

An abuse of surrogate markers for AIDS.  
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It should come as a shock, no doubt, to learn that if three laboratory tests somehow disappeared or were outlawed (HIV antibody test, CD4 cell count, PCR viral load test), then AIDS, as commonly understood, would formally vanish from the USA and Europe. The three laboratory tests in question are called surrogate markers because they stand in for either AIDS itself or for its supposed cause, HIV. According to the current definition of AIDS, no matter how sick an American or European is with AIDS-defining diseases, he or she cannot be classified as an AIDS case if antibodies to HIV are not present. In other words, for an American or European doctor to diagnose pneumonia, TB, dementia, cervical cancer, etc. as AIDS it is necessary to obtain laboratory test results that satisfy the definition of AIDS. Since the HIV-antibody test has been discussed in depth already, I will limit my remarks to CD4 cell counts and viral load.

At the beginning of the AIDS epidemic, it was already recognized as probably a mistake to use CD4 as a marker of AIDS or even a measure of therapeutic effectiveness. In 1981, James Goodwin, MD, wrote what he called "a diatribe against the measurement of T-cell subsets in human diseases" [1]. His "diatribe" began:

"It's starting again. ...The T- and B-cell measures--having run through the sick, the elderly, the young, the pregnant, the bereaved--had finally run out of diseases. Each condition was the subject of many reports; so that now, to give but one example, we can conclude with some assurance that T-cell numbers are up, down, or unchanged in old folks. And it's starting all over again, this time with T-cell subsets."

"What will they find?" he asked. "Sometimes the suppressor cell markers will be up and helper cells down; sometimes the suppressor cells will be down and the helper cells up; sometimes they'll be unchanged--and various combinations of the aforementioned. ...My strongest argument is this: Measurement of T and B cells and their subsets in diseases has no clinical meaning."

"Nonimmunologists have naturally assumed that any subject occupying so much journal space must be relevant in some way--a logical but incorrect assumption. ...And while the identification of T-cell subsets in mouse and man represents a major breakthrough in the understanding of immunoregulation, the enumeration of these subsets in myriad diseases largely represents a waste of time".

As recently as 1998, Mario Roederer of Stanford University confirmed Goodwin's assessment that an obsession with T-cell subsets in AIDS patients has been a mistake: "[T]he facts (1) that HIV uses CD4 as its primary receptor, and (2) that CD4+ T cell numbers decline during AIDS, are an unfortunate coincidence that have led us astray from understanding the immunopathogenesis of this disease" [2].

Prior to Roederer's remarks, the use of the CD4 (T-cell counts) as a surrogate marker of disease progression was also criticized by the authors of the Concorde Study, the largest clinical trial evaluating the use of AZT: The authors concluded that:

"The small but highly significant and persistent difference in CD4 count between the groups was not translated into a significant clinical benefit. Thus, analyses of the time until certain concentrations of CD4 were reached (eg, 200/ $\mu$ L, 350/ $\mu$ L, or 50% of baseline) revealed significantly shorter times in the Def[erred] group. Had such analyses been regarded as fundamental, the trial might have been stopped early with a false-positive result. This discrepancy in the differences between Imm[ediate] and Def groups in terms of changes of CD4 count and of long-term clinical response casts doubt on the uncritical use of CD4 counts as 'surrogate endpoints' in trials..." [3].

Thomas Fleming and David DeMets have stated that, "The use of surrogate end points has probably been more intensely discussed in the design and analysis of clinical trials of HIV infection and AIDS than in any other area" [4]. However, "Predictions having an accuracy of approximately 50%, such as the accuracy seen with the CD4 count in the HIV setting, are as uninformative as a toss of a coin." With regards to clinical trials and FDA approval of anti-HIV drugs, Fleming and DeMets have warned that, "Surrogate end points are rarely, if ever, adequate substitutes for the definitive clinical outcome in phase 3 trials" [4].

Indeed, a summary result from a 1993 state-of-the-art conference had previously concluded that the effect of treatment on the most popular surrogate, CD4 cell count, did not accurately predict the effect of treatment on the clinical outcomes, that is, progression to AIDS or time to death [5]. Nevertheless, with the exception of the early AZT clinical trials, all subsequent anti-HIV drug trials and FDA approvals have relied exclusively on the measurements of these surrogate markers and not on the real clinical outcomes, such as morbidity and mortality, that matter to most people.

A year later, Fleming stated that, "It is very apparent one cannot simply consider establishment of statistically significant treatment effects on CD4 cell counts to be a valid surrogate for either of the two clinical endpoints. When the progression to AIDS/death endpoint was positive, the CD4 endpoint appropriately was significantly positive in 7 of 8 trials; unfortunately however, the CD4 endpoint was significantly positive in 6 of 8 trials in which the progression to AIDS/death endpoint was negative. The relationship of CD4 effects and survival is even more unsatisfactory. The CD4 endpoint was significantly positive in only 2 of 4 trials in which the survival endpoint was positive; yet it was significantly positive in 6 of 7 trials in which the survival endpoint was negative. In three other trials, survival trends were observed which were in the opposite direction of significant treatment effects on CD4" [6].

The well-recognized problems with CD4 counts eventually led to its being replaced by the PCR viral-load test as the primary surrogate marker to be used in anti-HIV drug clinical trials. But, the "viral load" test has its share of problems. To start with, Roche's "AMPLICOR HIV-1 MONITOR Test is not intended to be used as a screening test for

HIV or as a diagnostic test to confirm the presence of HIV infection" (Roche Diagnostic Systems AMPLICOR HIV-1 MONITOR Test package insert, PMA No. BP950005/4).

To save space, below is a list of some of the problems with the viral load test that were published in the scientific, medical literature:

False positive or false negative? It depends on the answer you want. Apparently, absence of antibodies to HIV trumps a high viral load result.

Schwartz D. H. et al., "Extensive evaluation of a seronegative participant in an HIV-1 vaccine trial as a result of false-positive PCR" (1997) *The Lancet* 350: 256-259.

An individual tested positive by PCR, but was antibody negative. Therefore, the patient's viral load of 100,000 copies of RNA per ml was called false-positive. It took \$5000 worth of PCR testing in several labs to get the "right" answer: negative.

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Christine Defer et al., "Multicentre quality control of polymerase chain reaction [viral load] for detection of HIV DNA" (1992) *AIDS* 6: 659-663

"False-positive and false-negative results were observed in all laboratories (concordance with serology ranged from 40 to 100%)."

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Michael P. Busch et al., "Poor sensitivity, specificity, and reproducibility of detection of HIV-1 DNA in serum by polymerase chain reaction" (1992) *Journal of Acquired Immune Deficiency* 5: 872-877.

"The results indicate that current techniques for detecting cell-free HIV-1 DNA in serum lack adequate sensitivity, specificity, and reproducibility for widespread clinical applications."

"In any event, the levels of viral (and cellular) DNA in serum appear to be so low that reproducible detection, even with use of PCR, is not currently possible."

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Josiah D. Rich et al., "Misdiagnosis of HIV infection by HIV-1 plasma viral load testing: a case series" (1999) *Annals of Internal Medicine* 130: 37-39.

"The availability of sensitive assays for plasma HIV viral load and the trend toward earlier and more aggressive treatment of HIV infection has led to the inappropriate use of these assays as primary tools for the diagnosis of acute HIV infection."

"Physicians should exercise caution when using the plasma viral load assays to detect primary HIV infection..."

"Plasma viral load tests for HIV-1 were neither developed nor evaluated for the diagnosis of HIV infection..."

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M. Piatak et al., "High levels of HIV-1 in plasma during all stages of infection determined by competitive PCR" (1993) Science 259: 1749-1754.

"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."

In fact, 53% of the viral load positive patients had no culturable HIV.

"For HIV-1 propagated in vitro, total virions have been reported to exceed culturable infectious units by factors of 10,000 to 10,000,000, ratios similar to those we observed in plasma."

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Haynes W. Sheppard et al., "Viral burden and HIV disease" (1993) Nature 364: 291.

"...the high level of plasma virus observed by Piatak et al. [reference above] was about 99.9 per cent non-culturable, suggesting that it was either neutralized or defective. Therefore, rather than supporting a cytopathic model, this observation actually may help explain the relatively slow dissemination of the infected cell burden and thus the relative ineffectiveness of therapy with nucleoside analogues which target this process.

"...we question the longitudinal conclusions some of these investigators have drawn from cross-sectional data. The results presented are equally consistent with the conclusion that higher viraemia is a consequence of, rather than the proximate cause of, defective immune responses."

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Simply put: the AIDS surrogate markers are being abused. These surrogate markers are causing a great deal of harm by labeling people with myriad diseases and conditions--even healthy people who only have antibodies to HIV--as having incurable AIDS, which is said to be invariably fatal. The surrogate markers are also being used to obtain FDA approval of clinically ineffective AIDS chemotherapies that are highly toxic and even lethal if taken long enough.

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