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Management of the HIV-infected patient before the Development of AIDS

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Abstract
19th century and early 20th century physicians taught their students: "Know syphilis and you will know medicine." In this last decade of the 20th century, physicians could justifiably substitute the word 'AIDS' for 'syphilis'. Every aspect of human immunodeficiency virus (HIV) infection - whether the epidemiology, immunology, pathogenesis, diagnosis, management or prevention - presents an intellectual challenge to our profession. Politicians, educationalists, doctors and the lay public ignore this disease at their peril. We all have a duty to ourselves and to future generations to do everything possible to control and ultimately to eliminate HIV infection.

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James A Gray, Olim Præses

Dr. Gray was Senior President of the RMS in his day and during that time started the journal, 'Res Medica'. So we were 'well chuffed' when he offered to write an article for this resurrection of his creation, especially since it clarifies many of the incongruities presented in current literature concerning the clinical management of these special patients.

19th century and early 20th century physicians taught their students: "Know syphilis and you will know medicine." In this last decade of the 20th century, physicians could justifiably substitute the word 'AIDS' for 'syphilis'. Every aspect of human immunodeficiency virus (HIV) infection - whether the epidemiology, immunology, pathogenesis, diagnosis, management or prevention - presents an intellectual challenge to our profession. Politicians, educationalists, doctors and the lay public ignore this disease at their peril. We all have a duty to ourselves and to future generations to do everything possible to control and ultimately to eliminate HIV infection.

This article attempts to outline the general management of HIV-infected patients before they develop AIDS. To understand the philosophy behind such management, one must be conversant with the natural history of the infection. The Center of Communicable Disease Control (CDC), Atlanta, Georgia, has developed a system of classification which will be used throughout this article (see Figure1). Thus patients with the acute seroconversion illness which resembles glandular fever, if it is recognised for what it is - and often it is not or forgotten about - are classified as **Group 1**. There follows a long incubation period with a mean of 8-9 years (range 2-15 or longer) during which the patient remains largely well clinically (**Group 2**). This is the group upon which this article will concentrate. When the disease next becomes symptomatic the patient enters **Group 3** (formerly designated Persistent Generalised Lymphadenopathy or PGL) or else he or she develops full blown AIDS (**Group 4**).

New Classification System

Patients with AIDS may have minimal symptoms - say between attacks of opportunistic infection - or be desperately ill. The subgroups within Group 4 disease are :-

Sub-group A - fever persisting for longer than one month, involuntary weight loss in excess of 10% or diarrhoea lasting for more than one month without an alternative explanation. Sub-group A corresponds with the previously designated AIDS related

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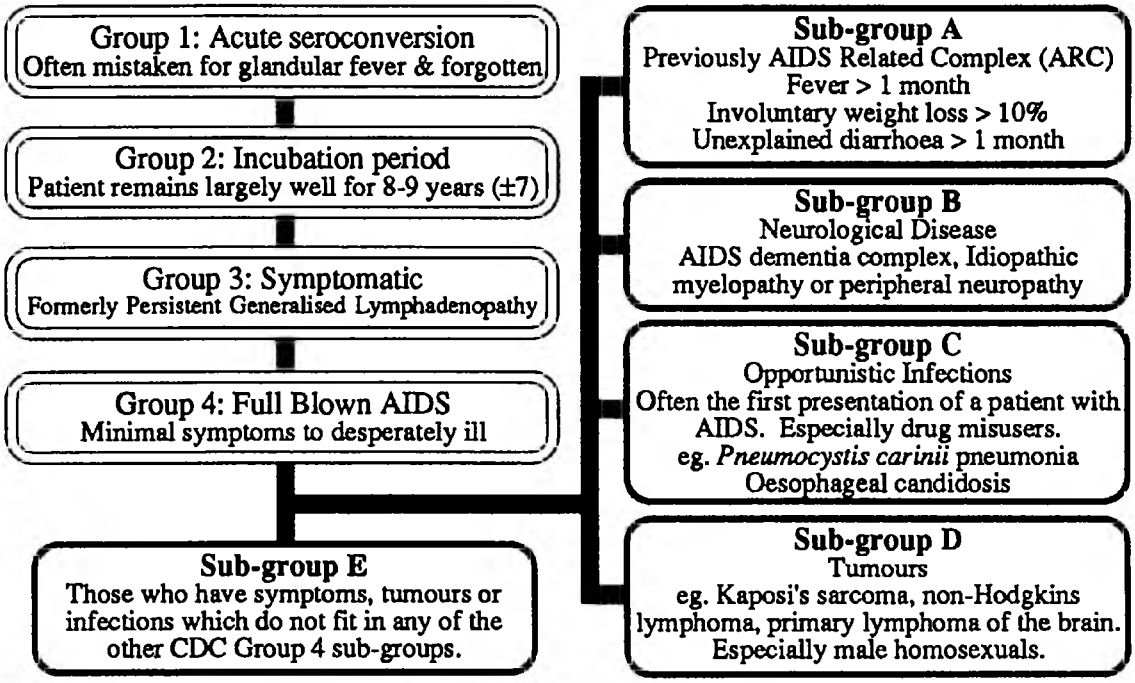


Figure 1: Abbreviated CDC classification of the natural history of HIV infection.

complex or ARC.

Sub-group B includes those patients with neurological disease like AIDS dementia complex, myelopathy or peripheral neuropathy without an alternative explanation.

Sub-group C represents those patients with opportunistic infections in the context of HIV infection or illness indicating a defect of cell mediated immunity. Many patients, especially those who have acquired their infection by intravenous drug misuse, first present with AIDS in this category by developing *Pneumocystis carinii* pneumonia (PCP), or other chronic or invasive parasitic, viral or fungal infections.

Sub-group D includes those patients with tumours such as Kaposi's sarcoma (KS), non-Hodgkins lymphoma or primary lymphoma of the brain. Many male homosexuals but very few intravenous drug misusers with HIV infection present with or are at some time affected by KS. The reason for this is not yet known.

Finally **Sub-group E** is a convenient category for patients with HIV infection whose symptoms, tumours or infections do not neatly fit into the other sub-groups of the CDC Group 4.

Without a clear knowledge of this classification, necessarily abbreviated here, the physician looking after HIV-infected patients who are asymptomatic to date cannot be aware of the many possible ways in which AIDS may present and so be able to investigate expeditiously and promptly treat serious disease when it does arise. Correct management of HIV infection is concerned with the intelligent anticipation of problems.

The length of any patient's stay in Group 2 (asymptomatic HIV infection) depends upon age, sex (including pregnancy), race

fitness at the start of the illness, lifestyle eg. persistent drug misuse, alcoholism, undernutrition, and probably also the infecting dose or doses of HIV and whether such insults are continuing. Ability to avoid other infections eg. sexually transmitted disease may reduce antigen load and also keep the patient asymptomatic for longer. Education is therefore an important factor in patient management, not only in reducing the risk of infection to others, but also in the encouragement of a lifestyle that will delay the onset of AIDS in that individual.

Another factor that may, in the future, help patients in Group 2 to keep well and delay the onset of AIDS is the judicious use of the anti-retroviral drug zidovudine (azido-thymidine, AZT or Retrovir). Antifungal, antiparasitic or other antiviral agents which are often used as *secondary* prophylaxis after AIDS has developed, may sometimes also be employed for *primary* prophylaxis. The decision about what drugs to use and when will depend on how the patient is, judged by *regular* clinical and laboratory screening. Whilst this monitoring and prophylaxis are proceeding, it is important to remember the psychological wellbeing of the HIV-infected individual who may also need the patient support of an experienced counsellor.

Expensive drugs like AZT are ill afforded even in the relatively affluent western world. In some parts of Africa where 30% of the population may be HIV infected, such therapy is simply unavailable.

A possible outline of management of the HIV-infected patient in CDC Group 2 follows, but it should be remembered that with our rapidly increasing understanding of the disease and the development of new drugs and strategies, this may require radical revision within months rather than years.

Zidovudine

At the time of writing the results of the British-French collaborative study (Concorde) on the use of AZT versus placebo in asymptomatic HIV-infected patients are not known. An American study by the National Institute of Allergy and Infectious Diseases reported in the summer of 1989 that 50 of the 713 participants who started on the study between 3 and 30 months before had progressed from early ARC (CDC Group 4 A) to more advanced ARC or full blown AIDS. Thirty-six of these 50 had been taking placebo and 14 of them 1,200mg AZT daily. AZT only seemed to benefit those with T4 lymphocyte counts of between 200 and 800 mm^{-3} (Normal range 500-1000 mm^{-3}).

AZT is better tolerated in asymptomatic patients fewer of whom develop bone marrow toxicity than when it is given to patients with AIDS. The theoretical risk of the development of AZT resistance by HIV *in vivo* has so far not been shown although it has been demonstrated *in vitro*.

It would therefore seem likely that CDC Group 2 patients could benefit from early treatment with AZT and that, despite the expense, not only of the drug itself, but also of the mandatory monitoring for toxicity that should accompany its use, it may in future be recommended at this stage of the disease. The dosage will depend upon the the results of the Concorde study but is likely to be less than that presently used. This will probably reduce dose-related toxicity and of course expense.

Clinical and laboratory monitoring

At each out-patient visit, perhaps every 3-6 months in the apparently well patient,

Symptoms to look for:

fever dyspnoea cough
skin rashes night sweats
weight loss oral thrush
reduced exercise tolerance
diarrhoea and vomiting
visual impairment

Less specific symptoms

headache poor memory
undue fatigue lethargy
malaise

Figure 2: Symptom checklist for CDC group 2 patient consultation.

enquiry should be made about symptomatology as detailed in Figure 2.

The patient must be weighed at each attendance. Examination should concentrate on a search for lymphadenopathy, skin rashes and tumours, an oral inspection for hairy leukoplakia and candidosis and finally ophthalmoscopy for evidence of retinitis caused by HIV itself, toxoplasma and cytomegalovirus.

If the patient is a known intravenous drug misuser, he or she must be questioned about any continuing habit and inspected both in likely and unlikely sites of venous access for puncture marks. Consideration may be given to registering the patient with the Home Office as a drug misuser and supplying him or her with maintenance methadone as a substitute for intravenously administered opiates like heroin.

Basic laboratory monitoring will depend upon whether AZT is being used in which case the patient should be seen every 1-2 months rather than less often. A full blood count, including platelets, should always be done and if available, a T4 lymphocyte count and a check for the HIV core antigen P24. A fall in peripheral blood lymphocytes (especially the T4 cells) or platelets, the development of anaemia, the presence of antigenaemia and elevation of ß-2 microgobulin and gamma-globulins generally suggest advancing disease.

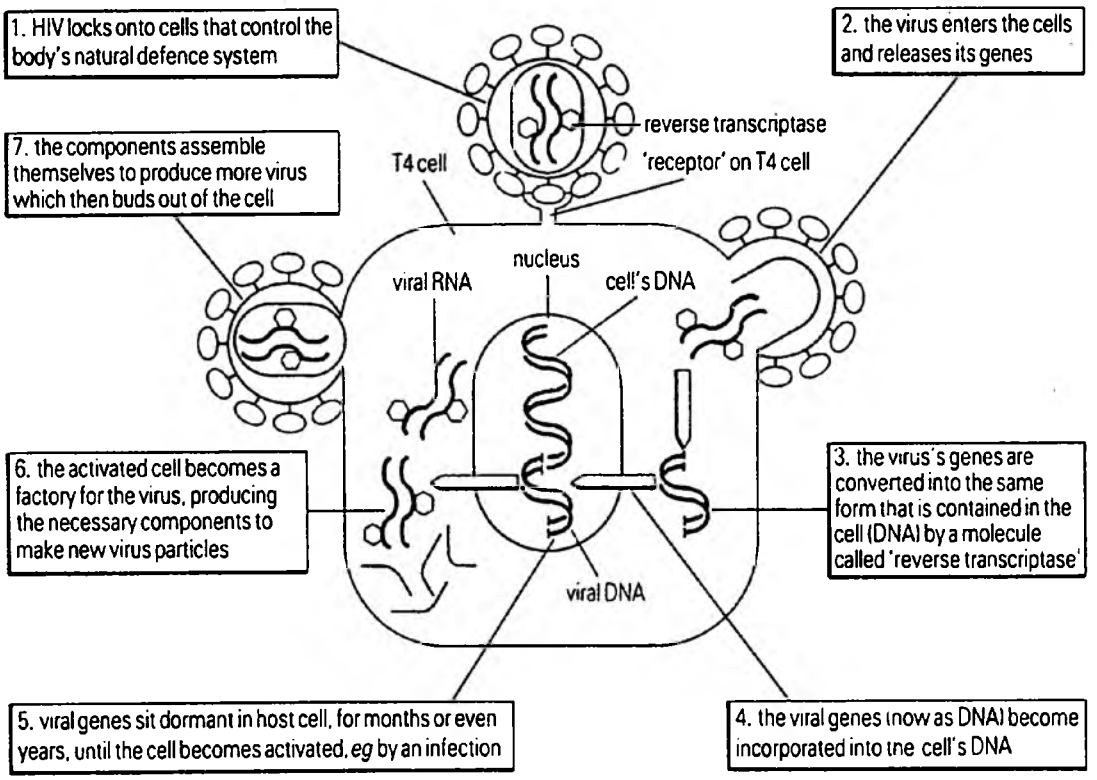
It may be necessary to stop or reduce the dose of AZT if the erythrocytes and granulocytes are much depleted. Transfusion of blood, platelets or the administration of gamma-globulin may be indicated. A haemoglobin below $8gdL^{-1}$ or a neutrophil count of less than $750mm^{-3}$ is an absolute indication for stopping AZT and for considering blood transfusion. AZT may be cautiously restarted in a reduced dose (i.e. less than the usual $3.5mgkg^{-1}$ 4hrly) if the haemoglobin has been well maintained after transfusion. AZT may be used occasionally as a platelet *booster*, but it is surprising how long HIV infected patients can tolerate very low platelet counts without bleeding.

The importance of monitoring T4 cells, other formed elements in the blood and antigenaemia is not simply to check for drug toxicity but also to anticipate if the patient is likely to be progressing towards CDC Groups 3 or 4 so that follow-up may be intensified and the general practitioner advised to refer the patient to hospital urgently if this seems appropriate. Early intervention in opportunistic infections is often life-saving but can only happen if anticipated. The earliest signs and symptoms must be recognised, investigated and appropriate treatment begun at once.

Primary prophylaxis for opportunistic infections

As about 50% of patients who progress to AIDS do so by developing PCP, primary

HOW HIV HIJACKS THE BODY'S T4 CELLS



prophylaxis against this disease would seem appropriate. Whereas cotrimoxazole prophylaxis against recurrence of PCP has been well tolerated, the administration of cotrimoxazole to prevent a first attack of PCP has been associated with a very high incidence of side-effects.

It is possible that inhaled pentamidine which again has a good record in the prevention of recurrences of PCP may in future have a place in primary prophylaxis but at the time of writing there is insufficient evidence to recommend it routinely. Fortnightly or 3-weekly doses of 300mg inhaled pentamidine are generally safe. If bronchospasm occurs it can usually be controlled in the next administration by inhalation of 2.5mg salbutamol immediately before the pentamidine. An alternative to inhaled pentamidine is the weekly administration of one tablet of pyrimethamine/sulfadoxine (Fansidar) although skin rashes and even the Stevens-Johnson Syndrome can result.

Other possibilities for primary prophylaxis which are less contentious include the administration of acyclovir to prevent *Herpes simplex* and *Herpes zoster* both of which can occur in milder forms without technically advancing the patient's CDC classification to Group 4. Antifungal prophylaxis with ketoconazole is sometimes associated with hepatic toxicity and the newer fluconazole in a daily dose of 50mg is more acceptable and has the advantage of crossing the blood-brain barrier and so, theoretically at least, lessening the risk of cryptococcal

meningitis.

Primary prophylaxis against toxoplasmosis, cryptosporidiosis, cytomegalovirus and mycobacterial infection may be goals for the future but often present problems of toxicity when tried.

Counselling, support and education

In addition to the morale boosting and support that a trained counsellor can provide, opportunities frequently exist when risk reduction for the patient, relatives and consorts can be discussed and reinforced. The provision of condoms and instruction in safe sexual practices, the exchange of dirty for clean syringes and needles for the drug abuser who will not desist from his or her habit or the establishment of a maintenance methadone substitution programme are all areas that may need to be explored.

A combined team approach is essential to the good management of HIV infected patients at whatever stage of their disease they happen to be in. Patients in the asymptomatic stages can enjoy a reasonably satisfactory lifestyle for many years if they are given the benefit of expert care and advice. New therapies may be developed. HIV-infected patients should therefore always be encouraged with a cautious but realistic degree of optimism.

Suggestions for further reading

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