

## Linkage and Independence of AIDS and Kaposi Disease: The Interaction of Human Immunodeficiency Virus and Some Coagents

**Summary:** Through epidemiological considerations we conclude that full-blown AIDS may occur only if the index patient is infected by the human immunodeficiency virus (HIV) and, in addition, by some other infectious coagent. Since the dynamical behaviour of the spread of AIDS cases with manifestation of Kaposi's sarcoma differs fundamentally from that of the non-Kaposi cases, we conjecture that two independent coagents (together with HIV) are responsible for the outbreak of full-blown AIDS with or without manifestation of Kaposi's sarcoma, respectively. Our formal epidemiological considerations appear to be supported by recent microbiological findings.

**Zusammenfassung:** *Kopplung und Unabhängigkeit von AIDS und Kaposi-Sarkom: Interaktion von humanem Immundefizienzvirus und anderen Koagenzien.* Aufgrund epidemiologischer Überlegungen wird geschlossen, daß Voll-AIDS möglicherweise nur dann auftritt, wenn der entsprechende Patient mit dem humanen Immundefizienzvirus (HIV) und außerdem mit einem weiteren infektiösen Koagens infiziert ist. Da sich die Ausbreitungsdynamik der AIDS-Fälle mit Manifestation von Kaposi-Sarkom wesentlich von der der Fälle ohne Kaposi-Sarkom unterscheidet, wird vermutet, daß für die Ausprägung von AIDS mit bzw. ohne Beteiligung von Kaposi-Sarkom jeweils eigenständige Koagenzien verantwortlich sind. Unsere formalen epidemiologischen Argumente scheinen durch neuere mikrobiologische Ergebnisse gestützt zu werden.

### HIV – A Necessary Condition for the Outbreak of AIDS

In 1983/1984 *L. Montagnier* and *R. C. Gallo* described the Human Immunodeficiency Virus (HIV) as the apparent causative agent of the newly observed acquired immune deficiency syndrome AIDS: HIV was found present in all AIDS patients regardless of the particular clinical manifestation and was detected, for example, in the blood, sperma, vaginal secretions, saliva, cerebrospinal fluid and various tissues of affected patients. Thus, HIV was recognized as *conditio sine qua non* of AIDS. Epidemiological studies showed that persons infected with HIV are likely to develop AIDS at least after an average incubation time of eight or more years. Thus, there is apparently no doubt about the causal role of HIV for the pathogenesis of AIDS. Looking more precisely at the outlined relationship between HIV and AIDS, we may only conclude that HIV is a *necessary* condition for the outbreak of full-blown

AIDS. However, as a consequence of principal methodological problems and considering the relatively short time of observation since 1981, it is more difficult to decide whether HIV is also *sufficient* for the development of full-blown AIDS so that any HIV infected person will progress to the final state of AIDS. Analysing the USA's AIDS incidence data we will show that the spread of AIDS does not behave like the spread of a disease that is caused by a single sexually transmitted agent. Rather we will see that some characteristics of the dynamical behaviour of the dissemination of AIDS can only be understood if there are two independent agents, namely HIV and some other postulated infectious agent, for example, COAIDS, that acting together cause AIDS. In the meantime, *S.-Ch. Lo* and *L. Montagnier* have found that, indeed, mycoplasma might be a coagent with the postulated properties [1–4]. Furthermore, when the AIDS cases with manifestation of Kaposi's sarcoma are depicted separately from those without Kaposi's sarcoma, one obtains a fundamentally different dynamical behaviour for the spread of the Kaposi cases and the remaining AIDS cases. These observations lead us to the conclusion that even three agents might be involved in the pathogenesis of AIDS and Kaposi's sarcoma. The essential point of our hypothesis on somehow interacting coagents is that some aspects of the spread of AIDS as well as that of Kaposi disease are not in agreement with the dynamics of a disease that is predominantly transmitted by sexual or blood contacts. Before we expound this seemingly strange statement in the next section, we will first discuss the usual arguments which seem to "prove unambiguously" that, in fact, AIDS is a sexually transmitted disease.

### Epidemiological Review

When the first AIDS cases were reported to CDC in the early eighties, the majority of cases were found in homosexual men. This type of sexual risk was so characteristic that AIDS' original name was GRID (gay related immunodeficiency). The increasing number of AIDS cases in i.v. drug abusers, hemophiliacs and recipients of blood transfusions required that (beside the sexual mode of transmission) any contact with contaminated blood, blood products or tissue involves a certain risk of contracting AIDS. The best argument for the causal role of sexual and blood contacts for the outbreak of AIDS is the distribution

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Prof. *H. J. Eggers*, Institut für Virologie, Universität zu Köln, Fürst-Pückler-Str. 56, Prof. Dr. *J. Weyer*, Mathematisches Institut, Universität zu Köln, Weywetal 86–90, W-5000 Köln 41, Germany.

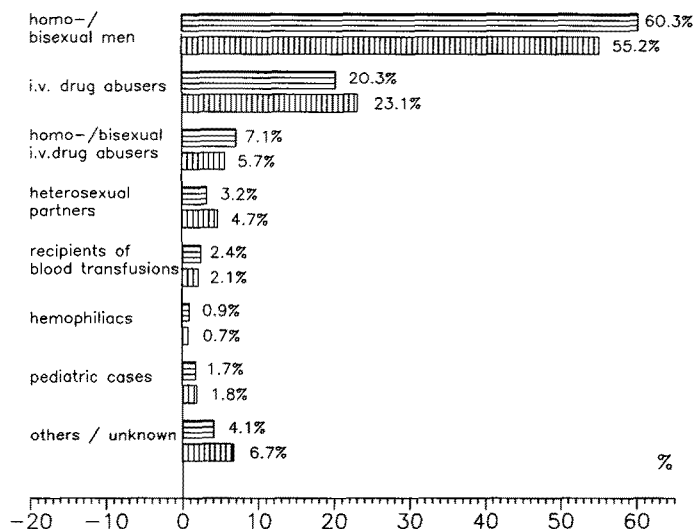


Figure 1: Distribution of the reported US AIDS cases; horizontal shading = January 1982 – June 1989, and vertical shading = July 1989 – June 1990.

of AIDS cases into several risk groups: Figure 1 shows the distribution of the cumulative US AIDS cases reported from January 1982 to June 1989 as well as the distribution of the incidence from July 1989 to June 1990. About 60.3% and 20.3% of the cumulative cases (until June 1989) are homo- or bisexual men and i.v. drug abusers, respectively [5]. An additional 7.1% of the cases are homo- or bisexual drug abusing men. Only 3.2% and 1.7% are heterosexual or pediatric cases, respectively; 0.9% and 2.4% are found in hemophiliacs and recipients of blood transfusions. Furthermore, in the time interval from July 1989 – June 1990 we find the following (actual) distribution for the AIDS incidence: homo- or bisexual men = 55.2%, i.v. drug abusers = 23.1%, homo- or bisexual drug abusers = 5.7%, heterosexual partners = 4.7%, pediatric cases = 1.8%, and recipients of blood transfusions = 2.1%. The overrepresentation of homo-/bisexual men and i.v. drug abusers strongly suggests that AIDS and its agent HIV are transmitted by sexual and blood contacts. Although the fraction of AIDS cases in heterosexual partners is continuously increasing with time, Figure 1 certainly does not really prove that AIDS is also heterosexually transmitted. However, retrospective investigations and interviews of heterosexual AIDS patients and HIV antibody positive persons show that (almost) all heterosexual AIDS patients and HIV positives had been at risk through sexual or blood contact. In this context, “to be at risk” means sexual intercourse with an HIV antibody positive person, i.v. drug abuse or treatment with contaminated blood or tissue constituents. Hence, there is no doubt of the mode of transmission of HIV by sexual and blood contacts, and since HIV is assumed to be the single and independent causative agent of AIDS one usually also concludes that AIDS is transmitted by sexual and blood contacts. The impression of a causative relationship between sexual or blood contacts and the risk of (full-blown) AIDS is also supported by previous

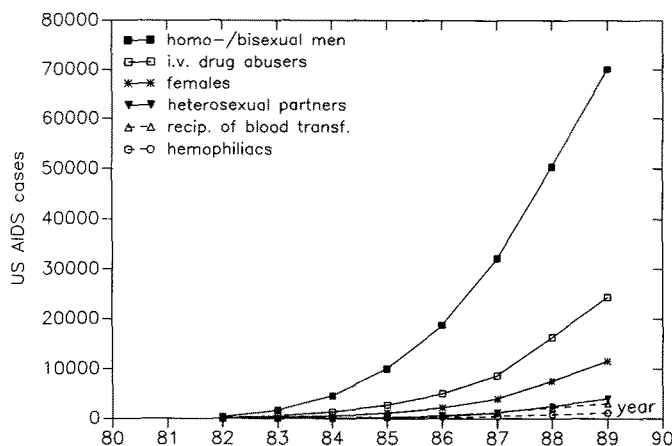


Figure 2: Cumulative number of reported US AIDS cases.

epidemiologic observations on the time development of the reported (or diagnosed) AIDS cases in the USA and some European countries. Figure 2 shows the time development of the cumulative number of reported US AIDS cases presented according to risk groups in an arithmetic scale<sup>1</sup>. Obviously, homosexual men, i.v. drug abusers, and some other risk groups are not only overrepresented in the number of AIDS cases as compared to the heterosexually generated cases, but intuitively one has the impression that the cases in homosexual men and i.v. drug abusers are even growing “more rapidly” when compared with the other groups as the gap between homosexual men or i.v. drug abusers and the other risk groups is continuously widening with time. The elevated *absolute number* of AIDS cases in homosexual men or i.v. drug abusers is commonly interpreted as an elevated *individual risk* of acquiring AIDS in these groups. However, in the next section we will see that the usual causal linkage of “overrepresentation and rapid increase of cases” and of “elevated individual risk in some subpopulations” is a seemingly plausible but superficial interpretation of the observed data. The essential point is how to measure “rapid” or “slow” growth. We shall argue that – in a certain sense – the increase of AIDS cases and individual risk are *independent* of the considered subpopulation and the corresponding sexual or drug behaviour. The characteristics of the increase of AIDS cases with manifestation of Kaposi’s sarcoma (KS) are very similar for all risk groups. Further, the characteristics of the increase of AIDS cases without manifestation of KS are also very similar for all risk groups. However, the characteristics of the increase of AIDS cases with manifestation of KS are so distinctly different from the characteristics of increase of AIDS cases without manifestation of KS that one can hardly speak of a “coherent” disease AIDS which includes both KS and non-KS cases (see next section).

<sup>1</sup> In Figures 2, 4–6 cases that are reported through the year n are recorded at the point of time n. Hence, these figures cover all cases reported until December 31, 1989. The reporting date is given by the variable “REPDATE” of the CDC definition [5].

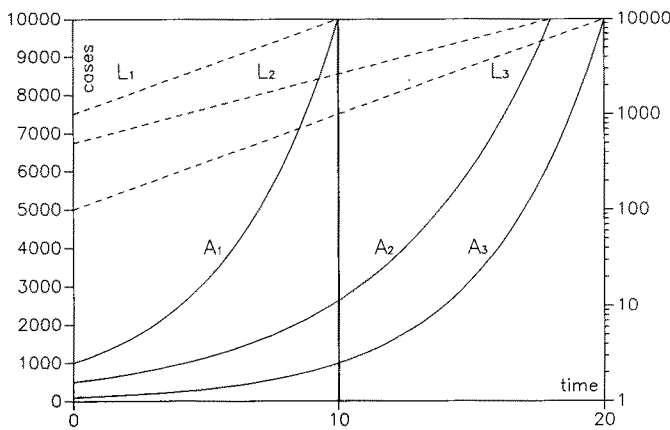


Figure 3: Spread of a fictive disease; left y-axis: arithmetic scale – curves  $A_i$ , right y-axis: logarithmic scale – curves  $L_i$ .

**Assessment of the Increase of AIDS and KS Cases**

Firstly, let us consider the time development of the spread of a fictive disease which is plotted in Figure 3. We assume that the curves  $A_1, A_2, A_3$  describe the spread of cases in some risk groups 1,2,3, respectively, by means of an arithmetic scale (left y-axis). If only the development for the time interval 0–10 is observed, it seems obvious that the number of cases in group 1 is growing “faster” than those of group 2, while group 3 is the slowest. However, if the time of reporting covers the longer time interval 0–20, the observer will be uncertain, whether curve  $A_1$  is growing “faster” than  $A_3$ . Indeed, for curve  $A_3$  exactly the same development is observed as in curve  $A_1$ ; one only has to consider a time delay of 10 time units. This means that curves  $A_1$  and  $A_3$  are running parallel with a time shift of 10 units. Hence, curve  $A_1$  does not represent a “faster” but only an “earlier” development of cases than curve  $A_3$ <sup>2</sup>. The relationship between the curves  $A_1, A_2$  and  $A_3$  becomes evident if we plot the same data on a logarithmic scale (right y-axis) so that curve  $A_1$  corresponds to the (dotted) logarithmic curve  $L_1, A_2$  to  $L_2$  and  $A_3$  to  $L_3$ , respectively. Now, the parallelism of  $L_1$  and  $L_3$  (and equivalently  $A_1$  and  $A_3$ ) is obvious, while  $L_2$  is skew relative to  $L_1$  and  $L_3$ . Although the *absolute* value of cases in group 2 is higher than the number of cases in 3 (at each instant time of the time interval 0–20), the *relative* increment of cases is “lower” in group 2 than in group 3 since the slope of curve  $L_2$  is lower than that of curve  $L_3$ . Here “relative increment” or “growth rate” means “increment of cases relative to the number of cases already present”. For example, if we con-

<sup>2</sup> Curve  $A_1$  is given by the formula  $y_1(t) = 1000 * \exp(0.2302585 * t)$  while  $A_2$  obeys  $y_2(t) = 500 * \exp(0.166429 * t)$ . Curve  $A_3$  is given by  $y_3(t) = 100 * \exp(0.2302585 * t) = y_1(t-10)$ .

<sup>3</sup> Mathematically, the relative increment or growth rate of a function  $y(t)$  is given by the quotient  $y'(t)/y(t)$ . If  $y(t)$  is the exponential function  $y(t) = a * e^{\beta t}$ , this quotient equals the constant  $\beta$ . In this case  $\beta$  is exactly the slope of the logarithmic straight lines of Figure 3.

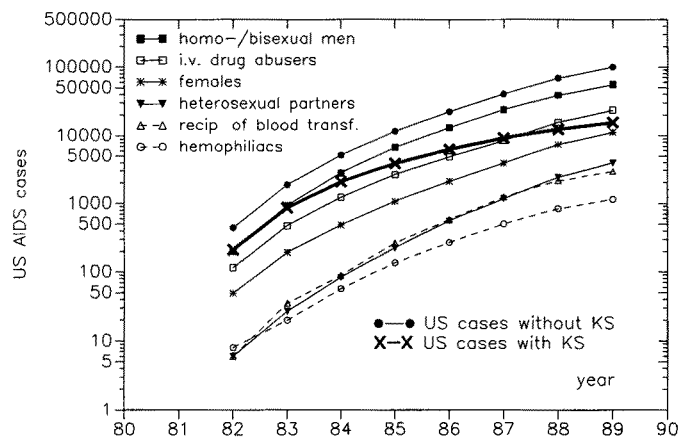


Figure 4: Cumulative number of US AIDS cases. Fine lines = cases without manifestation of KS. Heavy line = cases with manifestation of KS.

sider the growth of different populations it is obvious that a large population may have a higher absolute number of descendants than a small population, although the birth rate in the large population may be smaller<sup>3</sup>. Geometrically, the growth rate, i.e. the increment per head, corresponds to the slope of the straight line of Figure 3. Thus, the number of cases in group 2 is increasing more slowly than that in the other groups. Consequently, extrapolating all curves into the future, group 3 will “overtake” group 2, while groups 1 and 3, having the same relative increment, are “always” running parallel.

Now let us come back to reality. Making use of a logarithmic scale, Figures 4 and 5 show the time development of the cumulative number of US AIDS cases without and with manifestation of Kaposi’s sarcoma. The cases are divided into the well-known risk groups. Hence, in essence Figures 4 and 5 contain the same information as Figure 2; we have only separated the Kaposi cases from the non-Kaposi cases. Now, it is easy to see that all (thin) lines, representing different risk groups, are essentially running parallel (Figures 4 and 5). (As to the groups of recipients of blood transfusions and hemophiliacs see below.) Although semi-logarithmic diagrams like Figures 4 and 5 are commonly used for the description of the spread of AIDS, most epidemiologists failed to appreciate the meaning and consequence of the observed parallelism. However, we first note and strongly emphasize that the slightly more bent (dotted) lines describe groups with a reduced risk as a consequence of screening for HIV, so that the reduced incidence of HIV is a limiting factor for the development of AIDS in these groups (see next section).

<sup>4</sup> The observed parallelism also holds if one records the AIDS cases according to the date of diagnosis (DXDATE) instead of the date of reporting (REPDATE). As a consequence of delayed reporting the corresponding curves for the date of diagnosis would only cover a shorter period of time (1982–1988).

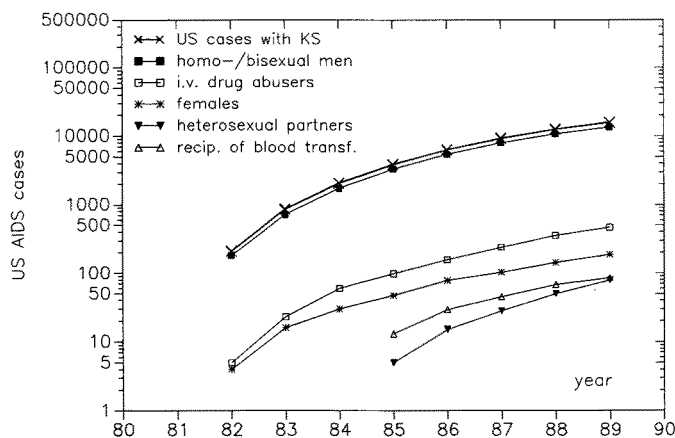


Figure 5: Cumulative number of US AIDS cases with manifestation of Kaposi's sarcoma.

As we have seen above, the parallelism of the epidemic curves means that a similar development is observed for all risk groups; one only has to consider a certain time shift for different groups. Since all logarithmic curves in Figures 4 and 5, except the heavy one, exhibit essentially the same slope<sup>4</sup> we conclude that the relative increment (i.e. the number of new cases relative to the actual number of cases) is the same for all risk groups. The identity of the relative increment for all risk groups is extremely surprising since AIDS is considered to be a sexually transmitted disease. For a sexually transmitted disease one intuitively expects that the relative increment of cases should depend on the sexual behaviour of the risk group considered. Hence, for groups with a high level of risky sexual or drug behaviour (homosexual men or i.v. drug abusers, for example) [6, 7] the growth rate – or equivalently the quotient of new cases  $y'(t)$  relative to the actual number of cases  $y(t)$  – should be greater than for groups with a lower level of risky behaviour (heterosexual partners, for example [8–10]). However, this difference of growth rates which is an essential property of sexually transmitted diseases is *not* observed for AIDS. The identity of the growth rates for all risk groups is in agreement with results of Padian et al. [11, 12], obtained from cohort studies, stating that the risk of AIDS infections is not correlated (in a linear way) with the level of sexual activity (number of partnerships) of the corresponding index person. The parallelism of the curves obtained from two groups with a totally different mode of transmission and different individual risk, viz. homo-/bisexual men and i.v. drug abusers, is particularly striking. To summarize, the parallelism of the epidemic curves for different risk groups means that, in a certain sense, the spread of AIDS does not behave like the spread of a sexually transmitted disease. On the other hand, AIDS *must* be correlated with sexual behaviour, as we have the overrepresentation of some high level risk groups, which has to be interpreted as an earlier but not faster development of cases in these groups. Furthermore, there is no doubt that HIV is transmitted by sexual or blood contacts. Thus, we

have a flagrant contradiction in the interpretation of the epidemiological data: the agent is sexually transmitted, but the manifest disease does not display the dynamics expected for epidemics transmitted by sexual or blood contacts. Before we resolve this contradiction in the next section, we will refer to another aspect of the parallel curves of Figures 4 and 5. While the curves for different groups with AIDS exhibiting Kaposi's sarcoma are running parallel (Fig. 5), each curve for a non-Kaposi group is skew relative to any curve for a group exhibiting Kaposi's sarcoma. This can be seen, if we consider the heavy line in Figure 4 which describes the time development of AIDS cases with Kaposi's sarcoma found in all risk groups, since the characteristically common slope for all Kaposi cases is considerably smaller than the common slope for all non-Kaposi cases. This means that the Kaposi cases spread "slower" than the non-Kaposi cases, and the spread of the two manifestations of AIDS does not fit the spread of a "coherent" disease. Here it is interesting to point out that Beral et al. [13] report that KS cases are more common among those who had acquired HIV by sexual contact than parenterally and that women are more likely to have KS if their partners have been bisexual men rather than i.v. drug abusers. Hence, one has to consider that Kaposi sarcoma is by itself a distinct communicable disease.

Until now we have always argued by the use of cumulative data. However, similar conclusions hold if we replace the curves for cumulative data by curves for the (yearly) incidence (Figure 6). Here, the same parallelism is observed, even if the effects for cumulative data are more striking, as the cumulation of data is a smoothing procedure damping statistical variance.

### Multiple Agents for AIDS and Kaposi's Sarcoma

The results of the preceding section may be summarized as follows: 1. There is no AIDS without a preceding HIV infection; 2. HIV is essentially transmitted by sexual or blood contacts; 3. The time development of the cumulative

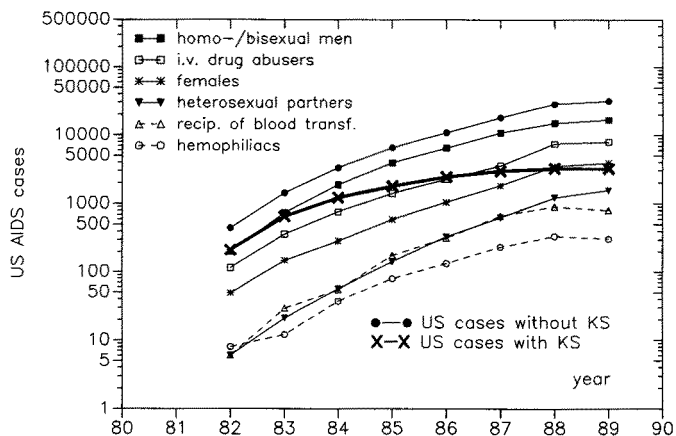


Figure 6: Yearly incidence of US AIDS cases. Fine lines = cases without manifestation of KS. Heavy line = cases with manifestation of KS.

AIDS cases (and of the AIDS incidence) split into special risk groups is essentially given by curves running parallel, so that the relative risk of acquiring AIDS is nearly the same for all risk groups; 4. Highly active groups (homo-/bi-sexual men, i.v. drug abusers) display an earlier but not faster increment of AIDS cases than groups with a lower level of sexual or drug activity (heterosexual partners, e.g.); 5. Statements 3 and 4 even hold if we restrict our considerations to AIDS cases with or without manifestation of Kaposi's sarcoma, respectively; and 6. The (logarithmic) curves describing the time development of KS cases for different risk groups are running parallel, and the corresponding curves of the non-KS cases are running parallel for different risk groups. However, all logarithmic curves for KS cases are skew relative to the corresponding curves for the non-KS cases.

At first sight, for example, there seems to be a contradiction between statements 2 and 3. If the agent of AIDS is sexually transmitted, then highly active groups should have a higher relative risk of acquiring AIDS and the curves for different risk groups should be skew. However, this is not observed. Precisely, the authors tried to explain the equalized relative risk by the low infectivity of HIV per contact [14]. However, a further mathematical analysis [15] showed that even the low probability of infection per contact is not sufficient to cause the leveling of the relative risk of highly and weakly active groups. The seemingly flagrant contradiction of statements 2 and 3 can be resolved by the assumption of two independent, somehow interacting agents. In addition, the fundamentally different dynamics of the spread of KS and non-KS cases requires the postulation of a third agent.

In order to understand the six empirical statements above we advance the following hypotheses [14]: I) AIDS and Kaposi's sarcoma (KS) are independent (but "closely linked") diseases. Here we denote by "AIDS" only cases of the Acquired Immunodeficiency Syndrome that do not involve KS; II) Full-blown AIDS (without KS) occurs only if HIV and some specific unknown coagent, say COAIDS, are present; III) AIDS with the manifestation of KS only occurs if HIV and some other specific unknown coagent, say COKS, are present. In exceptional cases, however, KS is observed in immune suppressed persons without preceding HIV infection; IV) HIV is sexually transmitted with exponential growth at the beginning of the disease. The rate of transmission of HIV depends on the sexual and drug behaviour of the considered subpopulation. In the phase of saturation the spread of HIV is damped like, for example, a logistic curve; V) The spread of the agents COAIDS and COKS occurs randomly so that the transmission of each of these agents is uniform and independent from the sexual and drug behaviour. Actually, we pass through the early phase of the spread of COAIDS and COKS, respectively, which happens to spread exponentially, too. The spread of COAIDS is independent of the spread of COKS. Both agents have their own dynamics and mode of transmission; VI) The initial doubling time of

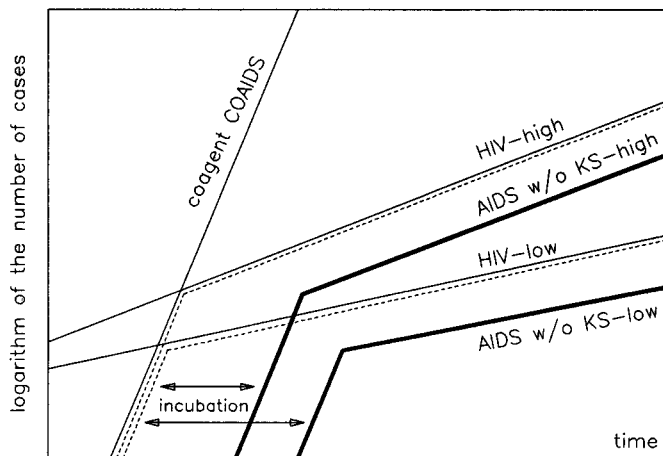


Figure 7: Postulated interaction of HIV and the hypothetical agent COAIDS.

COKS is significantly lower than that of COAIDS. The doubling rate for the spread of HIV infections is considerably lower than that of COAIDS and COKS, respectively, and depends on sexual behaviour. The starting point of the epidemic spread of HIV is some decades earlier than the beginning of the COAIDS and COKS epidemics, respectively; and VII) The incubation time for the outbreak of full-blown AIDS without or with manifestation of Kaposi's sarcoma starts when HIV and COAIDS or HIV and COKS, respectively, are present for the first time. In order to interpret the overrepresentation of groups with a high level of risky behaviour in the number of AIDS cases, we postulate that the duration of the incubation time is inversely related to the level of risky sexual and drug activity. With this assumption it is possible to understand the wide range of incubation times.

Next, we will describe why the hypotheses I-VII are an adequate base for the understanding of the previous statements 1-6. In particular, we will see that the strange phe-

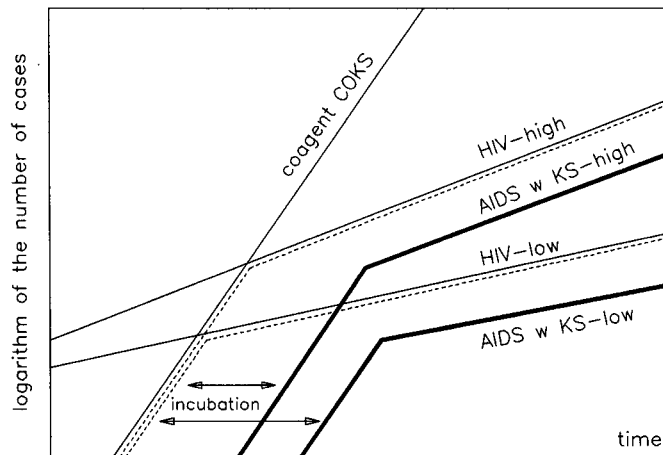


Figure 8: Postulated interaction of HIV and the hypothetical agent COKS.

nomenon of parallelism can be reproduced by computer simulation for groups with different levels of risky behaviour. Our arguments are illustrated in Figures 7 and 8 which schematically describe the time development of the number of cases by means of a logarithmic scale. We assume that the curve for COAIDS describes the spread of the coagent in the sample population. The spread of COAIDS (Figure 7) occurs randomly so that the slope of the COAIDS curve is valid for all groups. We further assume that the curves HIV-high and HIV-low describe the spread of HIV in some subpopulations with a high or low level of risky behaviour, respectively. Since HIV is sexually transmitted the different levels of risky behaviour will cause different slopes for the curves HIV-high and HIV-low. The incubation time only starts when both agents, HIV and COAIDS, are present in an organism for the first time. Hence, in a simplified way<sup>5</sup> the number of candidates for the subsequent outbreak of manifest AIDS can be illustrated by the dotted lines which correspond to the highly and weakly active subpopulations, respectively. After a certain incubation time, which is assumed to be shorter for persons with a high level of risky behaviour (see hypothesis VII), the carriers of both infections (indicated by the dotted lines) will develop full-blown AIDS. Hence, one only has to shift the dotted lines to the right in order to obtain the time development of the number of AIDS cases in the highly or weakly active population which are indicated by the heavy lines AIDS-high and AIDS-low. As the hypothetical coagent is COAIDS, which is assumed to be unrelated to the manifestation of Kaposi's sarcoma, the AIDS cases recorded in Figure 7 do not include KS cases. The time shift between the dotted and heavy lines is exactly the mean incubation time, depending on the risk group.

Hence the interaction of HIV and some coagent results in the overrepresentation of highly active groups in the number of AIDS cases and the parallelism of the curves for different groups in the early phase of the disease which is in good agreement with the observed data. It is an essential point that in the first phase of the disease the development of AIDS cases is controlled by the spread of COAIDS, which is the limiting factor causing the levelling of the increase of AIDS cases for different groups. In this phase the number of HIV infections exceeds the number of COAIDS infections. In the second phase of the disease, when the number of COAIDS infections exceeds the number of HIV infections, the spread of HIV will be the limiting factor for the spread of AIDS so that in the second phase the growth rate of AIDS cases indeed depends on the level of risky behaviour. Under these conditions, different slopes for different groups are observed. The observed sharp decrease of AIDS cases in hemophiliacs and recipients of blood transfusions (dotted lines of Figures 4 and 6) could

<sup>5</sup> More exactly, the number of persons in a certain risk group who are infected by both agents COAIDS and HIV is the absolute number of persons infected by COAIDS times the fraction of carriers of HIV in the considered subpopulation.

mean that these groups are passing through their "second phase" when the dynamics is controlled by the number of HIV infections which are strongly reduced by screening of blood and blood products. In general, assuming that the curves AIDS-high and AIDS-low describe observed data, most epidemiologists will interpret the crack in these curves as an effect of damping. However, if two agents are involved, the crack point only indicates that the control of the epidemiological dynamics changes from one agent to the other.

Until now we have discussed the influence of the spread of COAIDS. However, the above arguments analogously hold if the coagent COAIDS is replaced by the coagent COKS. In this case the curves describing the spread of AIDS (without manifestation of KS) are replaced by curves describing the spread of Kaposi's sarcoma (Figure 8). Now, it is assumed that HIV together with the coagent COKS is responsible for the outbreak of AIDS with manifestation of Kaposi's sarcoma. The candidates for the development of KS infected by the two agents HIV and COKS are symbolized by the dotted lines for different levels of risky behaviour. After a certain incubation time these persons will develop AIDS with manifestation of KS. The role of the two coagents COAIDS and COKS, responsible for full-blown AIDS (without KS) and Kaposi's sarcoma (Figures 7 and 8), respectively, will be obvious through the finding that the AIDS cases without and with manifestation of KS are described by curves with extremely different slopes (Figures 4 and 5). This effect can be understood if the KS cases have their own specific agent COKS and if the AIDS cases (without manifestation of KS) have their own specific coagent COAIDS which has a higher rate of infectivity than COKS so that the slope of any COKS curve is lower than the slope of all COAIDS curves (Figure 4). It has already been suggested by Beral et al. [13] that Kaposi's sarcoma in persons with AIDS might be caused by an as yet unidentified infectious agent.

Finally, Figure 9 describes the spread of a two-agent disease according to a simple mathematical model<sup>6</sup> [14]. We restrict our considerations to the spread of HIV, the spread of an arbitrary coagent CO which may be COAIDS or COKS, and the resulting disease, which may be AIDS (without manifestation of KS) or Kaposi's sarcoma, respectively. For a fictive population the figure describes the spread of the coagent CO, and the spread of HIV in five

<sup>6</sup> Let HIV and some cofactor spread in a sample population of  $N = 10^6$  individuals. It is assumed that HIV ( $i = 1$ ) is spreading according to the logistic law  $y_1(t) = y_1(T\gamma) \cdot N \cdot \{y_1(T\gamma) + (N - y_1(T\gamma)) \cdot \exp[-\gamma N(t - T\gamma)]\}^{-1}$  with  $T\gamma = -30$  and  $y_1(T\gamma) = 10$  so that there is a number of ten HIV carriers at the initial time  $T\gamma = -30$ . The initial growth rate  $\gamma$  depends on the level of risky behaviour. Furthermore, it is assumed that the coagent ( $i = 2$ ) is spreading according to  $y_2(t) = y_2(O) \cdot N \cdot \{y_2(O) + (N - y_2(O)) \exp(-\beta N t)\}^{-1}$  with  $y_2(O) = 100$  so that we find 100 carriers of the cofactor at the initial time  $t = O$ . Finally, it is assumed that the incubation time  $\delta$  of AIDS starts when both agents are present for the first time, where  $\delta$  is described by  $\delta = 2 + \sigma/\gamma$  with  $\sigma = 5 \cdot E^{-7}$ . Then the number of AIDS cases is given by  $y(t) = y_1(t - \delta) \cdot y_2(t - \delta)/N$ . This curve is plotted for different values of  $\gamma$ . Details are given in [14].

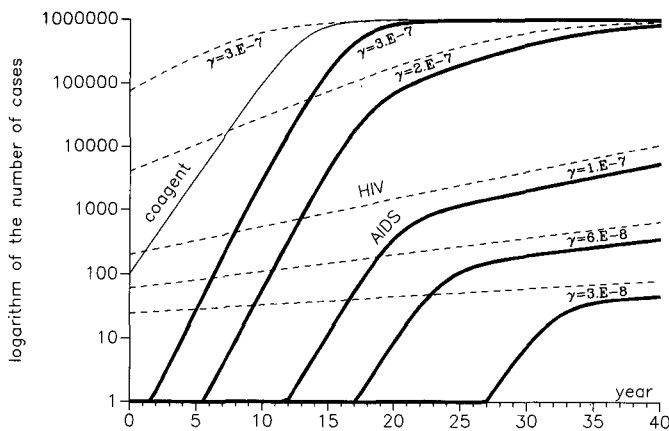


Figure 9: Interaction of HIV and some coagent leading to AIDS.

risk groups with different levels of risky activity (dotted lines) according to a logistic law. The heavy lines describe the number of patients contracting the full-blown disease (AIDS or KS, respectively). In this simple computer simulation the cracks of the corresponding heavy lines of Figure 9 become smoothed so that the dynamical control of the disease changes gradually from the coagent to HIV. Figure 9 also shows the overrepresentation of highly active groups and the parallelism of curves in the first phase while the curves for the full-blown disease become skew in

the second phase when HIV is a limiting factor. Even more sophisticated models [16] lead to similar results.

### Discussion of the Multi-Agent Theory

In the previous sections we showed that the specific structure of the spread of AIDS is *not* in agreement with the dynamics of a disease transmitted by sexual or blood contacts. On the other hand, there is no manifestation of AIDS without a preceding infection with HIV, which is transmitted by sexual or blood contacts. Furthermore, we observe the different growth rates for KS and non-KS cases. These seemingly contradicting statements can be untangled if HIV together with some coagent COAIDS causes full-blown AIDS (without manifestation of KS) while HIV together with some other coagent COKS is responsible for AIDS with Kaposi's sarcoma. The common component HIV of both diseases clears up the "close linkage" of AIDS and KS which is discussed by Beral et al. [13] who report that KS could also be a communicable disease. The concept of two independent infectious agents leading to disease is by far no novelty in microbiology. For example, influenza virus is activated by proteinases of *Staphylococcus aureus* or other bacteria. This activation leads to severe and often lethal pneumonia [17].

In the preceding sections we only argue by the structural properties of the reported data. In the meantime, the possible substantial nature of the cofactors, the existence of which is predicted by formal properties, seems to become a microbial reality [1-4, 13, 18-30].

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## Book Review

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A. J. Zuckerman, J. E. Banatvala, J. R. Pattison  
**Principles and Practice of Clinical Virology**  
Second edition, 643 pages  
John Wiley & Sons, Chichester, 1990  
Price: £ 85.00

This book gives a detailed description of all clinically important viruses. Most of the chapters are very up-to-date and contain some information rarely found in other textbooks. The chapter length is usually dependent on the clinical importance of a virus and on present knowledge. The book is composed of 27 chapters, arranged on 643 pages. A small disadvantage is that not a single coloured picture is included of the many clinical symptoms of viral lesions presented. As a general rule, all chapters cover the description of the virus, its pathogenicity, epidemiology, clinical features, treatment (when available) and prevention and mostly vaccines.

The first 140 pages deal with herpes viruses, specifically their latency and reactivation. Cytomegalovirus perinatal infection and presentation in the immunocompromised host is discussed in depth. A clear statement is made on the importance of human herpes virus 6. Hepatitis viruses are reviewed in 30 pages. The A and B virus are thoroughly presented, unfortunately the C virus only as a short annex. Viruses associated with acute diarrhoeal disease like rota, adeno, astro, Norwalk, calici, small round (par-

vo- and adeno-associated) corona viruses, Breda-like agents, their diagnosis and possibilities of vaccination are explained in 45 pages. Since treatment is not indicated, this is omitted.

Respiratory tract viruses are presented in 100 pages: influenza, parainfluenza, respiratory syncytial virus, adeno, rhino and corona viruses are described, also economic factors and special presentation and management in childhood. Measles and complications (20 pages), rubella and congenital infection (35 pages) and mumps virus (12 pages) and their prevention via vaccination are precisely outlined. The validity of enteroviruses is mentioned in 20 pages, especially polio virus vaccination. Pox viruses span 20 pages; in accordance with the reduced importance of human pox, the focus is on monkey pox, cow pox and molluscum contagiosum.

Alpha, flavi and Bunya viruses are presented in 12 pages, the overlapping viral haemorrhagic fevers take up 24 pages, and their pathogenesis 15 separate pages. A chapter on rabies virus gives very thorough information on pathogenesis and post exposure vaccination protocols. Forty pages deal with management and treatment of papova, papilloma and polyoma viruses. Human parvoviruses span ten pages, human retroviruses the last 50 pages; here an extensive review on leukemia viruses and immunodeficiency viruses, treatment and prevention is given.

L. Gürtler  
München