Heimlich Institute.
2. Rename malariotherapy "Immunotherapy" ["IT"].
3. Verify and elaborate on East Africa Phase II trial.
4. Explore further collaborating with Michele Ashby, the Denver Gold Group, and/or the CEOs, medical directors, &/or others of appropriate mining companies.
5. Complete and publish review of Immunotherapy.

Financial Next Steps

1. Write a budget for all activities: research, education, outreach, interventions, etc.
2. Secure funding.
3. Work with the Board of Directors to identify individuals, foundations, and corporations to solicit for financial support.
4. Contact Lynn Tilson to explore hosting a Cincinnati-located fundraiser (e.g., "Henry's Angels").
5. Contact Martha Jones regarding the Gates Foundation
6. Explore NIH for relevant RFAs [Requests for Applications] and RFPs [Requests for Proposals].

Institutional Next Steps

1. Negotiate with the Deaconess Associations Incorporated a relationship beneficial to all concerned.
2. Write a business plan that includes development, operations, and logistics.
3. Schedule a "retreat" for the Board of Directors.
4. Write a succession plan for Dr. Heimlich with clear milestones, assignments, and requisite resources.

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