

# Rethinking

# AIDS

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# VIRAL LOAD

For those who still think that HIV causes AIDS, the latest fad — along with protease inhibitors — is “viral load.” There was a time not so long ago when one of the best arguments against the HIV model was that there simply was not enough HIV in AIDS patients to account for any disease. Actually, it’s *still* one of the best arguments! No, you say? You’ve heard there’s some new technique that finds *tons* of HIV — high *viral load* — in AIDS patients? The old virus-counting method just wasn’t sensitive enough, they say. But a careful look at this new technique reveals serious problems. For one thing, it doesn’t measure HIV, it measures RNA associated with HIV. For another, nearly all of the RNA it finds is manufactured by the test itself! The *load* of HIV it measures is imaginary, and the theory it has spawned is, well, a load of crap.

In early 1995 research teams lead by David Ho [1] of New York University's Aaron Diamond AIDS Research Center and George Shaw [2] of the University of Alabama published adjacent papers in *Nature*. These papers were hailed as disproving the assertion that HIV is not active enough to cause the depletion of T4 cells observed in AIDS. Ho and Shaw claimed to have found an average of over 100,000 HIVs per mL of peripheral blood in their respective cohorts of AIDS patients. This was big news because all previous attempts to quantify HIV blood concentrations came up with averages of only about ten viruses per mL [3].

Four years earlier, in 1991, two other research teams had made a similar claim, reporting that they found "massive covert HIV infections lurking in the lymph nodes" of AIDS patients. That also was big news because all previous attempts to quantify the fraction of T4 cells infected by HIV in AIDS patients had come up with a paltry average of only about one-per-500 [3].

Before the "lurking lymph node" and Ho/Shaw papers, HIV enthusiasts had a very hard time explaining how HIV could possibly cause AIDS. Not only had HIV shown up in low blood concentrations and in small fractions of cells, it had demonstrated itself to be non-cytotoxic, meaning that when it

replicates, it does so without killing its host cell. When other viruses cause disease, they replicate in a manner that destroys the host cell, and are so prolific they show up at concentrations of hundreds of thousands to millions per mL of circulating blood, and infect one-third to two-thirds of all target cells [3].

So by existing standards of virology, HIV should have been dismissed as a non-pathogen. Since all the early AIDS patients were shown to have unusual, biologically-significant health factors such as street drug consumption, blood transfusions, and hemophilia, there really was no reason to pursue HIV as the only possible cause. But instead that's just what happened.

## Two-Front War

The virus hunters needed to explain how HIV, a biochemically inactive virus, could cause devastating disease. They set off in two directions.

Some went searching for mechanisms to explain how a virus (a non-cytotoxic one) could cause the death of more cells than it infected. The others, including Ho and Shaw, went searching for HIV itself, hoping to find large amounts of it by mining untapped areas of the body and using new instruments.

The first direction led only to

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unverified ponderings: What if HIV-infected cells bumped into uninfected cells, and imparted to them a "kiss of death," causing them to commit "cellular suicide" (known as apoptosis)? What if, by infecting even a few T4 cells, HIV caused T8 cells to kill *all* T4 cells, even those not infected?

Both of these ideas were warmly received and seriously considered by the best academic journals and the medical professoriate at large. Apparently nobody noticed that there was no confirmatory data [3,4]. Nor did anybody ask a very simple question: Why, if either of these ideas were true, did the many common viruses that infect immune cells — including some harbored by a majority of humans — do so without causing AIDS [5]?

The data dearth and logical fallacy of these ideas should have marooned them. Instead they are both considered viable, though their mention is no longer heard above the din of fabulous reports generated by scientists claiming to have finally uncovered lots of HIV.

### In Search of HIV

The HIV treasure hunters staked their first big claim in 1993, when *Nature* published tandem papers, one by the University of Minnesota's Ashley T. Haase [6], the other by Anthony Fauci [7], the government's lead HIV researcher. Most previous HIV excavators looked only in the easy-to-access peripheral blood, the stuff that comes out when you prick your finger. These authors removed the lymph nodes — in which a majority of immune cells reside — from the bodies of HIV-positive subjects, some with AIDS, some without. The authors claimed to have found "massive" amounts of HIV-infected T4 cells there, and confirmed that the general circulation contained very little. "Massive covert infection," Haase's team called it.

Immediately HIV was accepted as the agent responsible for wiping out the T4 population by some novel, unspecified process somehow limited to the lymph nodes.

The Ho/Shaw studies arrived two years later, in 1995, also in the form of adjacent papers published in *Nature* [1,2]. Using a new virus-counting technique, they claimed to have found "massive" amounts of HIV (as opposed to infected cells) in the peripheral blood of AIDS patients, and also specified a "covert" mechanism of AIDS pathogenesis.

### The "New View" is Born

Ho and Shaw combined their claims with those made in the lymph node papers and developed the "New View of HIV" [8] (also known as the "viral load hypothesis") which claims that:

1. Although infected cells do not die as a result of HIV replication, HIV replication is hyperactive. Infected cells churn out huge numbers of new HIV, resulting in a large portion of T4 cells in the lymph nodes becoming infected.
2. T8 cells, which kill any host cell harboring an active (virus-producing) infection, kill the T4 cells that are actively producing HIV.
3. Uninfected T4 cells replicate quickly in order to replace those killed by the T8 cells.
4. Because this process occurs quickly, few infected cells ever get a chance to make it to the general circulation. As a result, clinicians drawing blood samples had previously concluded,

erroneously, that only a low percentage of T4 cells are HIV-infected.

5. Although few infected cells ever make it out of the lymph nodes, lots of HIV does, and it is this HIV that Ho and Shaw claim to count with their new technique.
6. Over time — about a decade — the T4 population wears down trying to replace all of its members killed by the T8 cells.
7. There is no latency period for HIV. From the moment of initial infection, there is hyperactive HIV replication that quickly spreads to a large portion of T4 cells in the lymph nodes. This "massive covert infection," and the hyperactive "turnover" of T4 cells and HIV, continues unabated throughout a decade or more of clinical latency (no symptoms), into AIDS, and ultimately causes the patient to die.

According to this new view, the course of AIDS is best monitored by using the Ho/Shaw technique for measuring "viral load." Adherents recommend treatment immediately upon infection with powerful "antivirals," including old ones like AZT and new ones like protease inhibitors, and judge the efficacy of these drugs by the impact on "viral load."

### Debunking Viral Load

Ho and Shaw's viral load concept requires — even among symptom-free people who test HIV-positive — that there be massive HIV infections in the lymph nodes, that HIV be hyperactive, and that HIV be present at high levels in the circulating blood. But the viral load theory is falsified by both data and logic.

***HIV-positive people, even if they have AIDS, tend to have only insignificant HIV infections in their lymph nodes, even according to Haase and Fauci's own data.***

1. Haase studied just four HIV positive patients, three AIDS-free subjects who died of injection drug overdose, and one homosexual who died of "AIDS" while taking AZT. Although on average one-per-five lymph node T4 cells were HIV-infected (a hundred times more than the one-per-500 normally found in the periphery), one of the drug injectors had *no* infected cells at all. Only one-per-500 of the lymph node T4 cells were *actively* infected (one-per-100 of the one-per-five that were infected). Yet only actively-infected cells qualify as being relevant to the viral load mechanism, because only actively-infected T4 cells are killed by T8 cells.
2. Inexplicably, of the 12 patients Fauci studied, immune cell infection ratios are given only for three of them, and even then this data reports mononuclear cells in general, as opposed to just those mononuclear cells with the CD4 markers that are targeted by HIV. For the three selected subjects, Fauci reported HIV-infection ratios ranging from one-per-100 to one-per-10,000 mononuclear cells in the lymph nodes for the two who were symptom-free, and between one-per-ten and one-per-100 for the subject with AIDS. He commented that, compared with the infection ratios found in the peripheral blood, this is "in agreement with our previous study [which showed that] there is between 5 and 10 times greater frequency of infected cells in the lymphoid tissue" for symptom-free people who are HIV-

positive. Given the very small ratios Fauci found, this paper does not show anything resembling massive HIV infections in the lymph nodes.

3. In Fauci's "previous study," [9] he examined six HIV-positive subjects, five with no symptoms, one with AIDS. Again, he presented data for only some of the subjects, but this time the data was for T4 cells only. "We determined that one-per-100 lymph node CD4 T lymphocytes were infected with HIV, whereas one-per-1,000 were infected in peripheral blood," he concluded, hardly a case for "massive infection."
4. Fauci and Haase propose that HIV infection is different from other viral infections because it is hidden in the lymph nodes. Yet neither they nor anybody else show HIV as being more confined to the lymph nodes than any other virus that infects immune cells. In fact, concentrations of all such viruses are always greater in the lymph nodes than in the circulation. No data have ever been presented showing that the proportion of HIV-infected cells in AIDS patients is greater than the proportion of immune cells infected by these other viruses.
5. All other viruses believed to cause disease do so only when they infect about one-per-three target cells — or more — and do so actively [3], meaning virus is being produced. Although Haase found an infection ratio in three of his patients that was significant, the ratio of cells actively infected was trivial. And Fauci, who examined more subjects than Haase in two different studies, could find only insignificant ratios of inactive infections.
6. Significant infections in the lymph nodes cause a noticeable swelling that is usually not found in AIDS patients. Fauci and Haase did not even attempt to reconcile their claims of "massive" lymph node infections with the lack of this clinical symptom.

***There is neither high HIV activity nor high viral load in HIV-positive people, even if they have AIDS, even according to Ho and Shaw's own data.***

1. Rather than being hyperactive, HIV is one of the least active viruses ever studied. In the test tube, it is very difficult to induce infected cells to produce any HIV at all [3,4]. Usually, powerful, artificial stimulating agents called "mitogens" must be used to coax HIV to reproduce. Yet in the test tube infected cells produce much more virus than they do in the patient, where an active immune system works to suppress viral expression [3]. There is no rationale for why a virus that is dormant in the test tube could be active in the body.
2. There is no large number of circulating HIV as Ho and Shaw claim, although this is the linchpin of their theory. Rather than look for whole HIV, Ho and Shaw's technique looks for HIV RNA, the genetic material found in the viral core. They assume that since each HIV contains two HIV RNAs, there must be one HIV for every two HIV RNAs they count. But the large amount of HIV RNA they report is found only after sending blood samples through polymerase chain reactions (PCR). PCR is the "DNA fingerprinting" technology which takes tiny numbers of genetic molecules (RNA or DNA) and turns them into huge quantities. This is how police can transform a speck of blood into a large sample of criminal

evidence. One of the most startling aspects of the Ho/Shaw papers is that they reported finding over a hundred thousand HIVs per mL of peripheral blood, whereas all previous studies had found on average about ten, far too little for pathogenic effect. Although they don't mention it in their famous viral load papers, on other studies both Ho [10] and Shaw [11] quantified HIV using standard virus-counting techniques and compared the results with their new method of counting HIV RNA following PCR. The result: 100,000 HIVs counted using their PCR technique corresponded to less than ten actual HIVs [12]! In other words, Ho and Shaw's subjects had the same low numbers of HIV that have always been observed in AIDS patients. But if there are only ten HIVs, how did Ho and Shaw measure an extra 99,990? Some of these are HIVs that have been neutralized by antibodies, some are defective HIVs (those that did not form correctly), and some are free-floating HIV RNA. Though none of these entities has any pathological capacity, the viral load technique confuses them all with whole, infectious virus, the only kind that has any biological significance. Most of Ho and Shaw's "viral load," though, is probably just a mirage, huge numbers of HIV RNA bits generated by PCR, not whole RNA generated by HIV [12]. This explanation reconciles all the facts: a slow-replicating virus that infects only a very small fraction of cells (even in the lymph nodes) and is present in infectious form only at tiny concentrations.

3. If there was a lot of HIV in the periphery, it should infect lots of T4 cells. Instead, Ho and Shaw acknowledge there are few T4 cells infected in the periphery.
4. No explanation is given as to why the standard virus-counting techniques (that show low HIV levels in AIDS patients) should be discarded in favor of Ho and Shaw's new PCR method.
5. The Ho/Shaw PCR technique has never been validated by counting HIV RNA prior to application of PCR. After PCR is used, the Ho/Shaw method uses a conventional RNA-counting technique. If there is really lots of HIV, there should be lots of HIV RNA before application of PCR. Why not skip the PCR and just count the HIV RNA that is already there? Ho and Shaw probably use PCR for the same reason that everyone, including the police, use it: their samples don't contain as much genetic material as they want.
6. Since all the subjects examined by Ho and Shaw had late stage AIDS, even if there were high HIV loads, there is no rationale for concluding that this would also be the case in symptom-free patients. Yet it is essential for the Ho/Shaw thesis that HIV be active in the years of gradual immune suppression leading to AIDS. Otherwise, they are left to explain how it is that HIV can be inactive while driving the patient from symptom-free status to AIDS.

***The viral load concept requires that HIV be an extraordinary virus, but no data is ever presented comparing HIV to other viruses.***

1. There are many common viruses that infect various immune cells, including T4 cells. Among them, cytomegalovirus (which infects 40% of all Americans), Epstein-Barr virus (50%), hepatitis B virus (5%), herpes simplex virus-1 (65%),

and -2 (40%) [5]. T8 cells kill any cells harboring active infections with these viruses. Since these viruses do not cause AIDS, there is no reason to suppose that HIV might. And since these viruses are cytotoxic and actively infect one-third or more of their target cells, they are better candidates than HIV for AIDS causation.

2. These other viruses cause disease only when they manifest as acute infections, infecting about one-third or more of the cells they target, and are present in the blood at concentrations in excess of many thousand per mL. There is no logical reason to suppose that HIV can cause disease when actively infecting only tiny fractions of target cells and showing up only at trace blood concentrations.
3. Ho and Shaw imply that HIV is more active than these other viruses, but present no comparative data. However, the only available data for HIV shows it to be very inactive, which is consistent with the low fractions of actively-infected cells that Fauci and Haase found, and the low levels of real virus that Ho and Shaw found.
4. All the early AIDS patients were positive for these other viruses [5]. When these viruses show up as acute infections in AIDS patients, HIV advocates consider them to be "opportunists," springing out of dormancy to take advantage of an immune system suppressed by HIV. Even if AIDS

patients all had acute HIV infections (which clearly they do not), there is no logical reason to suppose that HIV is not just another opportunist taking advantage of an immune system suppressed by something else (street drugs, pharmaceutical drugs, etc.).

5. Most people positive for these other viruses do not have the diseases they are known to cause, so they do not suffer from acute infections. There exists no published data documenting the results of using the Ho/Shaw PCR technique for counting these other viruses in healthy, HIV-negative subjects. Would Ho and Shaw "find" in such people the same high "loads" of these other viruses that their new technique registers for HIV in AIDS patients? If so, this would confirm that their technique inaccurately indicates acute infections even in people harboring trace amounts of sleeping viruses.

Fauci, Haase, Ho and Shaw all fail to prove a role for HIV in AIDS because they fail to show that in AIDS patients there is an appreciable amount of HIV or HIV-infected cells, or why HIV should be considered different from any of the many other viruses that infect immune cells without causing AIDS. In addition, the Ho/Shaw method of measuring "viral load" does not measure HIV blood concentrations, and therefore is of dubious value as a diagnostic tool.

— Paul Philpott

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- (1) Ho, *Nature* 373, 1995, p123. (2) Wei, *Nature* 373, 1995, p117. (3) Duesberg, *Inventing the AIDS Virus*. (4) Papadopoulos-Eleopoulos, *Genetica* 1995, p5. (5) Root-Bernstein, *Rethinking AIDS*. (6) Embretson, *Nature* 362, 1993, p359. (7) Pantaleo, *Nature* 362, 1993, p355. (8) Maddox, *Nature* 373, 1993, p189. (9) Pantaleo, *Proc. Natl. Acad. Sci.* 88, 1991, p9838. (10) Chao, *New Engl. J. Med.* 332, 1995, p201. (11) Piatak, *Science* 259, 1993, p1749. (12) Duesberg, *Nature* 375, 1995, p197.

#### Mission Statement of the Rethinking AIDS Group

- 1 To develop, articulate, and promote rational scientific discourse on the subject of HIV and AIDS.
- 2 To advocate the absolute right of students, professors, physicians, scientists, government officials, and everyone else to think freely and speak openly on the subject of HIV and AIDS without fear of professional, social, political, economic, or criminal penalties.
- 3 To assemble scientists, physicians, and other informed people who support these views, and make those persons available for commentary and consultation to interested social groups, media outlets, government agencies, professional organizations, and individuals.

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#### Rethinking AIDS

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