A critical reading of Dr. Rebecca Culshaw's paper, *Mathematical Modeling of AIDS Progression: Limitations, Expectations, and Future Directions*, in the Journal of American Physicians and Surgeons (JPandS, Winter 2006).

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Summary: In her JPandS paper [1], Dr. Rebecca Culshaw argues that well-known mathematical models of HIV and AIDS have, in her view, achieved nothing but "abysmal failure." To Culshaw, all existing models have placed too little emphasis on the contributions of cofactors to disease. To replace these models, Culshaw proposes to model disease progression based solely upon measurements of glutathione and their impact on a "Th1-Th2 shift." As we demonstrate below, Culshaw's arguments rest upon multiple misunderstandings and misrepresentations of the literature (including the modeling literature) and of various aspects of the biology of HIV and AIDS, and Culshaw relies uncritically on the flawed and non-peer-reviewed writings of another mathematician. We also object to the fundamental inconsistency that overshadows Culshaw's work: while she claims elsewhere that HIV may not exist and that AIDS is a "sociopolitical" fabrication, Culshaw writes here from the assumption that HIV and AIDS do exist, and that the former may play a role in the latter. That Culshaw tries to have it both ways is, to us, evidence of intellectual dishonesty.

In this paper [1], Dr. Culshaw develops no mathematical formalism to analyze any aspect of HIV infection. The only model she writes down is a very general form of a model used in epidemiology, which she says is similar to the ones used for intra-host viral dynamics models. Although Culshaw is correct in formal terms, interpretation and justification of these intra-host models are obviously very different. Culshaw is probably right to note that we (as in everyone) have a "lack of complete understanding of the disease mechanism, as well as the fundamental nature of the immune system" – after all, this is the reason why we continue to conduct research into HIV/AIDS. However, she then proceeds to make arguments and innuendos that are very poor and misleading. Most of these are not related to mathematical models at all, but a few are. Below, we try to summarize those glaring ones that caught our attention immediately:

In "Limitations of HIV Models," fourth line: "…together with some patient data (which was not published together with the models themselves)…". It seems almost that Culshaw is accusing the authors of Ho et al [2] and Wei et al [3] (both 1995) of scientific fraud; she is at least hinting at it. It is true that they did not publish a table with every single measurement taken in all patients, nor is this common practice. They did publish summary tables, as well as plots of the viral load for representative patients. Interestingly enough, though, Culshaw doesn't criticize the main results of these papers directly – i.e., that viral turnover is very fast; she rather criticizes that this led to the concept that treatment should be "early and hard."

In "Limitations of HIV Models," second paragraph, Culshaw writes: "this strategy has been an abysmal failure in terms of eradication." It is clear that achieving eradication has not been possible, but she doesn't say anything about the huge benefits of treatment for countless HIV-infected patients. Nor does she apparently realize that 12 years have passed since the publication of those papers in 1995, and that we now realize that other factors (some of which have also been modeled) are important: long-lived cells, latently infected cells, drug sanctuaries, etc. Science evolves by discovery, hypothesis and testing, but Culshaw seems to view the first models as the beginning and end of work on HIV. She then goes on to say that there were important flaws in the assumptions.

In "Limitation of HIV Models," third paragraph: "… the biological assumptions and conclusions have been heavily criticized, largely in several papers published in 1998…" This is a huge distortion of the contents of the papers Culshaw cites. First of all, these papers do not criticize the viral dynamics models, nor do they criticize the conclusions from the mathematical models that viral turnover is very fast. These papers rather argue that part of the recovery of CD4+ T-cells after treatment is due to redistribution, and not, as assumed in the Ho et al and Wei et al papers, due to T-cell proliferation alone. Again, this is how science evolves – Ho et al and Wei et al never claimed to hold the absolute truth about HIV dynamics. Indeed, many letters to Nature immediately in the sequence of the original papers (in 1995) suggested that early CD4+ T-cell recovery could be due to redistribution. The irony is that this aspect definitely adds weight to the role of HIV infection in disregulating the immune system and the benefits of treatment. HIV infection occurring in the lymph nodes and its concomitant general activation of the immune system traps CD4+ T-cells in the lymph nodes, which are reduced when the viral load burden decreases during therapy.

Culshaw then says that "redistribution [of CD4+ T-cells] throughout the body is not an immunological advantage." This seems to be a strange declaration; after all, having normal number of cells in circulation, LN and tissue is not an "immunological advantage." But this affirmation is "consistent" with her later explanation (see below), which in essence says that redistribution is due to HAART-induced killing of B-cells, leaving the Th2 subset of CD4+ T-cells orphan in the lymph nodes (LN), whence they move out into the peripheral blood. We are not sure where Culshaw got this from, but she certainly did not find it in the paper she cites as a reference [4]. Interestingly, Gorochov et al, *do not even mention B-cells in their article*, much less that HAART kills them off, and they make no reference whatsoever to the Th2 subset of T-cells. This curious view of the immune system may come from the imaginative pronouncements of a German writer named Heinrich Kremer. Culshaw gives his book (in German [5]) as a reference elsewhere in her article, but the immunology ideas she uses uncited here are available in an English-language translation of an interview of Kremer by the *Raum und Zeit* newsletter (available at [6, 7]; although the translation is poor, the description of science and medicine is no more accurate in the original.)

Relating to the above point, even if one initial assumption—that increases in CD4+ T-cells after HAART are due only to proliferation—is no longer believed to be the whole explanation, many other papers, using different techniques, have convincingly shown that, indeed, proliferation rates of CD4+ T-cell are increased in the setting of HIV infection, and tend to decrease after treatment. These results are totally ignored by Culshaw. Here and elsewhere, she seems to view science in terms of absolutes. A model is either absolutely right and infallible or an "abysmal failure." Either every single point in a paper is accepted with praise, or the paper is meritless and should be discarded. Either everyone agrees on every aspect of a theory, or that theory is fundamentally flawed. If such a purist position were common in science, progress would be rare, indeed.

In "Limitations of HIV Models," fourth paragraph, Culshaw uses the arguments of Mark Craddock (a lecturer at the University of Technology, Sydney) as evidence that "The equations in the Ho/Shaw models were oversimplified…". Craddock's critique is posted on a denialist website [8] and also appears as part of a book published by prominent HIV denialist Peter Duesberg [9]. He is very bullish, but makes a number of mistakes. Culshaw's uncritical use of his flawed arguments is baffling. For clarity purposes, comments on Craddocks writings are appended (see below).

In the next 4 paragraphs, Culshaw expounds on why plasma viral load measurements are wrong, since QC-PCR is "inaccurate." She cites the 1993 paper by Piatak et al [10]. Culshaw's arguments simply rehash those of others (especially Mark Craddock), but introduce unique mistakes. For example, Culshaw does not seem to understand what "viral load" measures. She speaks of "viral load, referred to as the 'target' DNA," and later states that the assay "amplifies HIV DNA." Viral load, of course, quantifies HIV *RNA* in the blood, not DNA. Also, the assay measures any and all HIV RNA found free in the blood, including that of infectious particles—not just "viral fragments." Culshaw's misconceptions aside, the scientific community uses RT-PCR for countless different projects (besides HIV), with standards tested many times over, with consistent results. Logically, this technique cannot be so rife with problems as Culshaw and Craddock want us to believe. Moreover, Culshaw shoots herself in the foot, because if PCR is so unreliable "and there is no way to make an accurate estimation of infectious virus", then the results, showing a clear and consistent decrease in virus during therapy, must be "magic."

This is what Piatak et al [10] say about their measurements:

> Abstract: "Quantitative competitive polymerase chain reaction (QC-PCR) methods were used to quantify virion-associated human immunodeficiency virus type-i (HIV-1) RNA in plasma from 66 patients with Centers for Disease Control stage I to IVC1 infection. HIV-1 RNA, ranging from 100 to nearly 22,000,000 copies per milliliter of plasma (corresponding to 50 to 11,000,000 virions per milliliter), was readily quantified in all subjects, was significantly associated with disease stage and CD4+ T cell counts, and decreased by as much as 235-fold with resolution of primary infection or institution of antiretroviral therapy. Plasma virus levels determined by QC-PCR correlated with, but exceeded by an average of 60,000-fold, virus titers measured by endpoint dilution culture. Quantitation of HIV-1 in plasma by QC-PCR may be useful in assessing the efficacy of antiretroviral agents, especially in early stage disease when conventional viral markers are often negative."

> From the Conclusions: "the demonstration of significant associations between HIV-1 RNA levels and both disease stage and CD4' T cell counts argue strongly for a direct role for HIV-1 replication in the pathogenesis of HIV disease."

The high viral mutation rate, viral tropism, neutralization and other immune system successes…these are a few of the reasons why many viral particles produced in vivo are not infectious in laboratory assays. But these tests also seriously underestimate the infectivity of actual infectious particles because of the conditions that apply in vitro (particularly the very low cell density in culture vs. lymphoid tissue [11], and because cell-cell spread is more efficient than de novo infection by a virion). In culture, infection is limited by the diffusion rate of virions onto cells, which is slow. So in a traditional assay, only a small proportion of the added virions actually get a chance to infect the target cells. The ones that don't, the majority, are not necessarily defective, but the assay records them as being so. David Kabat showed in 1997 [12] that if one applies the same inoculum repeatedly over time to different sets of cells, the infectivity hardly changes. Much the same point is made recently by Haim et al [13].

In any case, as RT-PCR does not distinguish between RNA in infectious and non-infectious viral particles, what Culshaw calls "the 'efficiency' of PCR" has nothing to do with the infectious/non-infectious ratio. If it did, and PCR output varied wildly based upon the magnified, random error hypothesized by Culshaw and Craddock, we would logically expect an *under*estimation of viral load (as compared with TCID) in some samples, and an *over*estimation at approximately the same frequency. Instead, Culshaw sees all of the data from Piatak et al (and presumably all other viral load measurements, with their diverse protocols) as gross overestimates. (Note, as well, that a paper Culshaw cites as supporting her (mis)understanding of viral load vs. infectious virus [14] does not address viral load and T-cells, but refers to integrated provirus in mononuclear cells.)

The next point in Culshaw's paper is glowing praise for a "groundbreaking study published in JAMA." According to Culshaw, this study proves her point that viral load has no relation to CD4 count. Here is what Rodriguez et al [15] say:

> (From the Discussion): "Our findings confirm previous observations(5) that the magnitude of HIV viremia, as defined by broad categories of presenting HIV RNA level, is associated with the rate of CD4 cell loss and extend this observation to patient populations comprising both men and women. Despite this association, however, only a small proportion of the interindividual variability in the rate of CD4 cell decline can be explained by plasma HIV RNA level,…"

The point of this paper is that for each individual, there can be so much variation in HIV and CD4+ T-cell count levels that the association between them is weak (although from their plots, it seems significant). This then may make it difficult to take treatment decisions based on viral load – something that the current official treatment guidelines already acknowledge and support. However, from a pathogenesis point of view, and for the population as a whole, there is a clear association of higher viral loads and added CD4+ T-cell depletion (see quote above). This, "confirms previous observations," *i.e.* the Mellors et al. Ann Inter Med (1997) paper [16]. Despite the clear explanation of these results, both in the Rodriguez et al paper itself and in their clarifying document found HERE, Culshaw and other HIV/AIDS denialists insist on misrepresenting this publication.

Culshaw then proceeds to develop three more critiques of the mathematical modeling approach. One is that parameter estimation from the models for each individual patient is very difficult: "… parameter estimation may be impossible for a model that is meant to be applied to an individual patient." It would indeed be great if we had reached an era of individualized modeling (or even of individualized medicine), but clearly this is not yet possible. And in all likelihood, no modeler has claimed this. Rather, the models can help us understand general aspects of the disease and treatment. This is similar to Culshaw's misunderstanding of the Rodriguez et al. paper. It has been shown that higher viral loads correlate with lower CD4+ T-cells in the population; however, we still cannot, for a given individual, predict the full course of CD4+ T-cell depletion just by knowing his/her viral load at given time(s) in the past. This does not reduce the validity of the viral load/CD4+ T-cell correlation. As an example, we hear many times about this or that person who smoked *n* cigarettes a day and lived to 100 years of age. Sometimes this is used to "clearly argue" that smoking does not cause cancer or that it is not detrimental to health. This type of reasoning is very fallacious, and a misunderstanding of the meaning of statistical association. Yet it is precisely this reasoning that Culshaw employs here.

The second criticism is that models don't take into account the Th1/Th2 aspects of the immune response or the toxicity of the drugs (although Culshaw recognizes that some models did look at toxicity). Culshaw is free to think that there are aspects that should be modeled and were not so far – we could also think about other issues that have not been included in previous models. The most productive strategy for Culshaw would be to develop such models, this is how science advances. Not including these or other aspects does not make the models necessarily wrong, rather it may restrict the applicability to what the authors are studying at a given moment. As J.P. Moore et al observe, on the study of HIV pathogenesis, there are indeed many variables to consider:

> …(W)hen considering HIV-1 pathogenesis, it is important to fight the natural tendency for oversimplification by homogenization. HIV-1 can evolve complex phenotypes, humans are an outbred species (as too are macaques), and the efficiency with which the immune system responds to a viral infection varies between individuals. These are complex, interlocking variables. To fully understand HIV-1 pathogenesis on a population basis is, therefore, no easy task; each individual's overall response to the infecting strain is usually subtly, and sometimes profoundly, distinctive. Hence different answers to questions of HIV-1 pathogenesis can be obtained that depend upon who is studied, when during the course of his or her infection, and what properties are possessed by the infecting virus, a parameter that can itself vary markedly over time. Until recently, there has been a tendency for immunologists to overlook the complexities caused by the HIV-1 phenotypic variants, for virologists to consider all CD4+ T-cells as being much the same as one other, and for mathematical modelers to ignore most or all of the above variables as being beyond the scope of their equations. Perhaps the ever increasing knowledge of coreceptor expression and usage will enable HIV-1 infection to eventually be better understood than it is now [17].

Finally, in "Importance of the Th1/Th2 Balance in Immune Function," second paragraph, Culshaw says that "…all immunological models of HIV infection have failed to consider cofactors for HIV infection, or other possible viral or non-viral mechanisms of immune dysfunction…" This is a sweeping statement, since there are several models that include cofactors. A couple of these papers are even cited by her [18, 19]. Now, it may be true that no model considers non-HIV induced immune dysfunction, but that is because the overwhelming majority of evidence points to HIV as the (at least ultimate) cause of immune dysfunction. In any case, Culshaw is free to pursue such a model, if she thinks it could work and be consistent with the available data. Indeed, this is probably the objective of the last two sections of the paper. Significantly, Culshaw does not present any model here and her discussions are all based on a Th1/Th2 shift and the role of glutathione in that balance.

Culshaw is strongly encouraged to develop and present a model incorporating Th1 and Th2 responses and glutathione ratios. Before she can do this, however, she will have to make some strides in her understanding of immunology. Her presentation of T helper cell biology is not encouraging. Culshaw's strange interpretation of HAART, B-cells, and Th2 cells was noted above. Here are several more errors she makes:

-A simplistic division of CD4+ T-cells into Th1 and Th2, with neatly separate functions.
The co-discoverers of the Th1 and Th2 responses explicitly warn against this fallacy in the review Culshaw uses ([20]; here, as in her book, Culshaw repeatedly misspells Mosmann's name as "Mossman"). Th1 and Th2 have substantial functional overlap. Both Th1 and Th2 can stimulate antibody production, and both can act against at least some opportunistic infections, such as *Pneumocystis* (see table 8.1 of [21] and accompanying text for accurate information about Th1 and -2 cells and their actions). In addition, several new subsets of Th cells have been reported in the past few years (for a review, see [22]).
-A strict bodily compartmentalization of Th1 and Th2.
A paper cited by Culshaw ([23]) is one of many that demonstrate the problems with this assumption.
-An assertion that, "Th1 cells' production of nitric oxide (NO) gas, which destroys intracellular pathogens, is the main operational mode of the cellular arm of the immune system."
While Th1 cells can apparently produce NO, it is not this NO that kills most intracellular pathogens. Instead, helpers secrete interferon gamma (IFN-γ), which stimulates the activation of macrophages, including production of massive quantities of NO. Culshaw does not mention macrophages at all, despite their prominence in several of her references.
-A claim that HIV does not infect Th1 cells.
In fact, HIV does infect Th1 cells, as shown even by the paper cited by Culshaw [24]. Further studies have confirmed this, including strain-dependent replication [25-28].
-A statement that Immune Reconstitution Disease (IRD) results when Th2 cells enter the peripheral blood and, unable to make their own nitric oxide, cannot fight intracellular pathogens.

As mentioned in the review Culshaw cites [29], IRD occurs when the immune system begins to regenerate after the initiation of antiretroviral treatment. Inflammatory responses may get out of control and cause their own problems or reveal subclinical infections.

-A claim that HIV infection effects a Th1 to Th2 shift.

Although Culshaw presents this hypothesis as established, many articles have challenged the postulated shift or its scope. The Maggi et al paper cited by Culshaw [24] is one; a second article, from the same issue of *Science*, is another [30]. On balance, there do appear to be changes in cytokine profiles during the course of infection; it may, however, be best to refer to these changes as a "bias," rather than a "shift." It is disappointing that Culshaw completely ignores the healthy scientific debate in this area while exaggerating another debate (arising from Ho et al [2] and Wei et al [3], see above) to the point of "fundamental flaws" and "failure."

As for the role of oxidative stress in AIDS, hundreds of papers (at least) have examined aspects of this issue, and investigation is ongoing. Numerous studies measuring glutathione levels have already been published. In surveys of glutathione levels in patients, the results have been mixed: some groups report a link between glutathione and HIV or progression to AIDS [31, 32], others do not [33, 34]. Clinical trials have been conducted for several therapies designed to increase glutathione concentrations and thereby, it is hoped, improve immune system health. Therapeutic attempts to change Th1/Th2 ratios have also been initiated [35, 36] Again, Culshaw does not mention this work, even though it has quite a close bearing on her proposal. Is this because Culshaw is unaware of these papers, or because they cast doubt on her thesis? As Kidd reminds us in a 2003 review [37], "the early euphoria that Th1/Th2 manipulation would catalyze major immunotherapeutic breakthroughs has yet to be realized".

In our opinion, such a breakthrough is unlikely to result from replacing the current models with a simplistic Th1/Th2 balance estimation that leaves out the major players and ignores HIV partially or entirely, especially since HIV itself may contribute to oxidative stress in HIV-infection (see, for example, [38]). Culshaw does say in the first sentence of her last section "The role of HIV in the GSH:GSSG ratio remains unclear… ," thus seeming (at least) to allow a role for HIV, and we note that the JPandS paper, published in late 2006, unfolds from the implicit assumption that HIV exists and causes AIDS, a real medical syndrome.

Yet in her book, *Science Sold Out. Does HIV Really Cause AIDS?* [39] (which appeared at approximately the same time as the JPandS article), Culshaw disputes HIV's existence ("there is no bug," p.70), its ability to cause AIDS (pp.47 and 60), and even that AIDS is a medical syndrome (AIDS "is not a disease so much as a sociopolitical construct," p.7). Throughout Culshaw's small oeuvre, this intellectual schizophrenia looms large. HIV exists and it doesn't exist (in one internet forum, she refers to the Perth group, Rodney Richards, Etienne de Harven, and Heinrich Kremer as support for her HIV existence doubts [40]). Culshaw "had to learn an awful lot about the molecular biology of HIV" [41], but "no one really understands…what HIV really is" [39], pp.3-4, so there is no molecular biology to learn about. The link of HIV to AIDS by the "vultures" of science is a "psychosocial" crime motivated by "racism and homophobia" (*ibid*, pp.61-2, 65), and "it's SO obvious how racist and homophobic the hiv (sic) hypothesis of aids (sic) really is" [40]. Culshaw's strong opinions in this regard raise the question of why, exactly, she chose to support the HIV/AIDS "hypothesis" by publishing a paper on it half a year later. Indeed, Culshaw has presented work based on HIV and AIDS—a PhD thesis, several modeling articles, the JPandS paper, and conference presentations—for years after adopting the denialist position ("by the time she received her Ph.D. in 2002" [42]).

Culshaw cannot have it both ways. If she wishes to deny the existence of HIV, she is free to do so. But if Culshaw doubts that HIV exists, she cannot remain intellectually honest and continue to publish on HIV and AIDS in the biomedical literature. As we have seen in this paper, Culshaw demonstrates a remarkable depth of confusion on HIV and AIDS mathematical modeling, biology, immunology, and molecular techniques. She cites works that do not support her positions. She interprets healthy scientific debate and progress as symptoms of fraud and failure. And she presents, as novel, proposals that have been pursued for years, namely the connections between glutathione or Th1/Th2 responses and HIV. We hope that Dr. Culshaw will learn more about HIV and the immune system and correct her many mistakes in future.

Mark Craddock's critique of the Ho et al and Wei et al 1995 papers.

Craddock's critique of the Ho et al and Wei et al papers [2, 3] is posted on the website www.virusmyth.com. He is very bullish, but makes a number of mistakes. First, he criticizes those papers for supposedly presenting the viral load data with incredible precisions, he says: "The notation 10^4.6 is 10 to the power of 4.6, which you can work out on any scienific calculator. 10^4.6 =39810, or 19,905 virions per ml of blood. (…) Of course the accuracy given here is ludicrous. They can't really mean that they can measure things this accurately." This is an incredible mistake on Craddock's part. In fact, the results are presented as 10^4.6 virus; this means that the authors used two significant digits, thus the result of any calculation can also only be presented to two significant digits. In this case, $10^{4.6}=4.0\times10^4$. The concept of significant digits is basic, and Craddock is absolutely wrong here.

Craddock goes on to criticize the use of geometric mean in those papers: "Why have they used the geometric mean here? Well the only reason we could think of (myself and my colleague Sylvano Lucchetti, who is a statistician) is that the geometric mean smoothes out ratio changes." This is again a basic mistake and shows ignorance of simple principles of statistics. Here is what a standard and excellent statistics book says about the geometric mean: "Some beginners in statistics have difficulty accepting the fact that measures of location or central tendency other than the arithmetic mean are permissible and even desirable. They feel that the arithmetic mean is the 'logical' average and that any other mean would distort the data. This attitude raises the question of the proper scale of measurement for representing data; this scale is not always the linear scale familiar to everyone, but is sometimes by preference a logarithmic or reciprocal scale" ([43], page 44). Indeed, we want to use this mean exactly for something that varies logarithmically, such as the viral load.

Still on this topic, Craddock says, "If they are estimating changes in viral load by taking ratios of QC-PCR measurements at different times, then the geometric mean of these variations will show less variability than the arithmetic mean. It makes their results look more consistent than they really are." It is not apparent where he gets the measurements as being ratios of the assays at different times. Viral loads are measured independently at each time point, and there are no ratios taken between measurements at different times.

Then, Craddock again makes the argument about the unreliability of PCR, and Culshaw essentially just uses these uncritically, as mentioned above. He then complains about the use of linear regression and says "Have they never heard of polynomial interpolation, or Time series? Obviously not. The point is that there are advanced mathematical techniques for handling this kind of data,…" This is again totally off the mark. The point of the papers, and of good modeling in general, is not to find a line that goes exactly through the data points; rather we are interested in a simple (minimal) biological model that can describe the data with a minimum number of parameters. In this case, the authors do not use linear regression, they use a dynamical biological model for the dynamics of viral load whose solution (with appropriate simplifications) turns out to be a simple "linear regression" (indeed in both papers other more complicated models and solutions were also analyzed). No doubt, Craddock would have complained about the number of parameters used to fit the data, if more "advanced mathematical techniques", such as polynomial interpolation had been used. (By the way, there is nothing advanced about polynomial interpolation, in fact linear regression is a polynomial interpolation of degree 1.)

Finally, Craddock delves into criticism of the "mathematical modeling". His arguments are so bad, they are barely understandable, and at the very least demonstrate a total lack of comprehension about modeling. That is, he shows he knows how to solve very simple equations (such as the ones used in the papers), but he has no understanding of the concept of modeling a biological/physical system. Essentially, the models used in the papers were developed to describe what happens when drug treatment is administered. And all his criticism relies on what happens if you use these same equations/models during primary infection (or to describe HIV pathogenesis). This is akin to saying that applying Newtonian physics to describe the trajectory of the football is wrong because if we think of a football game near a black hole it would give the wrong answer. Any model has a realm of applicability, in this case drug treatment, that defines the circumstances under which it makes sense to use it. No one has ever claimed that we could describe the full behavior of HIV infection, from the primary stage to full blown AIDS with a two-equation model and four parameters (unfortunately, we can still not do this with any simple model). To pretend that this is the point of the paper is ridiculous.

Indeed, Craddock never criticizes or disputes the results of the models during treatment in demonstrating the fast turnover of HIV. Moreover, he seems not to have understood that the models used in these papers were very simplified to be applicable to the sparse data available. When he criticizes the model used for T-cells (in Ho et al), he doesn't even realize that this was just a conceptual model to show that the linear regression (here indeed a direct linear or exponential

regression) could only estimate minimum rates of production. Moreover, commenting on this issue he says that "There is also a major problem? Where is HIV? If they are assuming that the T cells are declining because of the effects of HIV, then this equation must contain some term involving the amount of virus present. It does not. So what the hell is it supposed to mean?" Well, again this was only a conceptual model used for discussion. Many other papers starting in 1996 presented a more complete and biologically relevant model, including the viral infection cycle. Again these models still can not explain the whole course of infection, nor do they claim to. Moreover, in the Ho et al paper the model was not used at all "assuming that the T cells are declining because of the effects of HIV," rather the model was used to analyze the increase of T-cells during therapy, when viral load is declining exponentially.

Putting all this together, Craddock says: "So Ho's model does not describe what actually happens in AIDS patients" – meaning that the model does not predict the long-term decay of CD4+ T-cells from early infection to AIDS. This is true, but completely beside the point. Finally, one of Craddock's minor criticisms is fair: he is right when he says about the T-cell model, "P here is the rate of T cells clearance [actually, he means production], and is not to be confused with P above [for the virus model]. They should use different notation." Indeed, it would have been nice if the authors had used different letters for the production of virus and the production of T-cells. However, this is hardly an important indictment of the overall design, results and conclusions of the papers.

In conclusion, Craddock's review demonstrates his own lack of sophistication regarding mathematical models of biological systems. In terms of basic mathematics, Craddock appears to be confused about significant digits, simple statistical concepts, and the usage of mathematical modeling in biology. Craddock's reading of the Ho et al and Wei et al papers is superficial and riddled with misunderstandings about techniques, biology, and what the papers do and do not claim. It is curious—and telling—that a professional mathematician such as Culshaw relies so heavily—and uncritically—on this flawed analysis in her JPandS article and other writings.

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