L&PS – Logic and Philosophy of Science
Vol. V, No. 1, 2007, pp. 9-32

The Sink and the Murder Scene: Rise and Fall of a Causal Model for AIDS Pathogenesis

Vincenzo Crupi
Department of Cognitive and Education Sciences, University of Trento (Italy)
e-mail: vincenzo.crupi@unitn.it

ABSTRACT. AIDS pathogenesis has been challenging researchers for more than two decades. The topic of this paper is an important episode in the history of AIDS science, concerning one of the most influential and discussed attempts to explain the onset of AIDS as an effect of HIV infection. The rise of the so-called "sink model" of AIDS pathogenesis is outlined on the background of the knowledge and anomalies emerging in AIDS research in the Nineties. Then a reconstruction is offered of the appraisal of the model against further experimental evidence, ultimately leading to the overcoming of the model itself and to a "paradigm shift" towards alternative views currently under scrutiny.

KEYWORDS: AIDS, causal model, HIV, paradigm shift, pathogenesis, sink model

1. Introduction

Although a remarkable body of relevant knowledge has been collected over the years, AIDS pathogenesis has been challenging researchers for more than two decades. In what follows we will focus on an important episode in the history

Published by L&PS – Logic and Philosophy of Science
http://www.units.it/~episteme/ – ISSN: 1826-1043

of AIDS: the proposal and overcoming of an account of AIDS pathogenesis, the "sink model", which has been widely influential and discussed. A brief exposition of the historical background and problem situation is given at first, followed by a reconstruction of the model and of its appraisal against evidence. Finally, further and more recent developments are outlined, which both shed new light on old issues and open up novel problems in research on the pathogenesis of AIDS.

2. Backstage: A brief history of AIDS research

The birth of AIDS research dates back to the beginning of the Eighties. Starting from 1980 a new mysterious pathological condition killing previously healthy persons was observed in the United States and soon recorded by the epidemiological surveillance federal agency CDC (Centers for Disease Control). First patients suffered from an unusually severe form of Kaposi's sarcoma and from opportunistic infections, such as *Pneumocystis Carinii* pneumonia. They especially included young homosexual males from big urban areas (Los Angeles and New York City)[1] and intravenous drugs users,[2] but soon other populations were identified as involved in the epidemic (such as hemofiliacs and infants).[3]

Susceptibility to opportunistic infections suggested a pathological lack of immunocompetence and was readily associated with lymphocytopenia observed in patients' blood.[4] This connection guided the first official definition of the newly observed clinical phenomenon as a *syndrome*, i.e., a condition which manifests itself as a collection of symptoms due to an underlying pathological condition, *immunodeficiency*, which is *acquired*, namely non-congenital.[5] Early aetiological hypotheses have been directed to the causal role of an infectious agent, at first suggested on the basis of epidemiological data,[6] as well as towards non-infectious pathogenic factors possibly associated with behavioral phenomena.[7] The former line of thought encouraged virus hunters: viruses were major candidates for aetiology given that antibiotics were clearly unable

[1] CDC (1981a; 1981b; 1981c); Friedman-Kien (1981); CDC (1982a; 1982b).

[2] CDC (1982c).

[3] CDC (1982d; 1982e; 1982f).

[4] CDC (1981a); Gottlieb *et al*. (1981); Masur *et al*. (1981); Siegal *et al*. (1981).

[5] CDC (1982g).

[6] CDC (1982a; 1982h; 1982i); Auerbach *et al*. (1984).

[7] Durack (1981); CDC (1982a; 1982b); Goedert *et al*. (1982); Marmor *et al*. (1982); McManus *et al*. (1982); Jaffe *et al*. (1983); Newell *et al*. (1984).

to control the disease and that, despite routine screening for bacteria in blood products, there was evidence of possible transfusion-associated AIDS.[8]

In 1983 and 1984 scientific reports by Luc Montagnier's, Robert Gallo's and Jay Levy's research teams appeared announcing the isolation of a newly discovered virus in AIDS patients, then still labeled LAV (Lymphoadenopathy Associated Virus),[9] HTLV-III (Human T-Lymphotropic retroVirus type III),[10] or ARV (AIDS-Related Virus).[11] The virus was found to target a family of immune system cells (T-lymphocytes) whose depletion was typically observed in AIDS patients' blood, and a decisive element of the chemical basis for this tropism was soon identified in the CD4 surface receptor.[12] Moreover, some *in vitro* cytopathic activity was observed.[13] Finally, several studies reported a strong association between infection by the virus and the clinical symptoms of AIDS.[14]

In a couple of years the viral approach in AIDS research was shaped in its essential lines and rapidly gained wide acceptance. In 1986 HIV (Human Immunodeficiency Virus) was established as a unifying label, partly as the widespread recognition of a causal link between the virus and the disease.[15] The same year, the HIV-AIDS research programme was authoritatively established by the influential volume *Confronting AIDS*, a survey of knowledge and a blueprint for action published by the US National Academy of Sciences' Institute of Medicine.[16] Prepared by a panel consisting of prominent virologists, clinicians, public health experts, and social scientists, the book encapsulated the official body of knowledge about AIDS at the time as centred around *three* main theses. First, the committee concluded that the isolation of HIV and later research "led to its definitive identification as the cause of AIDS".[17] Secondly, HIV is consid-

[8] CDC (1982i); Curran *et al*. (1984).

[9] Barré-Sinoussi *et al*. (1983); Montagnier *et al*. (1984).

[10] Popovic *et al*. (1984); Gallo *et al*. (1984).

[11] Levy *et al*. (1984).

[12] Dalgleish *et al*. (1984); Klatzmann *et al*. (1984).

[13] Levy *et al*. (1984); Montagnier *et al*. (1984); Popovic *et al*. (1984).

[14] Kitchen *et al*. (1984); Sarngadharan *et al*. (1984); Salahuddin *et al*. (1985); Ou *et al*. (1988); Darby *et al*. (1989).

[15] Coffin *et al*. (1986).

[16] USA Institute of Medicine (1986).

[17] *Ibid*., p. 39. The statement of the causal link between HIV-infection and the development of AIDS has been meant to imply that the increase in the probability of the occurrence of the disease provided by the occurrence of the infection *appoximates that from 0 to 1*: on one hand, HIV-infection is seen as a strictly *necessary* condition for AIDS, i.e., $p(\text{AIDS}|\text{not-HIV}) = 0$; on the other hand, it is considered as a *typically sufficient* condition, i.e., $p(\text{AIDS}|\text{HIV}) >> 50\%$. This is, I think, no overstatement of the prevailing position. For HIV as *necessary* see, for instance, Blat-

ered a pathogenic agent *newly* introduced in human populations in the last decades and *recently* spread worldwide. In fact, one of the most powerful factors driving AIDS research at its beginnings and contributing to the elaboration of the viral approach has been the quest for an answer to the obvious question: "Why AIDS *now*?" and, although the details of the microbiological mutations and inter-specific breakthrough allegedly leading to the epidemic have been and somehow remain debated, a "new disease, new agent" principle has been explicitly invoked.[18] Moreover, and finally, unprotected sexual intercourse and blood exchange are identified as typical ways of transmission of the infection, and hence of the disease. As a consequence, unsafe sex and shared usage of needles (common in intravenous drug consumption) are classified as major at risk behaviors for AIDS.

Meanwhile, AIDS epidemics were being registered in Europe[19] and Africa[20] and the AIDS case-definition was being importantly adjusted and expanded.[21] Moreover, a different but related retrovirus, called "HIV type 2" or simply "HIV-2", was isolated in West Africa and also found to be associated with AIDS disease.[22]

Then, between the end of the Eighties and the beginning of the Nineties, some researchers, notably Peter Duesberg and Robert Root-Bernstein, challenged essentially all the basic tenets of HIV-AIDS research and claimed that their acceptance had been premature and not well founded.[23] Duesberg, in particular, presented a partially renewed and extended version of early views, according to which different AIDS-related pathological conditions are produced by the exposition to non-infectious factors which severely damage the organism on chemical grounds, such as drugs consumption and malnutrition.[24] Mainstream HIV-AIDS researchers and distinguished scientific commentators have

tner, Gallo, and Temin (1988); Weiss and Jaffe (1990); Weiss (1993). Acquired immunodeficiency without HIV-infection has been classified as a separate clinical condition of unknown origins in need of further inquiry (see Fauci, 1993). For p(AIDS|HIV), see Weiss (1993) and Smith (1998).

[18] Gallo and Montagnier (1988); DeVita, Hellman, and Rosenberg (1997, pp. 5-6).

[19] Thomsen *et al*. (1981); Downs *et al*. (1987).

[20] Bayley (1984); Piot *et al*. (1984); Van de Perre *et al*. (1984); Serwadda *et al*. (1985); Quinn *et al*. (1986); Quinn *et al*. (1987).

[21] CDC (1985; 1987). Also see CDC (1992).

[22] Clavel *et al*. (1986); Clavel *et al*. (1987).

[23] Duesberg (1987; 1988); Root-Bernstein (1993). An epistemological analysis of this background controversy on the role of HIV in AIDS has been presented in Crupi (2000).

[24] Duesberg (1992); Duesberg and Rasnick (1998); Duesberg, Koehnlain, and Rasnick (2003).

repeatedly and vigorously rejected the criticisms[25] and the alternative views[26] of dissenters and have insisted on the necessity of continuous efforts to fully understand the pathogenetic processes involved in HIV infection in order to block more and more effectively its harmful consequences.[27]

In what follows, I will mostly focus on one particular attempt in this direction, which represents a remarkable episode in the history of AIDS research.[28]

3. The central paradox of AIDS pathogenesis

The guiding commitments of HIV-AIDS research constitute an original convergence of insights emerged in contemporary virology between the Sixties and Seventies. First, the suggestion of the existence of "slow viruses", i.e., viruses responsible for pathological conditions arising long after infection.[29] HIV has been clearly taken as being a slow virus in this sense.[30] Second, the involvement of viruses in the pathogenesis of some forms of cancer;[31] and third, the birth of human retrovirology.[32] HIV is itself a retrovirus, and among AIDS-defining conditions there are oncological pathologies, some of which are thought of as being virus-induced.

As far as pathogenetic mechanisms are concerned, however, early hypotheses have been quite traditional. Many well-known viral diseases develop because the agent causes target host cells' death as a consequence of active infection, the typical case being that of direct cell-destruction by cytolysis during the productive phase of the viral life cycle. From the beginning, it was clear that AIDS patients lacked immunocompetence and, as we have already seen, two specific kinds of experimental data drew much attention from the researchers:

---

[25] Blattner, Gallo, and Temin (1988); Weiss and Jaffe (1990); Cohen (1993); Maddox (1993a; 1995a); O'Brien and Goedert (1996).

[26] Ascher *et al*. (1993); Maddox (1993b); Schechter *et al*. (1993); Darby *et al*. (1995); Maddox (1995b).

[27] For a last statement of this position, see the Durban Declaration 2000.

[28] For more extensive treatments of the history of AIDS, see Epstein (1996), Grmek (1990), and Hellman (2001, ch. 10).

[29] Gajdusek, Gibbs, and Alpers (1965).

[30] See, for instance, Levy (1993, p. 185).

[31] Emmelot and Bentvelzen (1972); Tooze (1973).

[32] Blattner (1990).

(D.1) it turned out that disease progression is associated with loss of CD4+ T-lymphocytes in blood; and

(D.2) HIV was found to exhibit a strong tropism for these very immune system cells and to display some cytopathic activity against them.

Taken together, these data seemed to suggest a natural framework for pathogenesis, which can be summarized in two basic assumptions:

(B.1) the pathogenetically crucial consequence of infection is that HIV enters CD4+ T-cells and destroys them;

(B.2) this causes a general CD4+ lymphocytopenia, which progressively impairs physiological immune system functions, thus exposing the organism to classical opportunistic infections and other AIDS-related pathologies.

Over the years, a wide range of different mechanisms for CD4+ T-cells' destruction in AIDS have been considered and investigated (including cytolysis, formation of syncytiae, induction of apoptosis, and various immune and autoimmune host responses), and evidence has been reported of damages occurring in immune system cells of AIDS patients quite independently from active infection.[33] However, even if some alternative accounts have been proposed,[34] the most influential approach to pathogenesis has been for long the acceptance of the working hypothesis that the major event in AIDS is the destruction of immune system cells, largely due to active infection by HIV and causing their subsequent depletion.[35]

Yet this point of view had to face a serious anomaly: according to early estimates, mainly based on blood sample measurements, the ratio of actively infected T-cells, even in clinically compromised individuals, was *very low*. Figures ranged from a minimum of about 1 out of 10^5 to a maximum of about 1 out of 10^3.[36] On the basis of these numbers, the primary focus on direct cytopathic mechanisms did not allow a convincing account of immunological collapse even assuming that *all* actively infected cells are invariably killed *in vi-*

[33] For reviews and further references, see Weiss and Jaffe (1990), Levy (1993), Stevenson (2003).

[34] Ascher and Sheppard (1988); Nowak *et al*. (1991); Habeshaw, Hounsell, and Dalgleish (1992); Sheppard and Ascher (1992a, b); Adleman and Wofsy (1993); Margolick *et al*. (1993); Margolick *et al*. (1995).

[35] Fauci (1987; 1988).

[36] Harper *et al*. (1986); Schnittmann *et al*. (1989).

vo by HIV. As a consequence, a "HIV hunting" phase started. Ingenuity, determination and improvements in observational techniques yielded two partially encouraging results. First, it turned out that the virus was biologically active and significantly more widespread in lymphoid tissues.[37] Second, by ultrasensitive methods of detection (such as PCR) it was estimated that large quantities of viral RNA – and, therefore, high levels of "free floating" viral particles (viral load) – were present in plasma.[38]

The latter results, dating the beginning of the Nineties, were readily received as good news for research in AIDS pathogenesis[39] and soon incorporated into pathogenetical hypotheses and speculations.[40] Yet, according to these studies (as well as more recent ones),[41] even in lymphoid tissues actively infected T-cells are typically no more than 1 out of 100 – *still not enough* to be reconciliated with the then prevailing trends in AIDS pathogenetical research given the regenerative capacity of the immune system. Moreover, the overwhelming majority (~99.9%) of detected "free" viral particles appeared to be defective, i.e., unable to successfully infect cells.[42]

This puzzling state of affairs – i.e., evidence of low levels of active HIV infection despite substantial loss of immunocompetence and of circulating CD4+ T-cells in AIDS patients – has been labeled the "central paradox of HIV infection"[43] and has represented a major challenge in the study of AIDS pathogenesis. Some have observed that, assuming the view that AIDS is mainly caused by infection-mediated killing of immune system cells by HIV, it seems one is facing a "murder scene with more bodies than bullets".[44]

This was the situation when one of the most significant episodes in the history of the viral programme took place.

4. The sink model

In January 1995 David Ho's and George Shaw's research teams published two articles on *Nature* and shaped the "sink model" of immune cells "dynamics" in

[37] Pantaleo *et al*. (1991); Embretson *et al*. (1993); Pantaleo *et al*. (1993).
[38] Piatak *et al*. (1993).
[39] Cohen (1993); Maddox (1993a); Temin and Bolognesi (1993).
[40] See Pantaleo, Graziosi, and Fauci (1993); Weiss (1993).
[41] Haase *et al*. (1996); Chun *et al*. (1997).
[42] Piatak (1993); Sheppard, Ascher, and Krowka (1993).
[43] Sheppard, Ascher, and Krowka (1993).
[44] Ascher *et al*. (1995). Also see Anderson, Ascher, and Sheppard (1998).

AIDS pathogenesis.[45] Here is a summary reconstruction of the proposal, based on Ho *et al*.'s paper.

AIDS seems to be characterized by a pathological dynamics in immune cells populations. In its final stage, in particular, it develops through a severe decrease in counts of circulating CD4+ T-lymphocytes, which supposedly reflects a more general depletion (see statement **B.2** in paragraph 3). If x denotes the total number of CD4+ and t a time-variable, then dx/dt will be the rate of change of CD4+ levels in the organism. Then let P and K be, respectively, the rate of cell production and that of cell death. The basic equation of Ho's *et al*.'s model states that

(E) $dx/dt = P - K$.

This simply means that the rate of change of CD4+ T-cell total count is a function of cell production rate and cell death rate. According to the standard view, in the final stage of AIDS dx/dt typically assumes consistently negative values. However, before that, a long period of "incubation" or "latency" occurs during which CD4+ levels appear relatively stable. Suppose we idealize the incubation period as a "steady state" in which

(S) $dx/dt = 0$.

Clearly, **(E)** along with **(S)** imply that in the steady state $P = K$, but what is their value? The viral aetiology grounding the HIV-AIDS research programme suggests that there should be some biologically damaging activity by HIV leading to the final collapse of the immune system. As a consequence, Ho *et al*. conjecture that the value of K during the incubation period, modelled by the steady state, is *not the purely physiological cell death rate*. If so, it follows from **(E)** that the relatively constant levels of CD4+ in the incubation period must in fact be a surface effect of an underlying abnormal turnover induced by HIV infection.

The experimental intervention reported in the paper consisted in the administration to previously untreated patients, starting from time t_0, of a then new powerful kind of drugs (protease inhibitors) contrasting viral replication. Blood samples measurements obtained soon after t_0 suggested that HIV was indeed effectively being halted, showing a relatively unsurpring steep decrease of viral load. If HIV typically kills CD4+ T-cells by infecting them, one would reasonably expect fewer and fewer of them being killed, and therefore overall CD4+

[45] Ho *et al*. (1995); Wei *et al*. (1995).

levels to rise, i.e., $dx/dt > 0$ soon after t_0. Now consider the following important auxiliary assumptions:

(A.1) blood sample measurement are highly representative of *overall* CD4+ T-cell population;

(A.2) P remains constant before and soon after t_0, i.e., cell production rate is not influenced by drug administration.

(A.1) directly excludes major effects of *redistribution* among different compartments of the CD4+ T-lymphocytes pool; in particular, it excludes that an increase observed in the blood compartment be *compensated* by a decrease somewhere else (e.g., in lymphoid tissues). Moreover, since it is commonly estimated that overall CD4+ population is about $0{,}5 \bullet 10^2$ times CD4+ population in blood, **(A.1)** implies that increase in CD4+ levels in blood at any given time should approximately amount to the increase in overall levels (i.e., dx/dt) divided by $0{,}5 \bullet 10^2$.

On the other hand, **(A.2)** states that, after t_0, $dx/dt > 0$ *only because* K drastically drops down, i.e., because, by having halted HIV, fewer and fewer CD4+ T-cells are being killed. Assuming that soon after t_0 K virtually reduces to 0, by **(A.2)** the model implies that dx/dt soon after t_0 approximates P (i.e., overall CD4+ production rate). In particular, **(A.2)** implies that the increase in CD4+ levels soon after t_0 quite faithfully reflects the rate of cell production that, *before* t_0, was required to compensate for the HIV-induced cell destruction and keep CD4+ levels stable. Thus, **(A.1)** and **(A.2)** together imply that increase in CD4+ levels in blood soon after t_0, estimated by blood sample measurements, should amount to about P divided by $0{,}5 \bullet 10^2$, where P, in turn, equals K in the steady state (by **(E)** and **(S)** above).

By statistical analysis on raw data from 18 patients, Ho *et al*. estimated that, soon after t_0, CD4+ increase in blood is on average $3{,}51 \bullet 10^7$ per day, and used this figure to fix the value of parameter P in the model at $1{,}8 \bullet 10^9$ per day ($3{,}51 \bullet 10^7$ times $0{,}5 \bullet 10^2$). This number is meant to provide a measure of CD4+ turnover rate (daily production and destruction) in the steady state, that is, in the "incubation" or "latency" period in untreated HIV infection, when the virus is active and undisturbed.

According to the sink model, then, CD4+ T-cells dynamics during the incubation period is in fact characterized by a very high turnover consisting in continuous virus-mediated cell-destruction compensated by an ongoing effort of replenishment by the immune system. And here is the suggestion proposed in the often quoted last paragraph of the paper:

> The CD4+ T-lymphocytes depletion seen in advanced HIV infection may be likened to a sink containing a low water level, with the tap and drain both equally wide open. As the regenerative capacity of the immune system is not infinite, it is not difficult to see why the sink eventually empties.[46]

The sink model implies that the development of AIDS is backed by continuous CD4+ T-lymphocyte destruction and suggests that it is precisely this process that leads, through exhaustion, to the final depletion of this crucial population of cells. The proposal of this model offered a concrete, although still partial and tentative, insight as to the mechanisms leading to the collapse of the immune system.

5. Theory and evidence

The sink model drew much attention within as well as without the community of researchers. The *Time*, for instance, awarded David Ho with the title of Man of the Year in 1996. According to the magazine, "his pioneering experiments with protease inhibitors helped clarify how the virus ultimately overwhelms the immune system".[47] And in 1997 some critics defined the rise of the sink model as "spectacular", while complaining "that there is hardly any visible debate over this versus alternative theories" in the viral pathogenesis of AIDS and noting that, after the appearance of the model, previously well-known approaches seem to "have been fading away rather silently".[48]

Remarkably, commenting on the "new view" of HIV infection soon after the publication of the 1995 papers, the then editor of *Nature* John Maddox claimed that the "central paradox" had for the first time a plausible solution. In fact, assuming a mechanism of killing by infection as driving HIV infection to overt AIDS (and this assumption, although not explicitly involved, certainly inspired the construction of the sink model) along with a typically very short time-lag from cell-infection to cell-killing, there might be some hope of explaining why so few infected cells are detected and how, if so few are found to be infected, the virus can possibly destroy the immune system: large amounts of the CD4+ population in the blood at any given time may have been freshly created and not yet infected. In Maddox's words:

---

[46] Ho *et al*. (1995, p. 126).
[47] *Time*, 30 Dec. 1996.
[48] Grossman and Herberman (1997a, p. 936).

> In essence, the new developments resolve the paradox by showing that the T-cells in an infected person's blood are likely to have been created only in the few days previously. There will not have been time enough for more than a small proportion of them to have become infected, while those that harbour virus will be killed off very soon. So the scarcity of T-cells from which virus can be recovered in test-tube experiments is consistent with the assertion that the immune system is in overdrive from the onset of infection by HIV.[49]

First reactions among AIDS researchers, collected in the "Scientific Correspondence" section of the May 1995 issue of *Nature*, were by and large less enthusiastic. On the whole, critics did not question the experimental data reported by Ho's and Shaw's research teams, but were apparently reluctant to recognize those very results as genuinely supporting the sink model against other possible interpretations of the same data. Accordingly, substantial and recurrent doubts were raised about the assumptions involved, a major target being statement **(A.1)** above (see paragraph 4). In absence of direct evidence of T-lymphocytes' abnormal replication rates – so the argument run – increasing levels of T-cells counts in blood can well, and even more plausibly, be explained as an effect of redistribution from different compartments, in particular from lymphoid tissues into circulation.[50] This alternative reading amounts to a straight rejection of **(A.1)**: in this perspective, Ho *et al.*'s blood samples measurement were clearly *not* representative of overall T-cell population, since increase in blood levels did not reflect a more general proliferation, but rather was *compensated* by a decrease in other compartments harbouring T-cells.

However, the sink model shared at least one of the typical features of good and promising scientific hypotheses: it provided new empirically testable predictions on the basis of which its acceptance or rejection could be rationally evaluated. Although the sink model has been widely discussed, it seems plausible that its value had to be ultimately assessed by its capability to bear *additional* and *confirmed* empirical content.[51] The following are two particularly straightforward consequences (predictions) of the model:

(P.1) due to their rapid loss and the necessity of their ready replacement required to sustain the observed constant levels at the steady state, CD4+

[49] Maddox (1995b, p. 1).
[50] Dimitrov and Martin (1995); Mosier (1995); Sprent and Tough (1995).
[51] See Popper (1963) and Lakatos (1978).

production rate in naïve (untreated) HIV-positive patients should be higher than in HIV-negative controls;

(P.2) as a direct consequence of the suppression of viral replication by effective antiretroviral therapy in HIV-infected subjects, CD4+ T-cells should live, on average, significantly longer.

Several methods for investigating immune cells dynamics and testing the empirical predictions of the model have been devised and employed.[52] Arguably, this process culminated in 1999 with the publication on *Nature Medicine* of a sophisticated experimental study by Hellerstein and collegues, reporting results obtained by a research team based in San Francisco.[53] The observational technique involved allows "direct" monitoring of *in vivo* cell dynamics in humans. The procedure runs as follows. First, glucose or water are administred (either intravenuosly or orally) which have been labeled by means of deuterium, a safe and stable isotope of hydrogen which is incorporated in dividing cells by DNA synthesis. Then peripheral blood (or tissue) samples are obtained at various points in time, cell populations of interest (for instance, CD4+ T-lymphocytes) are purified, and isotopic enrichment of cellular DNA is assessed. By mathematical analysis, the time-dependence of the fraction of labeled DNA can be determined and this, in turn, allows the calculation of dynamically relevant data, such as production rate and survival time.

The 1999 CD4+ labeling study clearly showed both **(P.1)** and **(P.2)** empirically incorrect: CD4+ production rate has *not* been found to be significantly higher in naïve HIV-positive subjects than in healthy seronegative controls, and CD4+ survival time in HIV-positive previously untreated subjects was *not* significantly extended after 12 weeks of effective antiretroviral therapy. As the authors point out, even if "a definitive biological interpretation of the [...] results cannot be made at present", "some models [...] can be excluded".[54] In particular, according to AIDS researcher Giuseppe Pantaleo, commenting on the paper, the reported outcomes virtually "put an end to four years of exciting (although often harsch) debate about the CD4+ T-lymphocyte production/ destruction hypothesis"[55] – i.e., the sink model.

[52] Wolthers *et al*. (1996); Fleury *et al*. (1998); Sachsenberg *et al*. (1998); Zhang *et al*. (1998); Wolthers *et al*. (1999).

[53] Hellerstein *et al*. (1999).

[54] *Ibid*., p. 86.

[55] Pantaleo (1999).

6. Shifting the paradigm? From killing by infection to chronic immune activation

The construction of the sink model has been a major, and possibly the last, upshot of the view of AIDS as a relatively traditional viral disease mainly driven by the cytopathic activity of HIV. Beyond the observations quoted in the previous paragraph and directly discorfirming the sink model, a growing body of evidence has shown general limitations of this view. In particular, a serious problem has been the demonstration that in AIDS patients a different family of T-lymphocytes, called CD8+, which do *not* represent a natural target for HIV infection, suffer from abnormalities in biological behavior and population dynamics which are strikingly similar to those affecting CD4+ T-cells.[56] Worse still maybe, even among CD4+ T-cells, a major cell-killing process, i.e., apoptosis, predominantly occurs in *uninfected* cells.[57]

Some observers have identified a paradigm shift in recent research on AIDS pathogenesis.[58] The rise and fall of the sink model seems, in fact, to have come along with, and even to have stimulated, a fundamental change in perspective. A proposal which is gaining attention and consensus sees in an abnormal and chronic immune activation the crucial process associated with progression to AIDS,[59] and much recently reported experimental evidence seems to fit in a quite natural way into this framework but not into more traditional views. According to this emerging perspective, a crucial step is the inclusion into AIDS pathogenetical models of a more accurate and sophisticated version of our current knowledge of physiological immune system processes. Both CD4+ *and* CD8+ circulating T-lymphocytes include functionally distinct subpopulations. Essential components are represented by a large subset of long-lived "resting" cells consisting in pools of so-called "naïve" and "memory" cells, which regenerate and reproduce in a slow and relatively stable fashion. Upon antigenic exposure, a portion of (both naïve and memory) resting cells become activated, thereby starting a process of rapid proliferation and differentiation into so-called "effector" cells over a period of days or weeks. A large majority of activated cells typically die soon by activation-induced apoptosis, while a small fraction meets the pool of long-lived memory cells and serves as a persistent

[56] See, for instance, Roederer (1998); Hazenberg *et al*. (2000); Kovacs *et al*. (2001); Lempicki *et al*. (2000); McCune *et al*. (2000).

[57] Finkel (1995).

[58] Grossman *et al*. (2002); Silvestri and Feinberg (2003).

[59] Grossman and Herberman (1997b); Grossman *et al*. (2002).

reservoir for subsequent antigen-induced activation. It has been repeatedly reported that HIV-infected persons typically exhibit abnormal, chronic and up-regulated levels of immune system activation.[60]

Focussing on pathological immune activation as the basic process underlying progression to AIDS is providing researchers with several new insights, and gathers into a unified framework a cluster of intriguing experimental results. For instance, a marked preferential biological activity by HIV in activated CD4+ T-cells has been reported.[61] Consistent with these data, the immune activation approach suggests that it is precisely increased immune activation that sustains high HIV replication and viral load levels in (untreated) progression to AIDS. In other words, "activation is the machine driving virus production".[62] Moreover, the fact that antiretroviral theraphy may impact very quickly on viral load without immediately increasing average survival time of T-cells[63] suggests that, even if HIV is cytopathic *in vivo* to some extent, T-cells' death in HIV infection occurs largely independent of HIV. Rather, it may reflect apoptosis in a pathologically expanded population of activated T-cells. On the same basis, the finding of a typical susceptibility to apoptosis in circulating CD8+ cells and, in general, uninfected "bystanders" in HIV infection and AIDS can be quite simply explained. In fact, in a further labeling study in 2003, Hellerstein and collegues reported that in HIV/AIDS untreated patients the absolute number of circulating short-lived activated CD4+ cells is significantly higher than in healthy controls, while the number of circulating long-lived "resting" cells is drastically lower.[64]

Many aspects of the interplay between the immune activation model and experimental evidence are currently under scrutiny. Here I just would like to point out that the paradigm shift (assuming it is indeed occurring) has substantial, and partly puzzling, consequences on both old issues and further directions of inquiry. As a major example of the former case, it should be noticed that, from the standpoint of the new approach, inferring the basic pathogenetical hypotheses **(B.1)** and **(B.2)** from initial data **(D.1)** and **(D.2)** (see paragraph 3) seems to have taken AIDS research on a blind alley for years. For instance, AIDS researcher Mario Roederer has claimed that, contrary to the interpretation prevailing in the early times, "the fact that HIV uses CD4 as its primary receptor

[60] Gougeon *et al.* (1996); Giorgi *et al*. (1999); Sousa *et al*. (2002); Hunt *et al*. (2003).
[61] Roederer *et al*. (1997); Spina *et al*. (1997); Woods *et al*. (1997).
[62] Grossman *et al*. (2002, p. 321).
[63] Hellerstein *et al*. (1999); Kovacs *et al*. (2001).
[64] Hellerstein *et al*. (2003).

and that CD4+ T-cell numbers decline during AIDS are only an *unfortunate coincidence* that have led us astray from understanding the immunopathogenesis of this disease".[65] In fact, the very idea of an *overall* depletion of CD4+ T-cells as the hallmark of AIDS has been called into question in favour of the statement of a "*selective* depletion of 'resting' naïve and memory cells"[66] on the basis of the recent observation that, at least during asymptomatic infection, in an allegedly reliable animal model of AIDS CD4+ (and CD8+) T-cells' total counts seem actually to *increase*.[67]

As far as future prospects are concerned, it is fair to say that a satisfactory account of two crucial links in the causal chain from HIV infection to AIDS *via* immune activation still fail: in a recent review, while promoting the paradigm shift, Silvestri and Feinberg point out that "we still lack an explanation of why HIV appears to be uniquely powerful in inducing a chronic state of immune activation [...], and why the HIV-induced immune activation is so disruptive of the proper overall functioning of the immune system".[68] In view of documented observations that AIDS-like immune activation may occur without HIV infection[69] and that effective clinical improvement in AIDS patients on antiretroviral treatment can obtain despite evidence of modest inhibition of HIV replication,[70] investigation on these "missing links" seems a particularly urgent task for future research.

Acknowledgements
I would like to express my gratitude to Sharyn Clough, Gilberto Corbellini, Roberto Festa, Franz-Peter Griesmaier, Jonathan Kaplan, Diego Marconi, Pierpaolo Marrone, Matteo Motterlini, Alfred Tauber, Paolo Vineis, John Worrall, the participants to the LSE 2001/02 Research Seminar in the Philosophy of the Natural Sciences and to the 2001/02 Seminar on *Cognition, Choice, Decision* of the Laboratory of Cognitive Sciences in Rovereto (Italy) for useful and sometimes usefully critical comments on several previous presentations of material merged into this work. I also thank Raffaella Campaner, Edoardo Camurri, Gabriele Contessa, Francesca Guidi, Matteo Morganti, Silvia Pessione and Claudia Vittori for various helpful discussions on relevant issues. Any mistake falls, of course, under my own responsibility.

[65] Roederer (1998, p. 146, emphasis added).
[66] Grossman (2003).
[67] Sopper *et al*. (2003).
[68] Silvestri and Feinberg (2003, p. 823).
[69] Kalinkovich *et al*. (1998).
[70] Deeks *et al*. (2002).

REFERENCES

ADLEMAN, L.M., WOFSY, D. (1993): "T-Cell Homeostasis: Implications for HIV Infection", *Journal of Acquired Immune Deficiency Syndromes*, 6, pp. 144-152.

ANDERSON, R.W., ASCHER, M.S., SHEPPARD, H.W. (1998): "Direct HIV Cytopathicity Cannot Account for CD4 Decline in AIDS in the Presence of Homeostasis: A Worst-Case Dynamic Analysis", *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 17, pp. 245-252.

ASCHER, M.S., SHEPPARD, H.W. (1988): "AIDS as Immune System Activation: A Model for Pathogenesis", *Clinical & Experimental Immunology*, 73, pp. 165-167.

ASCHER, M.S. *et al*. (1993): "Does Drug Use Cause AIDS?", *Nature*, 362, pp. 103-104.

ASCHER, M.S. *et al*. (1995): "Paradox Remains", *Nature*, 375, p. 196.

AUERBACH, D.M. *et al*. (1984): "Cluster of Cases of Acquired Immune Deficiency Syndrome. Patients Linked by Sexual Contact", *The American Journal of Medicine*, 76, pp. 487-492.

BARRÉ-SINOUSSI, F. *et al*. (1983): "Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)", *Science*, 220, pp. 868-871.

BAYLEY, A.C. (1984): "Aggressive Kaposi's Sarcoma in Zambia", *Lancet*, 1, pp. 1318-1320.

BLATTNER, W.A., GALLO, R.C., TEMIN, H.M. (1988): "HIV Causes AIDS", *Science*, 241, pp. 514-517.

BLATTNER, W.A. (ed.) (1990): *Human Retrovirology: HTLV*, New York: Raven Press.

CDC (1981a): "*Pneumocystis* Pneumonia in Homosexual Men – Los Angeles', *Morbidity and Mortality Weekly Report*, 30, pp. 250-252.

——— (1981b): "Kaposi's Sarcoma and *Pneumocystis* Pneumonia among Homosexual Men – New York City and California", *Morbidity and Mortality Weekly Report*, 30, pp. 305-308.

——— (1981c): "Follow-up on Kaposi's Sarcoma and *Pneumocystis* Pneumonia", *Morbidity and Mortality Weekly Report*, 30, pp. 409-410.

——— (1982a): "A Cluster of Kaposi's Sarcoma and *Pneumocystis Carinii* Pneumonia among Homosexual Male Residents of Los Angeles and Orange Counties, California", *Morbidity and Mortality Weekly Report*, 31, pp. 305-307.

——— (1982b): "Epidemiologic Aspects of the Current Outbreak of Kaposi's Sarcoma and Opportunistic Infections", *The New England Journal of Medicine*, 306, pp. 248-252.

——— (1982c): "Update on Kaposi's Sarcoma and Opportunistic Infections in Previously Healthy Persons – United States", *Morbidity and Mortality Weekly Report*, 31, pp. 300-301.

——— (1982d): "Opportunistic Infections and Kaposi's Sarcoma among Haitians in the United States", *Morbidity and Mortality Weekly Report*, 31, pp. 353-354, 360-361.

——— (1982e): "*Pneumocystis Carinii* Pneumonia among Persons with Hemophilia A", *Morbidity and Mortality Weekly Report*, 31, pp. 365-367.

——— (1982f): "Unexplained Immunodeficiency and Opportunistic Infections in Infants – New York, New Jersey, California", *Morbidity and Mortality Weekly Report*, 31, pp. 665-667.

——— (1982g): "Update on Acquired Immune Deficiency Syndrome (AIDS) – United States", *Morbidity and Mortality Weekly Report*, 31, pp. 507-508, 513-514.

——— (1982h): "Acquired Immune Deficiency Syndrome (AIDS): Precautions for Clinical and Laboratory Staffs", *Morbidity and Mortality Weekly Report*, 31, pp. 577-580.

——— (1982i): "Possible Transfusion Associated AIDS – California", *Morbidity and Mortality Weekly Report*, 31, pp. 652-654.

——— (1985): "Revision of the Case Definition of Acquired Immunodeficiency Syndrome for National Reporting – United States", *Morbidity and Mortality Weekly Report*, 34, pp. 373-375.

——— (1987): "Revision of the CDC Surveillance Case Definition for Acquired Immunodeficiency Syndrome", *Morbidity and Mortality Weekly Report*, 36, p. 1S.

——— (1992): "1993 Revised Classification System for HIV-Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults", *Morbidity and Mortality Weekly Report*, 41, p. RR17.

CHUN, T.W. *et al*. (1997): "Quantification of Latent Tissue Reservoirs and Total Body Viral Load in HIV-1 Infection", *Nature*, 387, pp. 183-188.

CLAVEL, F. *et al*. (1986): "Isolation of a New Human Retrovirus from West African Patients with AIDS", *Science*, 233, pp. 343-346.

CLAVEL, F. *et al*. (1987): "Human Immunodeficiency Virus Type 2 Infection Associated with AIDS in West Africa", *The New England Journal of Medicine*, 316, pp. 1180-1185.

COFFIN, J. *et al*. (1986): "Human Immunodeficiency Viruses", *Science*, 232, p. 697.

COHEN, J . (1993): "AIDS Research. Keystone Blunt Message: 'It's the Virus, Stupid!'", *Science*, 260, pp. 292-293.

CRUPI, V. (2000): "Epistemologia del caso-AIDS: un *case-study* per la metodologia dei programmi di ricerca scientifici", *Epistemologia*, 23, pp. 243-280.

CURRAN, J.W. *et al*. (1984): "Acquired Immunodeficiency Syndrome (AIDS) Associated with Transfusions", *The New England Journal of Medicine*, 310, pp. 69-75.

DALGLEISH, A.G. *et al*. (1984): "The CD4 (T4) Antigen is an Essential Component of the Receptor for the AIDS Retrovirus", *Nature*, 312, pp. 763-767.

DARBY, S.C. *et al*. (1989): "Incidence of AIDS and Excess of Mortality Associated with HIV in Haemophiliacs in the United Kingdom: Report on Behalf of the Directors of Haemophilia Centers in the United Kingdom", *British Medical Journal*, 298, pp. 1064-1068.

DARBY, S.C. *et al*. (1995): "Mortality before and after HIV Infection in the Complete UK Population of Haemofiliacs", *Nature*, 377, pp. 79-82.

DEEKS, S.G. *et al*. (2002): "CD4+ T-Cell Kinetics and Activation in Human Immunodeficiency Virus-Infected Patients Who Remain Viremic despite Long-Term Treatment with Protease Inhibitor-Based Therapy", *The Journal of Infectious Diseases*, 185, pp. 315-323.

DEVITA, V.T., HELLMAN, S., ROSENBERG, S.A. (eds.) (1997): *AIDS. Biology, Diagnosis, Treatment and Prevention*, Philadelphia (PA): Lippincott-Raven Publishers.

DIMITROV, D.S., MARTIN, M.A. (1995): "CD4+ Cell Turnover", *Nature*, 375, pp. 194-195.

DOWNS, A.M. *et al*. (1987): "AIDS in Europe. Current Trends and Short-Term Predictions Estimated from Surveillance Data: January 1981 – June 1986", *AIDS*, 1, pp. 53-57.

DUESBERG, P.H. (1987): "Retroviruses as Carcinogens and Pathogens: Expectations and Reality", *Cancer Research*, 47, pp. 1199-1220.

——— (1988): "HIV is Not the Cause of AIDS", *Science*, 241, pp. 514-516.

——— (1992): "AIDS Acquired by Drug Consumption and Other Noncontagious Risk Factors", *Pharmacology & Therapeutics*, 55, pp. 201-277.

DUESBERG, P.H., KOEHNLAIN, C., RASNICK, D. (2003): "The Chemical Bases of the Various AIDS Epidemics: Recreational Drugs, Antiviral Chemotherapy and Malnutrition", *Journal of Biosciences*, 28, pp. 383-412.

DUESBERG, P.H., RASNICK, D. (1998): "The AIDS Dilemma: Drug Diseases Blamed on a Passenger Virus", *Genetica*, 104, pp. 85-132.

DURACK, D.T. (1981): "Opportunistic Infections and Kaposi's Sarcoma in Homosexual Men", *The New England Journal of Medicine*, 305, pp. 1465-1467.

EMBRETSON, J. *et al*. (1993): "Massive Covert Infection of Helper T-Lymphocytes and Macrophages by HIV during the Incubation Period of AIDS", *Nature*, 362, pp. 359-362.

EMMELOT, P., BENTVELZEN, P. (eds.) (1972): *RNA Viruses and Host Genome in Oncogenesis*, New York: American Elsevier Publishing.

EPSTEIN, S. (1996): *Impure science. AIDS, Activism and the Politics of Knowledge*, Berkeley: University of California Press.

FAUCI, A.S. (1987): "AIDS: Immunopathogenic Mechanisms and Research Strategies", *Clinical Research*, 35, pp. 503-510.

——— (1988): "The Human Immunodeficiency Virus: Infectivity and Mechanims of Pathogenesis", *Science*, 239, pp. 617-622.

——— (1993): "CD4+ Lymphocytopenia without HIV-Infection – No Lights, No Camera, just Facts", *The New England Journal of Medicine*, 328, pp. 429-431.

FINKEL, T.H. (1995): "Apoptosis Occurs Predominantly in Bystander Cells and Not in Productively Infected Cells of HIV- and SIV-Infected Lymph Nodes", *Nature Medicine*, 1, pp. 129-134.

FLEURY, S. *et al*. (1998): "Limited CD4+ T-Cell Renewal in Early HIV-1 Infection: Effects of Highly Active Antiretroviral Therapy", *Nature Medicine*, 4, pp. 794-801.

FRIEDMAN-KIEN, A.E.: "Disseminated Kaposi's Sarcoma Syndrome in Young Homosexual Men", *Journal of the American Academy of Dermatology*, 5, pp. 468-471.

GAJDUSEK, D.C., GIBBS, C.J., ALPERS, M. (1965): *Slow, Latent and Temperate Virus Infections*, Washington (DC): Government Printing Office.

GALLO, R.C. *et al*. (1984): "Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS", *Science*, 224, pp. 500-503.

GALLO, R.C., MONTAGNIER, L. (1988): "AIDS in 1988", *Scientific American*, 259, pp. 40-48.

GIORGI, J.V. *et al*. (1999): "Shorter Survival in Advanced Human Immunodeficiency Virus Type 1 Infection Is More Closely Associated with T-Lymphocyte Activation than with Plasma Virus Burden or Virus Chemokine Coreceptor Usage", *The Journal of Infectious Diseases*, 179, pp. 859-870.

GOEDERT, J.J. *et al*. (1982): "Amyl Nitrite May Alter T-Lymphocytes in Homosexual Men", *Lancet*, 1, pp. 412-416.

GOTTLIEB, M.S. *et al*. (1981): "*Pneumocystis Carinii* Pneumonia and Mucosal Candidiasis in Previously Healthy Homosexual Men: Evidence of a New Acquired Cellular Immunodeficiency", *The New England Journal of Medicine*, 305, pp. 1425-1431.

GOUGEON, M.L. *et al.* (1996): "Programmed Cell Death in Peripheral Lymphocytes from HIV-Infected Persons: Increased Susceptibility to Apoptosis of CD4 and CD8 T-Cells Correlates with Lymphocyte Activation and with Disease Progression", *Journal of Immunology*, 156, pp. 3509-3520.

GRMEK, M. (1990): *History of AIDS*, Princeton (NJ): Princeton University Press.

GROSSMAN, Z. (2003): "Is SIV Infection Associated with CD4+ T-Cell Depletion?", *Blood*, 101, p. 1209.

GROSSMAN, Z., HERBERMAN, R.B. (1997a): "Mathematical Models of HIV Pathogenesis", *Nature Medicine*, 9, p. 936.

——— (1997b): "T-Cell Homeostasis in HIV Infection is Neither Failing Nor Blind: Modified Cell Counts Reflect an Adaptive Response of the Host", *Nature Medicine*, 3, pp. 486-490.

GROSSMAN, Z. *et al*. (2002): "CD4+ T-Cell Depletion in HIV Infection: Are We Closer to Understanding the Cause?", *Nature Medicine*, 8, pp. 319-323.

HAASE, A. *et al*. (1996): "Quantitative Image Analysis of HIV-1 Infection in Lymphoid Tissue", *Science*, 274, pp. 985-989.

HABESHAW, J., HOUNSELL, E., DALGLEISH, A. (1992): "Does the HIV Envelope Induce a Chronic Graft-*versus*-Host-like Disease?", *Immunology Today*, 13, pp. 207-210.

HARPER, M.E. *et al*. (1986): "Detection of Lymphocytes Expressing Human T-Lymphotropic Virus Type III in Lymph Nodes and Peripheral Blood from Infected Individuals by *In Situ* Hybridization", *Proceedings of the National Academy of Sciences of United States of America*, 83, pp. 772-776.

HAZENBERG, M.D. *et al*. (2000): "T-Cell Division in Human Immunodeficiency Virus (HIV)-1 Infection Is Mainly Due to Immune Activation: A Longitudinal Analysis in Patients before and during Highly Active Antiretroviral Therapy (HAART)", *Blood*, 95, pp. 249-255.

HELLERSTEIN, M. *et al*. (1999): "Directly Measured Kinetics of Circulating T-Lymphocytes in Normal and HIV-1 Infected Humans", *Nature Medicine*, 5, pp. 83-89.

HELLERSTEIN, M. *et al*. (2003): "Subpopulations of Long-Lived and Short-Lived T-Cells in Advanced HIV-1 Infection", *Journal of Clinical Investigation*, 112, pp. 956-966.

HELLMAN, H. (2001): *Great Feuds in Medicine*, New York: Wiley.

HO, D.D. *et al*. (1995): "Rapid Turnover of Plasma Virios and CD4 Lymphocytes in HIV-1 Infection", *Nature*, 373, pp. 123-126.

HUNT, P.W. *et al*. (2003): "T-Cell Activation Is Associated with Lower CD4+ T-Cell Gains in Human Immunodeficiency Virus-Infected Patients with Sustained Viral Suppression during Antiretroviral Therapy", *The Journal of Infectious Diseases*, 187, pp. 1534-1543.

JAFFE, H.W. *et al*. (1983): "National Case-Control Study of Kaposi's Sarcoma and *Pneumocystis Carinii* Pneumonia in Homosexual Men – Part 1: Epidemiological Results", *Annals of Internal Medicine*, 99, pp. 145-151.

KALINKOVICH, A. *et al*. (1998): "Decreased CD4 and Increased CD8 Counts with T-Cell Activation Is Associated with Chronic Helminth Infection", *Clinical & Experimental Immunology*, 114, pp. 414-421.

KITCHEN, L.W. *et al*. (1984): "Aetiology of AIDS – Antibodies to Human T-Cell Leukemia Virus (Type III) in Haemofiliacs", *Nature*, 312, pp. 367-369.

KLATZMANN, D. *et al*. (1984): "T-Lymphocyte T4 Molecule Behaves as the Receptor for Human Retrovirus LAV", *Nature*, 312, pp. 767-768.

KOVACS, J.A. *et al*. (2001): "Identification of Dynamically Distinct Subpopulations of T-Lymphocytes that Are Differentially Affected by HIV", *The Journal of Experimental Medicine*, 194, pp. 1731-1741.

LAKATOS, I. (1978): *Philosophical Papers*. I: *The Methodology of Scientific Research Programmes*, Cambridge: Cambridge University Press.

LEMPICKI, R.A. *et al*. (2000): "Impact of HIV-1 Infection and Highly Active Antiretroviral Therapy on the Kinetics of CD4+ and CD8+ T-Cell Turnover in HIV-Infected Patients", *Proceedings of the National Academy of Sciences of United States of America*, 97, pp. 13778-13783.

LEVY, J.A. (1993): "Pathogenesis of Human Immunodeficiency Virus Infection", *Microbiological Reviews*, 57, pp. 183-289.

LEVY, J.A. *et al*. (1984): "Isolation of Lymphocytopathic Retroviruses from San Francisco Patients with AIDS", *Science*, 225, pp. 840-842.

MADDOX, J. (1993a): "Where the AIDS Virus Hides Away", *Nature*, 362, p. 287.

——— (1993b): "Has Duesberg a Right of Reply?", *Nature*, 363, p. 109.

——— (1995a): "Duesberg and the New View of HIV", *Nature*, 373, p. 189.

——— (1995b): "More Conviction on Hiv and Aids", *Nature*, 377, p. 1.

Margolick, J.B. *et al*. (1993): "Changes in T and Non-T Lymphocyte Subsets Following Seroconversion to Hiv-1: Stable CD3+ and Declining CD2-Populations Suggest Regulatory Responses Linked to Loss of CD4 Lymphocytes. The Multicenter Aids Cohort Study", *Journal of Acquired Immune Deficiency Syndromes*, 6, pp. 153-161.

Margolick, J.B. *et al*. (1995): "Failure of T-Cell Homeostasis Preceding Aids in Hiv-1 Infection. The Multicenter Aids Cohort Study", *Nature Medicine*, 1, pp. 674-680.

Marmor, M. *et al*. (1982): "Risk Factors for Kaposi's Sarcoma in Homosexual Men", *Lancet*, 1, pp. 1083-1087.

Masur, H. *et al*. (1981): "An Outbreak of Community-Acquired *Pneumocystis Carinii* Pneumonia: Initial Manifestation of Cellular Immune Dysfunction", *The New England Journal of Medicine*, 305, pp. 1431-1438.

McCune, J.M. *et al*. (2000): "Factors Influencing T-Cell Turnover in Hiv-1-Seropositive Patients", *Journal of Clinical Investigation*, 105, pp. R1-8.

McManus, T.J. *et al*. (1982): "Amyl Nitrite Use by Homosexuals", *Lancet*, 1, p. 503.

Montagnier, L. *et al*. (1984): "A New Human T-Lymphotropic Retrovirus: Characterization and Possible Role in Lymphoadenopathy and Acquired Immune Deficiency Syndromes", in R.C. Gallo, M.E. Essex, and L. Gross (eds.), *Human T-Cell Leukemia/Lymphoma Virus*, Cold Spring Harbor (NY): Cold Spring Harbor Laboratory, pp. 363-379.

Mosier, D.E. (1995): "CD4+ Cell Turnover", *Nature*, 375, pp. 193-194.

Newell, G.R. *et al*. (1984): "Toxicity, Immunosuppressive Effects, and Cancirogenic Potential of Volatile Nitrites: Possible Relationship to Kaposi's Sarcoma", *Pharmacotherapy*, 4, pp. 284-291.

Nowak, M.A. *et al*. (1991): "Antigenic Diversity Thresholds and the Development of Aids", *Science*, 254, pp. 963-969.

O'Brien, S., Goedert, J.J. (1996): "Hiv Causes Aids: Koch's Postulates Fulfilled", *Current Opinion in Immunology*, 8, pp. 613-618.

Ou, C.Y. *et al*. (1988): "Dna Amplification for Direct Detection of Hiv-1 in Dna of Peripheral Blood Mononuclear Cells", *Science*, 239, pp. 295-297.

Pantaleo, G. (1999): "Unraveling the Strands of Hiv's Web", *Nature Medicine*, 5, pp. 27-28.

Pantaleo, G. *et al*. (1991): "Lymphoid Organs Function as Major Reservoirs for Human Immunodeficiency Virus", *Proceedings of the National Academy of Sciences of United States of America*, 88, pp. 9838-9842.

Pantaleo, G. *et al*. (1993): "Hiv Infection is Active and Progressive in Lymphoid Tissue during the Clinically Latent Stage of Disease", *Nature*, 362, pp. 355-358.

Pantaleo, G., Graziosi, C., Fauci, A.C. (1993): "New Concepts in the Immunopathogenesis of Human Immunideficiency Virus Infection", *The New England Journal of Medicine*, 328, pp. 327-335.

PIATAK, M. *et al*. (1993): "High Levels of HIV-1 in Plasma during all Stages of Infection Determined by Competitive PCR", *Science*, 259, pp. 1749-1754.

PIOT, P. *et al*. (1984): "Acquired Immunodeficiency Syndrome in a Heterosexual Population in Zaire", *Lancet*, 2, pp. 65-69.

POPOVIC, M. *et al*. (1984): "Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS", *Science*, 224, pp. 497-500.

POPPER, K.R. (1963): *Conjectures and Refutations*, London: Routledge and Kegan Paul.

QUINN, T.C. *et al*. (1986): "AIDS in Africa: An Epidemiological Paradigm", *Science*, 234, pp. 955-663.

QUINN, T.C. *et al*. (1987): "Serologic and Immunologic Studies in Patients with AIDS in North America and Africa: The Potential Role of Cofactors in Human Immunodeficiency Virus Infection", *JAMA: The Journal of the American Medical Association*, 257, pp. 2617-2621.

ROEDERER, M. (1998): "Getting to the HAART of T-Cell Dynamics", *Nature Medicine*, 4, pp. 145-146.

ROEDERER, M. *et al*. (1997): "HIV Does Not Replicate in Naïve CD4 T-Cells Stimulated with CD3/CD28", *Journal of Clinical Investigation*, 99, pp. 1555-1564.

ROOT-BERNSTEIN, R.S. (1993): *Rethinking AIDS*, New York: Free Press Macmillan.

SACHSENBERG, N. *et al*. (1998): "Turnover of CD4+ and CD8+ T-Lymphocytes in HIV-1 Infection as Measured by Ki-67 Antigen", *The Journal of Experimental Medicine*, 187, pp. 1295-1303.

SALAHUDDIN, S.Z. *et al*. (1985): "Isolation of Infectious Human T-Cell Leukemia/Lymphotropic Virus Type III (HTLV-III) from Patients with Acquired Immunodeficiency Syndrome (AIDS) or AIDS-Related Complex (ARC) and from Healthy Carriers: A Study of Risk Groups and Tissue Sources", *Proceedings of the National Academy of Sciences of United States of America*, 82, pp. 5530-5534.

SARNGADHARAN, M.G. *et al*. (1984): "Antibodies Reactive with Human T-Lymphotropic Retroviruses (HTLV-III) in the Serum of Patients with AIDS", *Science*, 224, pp. 506-508.

SCHECHTER, M.T. *et al*. (1993): "HIV-1 and the Aetiology of AIDS", *Lancet*, 341, pp. 658-659.

SCHNITTMANN, M. *et al*. (1989): "The Reservoir for HIV-1 in Human Peripheral Blood is a T-Cell that Maintains Expression of CD4", *Science*, 245, pp. 305-308.

SERWADDA, D. *et al*. (1985): "Slim Disease: A New Disease in Uganda and Its Association with HTLV-III Infection", *Lancet*, 2, pp. 849-852.

SHEPPARD, H.W., ASCHER, M.S. (1992a): "The Relationship between AIDS and Immunologic Tolerance", *Journal of Acquired Immune Deficiency Syndromes*, 5, pp. 143-147.

——— (1992b): "The Natural History and Pathogenesis of HIV Infection", *Annual Review of Microbiology*, 46, pp. 533-564.

SHEPPARD, H.W., ASCHER, M.S., KROWKA, J.F. (1993): "Viral Burden and HIV Disease", *Nature*, 364, p. 291.

SIEGAL, F.P. *et al*. (1981): "Severe Acquired Immunodeficiency in Male Homosexuals Manifested by Chronic Perianal Ulcerative *Herpes Simplex* Lesions", *The New England Journal of Medicine*, 305, pp. 1439-1444.

SILVESTRI, G., FEINBERG, M.B. (2003): "Turnover of Lymphocytes and Conceptual Paradigms in HIV Infection", *Journal of Clinical Investigation*, 112, pp. 821-824.

SMITH, R.A. (ed.) (1998): *The Encyclopedia of AIDS*, Chicago: Fitzroy Dearborn Publishers.

SOPPER, S. *et al*. (2003): "Impact of Simian Immunodeficiency Virus (SIV) Infection on Lymphocyte Numbers and T-Cell Turnover in Different Organs of Rhesus Monkeys", *Blood*, 101, pp. 1213-1219.

SOUSA, A.E. *et al*. (2002): "CD4+ Cell Depletion Is Linked Directly to Immune Activation in the Pathogenesis of HIV-1 and HIV-2 but only Indirectly to Viral Load", *Journal of Immunology*, 169, pp. 3400-3406.

SPINA, C.A. *et al*. (1997): "Preferential Replication of HIV-1 in the CD45RO Memory Cell Subset of Primary CD4 Lymphocytes *In Vitro*", *Journal of Clinical Investigation*, 99, pp. 1774-1785.

SPRENT, J., TOUGH, D. (1995): "CD4+ Cell Turnover", *Nature*, 375, pp. 194.

STEVENSON, M. (2003): "HIV-1 Pathogenesis", *Nature Medicine*, 9, pp. 853-860.

TEMIN, H.M., BOLOGNESI, D.P. (1993): "AIDS: Where Has HIV Been Hiding?", *Nature*, 362, pp. 292-293.

THOMSEN, H.K. *et al*. (1981): "Kaposi Sarcoma among Homosexual Men in Europe", *Lancet*, 1, p. 688.

TOOZE, J. (1973): *The Molecular Biology of Tumor Viruses*, Cold Springer Harbor (NY): Cold Springer Harbor Laboratory.

USA INSTITUTE OF MEDICINE, *Confronting AIDS*, Washington (DC): National Academy Press.

VAN DE PERRE, P. *et al*. (1984): "Acquired Immunodeficiency in Rwanda", *Lancet*, 2, pp. 62-65.

WEI, X. *et al*. (1995): "Viral Dynamics in Human Immunodeficiency Virus Type 1 Infection", *Nature*, 373, pp. 117-122.

WEISS, R.A. (1993): "How Does HIV Cause AIDS?", *Science*, 260, pp. 1273-1279.

WEISS, R.A., JAFFE, H.W. (1990): "Duesberg, HIV and AIDS", *Nature*, 345, pp. 659-660.

WOLTHERS, K. *et al*. (1996): "T-Cell Telomere Length in HIV-1 Infection: No Evidence for Increased T-Cell Turnover", *Science,* 274, pp. 1543-1547.

WOLTHERS, K. *et al*. (1999): "Normal Telomere Lengths in Naïve and Memory CD4+ T-Cells in HIV Type 1 Infection: A Mathematical Interpretation", *AIDS Research and Human Retroviruses*, 15, pp. 1053-1062.

WOODS, T.C. *et al*. (1997): "Loss of Inducible Virus in CD45RA Naïve Cells after Human Immunodeficiency Virus-1 Entry Accounts for Preferential Viral Replication in CD45RO Memory Cells", *Blood*, 89, pp. 1635-1641.

ZHANG, Z.Q. *et al*. (1998): "Kinetics of CD4+ T-Cell Repopulation of Lymphoid Tissues after Treatment of HIV-1 Infection", *Proceedings of the National Academy of Sciences of United States of America*, 95, pp. 1154-1159.